Antihistamine H1RAs for COVID-19: real-time meta analysis of 15 studies

@CovidAnalysis, September 2024, Version 10
https://c19early.org/h1meta.html

Abstract

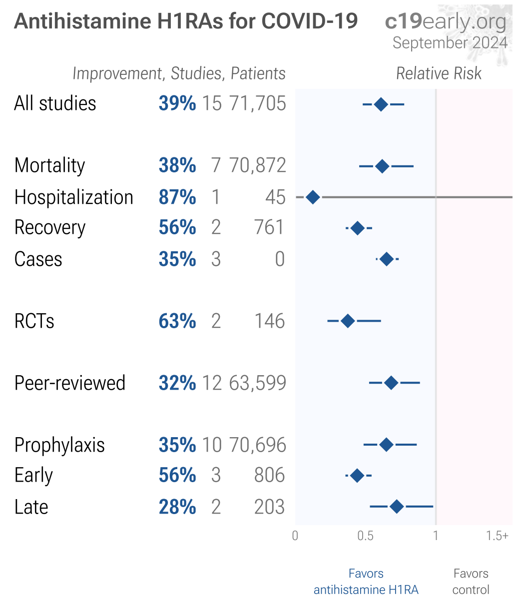
Statistically significant lower risk is seen for mortality, recovery, and cases. 8 studies from 7 independent teams in 4 countries show significant improvements.

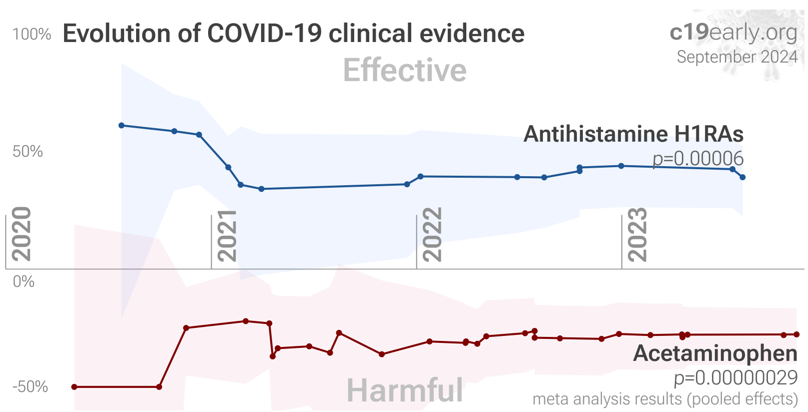
Meta analysis using the most serious outcome reported shows 39% [23-52%] lower risk. Results are similar for peer-reviewed studies and better for Randomized Controlled Trials. Early treatment is more effective than late treatment.

Results are very robust — in exclusion sensitivity analysis 8 of 15 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

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 may be more effective.

All data to reproduce this paper and sources are in the appendix.





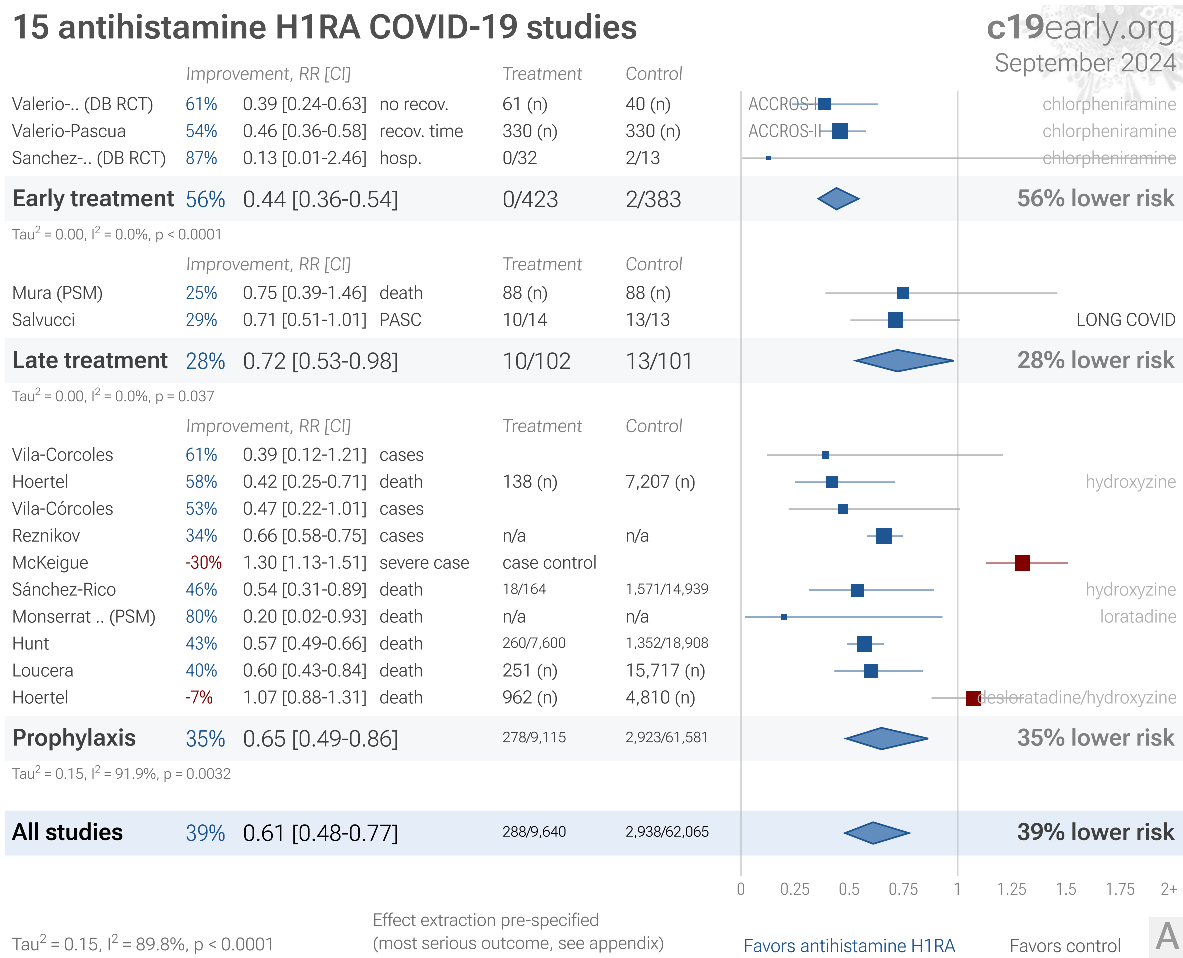
ANTIHISTAMINE H1RAS FOR COVID-19 — HIGHLIGHTS

Antihistamine H1RAs reduce risk with very high confidence for mortality, cases, and in pooled analysis, low confidence for recovery, and very low confidence for hospitalization.

10th treatment shown effective with ≥3 clinical studies in December 2020, now with *p* = 0.00006 from 15 studies.

Outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor.

Real-time updates and corrections, transparent analysis with all results in the same format, consistent protocol for 92 treatments.



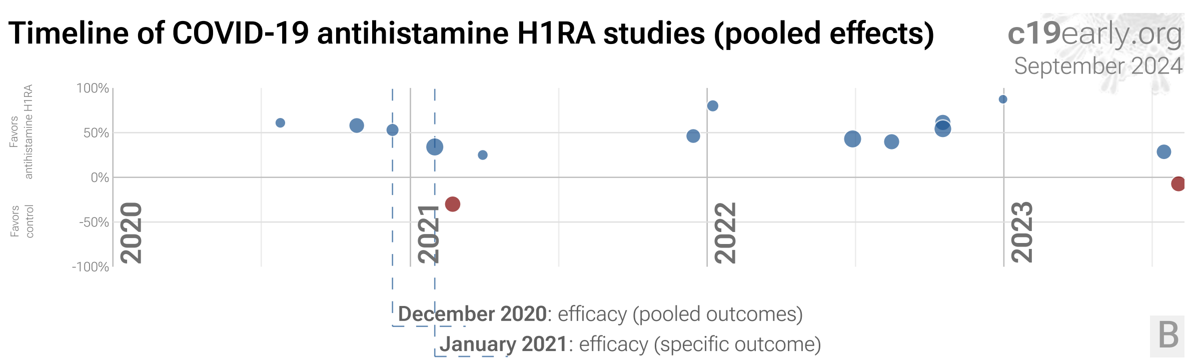


Figure 1. **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in antihistamine H1RA studies.** The marked dates indicate the time when efficacy was known with a statistically significant improvement of ≥10% from ≥3 studies for pooled outcomes and one or more specific outcome. Efficacy based on specific outcomes was delayed by 1.7 months, compared to using pooled outcomes.

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[1-9] and cognitive deficits[3,8], cardiovascular complications[10-12], 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,13-17], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 7,000 compounds may reduce COVID-19 risk[18], 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 Antihistamine H1RAs 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, and Randomized Controlled Trials (RCTs).

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.

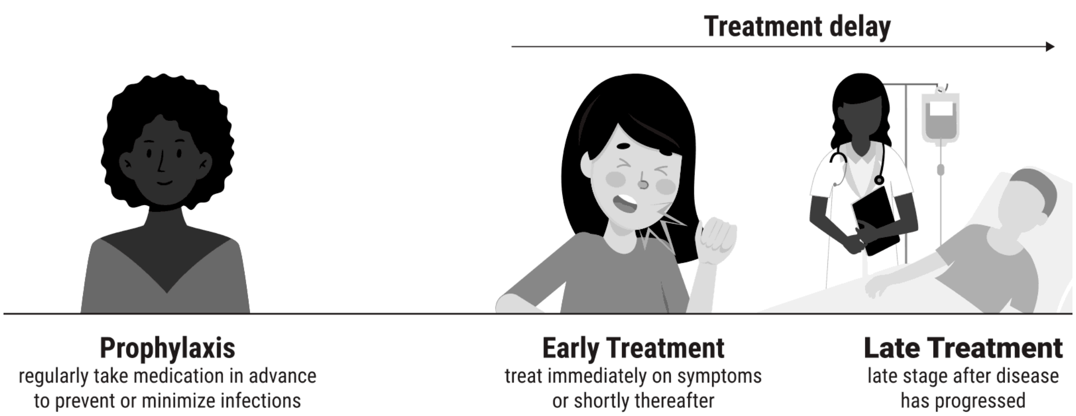


Figure 2. Treatment stages.

Preclinical Research

3 *In Silico* studies support the efficacy of antihistamine H1RAs[19-21].

7 *In Vitro* studies support the efficacy of antihistamine H1RAs[19,21-26].

2 *In Vivo* animal studies support the efficacy of antihistamine H1RAs[22,27].

