pHOXWELL for COVID-19: real-time meta analysis of 1 study

@CovidAnalysis, June 2025, Version 1

https://c19early.org/phxmeta.html

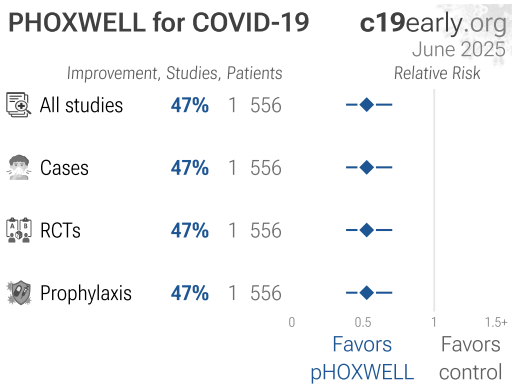
Abstract

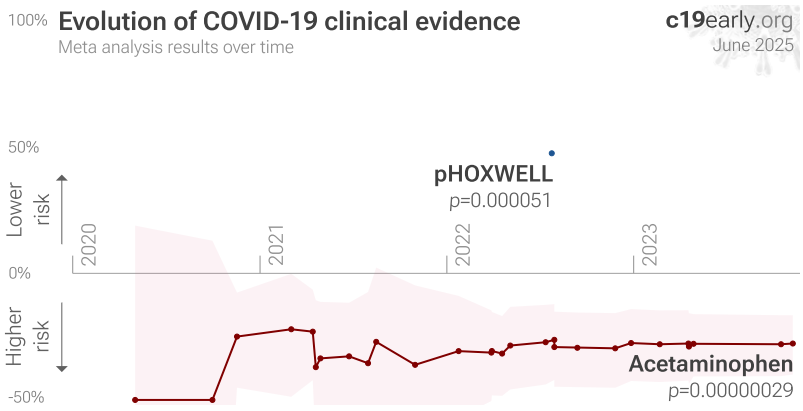
Significantly lower risk is seen for cases.

Meta analysis using the most serious outcome reported shows 47% [29-62%] lower risk.

Currently there is very limited data, with only one study to date.

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. pHOXWELL may affect the natural microbiome, especially with prolonged use. All data and sources to reproduce this analysis are in the appendix.



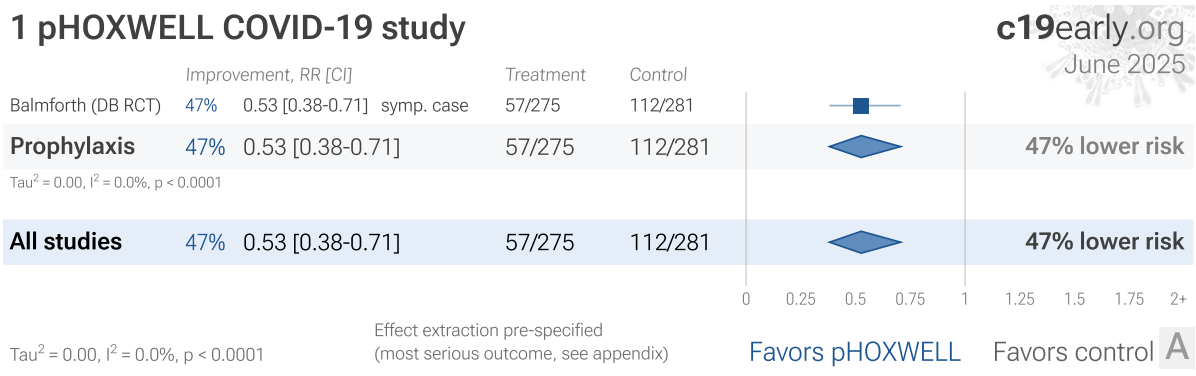


PHOXWELL FOR COVID-19 — HIGHLIGHTS

pHOXWELL reduces risk with low confidence for cases.

Real-time updates and corrections with a consistent protocol for 172 treatments. Outcome specific analysis and combined evidence from all studies including treatment delay, a primary confounding factor.

