Ribavirin for hantavirus: real-time meta-analysis of 3 studies

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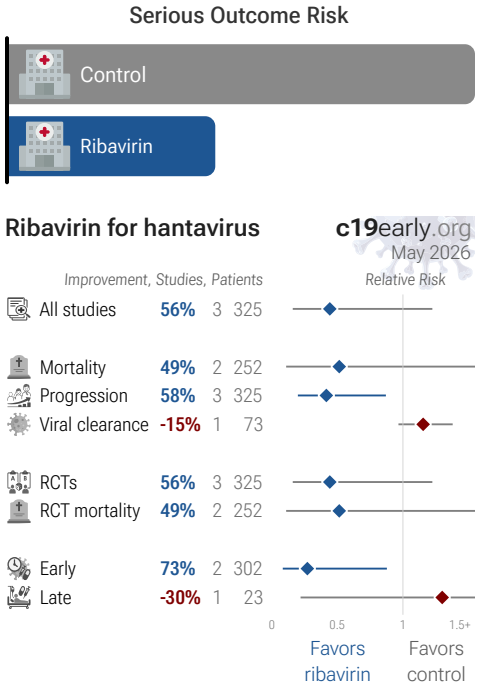
Abstract

Significantly lower risk is seen for progression. One study shows significant benefit.

Meta-analysis using the most serious outcome reported shows 56% [-22-84%] lower risk, without reaching statistical significance. Early treatment shows efficacy while late treatment does not, consistent with expectations for an antiviral treatment. Currently all studies are RCTs.

Currently there is limited data, with only 325 patients and only 13 control events for the most serious outcome in trials to date. Studies to date are from only 3 different groups.

No treatment is 100% effective. Protocols combine safe and effective options with individual risk/benefit analysis and monitoring. *Huggins et al.* shows efficacy for early treatment of HFRS. Ribavirin shows *in vitro* efficacy against Old World and New World hantaviruses, however no trial has evaluated early (prodromal) treatment for HCPS. Ribavirin has significant toxicity risks and careful risk-benefit analysis is required. All data and sources to reproduce this analysis are in the appendix.



Introduction

Immediate treatment recommended

Hantavirus is transmitted via the inhalation of aerosolized rodent excreta containing very small viral particles (<5 µm) that typically bypass the upper respiratory tract entirely, depositing directly into the deep lung alveoli without causing common cold symptoms. The virus primarily infects the alveolar macrophages and the pulmonary endothelial cells (the cells lining the microscopic blood vessels of the lungs), where it can cross directly into the bloodstream and circulate throughout the body. Once established, the infection primarily manifests as either Hemorrhagic Fever with Renal Syndrome (HFRS) or Hantavirus Cardiopulmonary Syndrome (HCPS), both beginning with a generic febrile prodrome.

Hantaviruses do not typically cause massive, direct cell death. Instead, they infect the microvascular endothelial cells lining the capillaries and trigger an immune response that causes those specific cell junctions to break down and leak fluid.

HCPS (New World Hantaviruses, e.g., Sin Nombre): these viruses have a highly specific tropism for the endothelial cells of the pulmonary capillaries. Even though the virus circulates systemically, the intense immune battle occurs primarily in the lungs. This localized endothelial dysfunction causes the pulmonary capillaries to leak plasma, rapidly flooding the lungs (non-cardiogenic pulmonary edema) and leading to cardiogenic shock.

HFRS (Old World Hantaviruses, e.g., Hantaan): these viruses have a strong tropism for the endothelial cells of the kidneys, specifically targeting the renal medullary capillaries, tubular cells, and glomerular podocytes. The immune-mediated capillary leakage happens primarily in the kidneys. This breakdown in the renal barrier leads to acute kidney injury, massive proteinuria (proteins leaking into the urine), and the systemic hemorrhagic manifestations (internal bleeding and drops in blood pressure) characteristic of HFRS.

Some hantaviruses such as Puumala virus are relatively mild, while Hantaan, Sin Nombre, Andes, and others are more severe with 5-50% mortality rates. Even among survivors, recovery is frequently incomplete, with high prevalence of morbidity. Minimizing replication as early as possible is recommended.

Many treatments are expected to modulate infection

Hantavirus infection and replication involves the complex interplay of over 100 viral and host factors, with core viral targets including Gn/Gc-mediated entry, endosomal fusion, nucleocapsid-RNA interactions, cap-snatching, RdRp-mediated transcription/replication, innate-immune evasion, endothelial barrier dysfunction, and host translation/ER-protein-processing pathways. Preclinical studies report dozens of treatments that may reduce hantavirus risk, either by directly minimizing infection and replication, by supporting immune system function, or by minimizing secondary complications.