Preclinical research is an important part of the development of treatments, however results may be very different in clinical trials. Preclinical results are not used in this paper.

Results

Table 1 summarizes the results for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes. Table 2 shows results by treatment stage. Figure 3 plots individual results by treatment stage. Figure 4, 5, 6, 7, 8, and 9 show forest plots for random effects meta-analysis of all studies with pooled effects, mortality results, hospitalization, recovery, cases, and peer reviewed studies.

	Improvement	Studies	Patients	Authors
All studies	39% [23-52%] ****	15	71,705	186
Peer-reviewed studies	32% [11-47%] **	12	63,599	136
Randomized Controlled Trials	63% [39-77%] ****	2	146	21
Mortality	38% [16-54%] **	7	70,872	92
Recovery	56% [45-64%] ****	2	761	32
Cases	35% [26-43%] ****	3	0	30

Table 1.* Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, for peer-reviewed studies, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval. * *p*<0.05 ** *p*<0.01 * *p*<0.0001.

	Early treatment	Late treatment	Prophylaxis
All studies	56% [46-64%] ****	28% [2-47%] *	35% [14-51%] **
Peer-reviewed studies	87% [-146-99%]	28% [2-47%] *	32% [8-50%] *
Randomized Controlled Trials	63% [39-77%] ****		
Mortality		25% [-46-61%]	40% [16-57%] **
Recovery	56% [45-64%] ****		
Cases			35% [26-43%] ****

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 ** *p*<0.01 * *p*<0.0001.

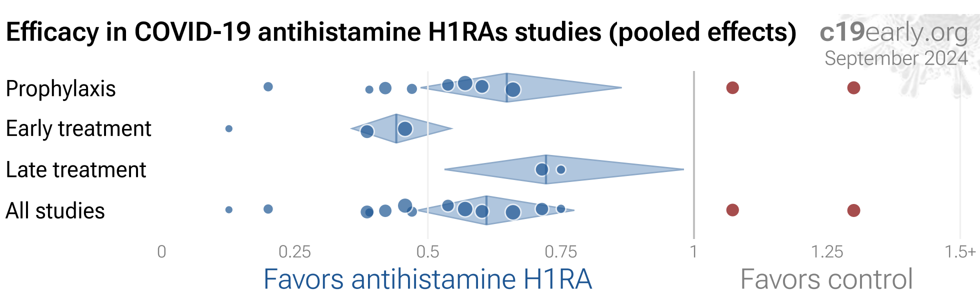


***Figure 3.* Scatter plot showing the most serious outcome in all studies, and for studies within each stage.** Diamonds shows the results of random effects meta-analysis.

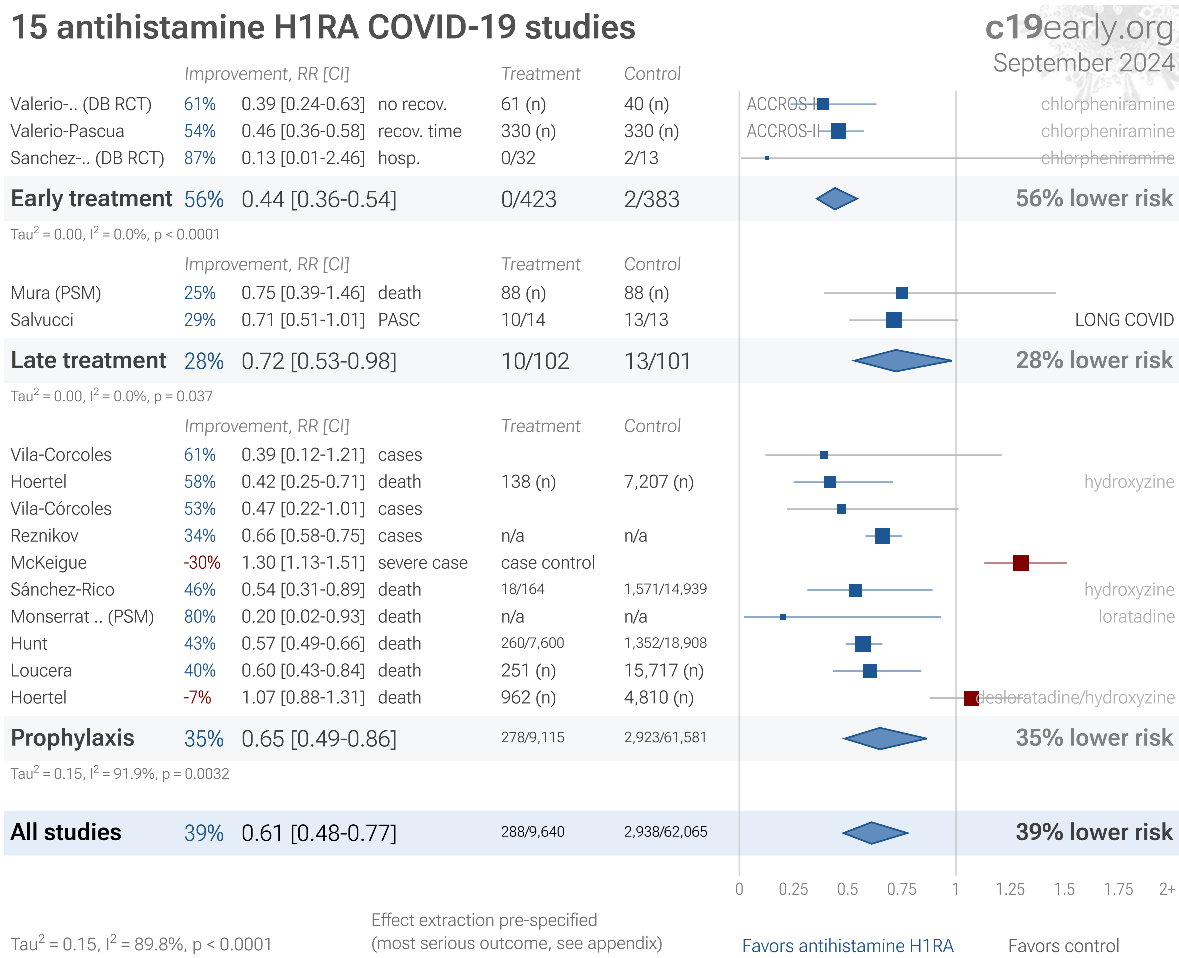


Figure 4. **Random effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

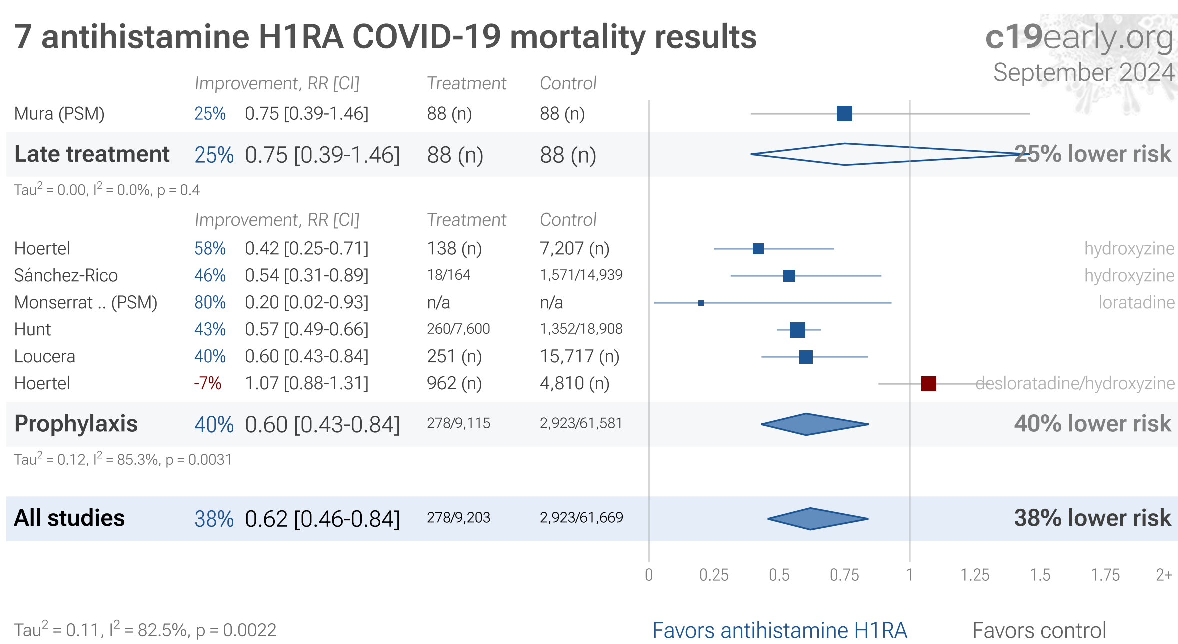


Figure 5. **Random effects meta-analysis for mortality results.**

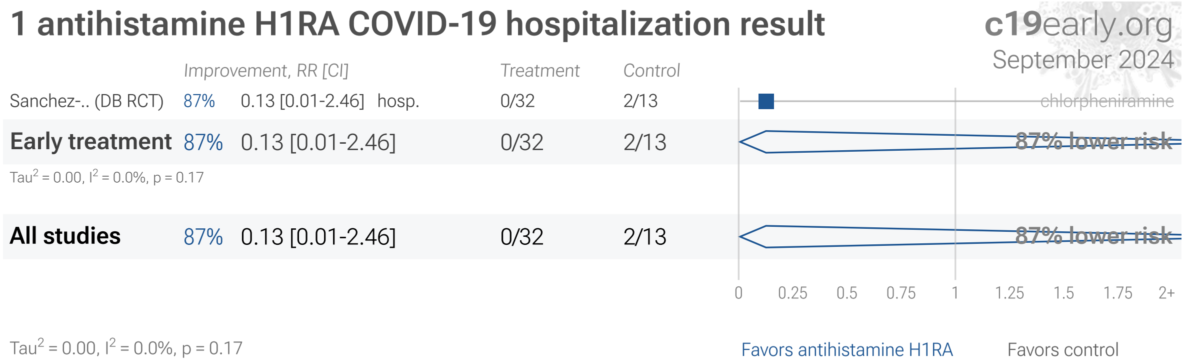


Figure 6. Random effects meta-analysis for hospitalization.