1 pHOXWELL COVID-19 study



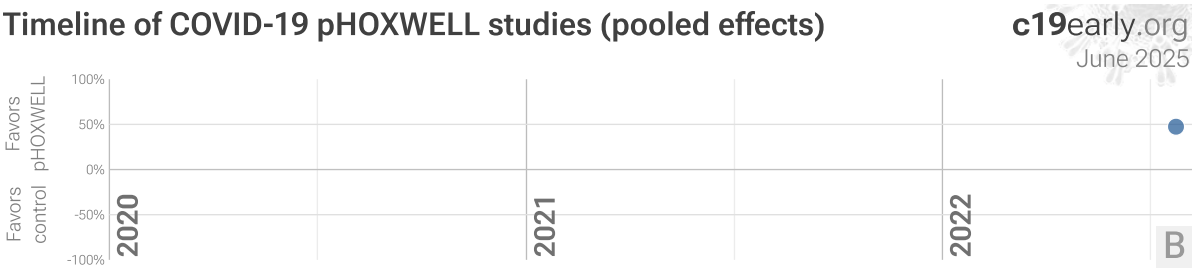


Figure 1. **A. Random effects meta-analysis.** Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix. **B. Timeline of results in pHOXWELL studies.**

Introduction

Immediate treatment recommended

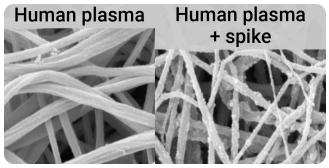


Figure 2. **SARS-CoV-2 spike protein fibrin binding leads to thromboinflammation and neuropathology, from [1].**

SARS-CoV-2 infection typically starts in the upper respiratory tract, and specifically the nasal respiratory epithelium. Entry via the eyes and gastrointestinal tract is possible, but less common, and entry via other routes is rare. Infection may progress to the lower respiratory tract, other tissues, and the nervous and cardiovascular systems. The primary initial route for entry into the central nervous system is thought to be the olfactory nerve in the nasal cavity[2]. Progression may lead to cytokine storm, pneumonia, ARDS, neurological injury[3-15] and cognitive deficits[6,11], cardiovascular complications[16-20], organ failure, and death. Even mild untreated infections may result in persistent cognitive deficits[21]—the spike protein binds to fibrin leading to fibrinolysis-resistant blood clots, thromboinflammation, and neuropathology. Systemic treatments may be insufficient to prevent neurological damage[10]. Minimizing replication as early as possible is recommended.

Targeted treatment to the primary location of initial infection

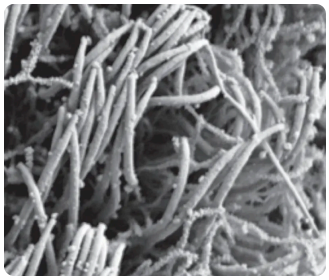


Figure 3. **SARS-CoV-2 virions attached to cilia of nasal epithelial cells, from Chien-Ting Wu[22,23].**

Logically, stopping replication in the upper respiratory tract should be simpler and more effective. *Wu et al.*, using an airway organoid model incorporating many *in vivo* aspects, show that SARS-CoV-2 initially attaches to cilia—hair-like structures responsible for moving the mucus layer and where ACE2 is localized in nasal epithelial cells[24]. The mucus layer and the need for ciliary transport slow down infection, providing more time for localized treatments[22,23]. Early or prophylactic nasopharyngeal/oropharyngeal treatment may avoid the consequences of viral replication in other tissues, and avoid the requirement for systemic treatments with greater potential for side effects.

Many treatments are expected to modulate infection

SARS-CoV-2 infection and replication involves the complex interplay of 100+ host and viral proteins and other factors[A,25-32], providing many therapeutic targets for which many existing compounds have known activity. Scientists have predicted that over 9,000 compounds may reduce COVID-19 risk[33], 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 pHOXWELL for COVID-19. Search methods, inclusion criteria, effect extraction criteria (more serious outcomes have priority), all individual study data, PRISMA answers, and statistical methods are detailed in Appendix 1. We present random effects meta-analysis results for all studies, individual outcomes, and Randomized Controlled Trials (RCTs).

Treatment timing

Figure 4 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.