Analysis

We analyze all significant controlled studies of ribavirin for hantavirus. 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).

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. Fig. 1 shows a timeline of the results in ribavirin studies. Fig. 2 plots individual results by treatment stage. Fig. 3, 4, 5, and 6 show forest plots for random-effects meta-analysis of all studies with pooled effects, mortality results, progression, and viral clearance.

	Relative Risk	Studies	Patients
All studies	0.44 [0.16-1.22]	3	325
RCTs	0.44 [0.16-1.22]	3	325
Mortality	0.51 [0.11-2.41]	2	252
RCT mortality	0.51 [0.11-2.41]	2	252

Table 1. **Random-effects meta-analysis for all stages combined, for Randomized Controlled Trials, and for specific outcomes.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$.

	Early treatment	Late treatment
All studies	0.27 [0.08-0.88] *	1.30 [0.22-7.69]
RCTs	0.27 [0.08-0.88] *	1.30 [0.22-7.69]
Mortality	0.26 [0.07-0.93] *	1.30 [0.22-7.69]
RCT mortality	0.26 [0.07-0.93] *	1.30 [0.22-7.69]

Table 2. **Random-effects meta-analysis results by treatment stage.** Results show the relative risk with treatment and the 95% confidence interval. * $p<0.05$.

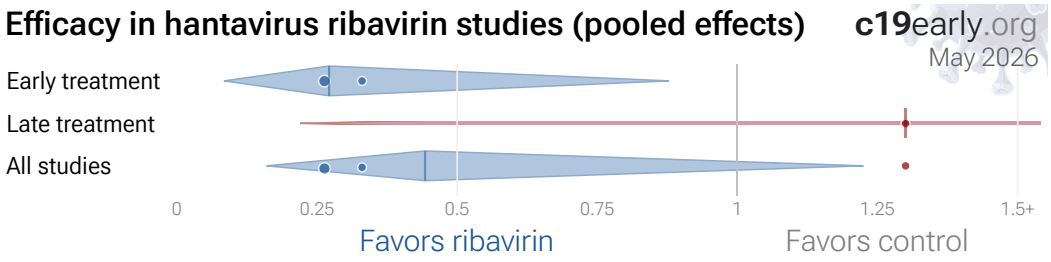


Fig. 2. Scatter plot showing the most serious outcome in all studies, and for studies within each stage. Diamonds shows the results of random-effects meta-analysis.

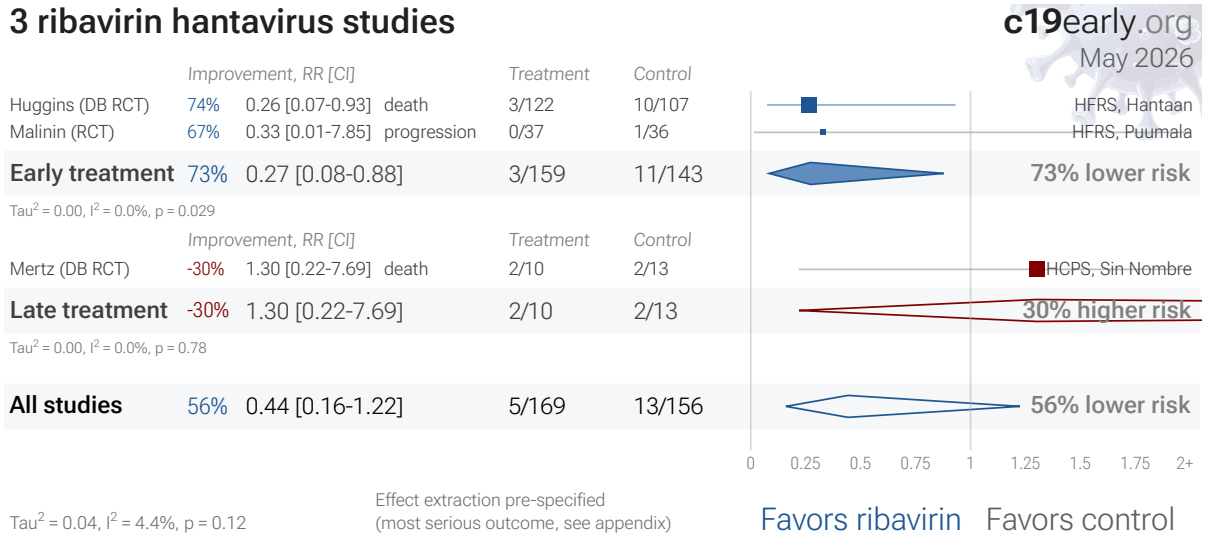


Fig. 3. **Random-effects meta-analysis for all studies.** This plot shows pooled effects, see the specific outcome analyses for individual outcomes. Effect extraction is pre-specified, using the most serious outcome reported. For details see the appendix.

