# Peginterferon Lambda for COVID-19: real-time meta analysis of 4 studies

@CovidAnalysis, March 2024, Version 7
https://c19early.org/ilmeta.html

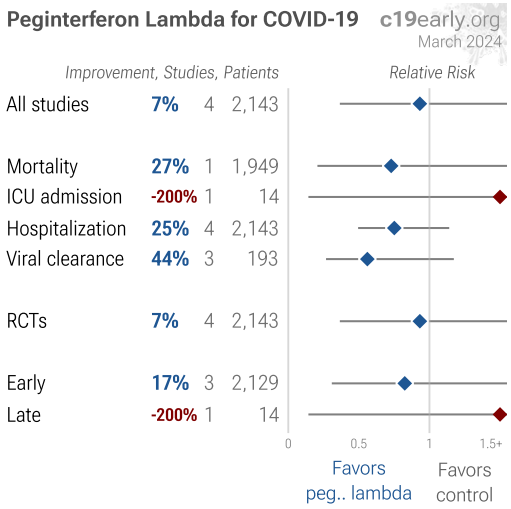
## Abstract

Meta analysis using the most serious outcome reported shows 7% [-138-63%] lower risk, without reaching statistical significance. Early treatment is more effective than late treatment. Currently all studies are RCTs.

2 studies from 2 independent teams in 2 countries show statistically significant improvements.

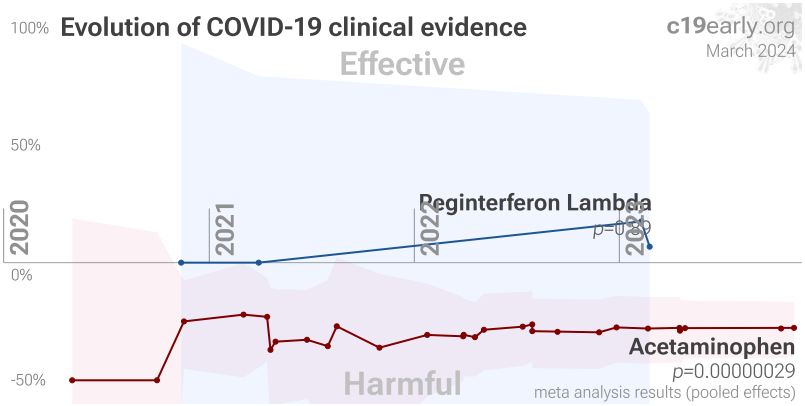
Currently there is limited data, with only 9 control events for the most serious outcome in trials to date.

The primary positive trial *Reis* has major anomolies *Kelleni*. Results from NCT04967430 have not been reported and contact information was deleted in the registry.




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.




## HIGHLIGHTS

Peginterferon Lambda reduces risk for COVID-19 with low confidence for viral clearance and very low confidence for hospitalization and progression, however increased risk is seen with very low confidence for ICU admission.

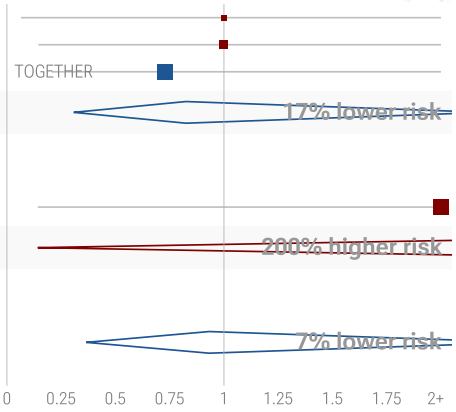
We show traditional outcome specific analyses and combined evidence from all studies, incorporating treatment delay, a primary confounding factor in COVID-19 studies.

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

## 4 peginterferon lambda COVID-19 studies

c19early.org
March 2024

| | Improvement, RR [CI] | | Treatment | Control |
|---|---|---|---|---|
| Feld (DB RCT) | 0% | 1.00 [0.07-15.3] hosp. | 1/30 | 1/30 |
| Jagannat.. (SB RCT) | 0% | 1.00 [0.15-6.87] hosp. | 2/60 | 2/60 |
| Reis (DB RCT) | 27% | 0.73 [0.21-2.58] death | 4/931 | 6/1,018 |
| **Early treatment** | 17% | 0.83 [0.31-2.21] | 7/1,021 | 9/1,108 |
| $Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.71$ | | | | |
| | Improvement, RR [CI] | | Treatment | Control |
| Kim (SB RCT) | -200% | 3.00 [0.14-63.2] ICU | 1/7 | 0/7 |
| **Late treatment** | -200% | 3.00 [0.14-63.2] | 1/7 | 0/7 |
| $Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.49$ | | | | |
| **All studies** | 7% | 0.93 [0.37-2.38] | 8/1,028 | 9/1,115 |