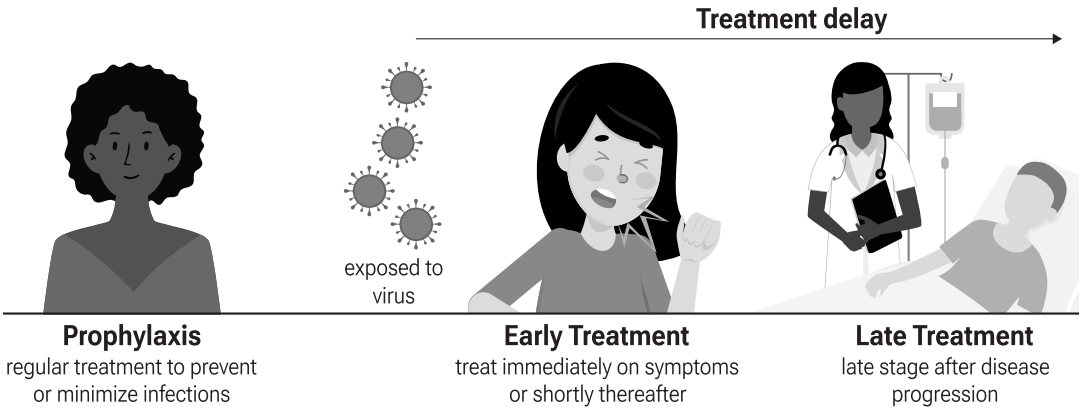


Figure 4. **Treatment stages.**

Results

Table 1 summarizes the results for all studies and for Randomized Controlled Trials. Figure 5 and 6 show forest plots for random effects meta-analysis of all studies with pooled effects and cases.

	Improvement	*Studies*	*Patients*	*Authors*
All studies	**47%** [29-62%] ****	1	556	15
Randomized Controlled Trials	**47%** [29-62%] ****	1	556	15

Table 1. **Random effects meta-analysis for all studies and for Randomized Controlled Trials.** Results show the percentage improvement with treatment and the 95% confidence interval. **** p<0.0001.

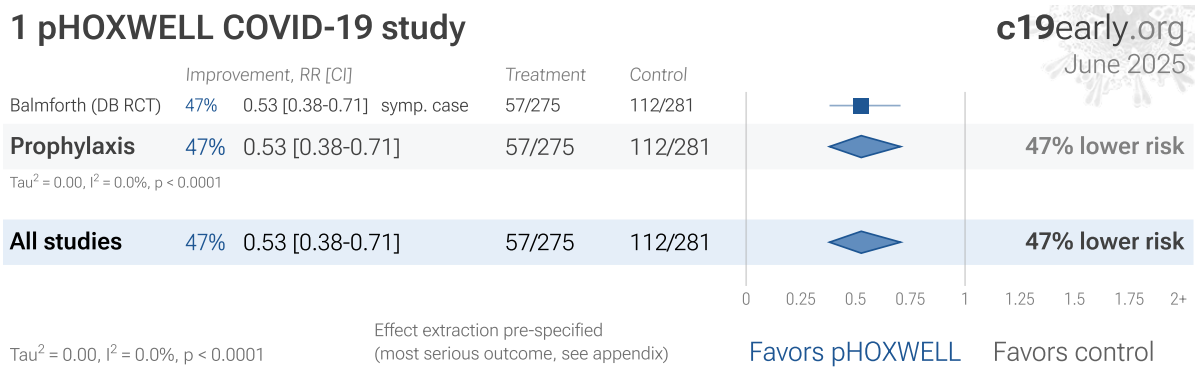


Figure 5. **Random effects meta-analysis for all studies.** Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