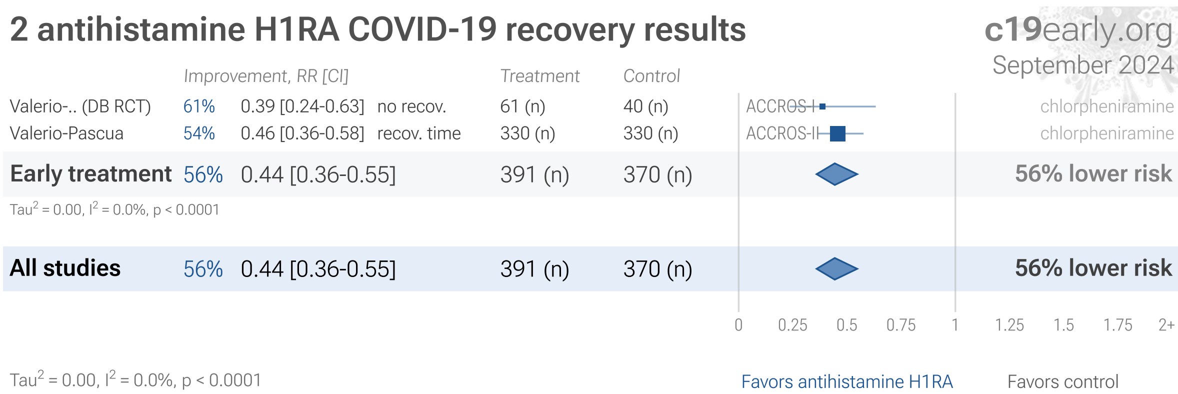


Figure 7. Random effects meta-analysis for recovery.

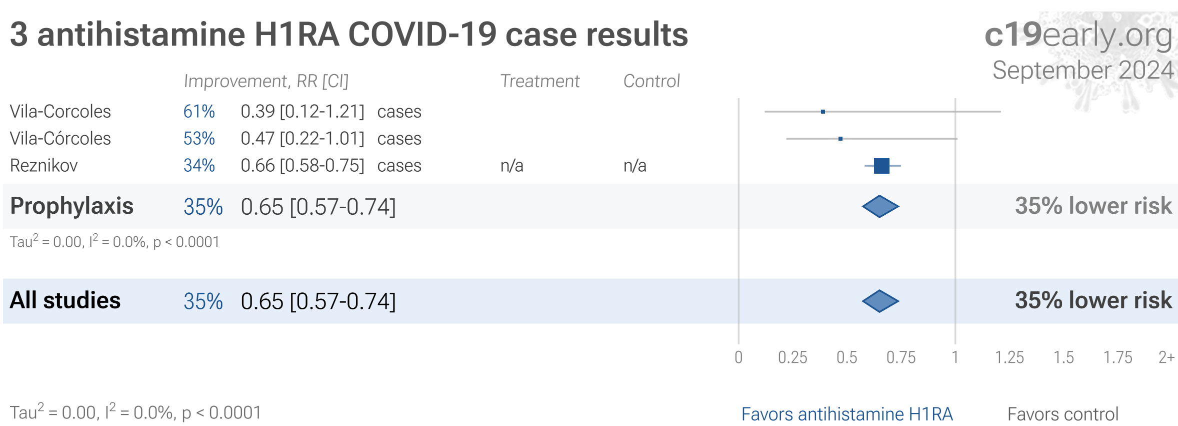


Figure 8. Random effects meta-analysis for cases.

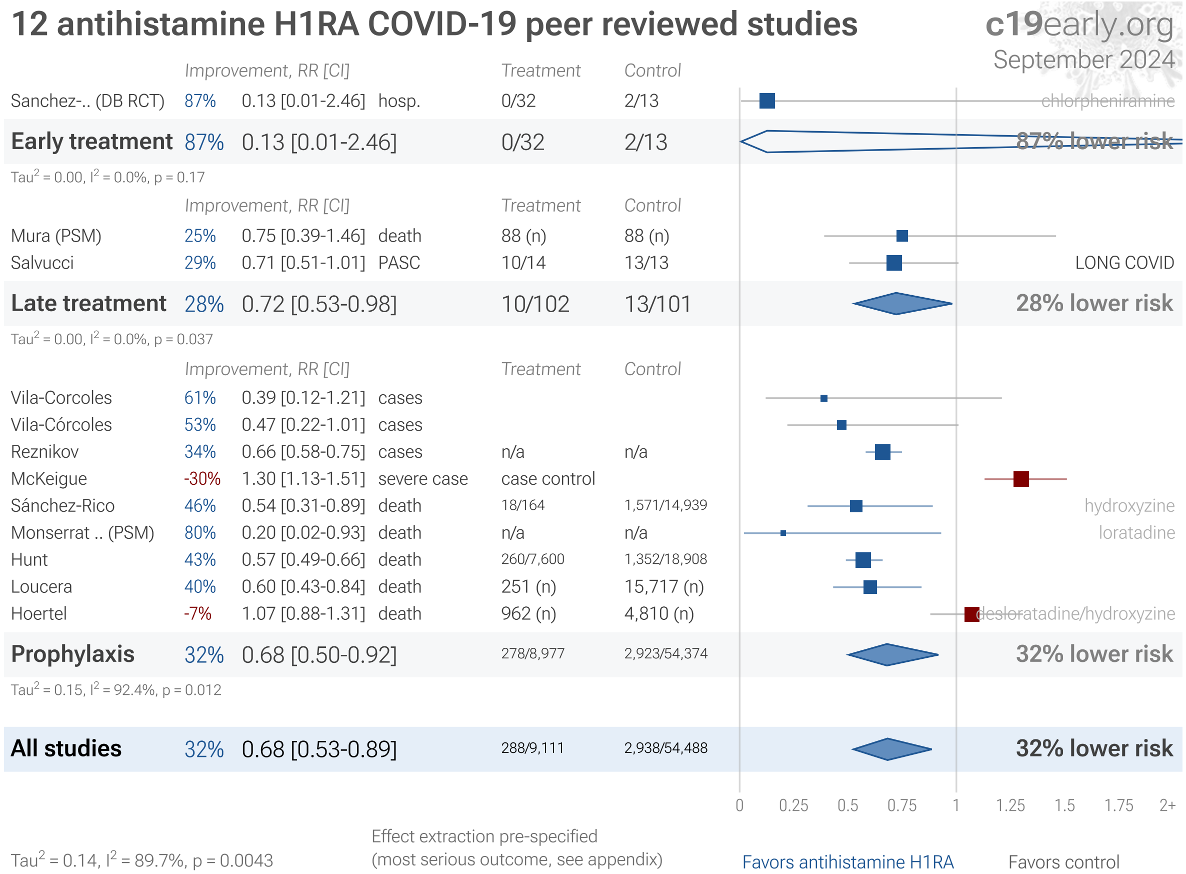


Figure 9. **Random effects meta-analysis for peer reviewed studies.** Effect extraction is pre-specified, using the most serious outcome reported, see the appendix for details. Analysis validating pooled outcomes for COVID-19 can be found below. *Zeraatkar et al.* analyze 356 COVID-19 trials, finding 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.

Randomized Controlled Trials (RCTs)

Figure 10 shows a comparison of results for RCTs and non-RCT studies. Random effects meta analysis of RCTs shows 63% improvement, compared to 36% for other studies. Figure 11 shows a forest plot for random effects meta-analysis of all Randomized Controlled Trials. RCT results are included in Table 1 and Table 2.

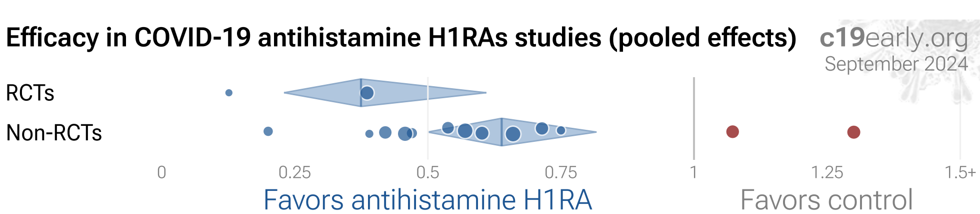


Figure 10. **Results for RCTs and non-RCT studies.**

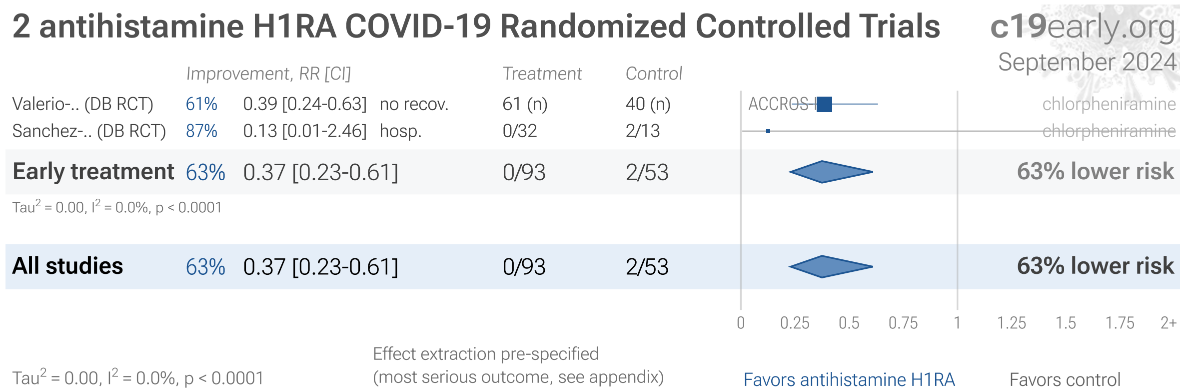


Figure 11. **Random effects meta-analysis for all Randomized Controlled Trials.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Analysis validating pooled outcomes for COVID-19 can be found below. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

RCTs have many potential biases. RCTs help to make study groups more similar and can provide a higher level of evidence, however they are subject to many biases [30], and analysis of double-blind RCTs has identified extreme levels of bias [31]. 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, reporting, 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 92 treatments we have analyzed, 64% 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 studies 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 may have a greater effect on results. Ethical issues may also prevent running RCTs for known effective treatments. For more on issues with RCTs see [36,37].

Using all studies identifies efficacy 7+ months faster (8+ months for low-cost treatments). 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. Of these, 30 have been confirmed in RCTs, with a mean delay of 6.9 months. When considering only low cost treatments, 25 have been confirmed with a delay of 8.2 months. For the 18 unconfirmed treatments, 4 have zero RCTs to date. The point estimates for the remaining 14 are all consistent with the overall results (benefit or harm), with 12 showing >20%. The only treatment showing >10% efficacy for all studies, but <10% for RCTs is sotrovimab.

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.