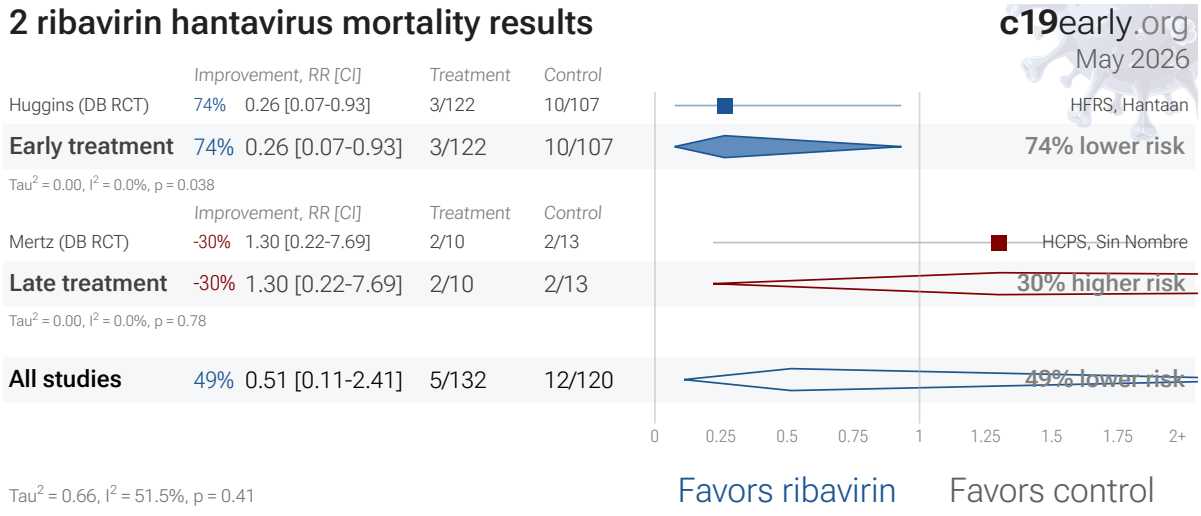


Fig. 4. Random-effects meta-analysis for mortality results.

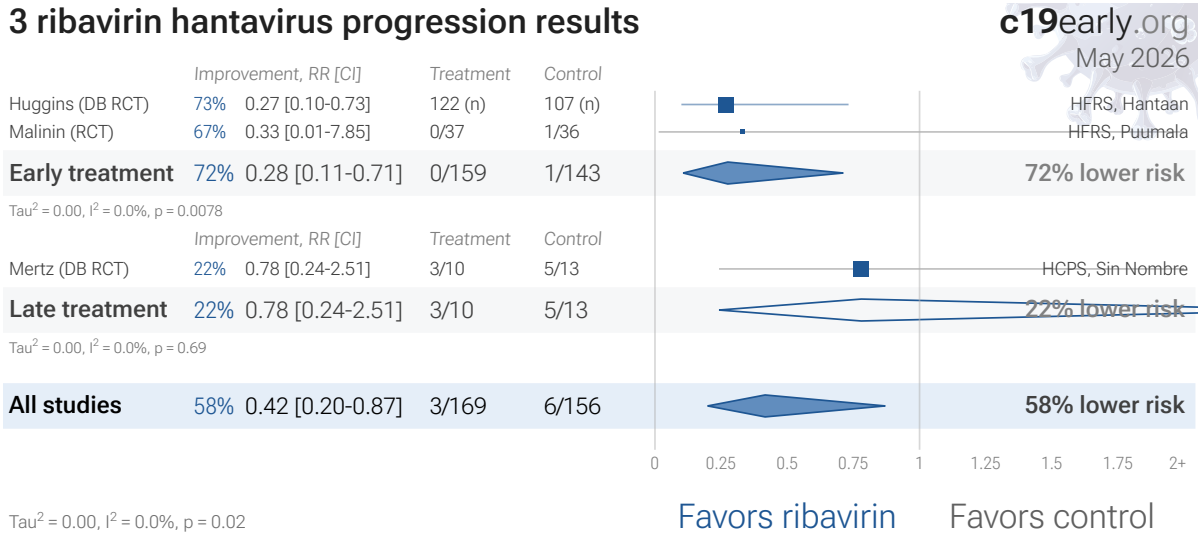


Fig. 5. Random-effects meta-analysis for progression.