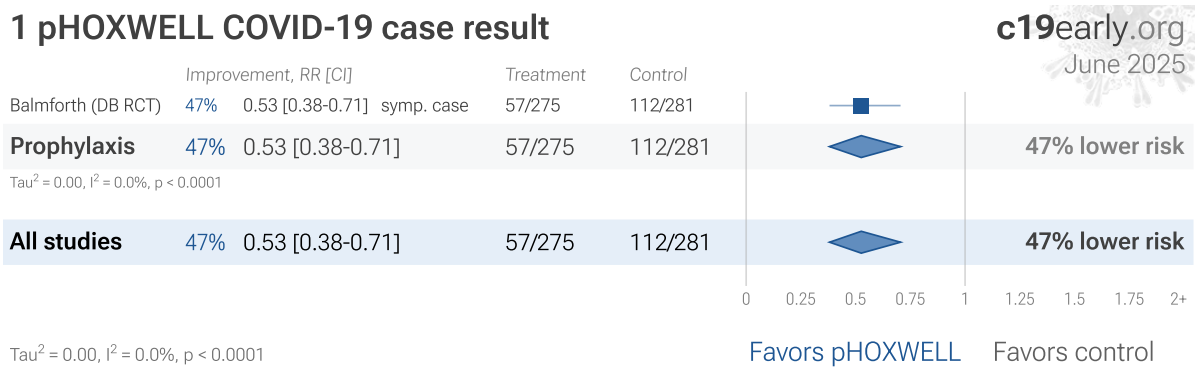


Figure 6. **Random effects meta-analysis for cases.**

Randomized Controlled Trials (RCTs)

Figure 7 shows a forest plot for random effects meta-analysis of all Randomized Controlled Trials. RCT results are included in Table 1. Currently there is only one study which is an RCT.

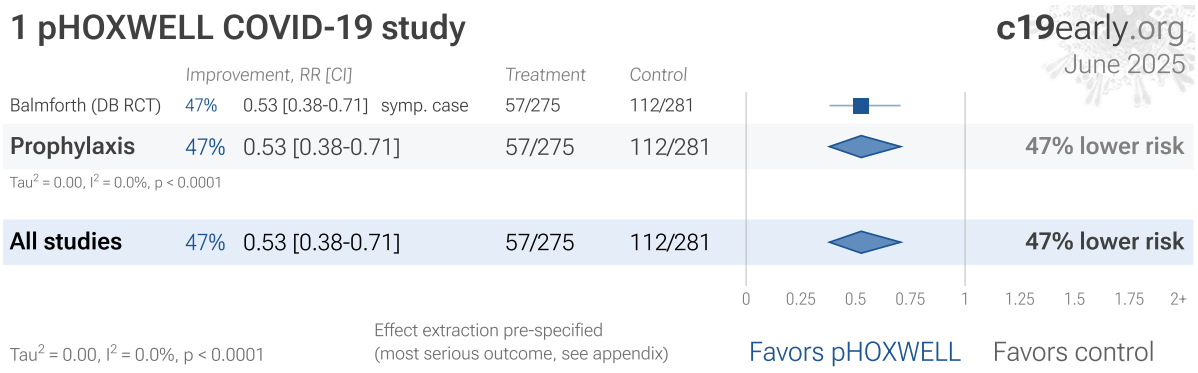


Figure 7. **Random effects meta-analysis for all Randomized Controlled Trials.** Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

Application

In addition to the dosage and frequency of administration, efficacy for nasopharyngeal/oropharyngeal treatments may depend on many other details. For example considering sprays, viscosity, mucoadhesion, sprayability, and application angle are important.

Akash et al. performed a computational fluid dynamics study of nasal spray administration showing 100x improvement in nasopharyngeal drug delivery using a new spray placement protocol, which involves holding the spay nozzle as horizontally as possible at the nostril, with a slight tilt towards the cheeks. The study also found the optimal droplet size range for nasopharyngeal deposition was ~7-17μm.

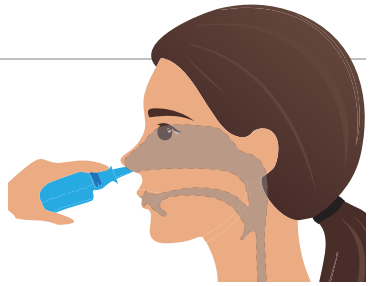


Figure 8. **Optimal spray angle may increase nasopharyngeal drug delivery 100x for nasal sprays, adapted from** *Akash et al.*

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[35,36]. 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[37]
<24 hours	-33 hours symptoms[38]
24-48 hours	-13 hours symptoms[38]
Inpatients	-2.5 hours to improvement[39]

Table 2. **Studies of baloxavir marboxil for influenza show that early treatment is more effective.**

Figure 9 shows a mixed-effects meta-regression for efficacy as a function of treatment delay in COVID-19 studies from 172 treatments, showing that efficacy declines rapidly with treatment delay. Early treatment is critical for COVID-19.