$Tau^2 = 0.00$, $I^2 = 0.0\%$, $p = 0.89$

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

Favors peg.. lambda  Favors control

A

## Efficacy in COVID-19 peginterferon lambda studies (pooled effects)

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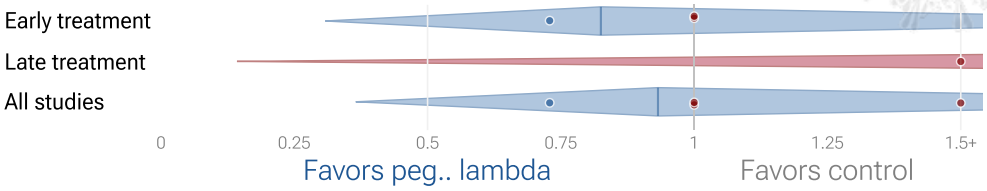
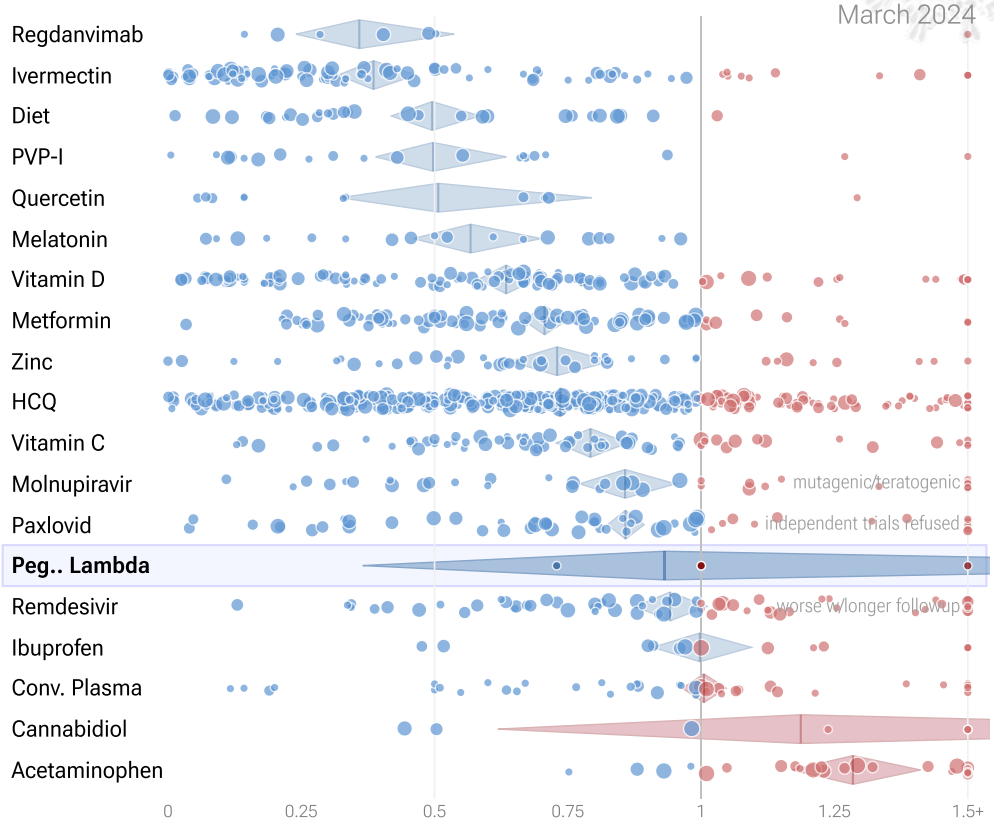



Favors peg.. lambda  Favors control

B

## Efficacy in COVID-19 studies (pooled effects)

c19early.org
March 2024




Lower risk  Increased risk

C

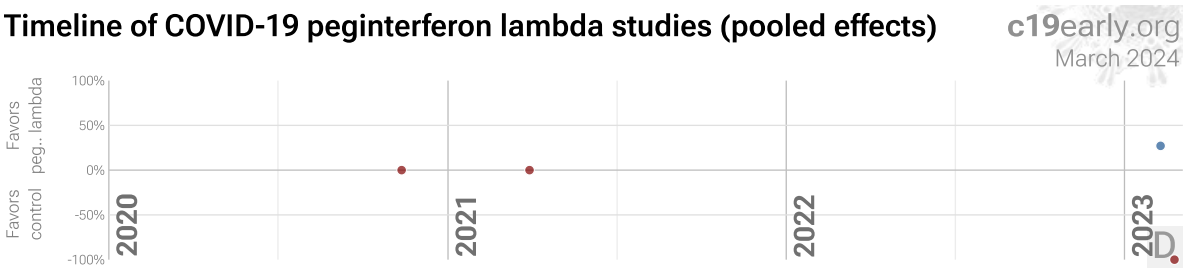



***Figure 1.*** **A. Random effects meta-analysis.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see 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 peginterferon lambda 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 peginterferon lambda 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, 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.

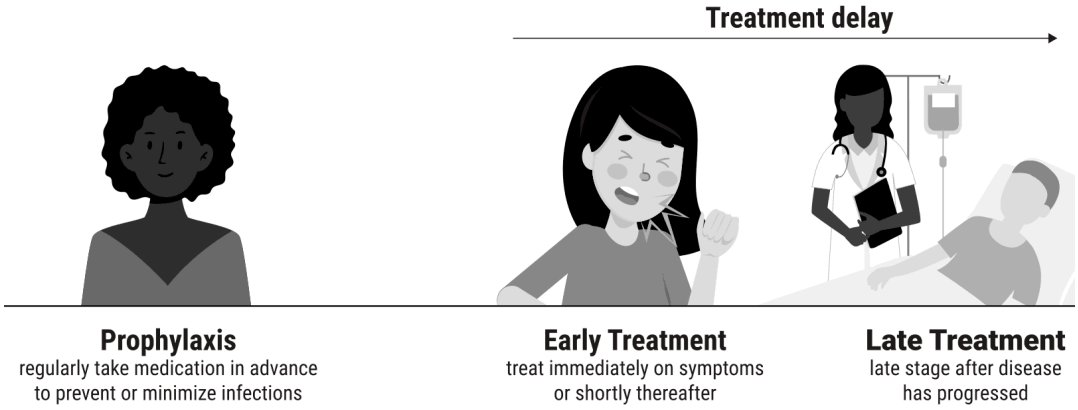



***Figure 2.*** Treatment stages.

## Results

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

| | *Improvement* | *Studies* | *Patients* | *Authors* |
|---|---|---|---|---|
| All studies | **7%** [-138-63%] | 4 | 2,143 | 112 |
| Randomized Controlled Trials | **7%** [-138-63%] | 4 | 2,143 | 112 |
| Hospitalization | 25% [-14-51%] | 4 | 2,143 | 112 |
| Viral | 44% [-17-73%] | 3 | 193 | 71 |
| RCT hospitalization | 25% [-14-51%] | 4 | 2,143 | 112 |