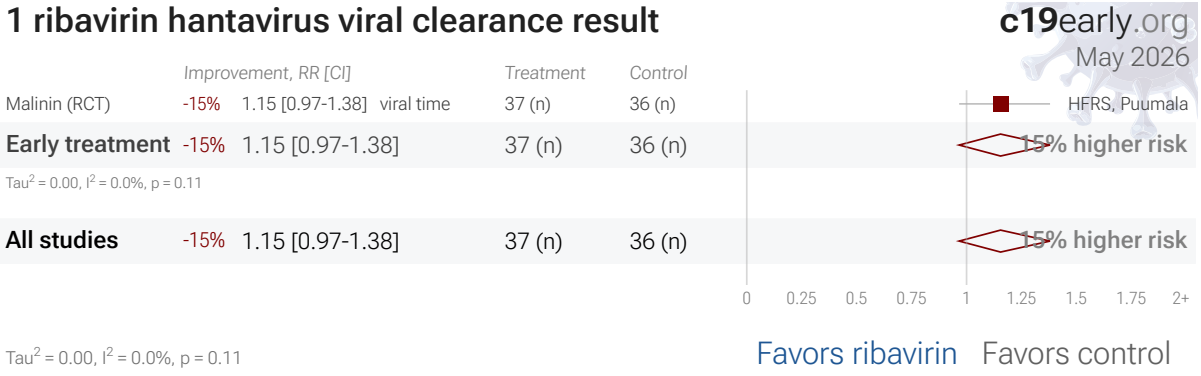


Fig. 6. Random-effects meta-analysis for viral clearance.

Randomized Controlled Trials (RCTs)

Currently all studies are RCTs.

Discussion

HFRS vs. HCPS

Huggins et al. shows efficacy of intravenous ribavirin for reducing mortality and the incidence of oliguria when administered early in Hemorrhagic Fever with Renal Syndrome (HFRS), however efficacy for Hantavirus Cardiopulmonary Syndrome (HCPS) remains unknown. Mechanistically, ribavirin inhibits the replication of both Old and New World hantaviruses *in vitro*, however, no clinical trial has evaluated early (prodromal) treatment for HCPS.

Intravenous administration of ribavirin achieves therapeutic antiviral concentrations in the lungs, however, ribavirin is a prodrug that may require days of continuous infusion to reach steady-state, active intracellular levels. Therefore, rapid identification of cases and earlier initiation of treatment may critical for HCPS. For HFRS, *Huggins et al.* note that "*early treatment (initiated on or before day 4 of illness) resulted in a more pronounced treatment effect*".

Additionally, because ribavirin is primarily eliminated via the kidneys, it naturally concentrates at much higher levels in renal tissue, potentially providing a therapeutic advantage for HFRS that is not mirrored in the pulmonary-centric pathogenesis of HCPS.

Safety

Use of intravenous ribavirin is constrained by its substantial toxicity profile, notably the induction of a pronounced, though generally reversible, hemolytic anemia. Because the early, prodromal symptoms of severe hantavirus infections are virtually indistinguishable from common, benign viral illnesses, empirical treatment risks inflicting severe hematological toxicity on patients who do not actually have the disease. Risk-benefit analysis recommends against the presumptive use of high-dose intravenous ribavirin. Administration may only be recommended for cases where the infection is definitively confirmed via diagnostics such as PCR, and where the patient faces a significant risk that outweighs the drug's established adverse hematological effects.

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.

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.

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 [2-19]. 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.

Conclusion

Significantly lower risk is seen for progression. One study shows significant benefit. Meta-analysis using the most serious outcome reported shows 56% [-22-84%] lower risk, without reaching statistical significance. Early treatment shows efficacy while late treatment does not, consistent with expectations for an antiviral treatment. Currently all studies are RCTs.

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Ribavirin has significant toxicity risks and careful risk-benefit analysis is required.

Contact. Contact us on X at @CovidAnalysis.

Funding. We have received no funding or compensation in any form, and do not accept donations. This is entirely volunteer work.

Conflicts of interest. We have no conflicts of interest. We have no affiliation with any pharmaceutical companies, supplement companies, governments, political parties, or advocacy organizations.

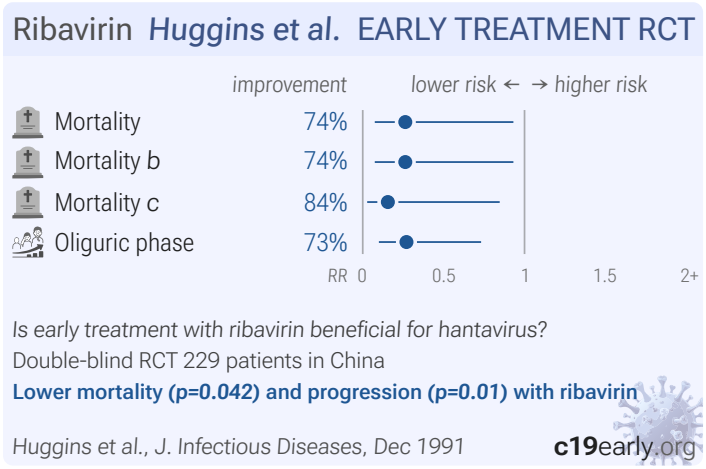
Disclaimer. We do not provide medical advice. No treatment is 100% effective, and all may have side effects. Protocols combine multiple treatments. Consult a qualified physician for personalized risk/benefit analysis.