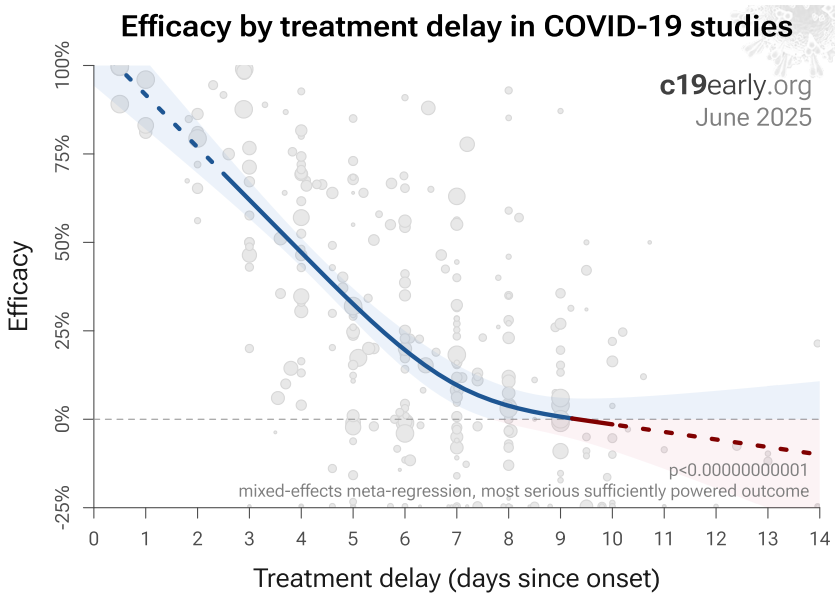


Figure 9. **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 172 treatments.

Patient demographics

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

SARS-CoV-2 variants

Efficacy may depend critically on the distribution of SARS-CoV-2 variants encountered by patients. Risk varies significantly across variants [41], for example the Gamma variant shows significantly different characteristics [42-45]. 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 [46,47].

Treatment regimen

Effectiveness may depend strongly on the dosage and treatment regimen.

Medication quality

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

Other treatments

The use of other treatments may significantly affect outcomes, including supplements, other medications, or other interventions such as prone positioning. Treatments may be synergistic [50-66], therefore efficacy may depend strongly on combined treatments.

Effect measured

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

Meta analysis

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

Discussion

Nasopharyngeal/oropharyngeal administration

Studies to date use a variety of administration methods to the respiratory tract, including nasal and oral sprays, nasal irrigation, oral rinses, and inhalation. Table 3 shows the relative efficacy for nasal, oral, and combined administration. Combined administration shows the best results, and nasal administration is more effective than oral. Precise efficacy depends on the details of administration, e.g., mucoadhesion and sprayability for sprays.

Nasal/oral administration to the respiratory tract	*Improvement*	*Studies*
Oral spray/rinse	38% [25-49%]	11
Nasal spray/rinse	58% [49-65%]	20
Nasal & oral	91% [74-97%]	7

Table 3. **Respiratory tract administration efficacy. Relative efficacy of nasal, oral, and combined nasal/oral administration for treatments administered directly to the respiratory tract, based on studies for astodrimer sodium, chlorhexidine, cetylpyridinium chloride, chlorpheniramine, iota-carrageenan, hydrogen peroxide, nitric oxide, povidone-iodine, plasma-activated water, alkalinization, phthalocyanine, sodium bicarbonate, pHOXWELL, and sentinox. Results show random effects meta analysis for the most serious outcome reported for all prophylaxis and early treatment studies.**

Impact on the microbiome

Nasopharyngeal/oropharyngeal treatments may not be highly selective. In addition to inhibiting or disabling SARS-CoV-2, they may also be harmful to beneficial microbes, disrupting the natural microbiome in the oral cavity and nasal passages that have important protective and metabolic roles[67]. This may be especially important for prolonged use or overuse. Table 4 summarizes the potential for common nasopharyngeal/oropharyngeal treatments to affect the natural microbiome.