***Table 1.*** **Random effects meta-analysis for all stages combined, for Randomized Controlled Trials, and for specific outcomes.** Results show the percentage improvement with treatment and the 95% confidence interval.

| | *Early treatment* | *Late treatment* |
|---|---|---|
| All studies | **17%** [-121-69%] | -200% [-6215-86%] |
| Randomized Controlled Trials | **17%** [-121-69%] | -200% [-6215-86%] |
| Hospitalization | 39% [-0-63%] | -25% [-173-43%] |
| Viral | 58% [-6-83%] | **12%** [-144-69%] |
| RCT hospitalization | 39% [-0-63%] | -25% [-173-43%] |

***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.

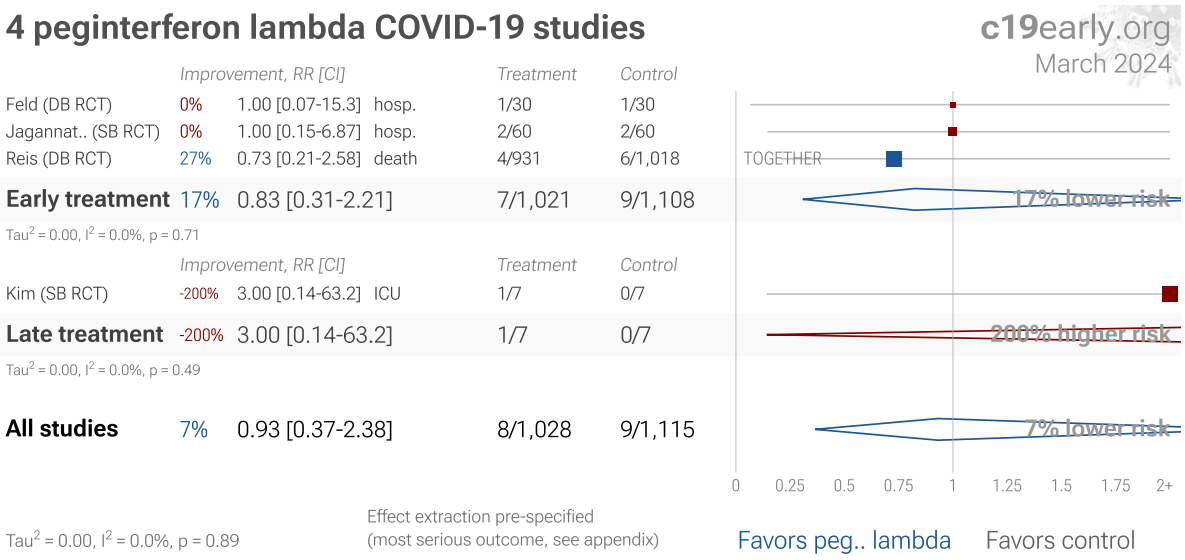



***Figure 3.*** **Random effects meta-analysis for all studies with pooled effects.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes, and the heterogeneity section for discussion. Effect extraction is pre-specified, using the most serious outcome reported. For details of effect extraction see the appendix.

