Agreement of treatment effects estimates from observational studies and randomized clinical trials evaluating therapeutics for COVID-19

Osman Moneer[1], Garrison Daly[2], Joshua J. Skydel[3], Kate Nyhan[4, 5], Peter Lurie[2], Joseph S. Ross[6,7,8], Joshua D. Wallach[5]

[1]Yale School of Medicine, Yale University, New Haven, CT, USA
[2]Center for Science in the Public Interest, Washington, DC, USA
[3]Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA
[4]Harvey Cushing/John Hay Whitney Medical Library, Yale University, New Haven, CT, USA
[5]Department of Environmental Health Sciences, Yale School of Public Health, New Haven, CT, USA
[6]Section of General Medicine and the National Clinician Scholars Program, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA
[7]Center for Outcomes Research and Evaluation, Yale-New Haven Health System, New Haven, CT, USA
[8]Department of Health Policy and Management, Yale School of Public Health, New Haven, CT, USA

Correspondence to: J D Wallach Joshua.wallach@yale.edu (or @JoshuaDWallach on Twitter)

Conflicts of Interest: Dr. Ross is the U.S. Outreach and Associate Research Editor at the BMJ and currently receives research support through Yale University from Johnson and Johnson to develop methods of clinical trial data sharing, from the Medical Device Innovation Consortium as part of the National Evaluation System for Health Technology (NEST), from the Food and Drug Administration for the Yale-Mayo Clinic Center for Excellence in Regulatory Science and Innovation (CERSI) program (U01FD005938), from the Agency for Healthcare Research and Quality (R01HS022882), from the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH) (R01HS025164, R01HL144644), and from the Laura and John Arnold Foundation to establish the Good Pharma Scorecard at Bioethics International; in addition, Dr. Ross is an expert witness at the request of Relator's attorneys, the Greene Law Firm, in a qui tam suit alleging violations of the False Claims Act and Anti-Kickback Statute against Biogen Inc. Dr. Wallach currently received research support from the Food and Drug Administration and through Yale University from Johnson & Johnson, Inc to develop methods of clinical trial data sharing. There are no other competing interests.

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Objective: To systematically identify, match, and compare treatment effect estimates and study demographics from observational studies and randomized clinical trials (RCTs) evaluating the same COVID-19 therapeutics, comparators, and outcomes.
Design: In this meta-epidemiological study, individual RCTs or meta-analyses of RCTs reported in a *BMJ* living review directly comparing any of the three most frequently studied therapeutic interventions for COVID-19 (hydroxychloroquine/chloroquine, lopinavir/ritonavir, or dexamethasone) were identified for any safety and efficacy outcomes.[1] Using the Epistemonikos "Living OVerview of Evidence" evidence database, individual observational studies evaluating the same interventions, comparisons, and outcomes reported in the *BMJ* review were identified. Treatment effect estimates from observational studies were identified, standardized, and when possible meta-analyzed to match individual RCTs or meta-analyses of RCTs with the same interventions, comparisons, and outcomes (i.e., matched pairs). The direction and statistical significance (both $P<0.05$ or $P\geq0.05$) of treatment effect estimates and the distribution of study demographics from matched pairs was then compared. Concordance of effect size was not considered given the heterogeneity of endpoints.
Results: 17 new, independent meta-analyses of observational studies were conducted of hydroxychloroquine/chloroquine, lopinavir/ritonavir, or dexamethasone vs. an active or placebo comparator for any safety or efficacy outcomes and matched and compared to 17 meta-analyses of RCTs reported in the *BMJ* review. 10 additional matched pairs with only one observational study and/or only one RCT were identified. Across all 27 matched pairs, 22 included any demographic and clinical data for all individual studies. All 22 matched pairs had studies with overlapping distributions of sex, age, and disease severity. Overall, 21 (78%) of the 27 matched pairs had effect estimates that agreed in terms of direction and statistical significance. Higher levels of concordance were observed among the 17 matched pairs consisting of meta-analyses of observational studies and meta-analyses of RCTs (14, 82%) than the 10 matched pairs consisting of only one observational study and/or only one RCT (7, 70.0%). The 18 matched pairs with relative treatment effect estimates also had higher levels of agreement (16, 89%) than the 9 matched pairs with continuous treatment effect estimates (5, 56%). While 39 (85%) of the 46 individual observational studies were referenced by at least one RCT, only 14 (38%) of the 37 individual RCTs were referenced by any observational study.
Conclusions: More than three quarters of the matched pairs had treatment effects that were in agreement. Meta-analyses of observational studies and RCTs evaluating therapeutics for the treatment of COVID-19 more often than not have summary treatment effect estimates that are in agreement in terms of direction and statistical significance. Although concerns have been raised about the evidence produced by individual observational studies evaluating therapeutics for COVID-19,[2] meta-analyzed evidence from observational studies may complement evidence collected from RCTs.

References

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Table 1. Concordance between treatment effect estimates from matched observational study and RCT pairs, No=27 (pairs classified as concordant in bold)				
Observational study treatment effect estimates	**RCT treatment effect estimates**			
	Increased, statistically significantly	Decreased, statistically significantly	Increased, but not statistically significantly	Decreased, but not statistically significantly
Matched pairs consisting of meta-analyses of observational studies and meta-analyses of RCTs				
*Increased, significantly**	**0**	0	2	0
*Decreased, significantly**	0	**0**	0	0
Increased, but not significantly†	0	0	**4**	**2**
Decreased, but not significantly†	0	1	**5**	**3**
Additional matched pairs consisting of one observational study and/or one RCT				
*Increased, significantly**	**0**	0	0	1
*Decreased, significantly**	0	**0**	0	1
Increased, but not significantly†	1	0	**3**	**1**
Decreased, but not significantly†	0	0	**1**	**2**
No, number; RCT, randomized clinical trial *Statistically significant based on P<0.05. †Not statistically significant based on P ≥0.05.				