AI. We use AI models (Gemini, Grok, Claude, and ChatGPT) tasked with functioning as additional peer-reviewers to check for errors, suggest improvements, and review spelling and grammar. Any corrections are verified and applied manually. Our preference for em dashes is independent of AI.

Dedication. This work is dedicated to those who risked their career to save lives under extreme censorship and persecution from authorities and media that have not even reviewed most of the science. In alphabetical order, those that paid the ultimate price: Dr. Thomas J. Borody, Dr. Jackie Stone, Dr. Vladimir (Zev) Zelenko; and those that continue to risk their careers to save lives: Dr. Mary Talley Bowden, Dr. Flavio Cadegiani, Dr. Shankara Chetty, Dr. Ryan Cole, Dr. George Fareed, Dr. Sabine Hazan, Dr. Pierre Kory, Dr. Tess Lawrie, Dr. Robert Malone, Dr. Paul Marik, Dr. Peter McCullough, Dr. Didier Raoult, Dr. Harvey Risch, Dr. Brian Tyson, Dr. Joseph Varon, and the estimated over one million physicians worldwide that prescribed one or more low-cost COVID-19 treatments known to reduce risk, contrary to authority beliefs.

Study Notes

Huggins



RCT 242 hospitalized patients with hemorrhagic fever with renal syndrome (HFRS) from Hantaan virus (the first hantavirus isolated) showing significantly lower mortality with intravenous ribavirin treatment. Ribavirin-treated patients had a sevenfold lower risk of death compared to placebo when adjusted for baseline variables. A notable adverse effect was a reversible hemolytic anemia during treatment, with significantly more ribavirin-treated patients reaching hematocrit below 30%, though no patients required withdrawal from the protocol. The study was conducted over two seasons in Hubei Province, China, with some baseline imbalances between treatment groups noted across the two seasons. Authors hypothesize the primary mechanism of benefit is reduction of viral replication, thereby preventing oliguria and subsequent organ damage.

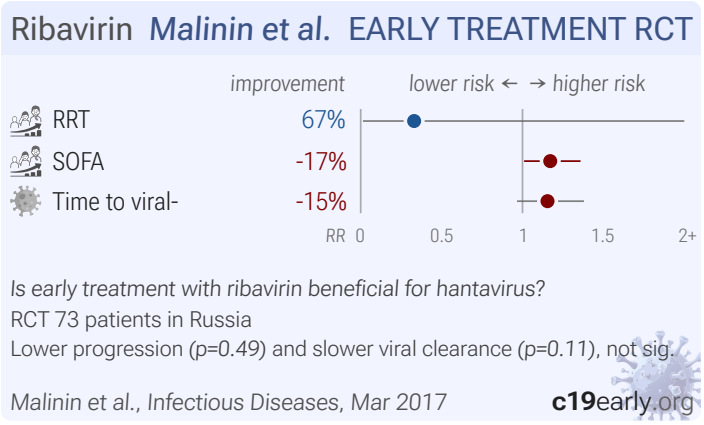
The mean duration of fever at the time of enrollment was 3.7 days during the 1985-1986 season, and 4.3 days during the 1986-1987 season. About 90% of patients were enrolled prior to the oliguric phase.

Authors noted that early treatment - defined as on or before day 4 of illness - was more effective.

Using the unadjusted raw counts to estimate mortality may be more reliable - the adjusted result relies on an unstable logistic regression model driven by only 13 total deaths, resulting in a very wide confidence interval that makes the exact magnitude of the reduction statistically fragile. The adjusted model used baseline Total Serum Protein and AST. Researchers used a mean-imputation strategy for missing baseline data, therefore the specific covariate values fed into this already fragile model may have been artificially smoothed out.

All three ribavirin-treated patients who died were oliguric on presentation.