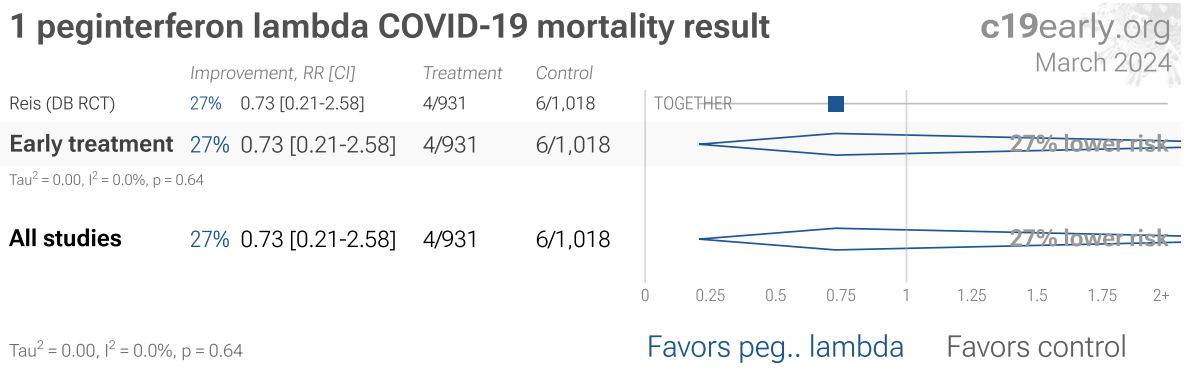



***Figure 4.*** **Random effects meta-analysis for mortality results.**

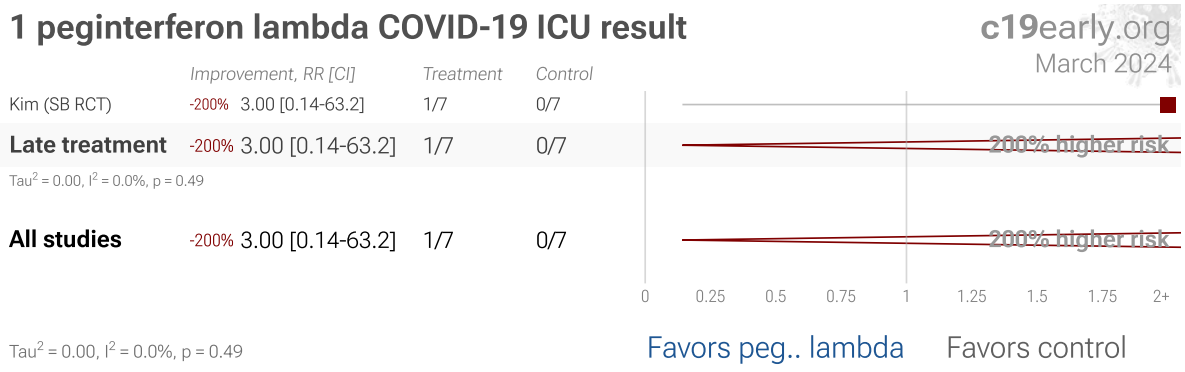



***Figure 5.*** **Random effects meta-analysis for ICU admission.**

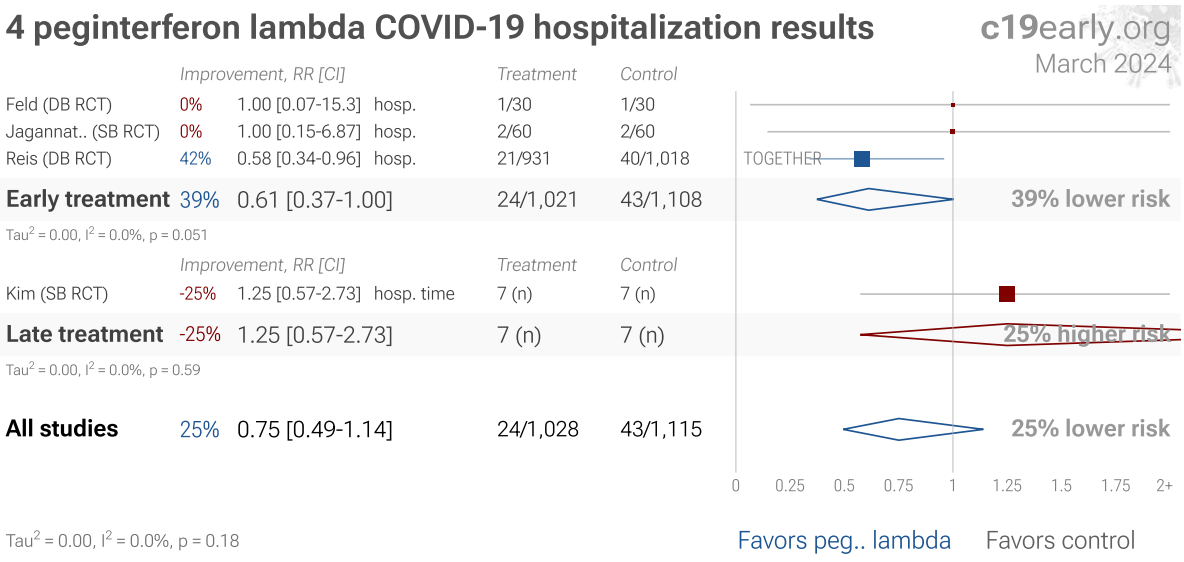



***Figure 6.*** Random effects meta-analysis for hospitalization.

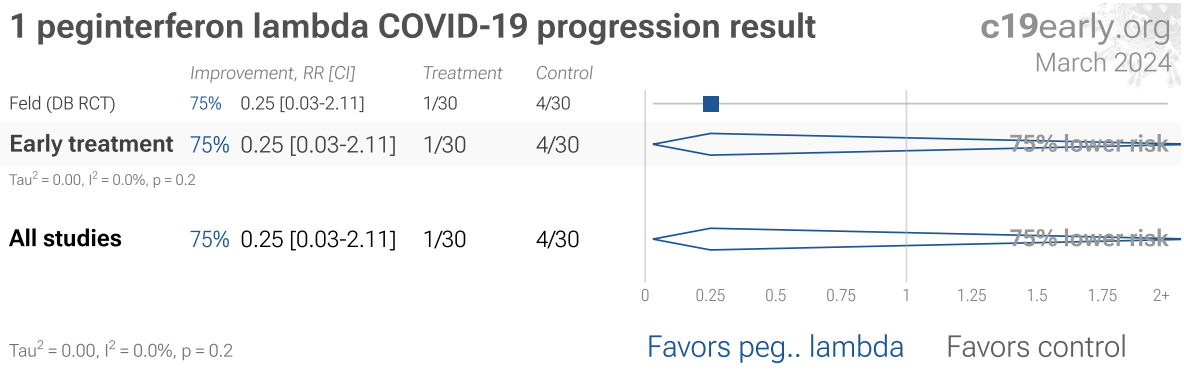



***Figure 7.*** Random effects meta-analysis for progression.

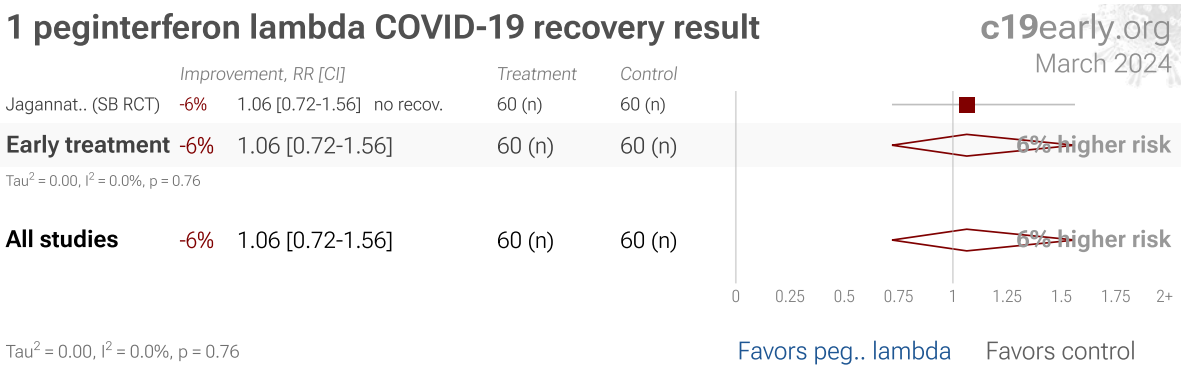



***Figure 8.*** Random effects meta-analysis for recovery.

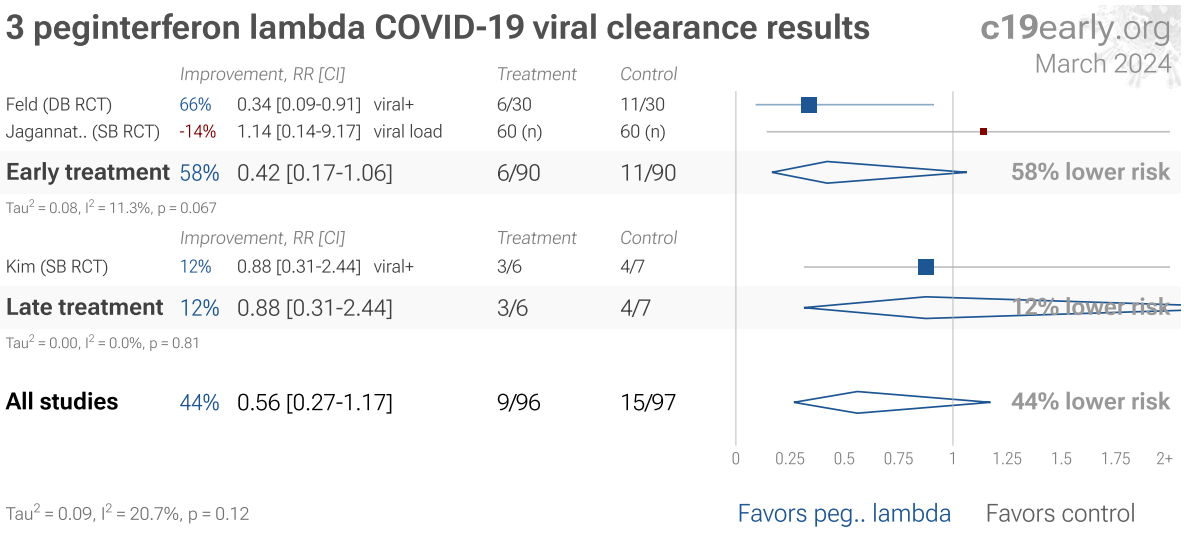



***Figure 9.*** **Random effects meta-analysis for viral clearance.**

## Randomized Controlled Trials (RCTs)

Currently all studies are RCTs.