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[38,39]. 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[40]
<24 hours	-33 hours symptoms[41]
24-48 hours	-13 hours symptoms[41]
Inpatients	-2.5 hours to improvement[42]

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

Figure 12 shows a mixed-effects meta-regression of efficacy as a function of treatment delay in COVID-19 antihistamine H1RA studies, with group estimates for different stages when a specific value is not provided. For comparison, Figure 13 shows a meta-regression for all studies providing specific values across 92 treatments. Efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

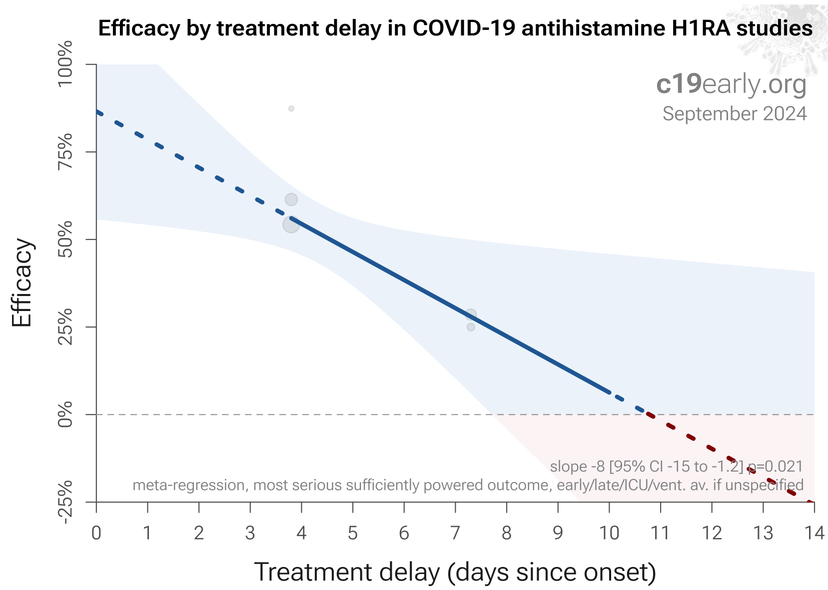


Figure 13. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 antihistamine H1RA studies.

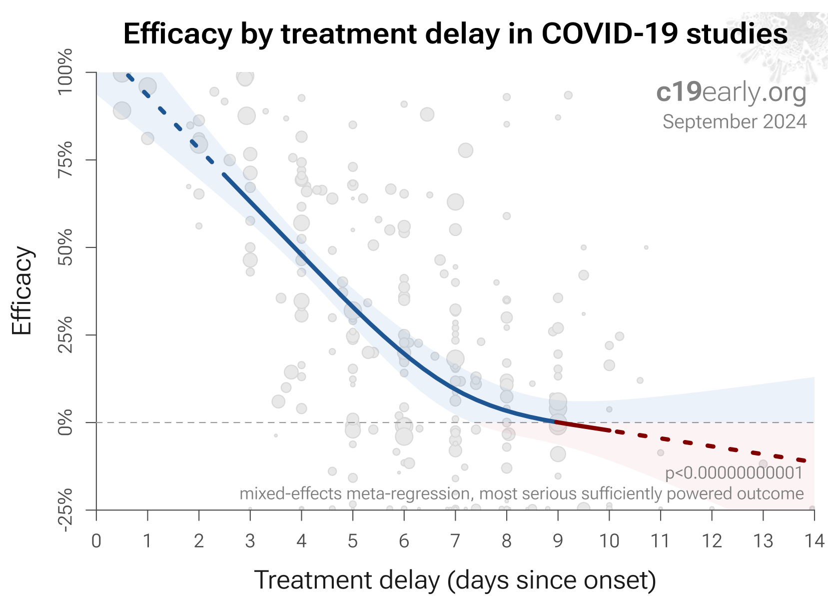


Figure 13. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 92 treatments.

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.

Variants. Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants[44], for example the Gamma variant shows significantly different characteristics[45-48]. 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[49,50].

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

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[51-61], therefore efficacy may depend strongly on combined treatments.

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.

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

Pooled effects are no longer required to show efficacy as of January 2021. This section validates the use of pooled effects for COVID-19, which enables earlier detection of efficacy, however note that pooled effects are no longer required for antihistamine H1RAs as of January 2021. Efficacy is now known based on specific outcomes. Efficacy based on specific outcomes was delayed by 1.7 months, compared to using pooled outcomes.

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.

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.

Using more information. Another way to view pooled analysis is that we are using more of the available information. Logically we should, and do, use additional information. For example dose-response and treatment delay-response relationships provide significant additional evidence of efficacy that is considered when reviewing the evidence for a treatment.

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 collection of evidence.

Improvement across outcomes. 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.

Validating pooled outcome analysis for COVID-19. Analysis of the the association between different outcomes across studies from all 92 treatments we cover confirms the validity of pooled outcome analysis for COVID-19. Figure 14 shows that lower hospitalization is very strongly associated with lower mortality (*p < 0.000000000001*). Similarly, Figure 15 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 16 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 = 0.0000013* to *p = 0.000000015*.

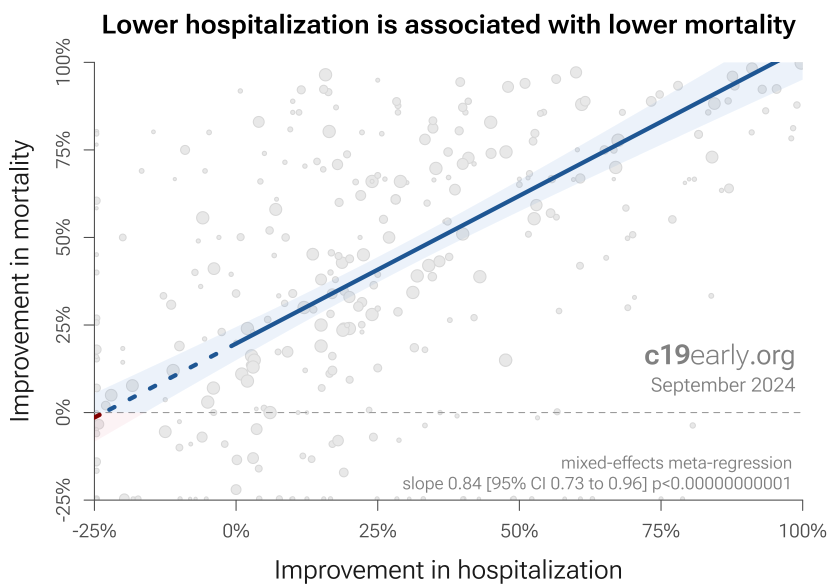


Figure 14. **Lower hospitalization is associated with lower mortality, supporting pooled outcome analysis.**

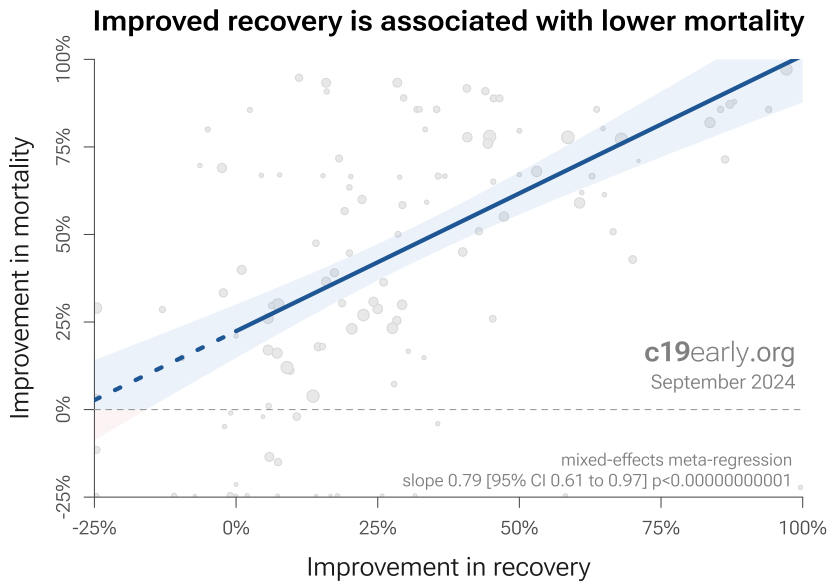


Figure 15. **Improved recovery is associated with lower mortality, supporting pooled outcome analysis.**

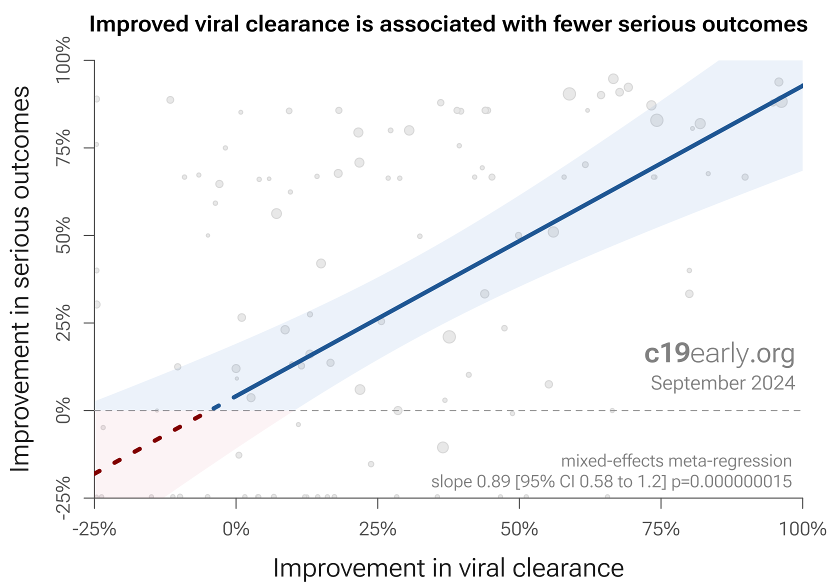


Figure 14. **Improved viral clearance is associated with fewer serious outcomes, supporting pooled outcome analysis.**

Pooled outcomes identify efficacy 5 months faster (6 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 5.1 months. When restricting to RCTs only, 54% of treatments showing statistically significant efficacy/harm with pooled effects have been confirmed with one or more specific outcomes, with a mean delay of 6.4 months. Figure 17 shows when treatments were found effective during the pandemic. Pooled outcomes often resulted in earlier detection of efficacy.