Malinin

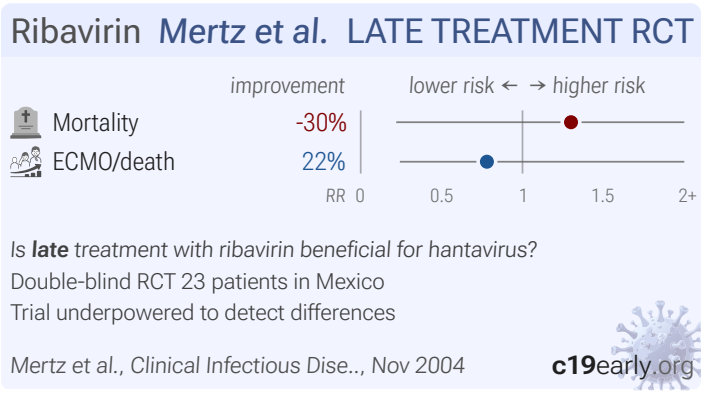


RCT 73 hospitalized patients showing no significant differences with intravenous ribavirin for treatment of haemorrhagic fever with renal syndrome (HFRS) caused by Puumala virus (PUUV). Puumala virus is relatively mild compared to other hantaviruses like Andes and there were no deaths, and only one patient in the control group required RRT.

Authors hypothesize that the lack of efficacy may be due to late initiation of therapy, the fact that PUUV disease severity is not strongly correlated with viral load (unlike Hantaan virus).

Authors do not report the baseline disease phase for patients. A secondary outcome compares patients in the oliguric phase, but authors do not report how many patients started or entered this phase.

Mertz



RCT 36 patients (23 with confirmed hantavirus cardiopulmonary syndrome, HCPS) showing no significant differences with intravenous ribavirin treatment. Mortality and the proportion of patients surviving without extracorporeal membrane oxygenation was similar between groups. Two ribavirin recipients and two placebo recipients died.

All patients were enrolled late in the cardiopulmonary phase. Major limitations include the very small sample size (far below the target of 130), inability to enroll any patients during the prodrome phase, and the rapid disease progression once the cardiopulmonary phase began (median time to death or ECMO initiation was only 4 hours after drug initiation in ribavirin recipients), which may have precluded any therapeutic benefit.

Authors hypothesize that ribavirin is likely ineffective in the cardiopulmonary stage due to the rapid rate of disease progression compared to hemorrhagic fever with renal syndrome, where ribavirin showed benefit.

Appendix 1. Methods and Data

Search methods

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, which regularly receives notification of studies upon publication. Search terms are ribavirin and hantavirus. Automated searches are performed twice daily, with all matches reviewed for inclusion. All studies regarding the use of ribavirin for Hantavirus 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.

Effect extraction

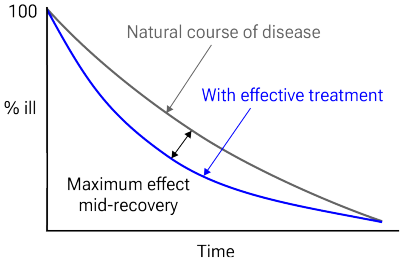


Fig. 7. Mid-recovery results can more accurately reflect efficacy when almost all patients recover. *Mateja et al.* confirm that intermediate viral load results more accurately reflect hospitalization/death.

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 [22]. 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.

Statistical methods

Forest plots are computed using PythonMeta [23] 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. 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 [27]. 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 (3.14.4) with scipy (1.17.1), pythonmeta (1.26), numpy (2.4.4), statsmodels (0.14.6), and plotly (6.7.0). 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.

When evaluating potential effect modification across groups, we use an interaction test as described by *Altman (C) et al.* We compared the log-transformed relative risks using a *z*-test, deriving the standard error of the difference from the 95% confidence intervals. A two-sided interaction *p*-value of < 0.05 was considered a statistically significant difference in treatment effect between the groups.

Quality evaluation

Our quality evaluation focuses on known issues and bias, and the potential impact on outcomes, rather than just the risk of bias. The estimated potential impact of each confounding factor, and the direction of the impact is considered. For example, consider a study that shows significantly lower risk, the value of the study varies significantly if confounding points to an underestimate or an overestimate of efficacy. In one case, the real effect may be null, while the other case provides stronger evidence of efficacy (which may be greater than the study shows). Analysis focusing on the risk of bias, while simpler, may penalize studies for theoretical or technical issues that have no or minimal impact on outcomes. Analysis also depends on the outcome, for example certain issues are less relevant for objective outcomes such as mortality. Inaccurate penalization, and inaccurate high-quality evaluation in the face of known major issues affecting outcomes, increases in significance during a pandemic when immediate recognition of new evidence is critical, and when considering all global studies, as required during a pandemic. Investigators in other countries may have different customs for design, analysis, and reporting, and different English language skills, however they may not be less diligent or have greater bias. Investigators in lower-pharmaceutical-profit countries may have lower bias towards profitable interventions.