## Heterogeneity

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

**Treatment delay.** The time between infection or the onset of symptoms and treatment may critically affect how well a treatment works. For example an antiviral may be very effective when used early but may not be effective in late stage disease, and may even be harmful. Oseltamivir, for example, is generally only considered effective for influenza when used within 0-36 or 0-48 hours *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 10 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.

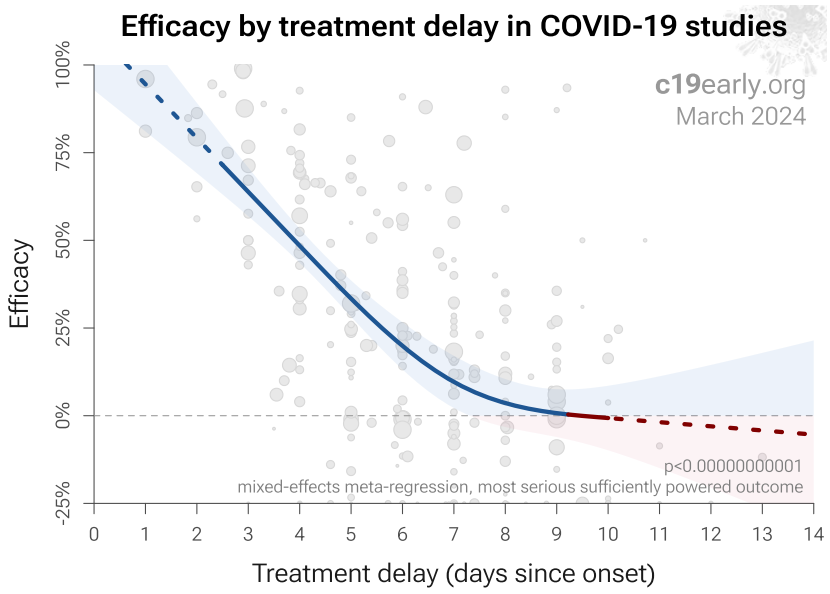



***Figure 10.*** **Early treatment is more effective.** Meta-regression showing efficacy as a function of treatment delay in COVID-19 studies from 66 treatments.