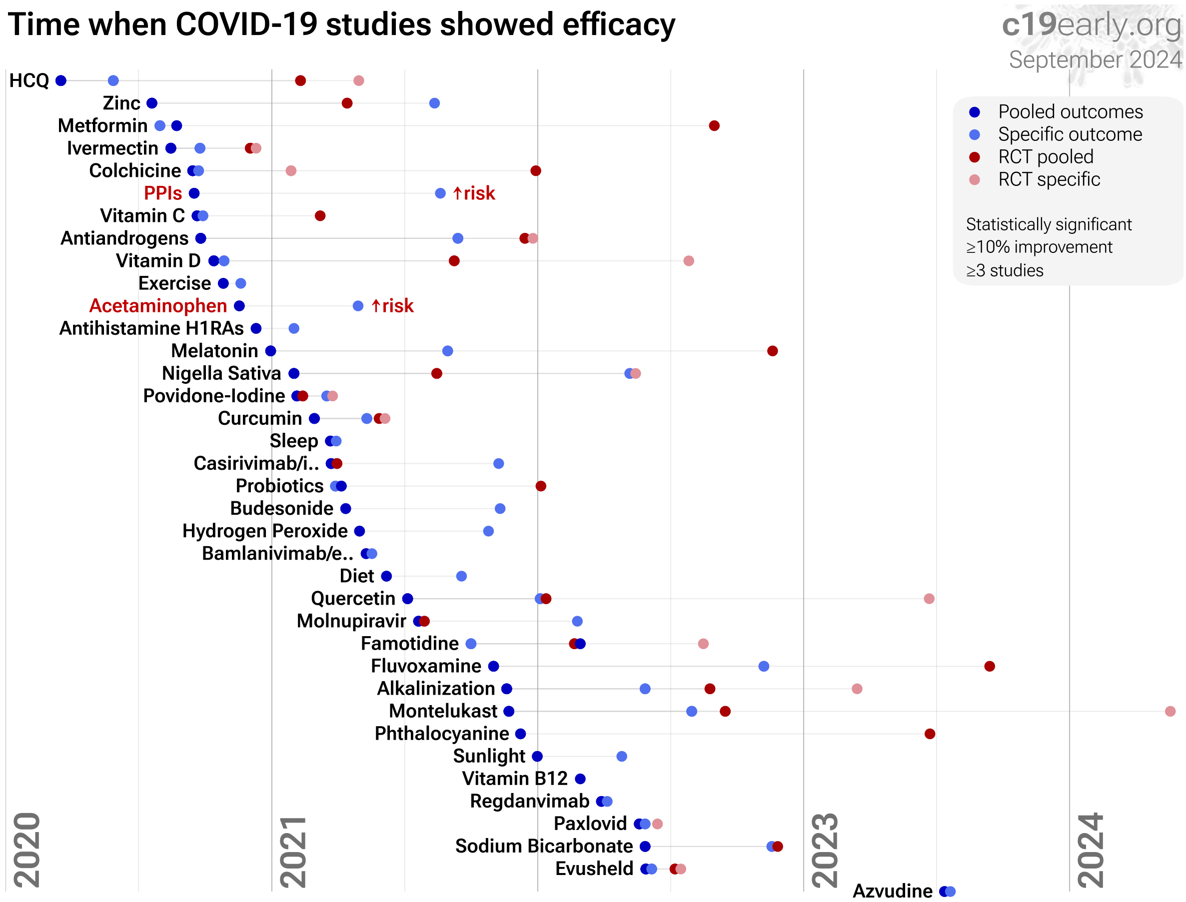


Figure 17. **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting 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, 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[65-68]. For antihistamine H1RA, there is currently not enough data to evaluate publication bias with high confidence.

One method to evaluate bias is to compare prospective vs. retrospective studies. Prospective studies are more likely to be published regardless of the result, while retrospective studies are more likely to exhibit bias. For example, researchers may perform preliminary analysis with minimal effort and the results may influence their decision to continue. Retrospective studies also provide more opportunities for the specifics of data extraction and adjustments to influence results.

Figure 18 shows a scatter plot of results for prospective and retrospective studies. 54% of retrospective studies report a statistically significant positive effect for one or more outcomes, compared to 50% of prospective studies, showing similar results. The median effect size for retrospective studies is 43% improvement, compared to 74% for prospective studies, suggesting a potential bias towards publishing results showing lower efficacy.

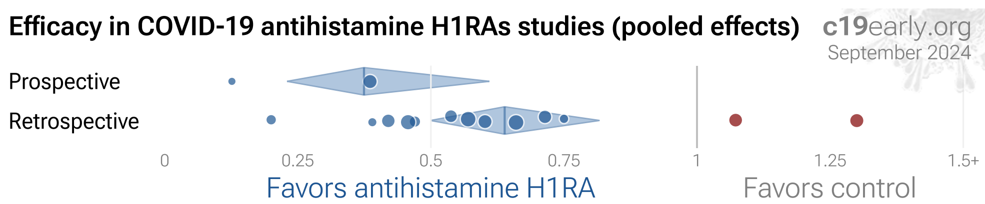


Figure 18. **Prospective vs. retrospective studies. The diamonds show the results of random effects meta-analysis.**

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 $p < 0.05$[69-76]. 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.

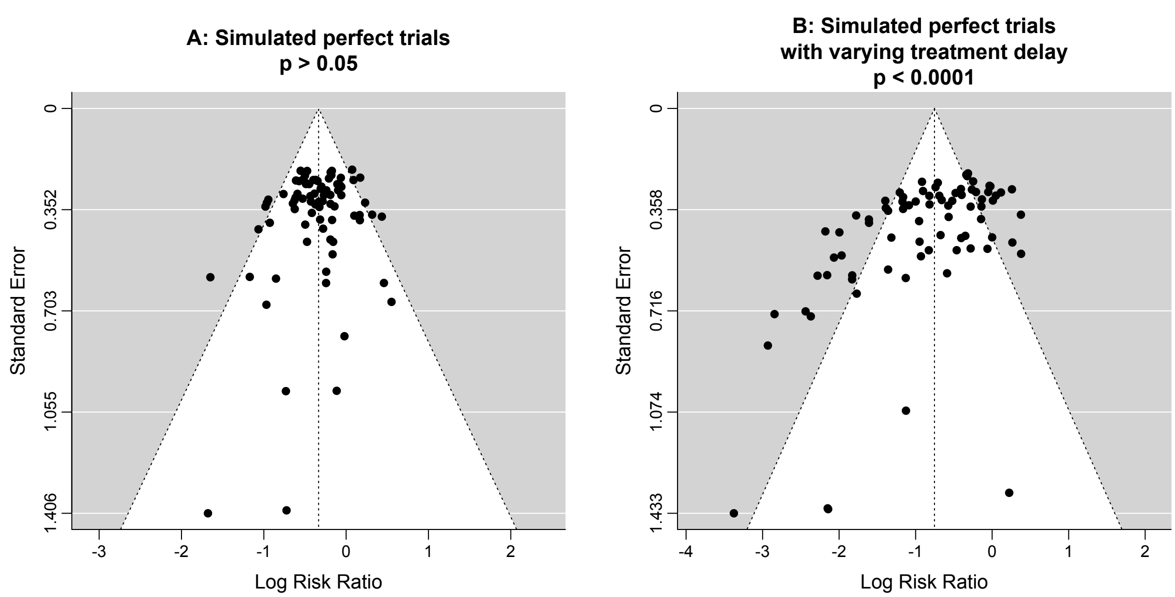


Figure 19. **Example funnel plot analysis for simulated perfect trials.**

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. Antihistamine H1RA for COVID-19 lack this because they are generally inexpensive and widely available. In contrast, most COVID-19 antihistamine H1RA 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 antihistamine H1RA 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 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[51-61]. 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.

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[13-17], providing many therapeutic targets. Over 7,000 compounds have been predicted to reduce COVID-19 risk[18], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 20 shows an overview of the results for antihistamine H1RAs in the context of multiple COVID-19 treatments, and Figure 21 shows a plot of efficacy vs. cost for COVID-19 treatments.

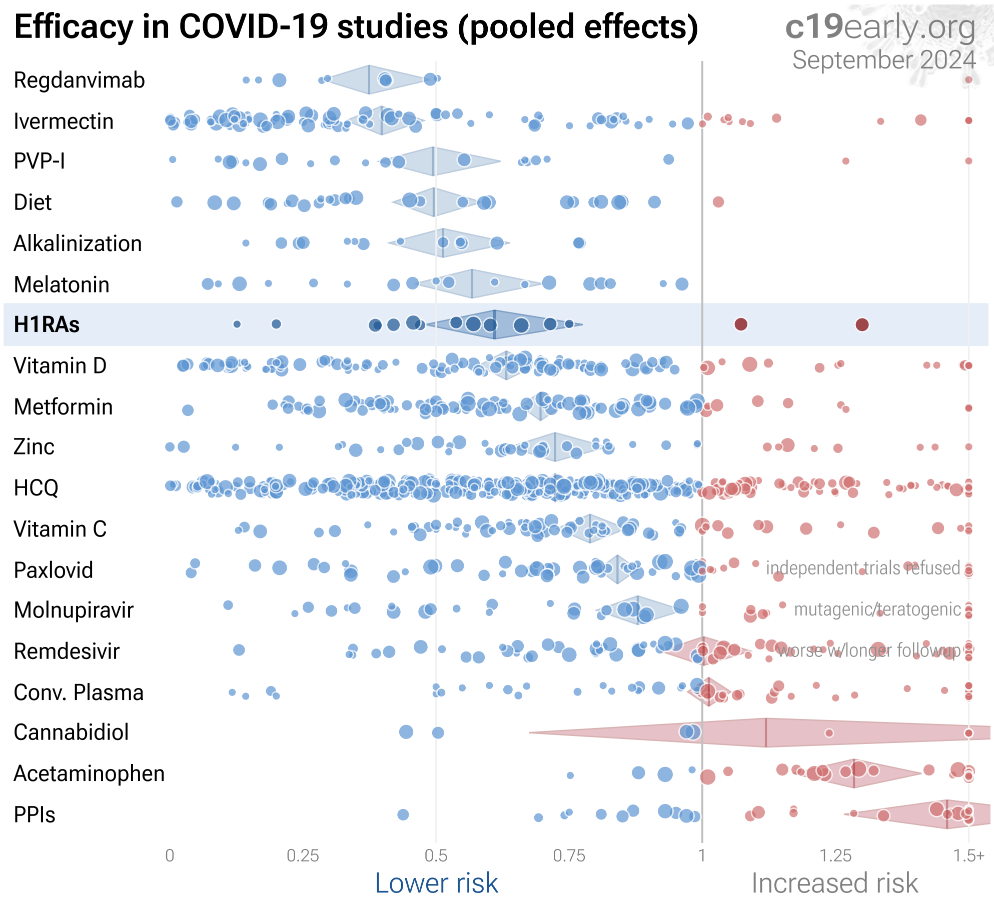


Figure 20. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 7,000+ proposed treatments show efficacy[77].