Living analysis

This is a living analysis and is updated regularly. We received no funding, this research is done in our spare time. We have no affiliation with any pharmaceutical companies, supplement companies, governments, political parties, or advocacy organizations.

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

Huggins, 12/1/1991, Double Blind Randomized Controlled Trial, placebo-controlled, China, peer-reviewed, 15 authors, HFRS, Hantaan.	risk of death, 73.7% lower, RR 0.26, *p* = 0.04, treatment 3 of 122 (2.5%), control 10 of 107 (9.3%), NNT 15, p-value adjusted for treatment site and stratification by seasons.
	risk of death, 73.7% lower, RR 0.26, *p* = 0.04, treatment 3 of 122 (2.5%), control 10 of 107 (9.3%), NNT 15, unadjusted.

	risk of death, 84.5% lower, RR 0.16, $p = 0.03$, treatment 3 of 122 (2.5%), control 10 of 107 (9.3%), adjusted per study, inverted to make RR<1 favor treatment, odds ratio converted to relative risk.
	oliguric phase, 73.0% lower, OR 0.27, $p = 0.01$, treatment 122, control 107, inverted to make OR<1 favor treatment, RR approximated with OR.
Malinin, 3/3/2017, Randomized Controlled Trial, Russia, peer-reviewed, 2 authors, HFRS, Puumala.	RRT, 67.0% lower, RR 0.33, $p = 0.49$, treatment 0 of 37 (0.0%), control 1 of 36 (2.8%), NNT 36, relative risk is not 0 because of continuity correction due to zero events (with reciprocal of the contrasting arm).
	SOFA, 17.1% higher, RR 1.17, $p = 0.04$, treatment mean 4.1 (±1.2) n=37, control mean 3.5 (±1.2) n=36.
	time to viral-, 15.5% higher, relative time 1.15, $p = 0.11$, treatment mean 11.2 (±4.0) n=37, control mean 9.7 (±4.0) n=36.

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.

Mertz, 11/1/2004, Double Blind Randomized Controlled Trial, placebo-controlled, Mexico, peer-reviewed, 15 authors, HCPS, Sin Nombre.	risk of death, 30.0% higher, RR 1.30, $p = 1.00$, treatment 2 of 10 (20.0%), control 2 of 13 (15.4%).
	ECMO/death, 22.0% lower, RR 0.78, $p = 1.00$, treatment 3 of 10 (30.0%), control 5 of 13 (38.5%), NNT 12.