**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 11. 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.

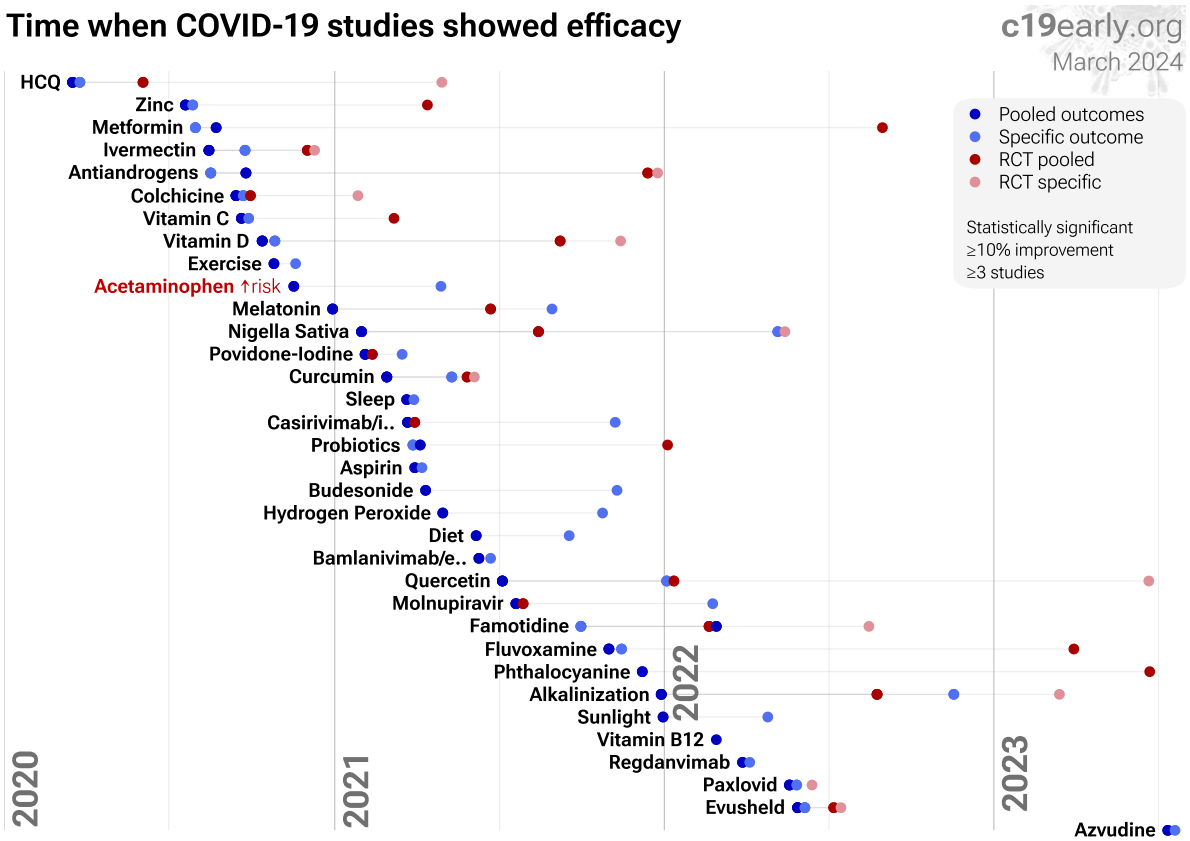



***Figure 11.*** **The time when studies showed that treatments were effective, defined as statistically significant improvement of ≥10% from ≥3 studies.** Pooled results typically show efficacy earlier than specific outcome results. Results from all studies often shows efficacy much earlier than when restricting to RCTs. Results reflect conditions as used in trials to date, these depend on the population treated, treatment delay, and treatment regimen.

**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. Trials with patented drugs may have a financial conflict of interest that results in positive studies being more likely to be published, or bias towards more positive results. For example with molnupiravir, trials with negative results remain unpublished to date (CTRI/2021/05/033864 and CTRI/2021/08/0354242). For peginterferon lambda, 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 12 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.