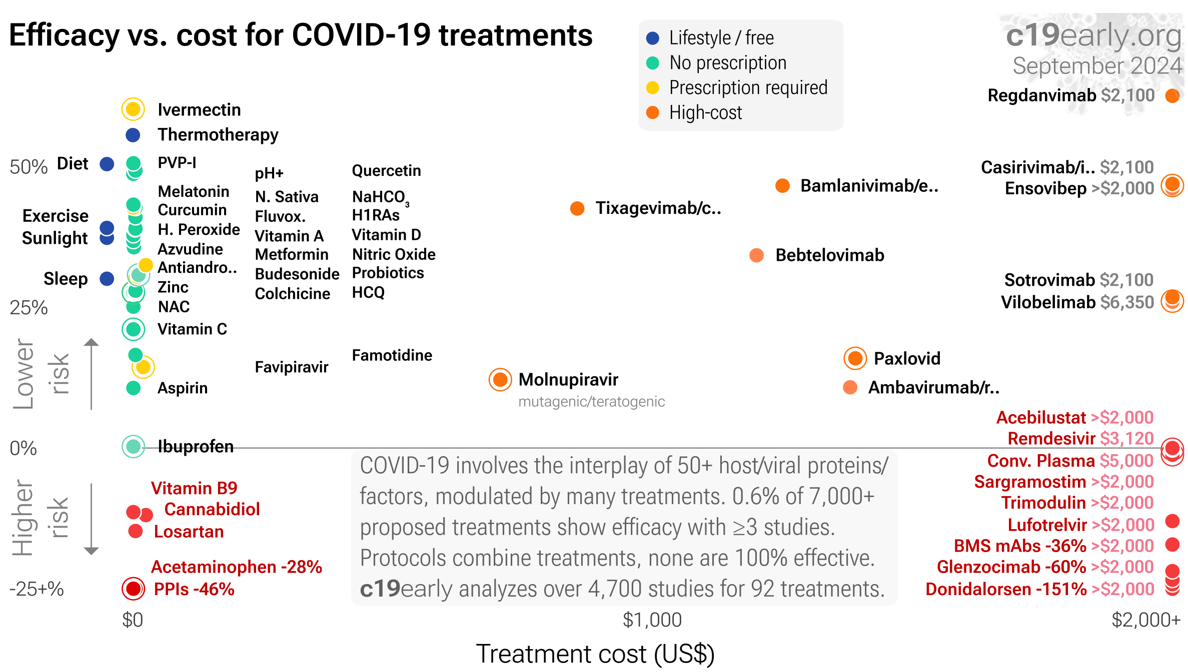


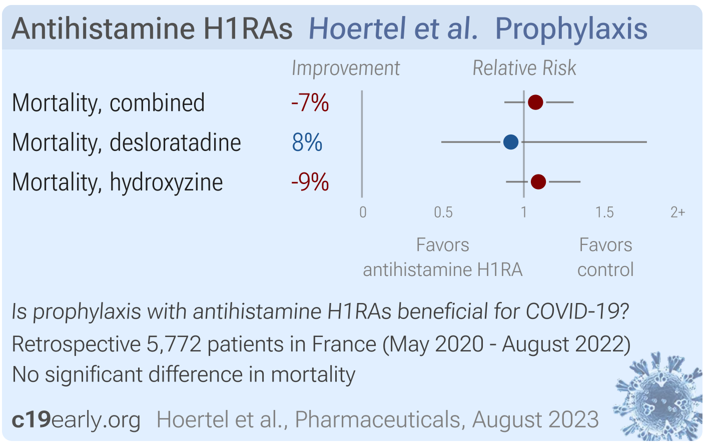
Figure 21. Efficacy vs. cost for COVID-19 treatments.

Conclusion

Antihistamine H1RAs are an effective treatment for COVID-19. Statistically significant lower risk is seen for mortality, recovery, and cases. 8 studies from 7 independent teams in 4 countries show significant improvements. Meta analysis using the most serious outcome reported shows 39% [23-52%] lower risk. Results are similar for peer-reviewed studies and better for Randomized Controlled Trials. Early treatment is more effective than late treatment. Results are very robust — in exclusion sensitivity analysis 8 of 15 studies must be excluded to avoid finding statistically significant efficacy in pooled analysis.

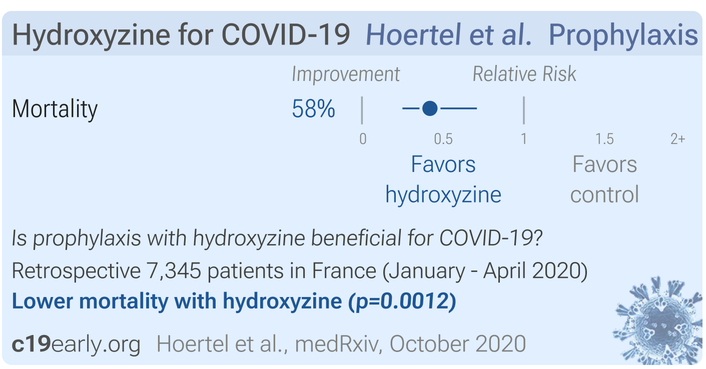
Study Notes

Hoertel



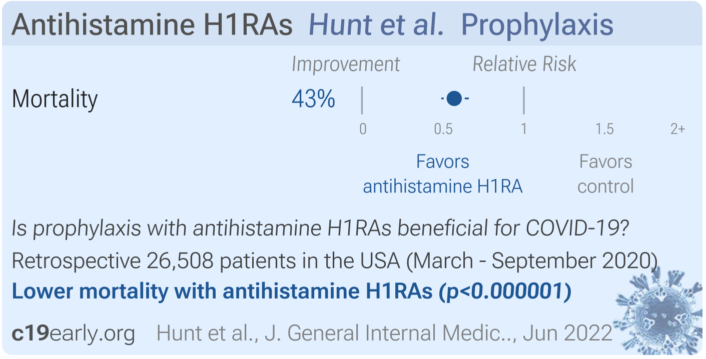
Hoertel: Retrospective 72,105 COVID+ hospitalized patients in France, showing no significant difference in mortality with antihistamine H1RAs desloratadine and hydroxyzine.

Hoertel



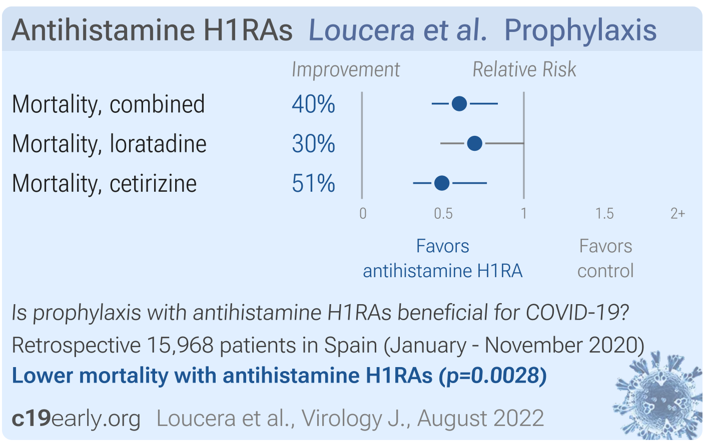
Hoertel (B): Retrospective 7,345 hospitalized COVID-19 patients in France showing lower mortality with hydroxyzine use, with a significant dose-response relationship. Hydroxyzine was also associated with a faster decrease in inflammatory markers.

Hunt



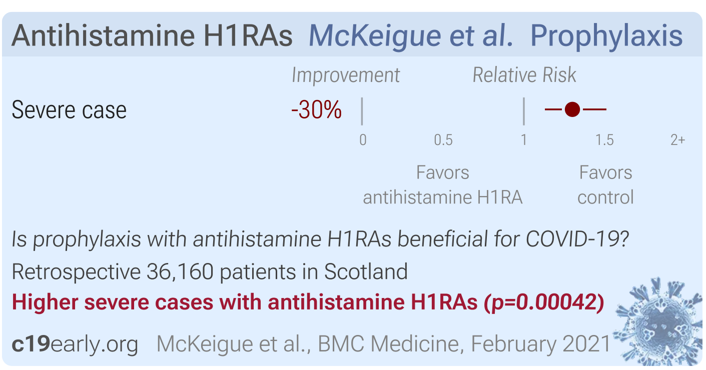
Hunt: Retrospective 26,508 consecutive COVID+ veterans in the USA, showing lower mortality with multiple treatments including antihistamines. Treatment was defined as drugs administered ≥50% of the time within 2 weeks post-COVID+, and may be a continuation of prophylactic treatment. Further reduction in mortality was seen with combinations of treatments.

Loucera



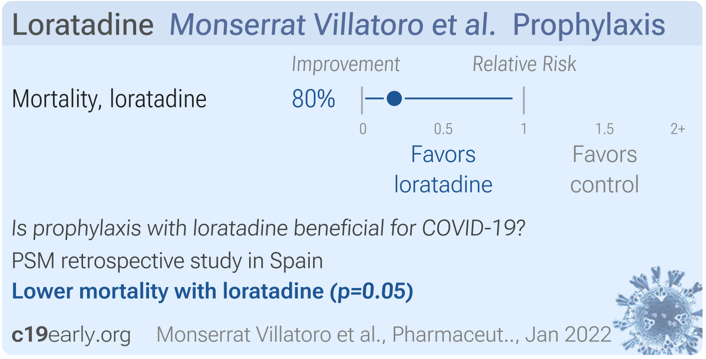
Loucera: Retrospective 15,968 COVID-19 hospitalized patients in Spain, showing lower mortality with antihistamine H1RAs, without statistical significance. Since only hospitalized patients are included, results do not reflect different probabilities of hospitalization across treatments.

McKeigue



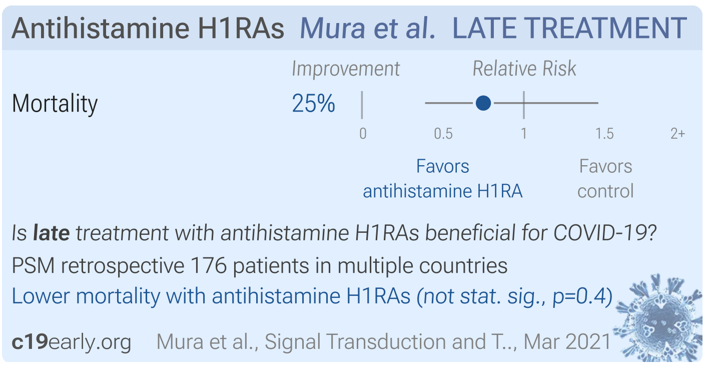
McKeigue: Retrospective 4,251 severe COVID-19 cases and 36,738 matched controls in Scotland showing increased risk of severe COVID-19 with PPI use and antihistamine H1RA use. Adjusted results are only provided for the patients not in care homes (2,357 cases and 33,803 controls).