Treatment	*Microbiome disruption potential*	*Notes*
Iota-carrageenan	Low	Primarily antiviral, however extended use may mildly affect the microbiome
Nitric Oxide	Low to moderate	More selective towards pathogens, however excessive concentrations or prolonged use may disrupt the balance of bacteria
Alkalinization	Moderate	Increases pH, negatively impacting beneficial microbes that thrive in a slightly acidic environment
Cetylpyridinium Chloride	Moderate	Quaternary ammonium broad-spectrum antiseptic that can disrupt beneficial and harmful bacteria
Phthalocyanine	Moderate to high	Photodynamic compound with antimicrobial activity, likely to affect the microbiome
Chlorhexidine	High	Potent antiseptic with broad activity, significantly disrupts the microbiome
Hydrogen Peroxide	High	Strong oxidizer, harming both beneficial and harmful microbes
Povidone-Iodine	High	Potent broad-spectrum antiseptic harmful to beneficial microbes

Table 4. **Potential effect of treatments on the nasophyrngeal/oropharyngeal microbiome.**

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[68-71]. For pHOXWELL, there is currently not enough data to evaluate publication bias with high confidence.

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. pHOXWELL for COVID-19 lacks this because it is off-patent, has multiple manufacturers, and is very low cost. In contrast, most COVID-19 pHOXWELL 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 pHOXWELL 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[50-66]. 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 100+ host and viral proteins and other factors[25-32], providing many therapeutic targets. Over 9,000 compounds have been predicted to reduce COVID-19 risk[33], either by directly minimizing infection or replication, by supporting immune system function, or by minimizing secondary complications. Figure 10 shows an overview of the results for pHOXWELL in the context of multiple COVID-19 treatments, and Figure 11 shows a plot of efficacy vs. cost for COVID-19 treatments.

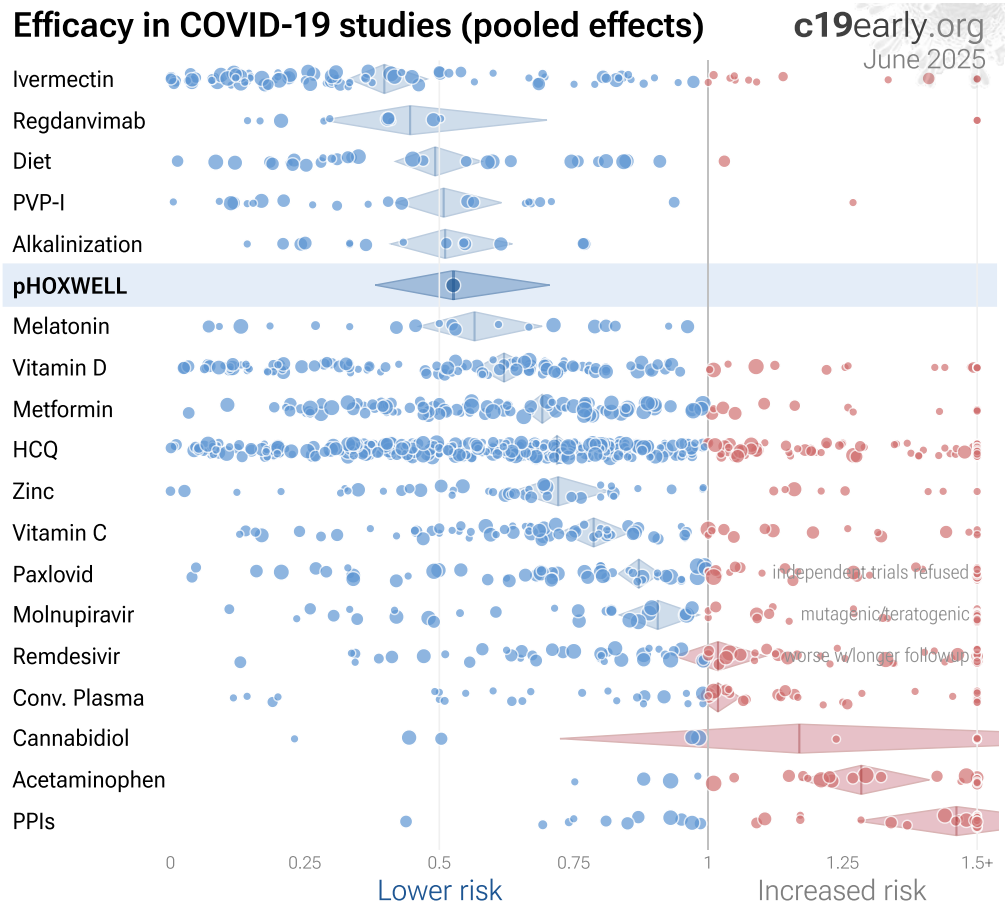


Figure 10. **Scatter plot showing results within the context of multiple COVID-19 treatments.** Diamonds shows the results of random effects meta-analysis. 0.6% of 9,000+ proposed treatments show efficacy[73].