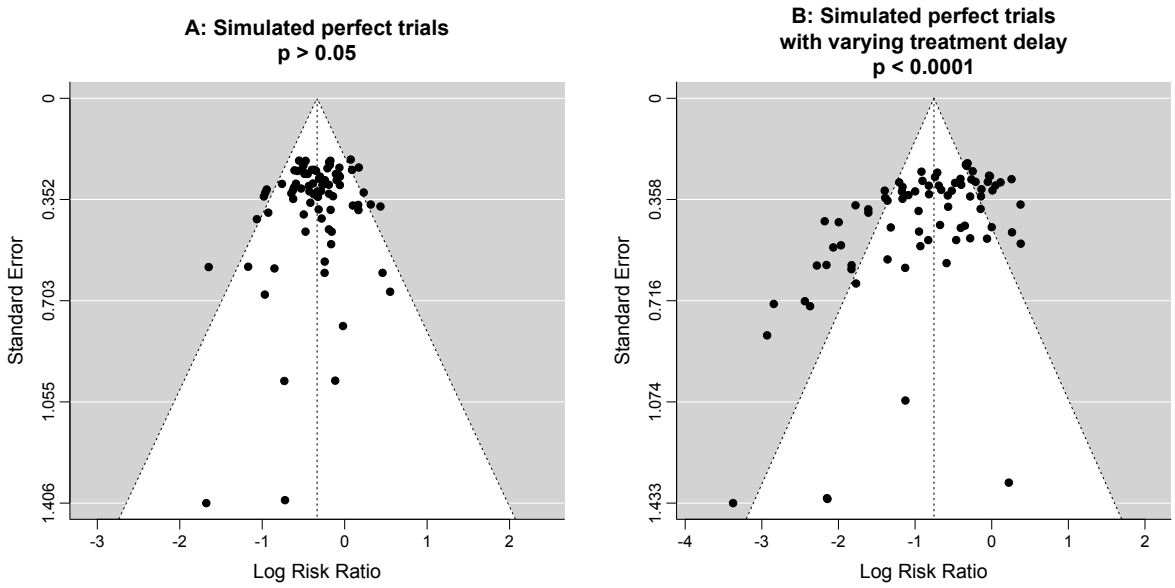



***Figure 12.*** Example funnel plot analysis for simulated perfect trials.

**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.

**Reviews.** *Kelleni et al.* present a review covering peginterferon lambda for COVID-19.

## Conclusion

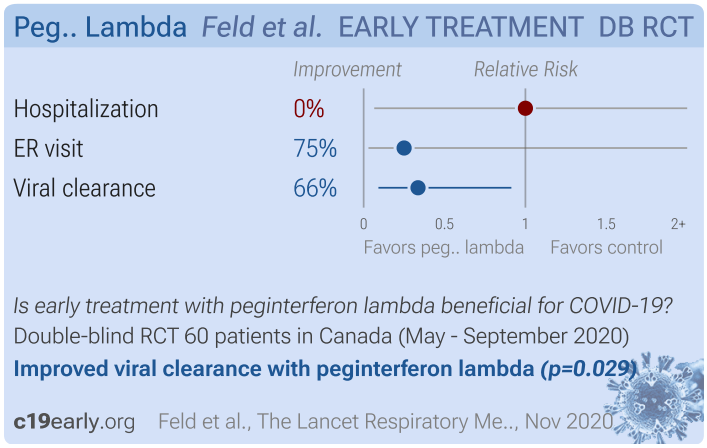
Meta analysis using the most serious outcome reported shows 7% [-138-63%] lower risk, without reaching statistical significance. Early treatment is more effective than late treatment. Currently all studies are RCTs. 2 studies from 2 independent teams in 2 countries show statistically significant improvements.

Currently there is limited data, with only 9 control events for the most serious outcome in trials to date.

The primary positive trial *Reis* has major anomolies *Kelleni*. Results from NCT04967430 have not been reported and contact information was deleted in the registry.

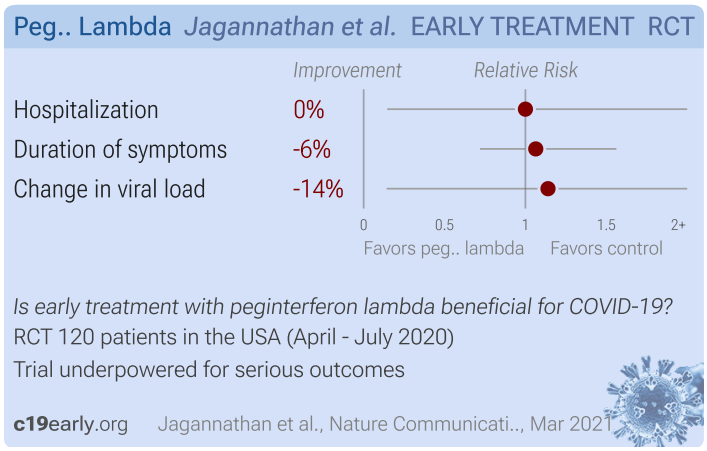
## Study Notes

### Feld



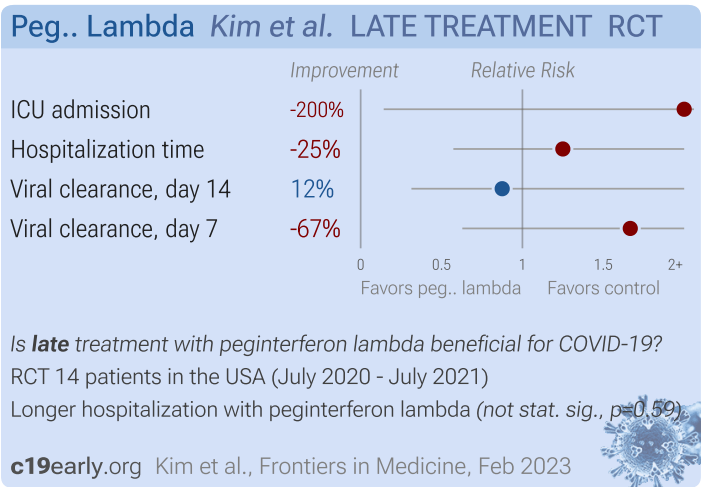

*Feld*: Small outpatient RCT with 30 peginterferon lambda and 30 control patients, showing improved viral clearance with treatment. Single subcutaneous injection of peginterferon lambda 180µg. NCT04354259.

### Jagannathan



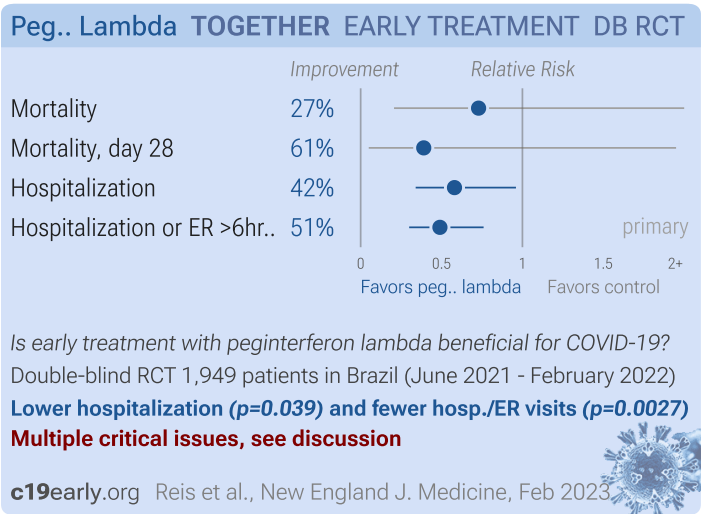

*Jagannathan*: RCT 120 outpatients with mild/moderate COVID-19, showing no significant differences with peginterferon lambda-1a treatment. 180µg subcutaneous peginterferon lambda-1a. NCT04331899.