Monserrat Villatoro



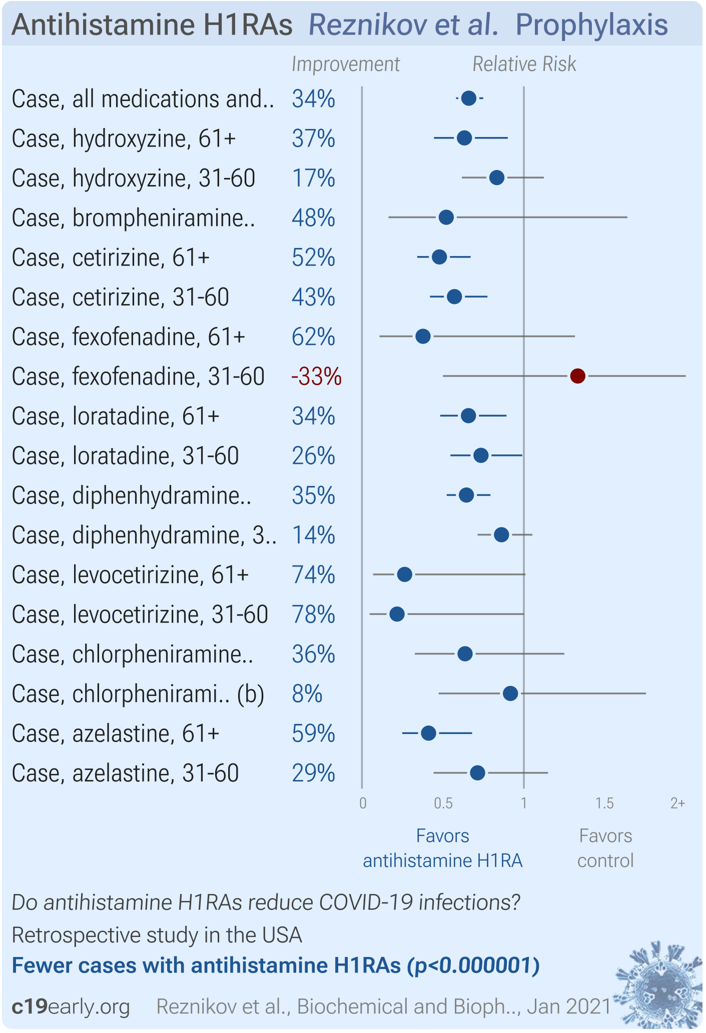
Monserrat Villatoro: PSM retrospective 3,712 hospitalized patients in Spain, showing lower mortality with existing use of loratadine.

Mura



Mura: PSM retrospective TriNetX database analysis of 1,379 severe COVID-19 patients requiring respiratory support, showing lower mortality with H1RAs+H2RAs versus famotidine alone, without statistical significance.

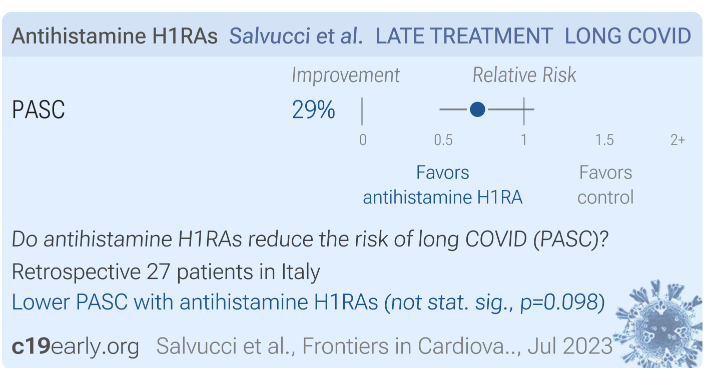
Reznikov



Reznikov: Retrospective 219,000 patients showing lower risk of COVID-19 with antihistamine H1RA use.

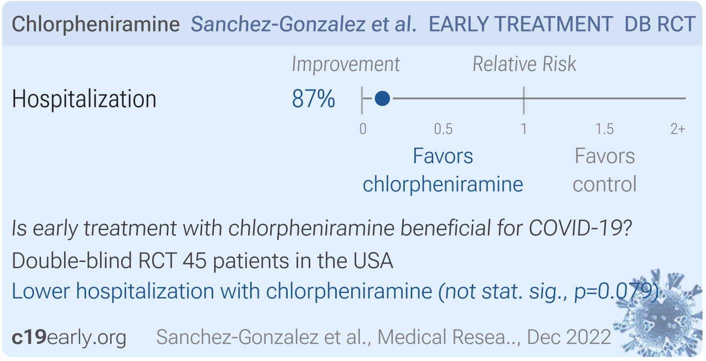
In Vitro study showing these drugs exhibit direct antiviral activity against SARS-CoV-2. Molecular docking suggests hydroxyzine and azelastine may exert antiviral effects by binding ACE2 and the sigma-1 receptor.

Salvucci



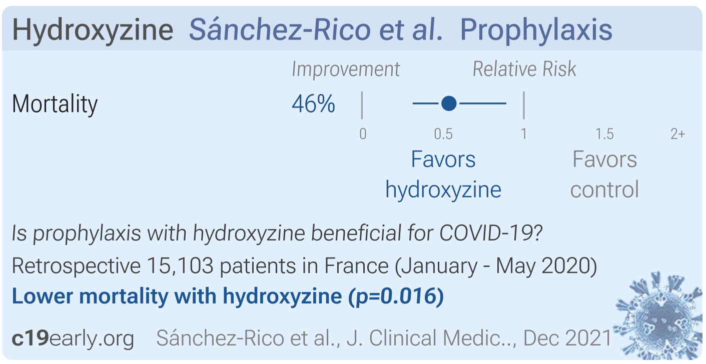
Salvucci: Retrospective 14 patients with long-COVID symptoms attributed to mast cell activation treated with H1 and H2 antihistamines compared to 13 control patients, showing significant improvements in several symptoms in the treatment group compared to controls after 20 days. 29% of treated patients had complete resolution of long-COVID symptoms, compared with none in the control group.

Sanchez-Gonzalez



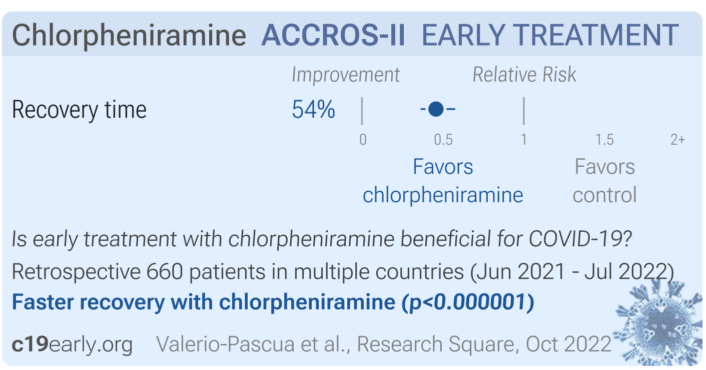
Sanchez-Gonzalez: Small RCT showing significantly improved recovery with intranasal chlorpheniramine maleate. Authors also perform an In Vitro study showing efficacy with a highly differentiated three-dimensional model of normal, human-derived tracheal/bronchial epithelial cells.

Sánchez-Rico



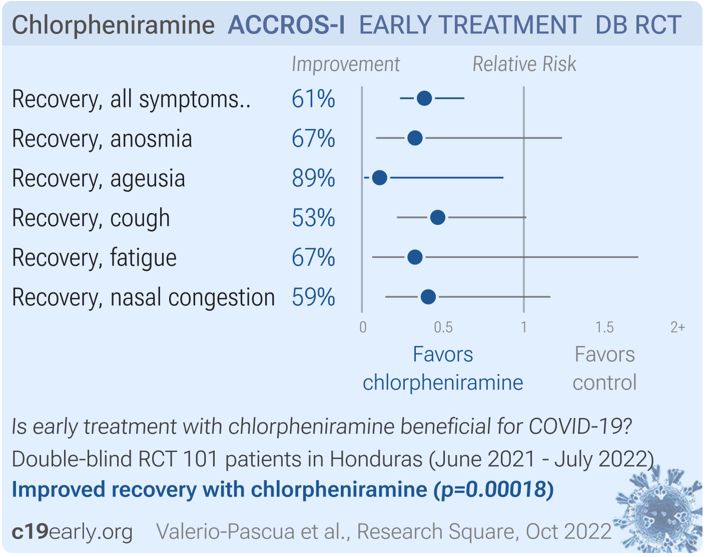
Sánchez-Rico: Retrospective 15,103 hospitalized COVID-19 patients in France showing lower mortality with hydroxyzine use.

Valerio-Pascua



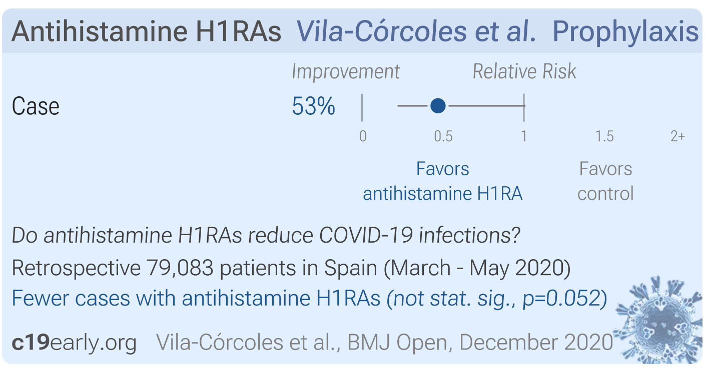
Valerio-Pascua: RCT and retrospective study of chlorpheniramine nasal spray for COVID-19. The retrospective study included 660 outpatients showing fewer days with general COVID-19 symptoms, cough, anosmia, and ageusia compared to standard of care alone. The RCT results are listed separately[88].

Valerio-Pascua



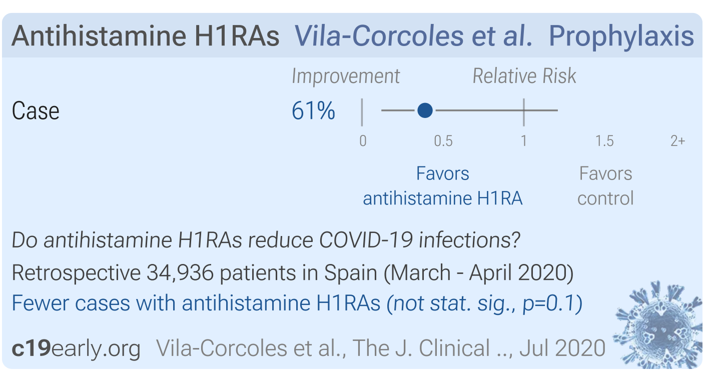
Valerio-Pascua (B): RCT and retrospective study of chlorpheniramine nasal spray for COVID-19. The RCT included 101 outpatients showing significantly faster recovery with treatment. The retrospective study results are listed separately[87].