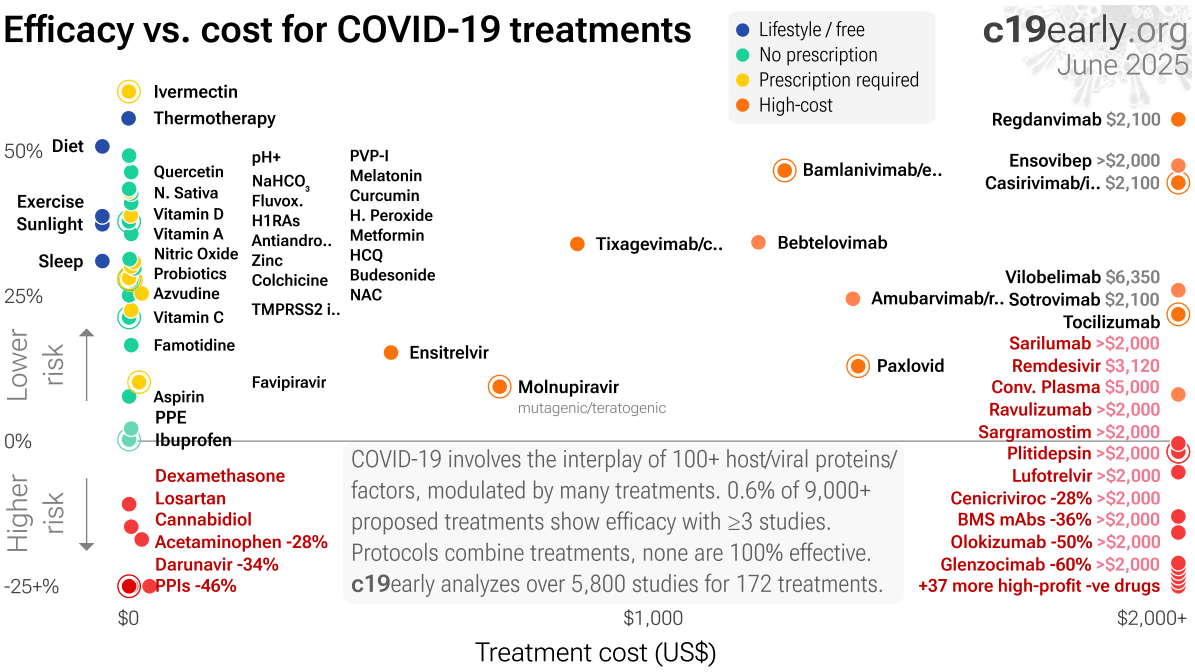


Figure 11. Efficacy vs. cost for COVID-19 treatments.

Conclusion

SARS-CoV-2 infection typically starts in the upper respiratory tract. Progression may lead to cytokine storm, pneumonia, ARDS, neurological issues, organ failure, and death. Stopping replication in the upper respiratory tract, via early or prophylactic nasopharyngeal/oropharyngeal treatment, can avoid the consequences of progression to other tissues, and avoid the requirement for systemic treatments with greater potential for side effects.

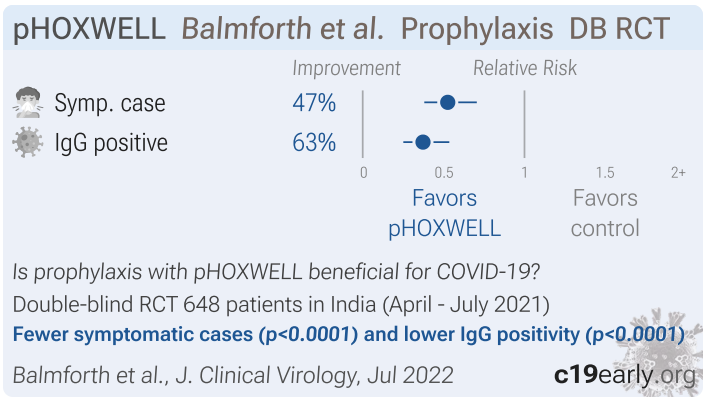
Studies to date show that pHOXWELL is an effective treatment for COVID-19. Significantly lower risk is seen for cases. Meta analysis using the most serious outcome reported shows 47% [29-62%] lower risk.

