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Viral clearance as a surrogate of clinical efficacy for COVID-19 therapies in outpatients: a systematic review and meta-analysis

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Summary

Background Surrogates of antiviral efficacy are needed for COVID-19. We aimed to investigate the relationship between the virological effect of treatment and clinical efficacy as measured by progression to severe disease in outpatients treated for mild-to-moderate COVID-19.

Methods In this systematic review and meta-analysis, we searched PubMed, Scopus, and medRxiv from database inception to Aug 16, 2023, for randomised placebo-controlled trials that tested virus-directed treatments (ie, any monoclonal antibodies, convalescent plasma, or antivirals) in non-hospitalised individuals with COVID-19. We only included studies that reported both clinical outcomes (ie, rate of disease progression to hospitalisation or death) and virological outcomes (ie, viral load within the first 7 days of treatment). We extracted summary data from eligible reports, with discrepancies resolved through discussion. We used an established meta-regression model with random effects to assess the association between clinical efficacy and virological treatment effect, and calculated I^2 to quantify residual study heterogeneity.

Findings We identified 1718 unique studies, of which 22 (with a total of 16 684 participants) met the inclusion criteria, and were in primarily unvaccinated individuals. Risk of bias was assessed as low in 19 of 22 studies for clinical outcomes, whereas for virological outcomes, a high risk of bias was assessed in 11 studies, some risk in ten studies, and a low risk in one study. The unadjusted relative risk of disease progression for each extra $\log_{10}$ copies per mL reduction in viral load in treated compared with placebo groups was 0·12 (95% CI 0·04–0·34; p<0·0001) on day 3, 0·20 (0·08–0·50; p=0·0006) on day 5, and 0·53 (0·30–0·94; p=0·030) on day 7. The residual heterogeneity in our meta-regression was estimated as low (I^2=0% [0–53] on day 3, 0% [0–71] on day 5, and 0% [0–43] on day 7).

Interpretation Despite the aggregation of studies with differing designs, and evidence of risk of bias in some virological outcomes, this review provides evidence that treatment-induced acceleration of viral clearance within the first 5 days after treatment is a potential surrogate of clinical efficacy to prevent hospitalisation with COVID-19. This work supports the use of viral clearance as an early phase clinical trial endpoint of therapeutic efficacy.

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Introduction

Several effective therapies have been developed for COVID-19, including both monoclonal antibodies and small molecule antivirals. These therapies have been shown to be most effective when administered early in infection, with the aim of preventing progression to severe infection.[1,2] However, the emergence of SARS-CoV-2 immune escape variants has led to a major loss of effectiveness of monoclonal antibody products, leading to reliance on a small number of antivirals.[3] Accelerated development of new antivirals is urgently needed. Although placebo-controlled trials based on clinical outcomes remain the gold standard, validated surrogate measures of treatment efficacy could accelerate efforts to develop and deploy effective COVID-19 therapies. Speeding up the process of finding and validating the efficacy of novel COVID-19 therapies could reduce mortality, especially among those most at risk.

Surrogate measures of treatment effect have been a mainstay of clinical drug development.[4] In particular, during preclinical or early clinical development of a candidate antimicrobial treatment or monitoring of ongoing effectiveness against a potentially resistant pathogen, it is common to use a surrogate measure that is thought to predict therapeutic efficacy, such as pathogen clearance time.[5–8] In the case of antiviral agents for COVID-19, viral clearance has been proposed as a surrogate of clinical efficacy,[9,10] and many phase 2 trials have compared the reduction in viral load between treated and control groups at different times after therapy as a surrogate marker of

Research in context

Evidence before this study

Several treatments for COVID-19 have been approved or recommended for use on the basis of evidence from randomised controlled trials showing improved clinical outcomes. Many studies have also analysed the effects of treatment on viral concentrations after treatment. No separate systematic literature search was conducted before beginning the systematic review described in this study. However, we are aware of two relevant studies published before the work reported here. One study (published in 2021) described the need to assess whether the virological effect of treatment was a valid surrogate of the clinical efficacy of COVID-19 therapeutics. Another study published in 2022 provided preliminary evidence to support the hypothesis that the virological treatment effect is associated with clinical outcomes, but this association had not been validated in a systematic review of the available data, and careful consideration of the timing of viral clearance outcomes, risk of bias of included studies, and other potential confounders was still required.

Added value of this study

In our study we used a meta-analytical approach to integrate data from a systematic search of the literature, and identified a correlation between the virological effect of the different COVID-19 treatments measured on day 3, 5, or 7 following treatment and the corresponding clinical efficacy of these treatments in mostly unvaccinated individuals. We identified 1718 unique studies and included 22 eligible studies that reported both clinical and virological outcomes of a candidate COVID-19 treatment. These treatments included both monoclonal antibodies and small molecule antivirals and ranged in their reported clinical efficacy (defined using the relative risk of hospitalisation, progression to severe COVID-19, or death *vs* no treatment) from –51% to 89%.