Vila-Córcoles



Vila-Córcoles: Retrospective 79,083 adults aged ≥50 years in Spain showing lower with of PCR-confirmed COVID-19 with antihistamine use, close to statistical significance.

Vila-Corcoles



Vila-Corcoles: Retrospective 34,936 hypertensive outpatients in Spain showing no significant difference in COVID-19 cases with PPIs and antihistamine H1RAs.

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 antihistamine H1RA 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 antihistamine H1RA 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 [91]. 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 [94]. 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 (3.12.5) with scipy (1.14.1), pythonmeta (1.26), numpy (1.26.4), statsmodels (0.14.2), and plotly (5.23.0).

Forest plots are computed using PythonMeta [95] 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 [38,39].

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/h1meta.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.

Sanchez-Gonzalez, 12/31/2022, Double Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, mean age 44.5, 5 authors.	risk of hospitalization, 87.4% lower, RR 0.13, $p = 0.08$, treatment 0 of 32 (0.0%), control 2 of 13 (15.4%), NNT 6.5, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
Valerio-Pascua, 10/18/2022, retrospective, multiple countries, preprint, 16 authors, study period June 2021 - July 2022, trial NCT05520944 (history) (ACCROS-II).	recovery time, 54.3% lower, relative time 0.46, $p < 0.001$, treatment mean 4.97 (±3.32) n=330, control mean 10.88 (±6.64) n=330.
Valerio-Pascua (B), 10/18/2022, Double Blind Randomized Controlled Trial, placebo-controlled, Honduras, preprint, 16 authors, study period June 2021 - July 2022, trial NCT05449405 (history) (ACCROS-I).	risk of no recovery, 61.4% lower, RR 0.39, $p < 0.001$, treatment 61, control 40, all symptoms combined.
	risk of no recovery, 67.2% lower, RR 0.33, $p = 0.15$, treatment 3 of 61 (4.9%), control 6 of 40 (15.0%), NNT 9.9, day 7, anosmia.
	risk of no recovery, 89.1% lower, RR 0.11, $p = 0.01$, treatment 1 of 61 (1.6%), control 6 of 40 (15.0%), NNT 7.5, day 7, ageusia.
	risk of no recovery, 53.2% lower, RR 0.47, $p = 0.05$, treatment 10 of 61 (16.4%), control 14 of 40 (35.0%), NNT 5.4, day 7, cough.
	risk of no recovery, 67.2% lower, RR 0.33, $p = 0.21$, treatment 2 of 61 (3.3%), control 4 of 40 (10.0%), NNT 15, day 7, fatigue.
	risk of no recovery, 59.0% lower, RR 0.41, $p = 0.13$, treatment 5 of 61 (8.2%), control 8 of 40 (20.0%), NNT 8.5, day 7, nasal congestion.

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.

Mura, 3/31/2021, retrospective, database analysis, multiple countries, peer-reviewed, 6 authors.	risk of death, 25.0% lower, OR 0.75, $p = 0.40$, treatment 88, control 88, H1+H2 vs. famotidine, propensity score matching, RR approximated with OR.
Salvucci, 7/17/2023, retrospective, Italy, peer-reviewed, 9 authors.	risk of PASC, 28.6% lower, RR 0.71, $p = 0.10$, treatment 10 of 14 (71.4%), control 13 of 13 (100.0%), NNT 3.5.

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.

Hoertel, 8/4/2023, retrospective, France, peer-reviewed, 14 authors, study period 2 May, 2020 - 31 August, 2022.	risk of death, 7.2% higher, HR 1.07, *p* = 0.50, treatment 962, control 4,810, adjusted per study, combined.
	risk of death, 8.0% lower, HR 0.92, *p* = 0.81, treatment 11 of 94 (11.7%), control 62 of 470 (13.2%), NNT 67, adjusted per study, desloratadine, multivariable, Cox proportional hazards, day 28.
	risk of death, 9.0% higher, HR 1.09, *p* = 0.40, treatment 104 of 962 (10.8%), control 591 of 4,810 (12.3%), adjusted per study, hydroxyzine, multivariable, Cox proportional hazards, day 28.
Hoertel (B), 10/27/2020, retrospective, France, preprint, 18 authors, study period 24 January, 2020 - 1 April, 2020.	risk of death, 58.0% lower, HR 0.42, *p* = 0.001, treatment 138, control 7,207, adjusted per study, propensity score weighting, multivariable.
Hunt, 6/29/2022, retrospective, USA, peer-reviewed, 8 authors, study period 1 March, 2020 - 10 September, 2020.	risk of death, 43.0% lower, RR 0.57, *p* < 0.001, treatment 260 of 7,600 (3.4%), control 1,352 of 18,908 (7.2%), NNT 27, adjusted per study, day 30.
Loucera, 8/16/2022, retrospective, Spain, peer-reviewed, 8 authors, study period January 2020 - November 2020.	risk of death, 39.8% lower, HR 0.60, *p* = 0.003, treatment 251, control 15,717, combined.
	risk of death, 30.4% lower, HR 0.70, *p* = 0.05, treatment 251, control 15,717, loratadine, Cox proportional hazards, day 30.
	risk of death, 50.6% lower, HR 0.49, *p* = 0.002, treatment 233, control 15,735, cetirizine, Cox proportional hazards, day 30.
McKeigue, 2/22/2021, retrospective, Scotland, peer-reviewed, 18 authors, trial EUPAS35558.	risk of severe case, 30.0% higher, OR 1.30, *p* < 0.001, treatment 263 of 2,357 (11.2%) cases, 2,556 of 33,803 (7.6%) controls, adjusted per study, case control OR.
Monserrat Villatoro, 1/8/2022, retrospective, propensity score matching, Spain, peer-reviewed, 18 authors.	risk of death, 80.0% lower, OR 0.20, *p* = 0.05, loratadine, RR approximated with OR.
Reznikov, 1/31/2021, retrospective, USA, peer-reviewed, 9 authors.	risk of case, 34.0% lower, RR 0.66, *p* < 0.001, adjusted per study, all medications and age groups combined.
	risk of case, 36.7% lower, OR 0.63, *p* = 0.01, adjusted per study, inverted to make OR<1 favor treatment, hydroxyzine, 61+, multivariable, RR approximated with OR.
	risk of case, 16.7% lower, OR 0.83, *p* = 0.24, adjusted per study, inverted to make OR<1 favor treatment, hydroxyzine, 31-60, multivariable, RR approximated with OR.
	risk of case, 47.9% lower, OR 0.52, *p* = 0.27, adjusted per study, inverted to make OR<1 favor treatment, brompheniramine , 31-60, multivariable, RR approximated with OR.

	risk of case, 52.2% lower, OR 0.48, p < 0.001, adjusted per study, inverted to make OR<1 favor treatment, cetirizine, 61+, multivariable, RR approximated with OR.
	risk of case, 42.9% lower, OR 0.57, p < 0.001, adjusted per study, inverted to make OR<1 favor treatment, cetirizine, 31-60, multivariable, RR approximated with OR.
	risk of case, 62.3% lower, OR 0.38, p = 0.13, adjusted per study, inverted to make OR<1 favor treatment, fexofenadine, 61+, multivariable, RR approximated with OR.
	risk of case, 33.3% higher, OR 1.33, p = 0.58, adjusted per study, inverted to make OR<1 favor treatment, fexofenadine, 31-60, multivariable, RR approximated with OR.
	risk of case, 34.2% lower, OR 0.66, p = 0.008, adjusted per study, inverted to make OR<1 favor treatment, loratadine, 61+, multivariable, RR approximated with OR.
	risk of case, 26.5% lower, OR 0.74, p = 0.04, adjusted per study, inverted to make OR<1 favor treatment, loratadine, 31-60, multivariable, RR approximated with OR.
	risk of case, 35.5% lower, OR 0.65, p < 0.001, adjusted per study, inverted to make OR<1 favor treatment, diphenhydramine, 61+, multivariable, RR approximated with OR.
	risk of case, 13.8% lower, OR 0.86, p = 0.13, adjusted per study, inverted to make OR<1 favor treatment, diphenhydramine, 31-60, multivariable, RR approximated with OR.
	risk of case, 73.6% lower, OR 0.26, p = 0.05, adjusted per study, inverted to make OR<1 favor treatment, levocetirizine, 61+, multivariable, RR approximated with OR.
	risk of case, 78.3% lower, OR 0.22, p = 0.0496, adjusted per study, inverted to make OR<1 favor treatment, levocetirizine, 31-60, multivariable, RR approximated with OR.
	risk of case, 36.3% lower, OR 0.64, p = 0.19, adjusted per study, inverted to make OR<1 favor treatment, chlorpheniramine, 61+, multivariable, RR approximated with OR.
	risk of case, 8.3% lower, OR 0.92, p = 0.81, adjusted per study, inverted to make OR<1 favor treatment, chlorpheniramine, 31-60, multivariable, RR approximated with OR.
	risk of case, 58.8% lower, OR 0.41, p < 0.001, adjusted per study, inverted to make OR<1 favor treatment, azelastine, 61+, multivariable, RR approximated with OR.
	risk of case, 28.6% lower, OR 0.71, p = 0.17, adjusted per study, inverted to make OR<1 favor treatment, azelastine, 31-60, multivariable, RR approximated with OR.

Sánchez-Rico, 12/15/2021, retrospective, France, peer-reviewed, 20 authors, study period 24 January, 2020 - 1 May, 2020.	risk of death, 46.2% lower, RR 0.54, *p* = 0.02, treatment 18 of 164 (11.0%), control 1,571 of 14,939 (10.5%), adjusted per study, odds ratio converted to relative risk, multivariable.
Vila-Córcoles, 12/10/2020, retrospective, Spain, peer-reviewed, 10 authors, study period 1 March, 2020 - 23 May, 2020.	risk of case, 53.0% lower, HR 0.47, *p* = 0.05, treatment 3,264, control 75,819, adjusted per study, multivariable, Cox proportional hazards, RR approximated with OR.
Vila-Corcoles, 7/25/2020, retrospective, Spain, peer-reviewed, mean age 70.9, 11 authors, study period 1 March, 2020 - 30 April, 2020.	risk of case, 61.0% lower, HR 0.39, *p* = 0.10, treatment 1,579, control 33,357, adjusted per study, multivariable, Cox proportional hazards.

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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