Currently there is very limited data, with only one study to date.

pHOXWELL may affect the natural microbiome, especially with prolonged use.

Study Notes

Balmforth



648 patient RCT pHOXWELL nasal spray in India, showing significantly lower IgGS+ and significantly lower symptomatic cases with treatment.

pHOXWELL includes a combination of natural virucidal agents and is designed to mimic the fluid surrounding healthy cells. The spray included xylitol, zinc chloride, polyethylene glycol 400, poloxamer, disodium hydrogen phosphate, sodium chloride, hydroxypropyl methylcellulose, ginger oil, eucalyptus oil, basil oil, clove oil, sodium hydrogen carbonate, potassium dihydrogen phosphate, ethylenediaminetetraacetic acid, sodium hyaluronate, calcium chloride dihydrate, benzalkonium chloride, magnesium chloride hexahydrate, potassium chloride, and glycerol. The spray was administered up to three times per day (TID) 140 µl/nostril for 45 days, with a gap of 6-8 hours between doses.

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 pHOXWELL 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 pHOXWELL for COVID-19 that report a comparison with a control group are included in the main analysis. Studies with major unexplained data issues, for example major outcome data that is impossible to be correct with no response from the authors, are excluded. This is a living analysis and is updated regularly.

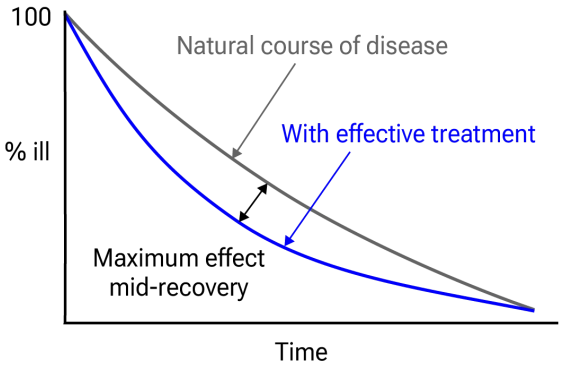


Figure 12. **Mid-recovery results can more accurately reflect efficacy when almost all patients recover.** *Mateja et al.* **confirm that intermediate viral load results more accurately reflect hospitalization/death.**

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 reported then they are both used in specific outcome analyses, while mortality is used for pooled analysis. If symptomatic results are reported at multiple times, we use 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 outcomes. 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. An IPD meta-analysis confirms that intermediate viral load reduction is more closely associated with hospitalization/death than later viral load reduction [74]. 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 et al.* Reported confidence intervals and *p*-values are used when available, and adjusted values are used 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 [78]. Results are expressed with RR < 1.0 favoring treatment, and using the risk of a negative outcome when applicable (for example, the risk of death rather than the risk of survival). If studies only report relative continuous values such as relative times, the ratio of the time for the treatment group versus the time for the control group is used. Calculations are done in Python (3.13.4) with scipy (1.15.3), pythonmeta (1.26), numpy (2.3.0), statsmodels (0.14.4), and plotly (6.1.2).

Forest plots are computed using PythonMeta[79] 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 0.8.2 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[35,36].

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/phxmeta.html.

Prophylaxis

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

Balmforth, 7/25/2022, Double Blind Randomized Controlled Trial, placebo-controlled, India, peer-reviewed, 15 authors, study period April 2021 - July 2021, trial CTRI/2021/04/032989.	risk of symptomatic case, 47.4% lower, RR 0.53, $p < 0.001$, treatment 57 of 275 (20.7%), control 112 of 281 (39.9%), NNT 5.2, odds ratio converted to relative risk.
	risk of IgG positive, 62.7% lower, RR 0.37, $p < 0.001$, treatment 36 of 275 (13.1%), control 97 of 281 (34.5%), NNT 4.7, adjusted per study, odds ratio converted to relative risk, multivariable.

Supplementary Data

Supplementary Data

Footnotes

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

References

1. ***Ryu*** et al., *Fibrin drives thromboinflammation and neuropathology in COVID-19*, Nature, doi:10.1038/s41586-024-07873-4.
2. ***Dai*** et al., *Neurological complications of COVID-19*, QJM: An International Journal of Medicine, doi:10.1093/qjmed/hcac272.
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