Supplementary Data

Supplementary Data

References

1. **Huggins** et al., *Prospective, Double-Blind, Concurrent, Placebo-Controlled Clinical Trial of Intravenous Ribavirin Therapy of Hemorrhagic Fever with Renal Syndrome*, Journal of Infectious Diseases, doi:10.1093/infdis/164.6.1119.
2. **Jitobaom** et al., *Favipiravir and Ivermectin Showed in Vitro Synergistic Antiviral Activity against SARS-CoV-2*, Research Square, doi:10.21203/rs.3.rs-941811/v1.
3. **Jitobaom (B)** et al., *Synergistic anti-SARS-CoV-2 activity of repurposed anti-parasitic drug combinations*, BMC Pharmacology and Toxicology, doi:10.1186/s40360-022-00580-8.
4. **Jeffreys** et al., *Remdesivir-ivermectin combination displays synergistic interaction with improved in vitro activity against SARS-CoV-2*, International Journal of Antimicrobial Agents, doi:10.1016/j.ijantimicag.2022.106542.
5. **Ostrov** et al., *Highly Specific Sigma Receptor Ligands Exhibit Anti-Viral Properties in SARS-CoV-2 Infected Cells*, Pathogens, doi:10.3390/pathogens10111514.
6. **Alsaidi** et al., *Griffithsin and Carrageenan Combination Results in Antiviral Synergy against SARS-CoV-1 and 2 in a Pseudoviral Model*, Marine Drugs, doi:10.3390/md19080418.
7. **Andreani** et al., *In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect*, Microbial Pathogenesis, doi:10.1016/j.micpath.2020.104228.
8. **De Forni** et al., *Synergistic drug combinations designed to fully suppress SARS-CoV-2 in the lung of COVID-19 patients*, PLoS ONE, doi:10.1371/journal.pone.0276751.
9. **Wan** et al., *Synergistic inhibition effects of andrographolide and baicalin on coronavirus mechanisms by downregulation of ACE2 protein level*, Scientific Reports, doi:10.1038/s41598-024-54722-5.
10. **Said** et al., *The effect of Nigella sativa and vitamin D3 supplementation on the clinical outcome in COVID-19 patients: A randomized controlled clinical trial*, Frontiers in Pharmacology, doi:10.3389/fphar.2022.1011522.
11. **Fiaschi** et al., *In Vitro Combinatorial Activity of Direct Acting Antivirals and Monoclonal Antibodies against the Ancestral B.1 and BQ.1.1 SARS-CoV-2 Viral Variants*, Viruses, doi:10.3390/v16020168.
12. **Xing** et al., *Published anti-SARS-CoV-2 in vitro hits share common mechanisms of action that synergize with antivirals*, Briefings in Bioinformatics, doi:10.1093/bib/bbab249.
13. **Chen** et al., *Synergistic Inhibition of SARS-CoV-2 Replication Using Disulfiram/Ebselen and Remdesivir*, ACS Pharmacology & Translational Science, doi:10.1021/acsptsci.1c00022.
14. **Hempel** et al., *Synergistic inhibition of SARS-CoV-2 cell entry by otamixaban and covalent protease inhibitors: pre-clinical assessment of pharmacological and molecular properties*, Chemical Science, doi:10.1039/D1SC01494C.
15. **Schultz** et al., *Pyrimidine inhibitors synergize with nucleoside analogues to block SARS-CoV-2*, Nature, doi:10.1038/s41586-022-04482-x.
16. **Ohashi** et al., *Potential anti-COVID-19 agents, cepharanthine and nelfinavir, and their usage for combination treatment*, iScience, doi:10.1016/j.isci.2021.102367.
17. **Al Krad** et al., *The protease inhibitor Nirmatrelvir synergizes with inhibitors of GRP78 to suppress SARS-CoV-2 replication*, bioRxiv, doi:10.1101/2025.03.09.642200.
18. **Abd Elsalam** et al., *Anti-COVID-19 activity and simple HPLC method for concurrent detection of repurposed drugs in novel binary mixtures*, AMB Express, doi:10.1186/s13568-026-02030-8.
19. **Thairu** et al., *A Comparison of Ivermectin and Non Ivermectin Based Regimen for COVID-19 in Abuja: Effects on Virus Clearance, Days-to-discharge and Mortality*, Journal of Pharmaceutical Research International, doi:10.9734/jpri/2022/v34i44A36328.
20. **Malinin** et al., *Insufficient efficacy and safety of intravenous ribavirin in treatment of haemorrhagic fever with renal syndrome caused by Puumala virus*, Infectious Diseases, doi:10.1080/23744235.2017.1293841.
21. **Mertz** et al., *Placebo-Controlled, Double-Blind Trial of Intravenous Ribavirin for the Treatment of Hantavirus Cardiopulmonary Syndrome in North America*, Clinical Infectious Diseases, doi:10.1086/425007.
22. **Mateja** et al., *The choice of viral load endpoint in early phase trials of COVID-19 treatments aiming to reduce 28-day hospitalization and/or death*, The Journal of Infectious Diseases, doi:10.1093/infdis/jiaf282.
23. **Deng**, H., *PyMeta, Python module for meta-analysis*, www.pymeta.com/.
24. **Zhang** et al., *What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes*, JAMA, 80:19, 1690, doi:10.1001/jama.280.19.1690.
25. **Altman**, D., *How to obtain the P value from a confidence interval*, BMJ, doi:10.1136/bmj.d2304.
26. **Altman (B)** et al., *How to obtain the confidence interval from a P value*, BMJ, doi:10.1136/bmj.d2090.
27. **Sweeting** et al., *What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data*, Statistics in Medicine, doi:10.1002/sim.1761.

28. **Altman (C)** et al., *Interaction revisited: the difference between two estimates*, BMJ, doi:10.1136/bmj.326.7382.219.

29. **Michelucci** et al., *SARS-CoV-2 ORF3a accessory protein is a water-permeable channel that induces lysosome swelling*, Communications Biology, doi:10.1038/s42003-024-07442-5.

30. **Ghosh** et al., *β-Coronaviruses Use Lysosomes for Egress Instead of the Biosynthetic Secretory Pathway*, Cell, doi:10.1016/j.cell.2020.10.039.

31. **Kamga Kapchoup** et al., *In vitro effect of hydroxychloroquine on pluripotent stem cells and their cardiomyocytes derivatives*, Frontiers in Pharmacology, doi:10.3389/fphar.2023.1128382.

32. **Bobrowski** et al., *Synergistic and Antagonistic Drug Combinations against SARS-CoV-2*, Molecular Therapy, doi:10.1016/j.ymthe.2020.12.016.

33. **Peters** et al., *Outcomes of Persons With COVID-19 in Hospitals With and Without Standard Treatment With (Hydroxy)chloroquine*, Clinical Microbiology and Infection, doi:10.1016/j.cmi.2020.10.004.

34. **Mahévas** et al., *Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data*, BMJ 2020, doi:10.1136/bmj.m1844.