### Kim




*Kim*: Very small RCT with 14 hospitalized patients in the USA showing no significant differences with peginterferon lambda. Viral load was improved, however 86% of treatment versus 14% of control patients received remdesivir, and the median baseline viral load for treatment patients was 3.6 log10 copies/ml versus 0 for control.

### Reis




*Reis*: High-risk outpatient RCT with 931 peginterferon lambda patients and 1,018 control patients, showing significantly lower hospitalization/ER visits with treatment. Single subcutaneous injection.

There were 85/931 and 286/1018 patients for which baseline SARS-CoV-2 status was unknown, p = 1.4e-27 (about 1 in 704 septillion).

The most frequent risk factors were more common in the placebo group, for example obesity 39.1% control vs. 34.5% treatment, p = 0.04.

Authors claim patients were unaware or the randomization assignments, however some patients received oral placebo in a trial of a treatment requiring subcutaneous injection.

The numbers in Table 1 and Table S1 do not match, e.g., the text and Table 1 indicate 931 ITT interferon patients, while Table S1 shows 916.

All deaths in the placebo arm were attributed to COVID-19, while only 50% were in the interferon arm. One placebo death is listed as both due to COVID-19 and due to acute myeloid leukemia (Table S6).

See also *Kelleni*.

The TOGETHER trial has extreme COI, impossible data, blinding failure, randomization failure, uncorrected errors, and many protocol violations. Authors do not respond to these issues and they have refused to release the data as promised. Some issues may apply only to specific arms. For more details see *Reis (B), Reis (C), Reis (D), Reis (E), Reis (F)*.

## 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 peginterferon lambda 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 peginterferon lambda 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 *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].

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

| | |
|---|---|
| *Feld*, 11/12/2020, Double Blind Randomized Controlled Trial, placebo-controlled, Canada, peer-reviewed, 35 authors, study period 18 May, 2020 - 4 September, 2020, average treatment delay 4.3 days, trial NCT04354259 (history). | risk of hospitalization, no change, RR 1.00, $p = 1.00$, treatment 1 of 30 (3.3%), control 1 of 30 (3.3%). |
| | risk of ER visit, 75.0% lower, RR 0.25, $p = 0.35$, treatment 1 of 30 (3.3%), control 4 of 30 (13.3%), NNT 10.0. |
| | risk of no viral clearance, 66.4% lower, RR 0.34, $p = 0.03$, treatment 6 of 30 (20.0%), control 11 of 30 (36.7%), NNT 6.0, inverted to make RR<1 favor treatment, odds ratio converted to relative risk, adjusted for baseline viral load, day 7. |
| *Jagannathan*, 3/30/2021, Single Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, 27 authors, study period 25 April, 2020 - 17 July, 2020, average treatment delay 5.0 days, trial NCT04331899 (history). | risk of hospitalization, no change, RR 1.00, $p = 1.00$, treatment 2 of 60 (3.3%), control 2 of 60 (3.3%), day 28. |
| | duration of symptoms, 6.4% higher, HR 1.06, $p = 0.76$, treatment 60, control 60, inverted to make HR<1 favor treatment. |
| | relative change in viral load, 14.0% worse, RR 1.14, $p = 0.91$, treatment 60, control 60, day 14. |
| *Reis*, 2/9/2023, Double Blind Randomized Controlled Trial, placebo-controlled, Brazil, peer-reviewed, 41 authors, study period 24 June, 2021 - 7 February, 2022, trial NCT04727424 (history) (TOGETHER). | risk of death, 27.1% lower, RR 0.73, $p = 0.76$, treatment 4 of 931 (0.4%), control 6 of 1,018 (0.6%), NNT 626, all-cause, Table S6. |
| | risk of death, 61.0% lower, RR 0.39, $p = 0.32$, treatment 1 of 931 (0.1%), control 4 of 1,018 (0.4%), adjusted per study, attributed to COVID, day 28. |
| | risk of hospitalization, 42.0% lower, RR 0.58, $p = 0.04$, treatment 21 of 931 (2.3%), control 40 of 1,018 (3.9%), NNT 60, adjusted per study, day 28. |
| | hospitalization or ER >6hrs, 51.0% lower, RR 0.49, $p = 0.003$, treatment 25 of 931 (2.7%), control 57 of 1,018 (5.6%), NNT 34, adjusted per study, day 28, primary outcome. |

## 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.

| | |
|---|---|
| *Kim*, 2/24/2023, Single Blind Randomized Controlled Trial, placebo-controlled, USA, peer-reviewed, median age 54.0, 9 authors, study period 14 July, 2020 - 16 July, 2021, trial NCT04343976 (history). | risk of ICU admission, 200.0% higher, RR 3.00, $p$ = 1.00, treatment 1 of 7 (14.3%), control 0 of 7 (0.0%), continuity correction due to zero event (with reciprocal of the contrasting arm). |
| | hospitalization time, 25.0% higher, relative time 1.25, $p$ = 0.59, treatment median 5.0 IQR 4.0 n=7, control median 4.0 IQR 5.0 n=7. |
| | risk of no viral clearance, 12.5% lower, RR 0.88, $p$ = 1.00, treatment 3 of 6 (50.0%), control 4 of 7 (57.1%), NNT 14, day 14. |
| | risk of no viral clearance, 66.7% higher, RR 1.67, $p$ = 0.59, treatment 5 of 7 (71.4%), control 3 of 7 (42.9%), day 7. |

## 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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