Implications of all the available evidence

Although we only examined studies in primarily unvaccinated individuals, this meta-analysis of COVID-19 therapies provides strong support of the hypothesis and preliminary evidence that virological treatment effect is a potential surrogate marker of the clinical efficacy of treatment in preventing more severe forms of COVID-19. Such a surrogate is likely to be useful in early-stage clinical trials, as a means of predicting clinical protection of candidates, to aid in dose selection, and to accelerate the development of new COVID-19 therapies. Further, validating this surrogate of therapeutic efficacy in other populations, including in vaccinated, previously infected, and immune-compromised individuals, is still required.

therapeutic effect. For example, participants with COVID-19 treated with nirmatrelvir–ritonavir were shown to have greater reduction in viral loads than controls at day 3 (0·55 $\log_{10}$ copies per mL lower *vs* placebo) and day 5 (0·80 $\log_{10}$ copies per mL lower) after treatment.[11] The virological effect of treatment (the extent to which it reduces viral load compared with placebo) has been widely used in studies of COVID-19 therapeutics, but whether it is predictive of a treatment's clinical efficacy in preventing progression to severe outcomes, and what the optimal time is for measuring this difference, have not been established. We aimed to address these questions by aggregating the available studies that report the virological effects of treatment and the clinical efficacy of treatment in the same trial. We focus on analysis of treatments administered early in infection in outpatients, as these treatments have shown higher efficacy than therapies used later in patients treated in hospital.[1,2]

Methods

Search strategy and selection criteria

See Online for appendix

In this systematic review and meta-analysis, we followed the PRISMA statement for study design (appendix pp 28–31).[12,13] We searched PubMed, Scopus, and medRxiv for randomised placebo-controlled trials of various treatments for COVID-19 in non-hospitalised individuals with COVID-19, published from database inception until Aug 16, 2023 (see appendix pp 2–3 for full search strategy). The search was restricted to articles published in English. Articles were screened to determine eligibility for final inclusion (by SRK) using inclusion and exclusion criteria outlined in the appendix (pp 2–3). Publications that were reviews or protocols, animal or in-vitro studies, observational or case studies, and studies of vaccines, host-directed therapies, or antibiotics were excluded. We included all identified randomised controlled trials testing virus-directed COVID-19 therapies (ie, any monoclonal antibodies, convalescent plasma, or antivirals) in non-hospitalised individuals, and which reported both viral load data for at least one timepoint on or before day 7, and rates of progression to either hospitalisation or death (appendix pp 4–11). To be unbiased, we included studies regardless of whether the treatments were found to be effective. We also screened the references of eligible studies to identify any other relevant publications. This work was approved under the University of New South Wales Sydney Human Research Ethics Committee (approval HC200242). A systematic review protocol was not pre-registered for this review.

Data extraction

We extracted all summary data from the included studies on viral load at baseline and after treatment at all available timepoints up to 14 days, for treatment and control groups of the studies, as well as number of individuals in each group and the number of outcomes (ie, progression of disease as defined by the study; appendix pp 4–8). Other study data that were collected included inclusion and exclusion criteria for participants in each of the randomised controlled trials, treatment administered (including dosing and timing information), and viral load quantification

method (appendix pp 4–8). Data extraction of summary estimates from the selected studies was performed independently by two researchers (KME and SRK). When data were not provided in tables or text, but were available in figures, they were extracted from the figures using WebPlotDigitizer (version 4·6); discrepancies were resolved through discussion and consensus among data extractors. We have indicated if any relevant data were not available in a given study in the appendix (pp 4–11). If two publications were identified that reported data from the same study, only the publication reporting the most complete and disaggregated data was used (appendix pp 4–8). The revised tool for risk of bias in randomised trials (RoB 2·0) was used to assess the studies, and the robvis web app was used to generate charts.[14,15] The risk of bias assessment of the included studies was performed by KME and SRK independently, and any disagreements were resolved through discussion.

Clinical efficacy of treatment

To visualise the clinical efficacy observed in each study, the relative risk (RR) of hospitalisation with and without treatment was calculated along with 95% CI (using the Katz-log method[16]), and was converted to efficacy (E) using the formula $E = 100\% \times (1 - \mathrm{RR})$. When a trial contained multiple treatment groups with different treatment combinations, doses, or routes of administration, we considered different treatment combinations separately (eg, bamlanivimab *vs* bamlanivimab and etesevimab), but pooled groups with different doses or administration routes using the same treatment (ie, the same drug or the same monoclonal combination).

Virological effect of treatment

For studies in which the drop in viral load from baseline (day 1) to day d was not provided, we calculated it for any study group (G) at day d using the formula $\mathrm{Drop}_{G,d} = \mathrm{VL}_1 - \mathrm{VL}_d$ where VL_d is the $\log_{10}$ viral load at day d. The virological treatment effect (V), associated with day d, for all treatment groups was defined as $V_d = \mathrm{Drop}_{\mathrm{trt},d} - \mathrm{Drop}_{\mathrm{ctrl},d}$ where $\mathrm{Drop}_{\mathrm{trt},d}$ and $\mathrm{Drop}_{\mathrm{ctrl},d}$ are the $\log_{10}$ drops in the treated (trt) and control (ctrl) groups from day 1 to day d, respectively. We calculated the virological treatment effect for each day (d) for which viral load data were provided in each study. When possible, we derived 95% CIs from published data of the spread of the virological treatment effect by using methods summarised in the appendix (p 18). We calculated the day on which the maximum virological treatment effect was observed for studies in which a treatment effect was observed and at least one datapoint was available after day 7.

Statistical analysis

Data on the number of clinical events in each study were aggregated using a linear mixed effects meta-regression model (using the rma.mv function with maximum likelihood estimation from the metafor package in R version 4.2.1), and stratified by treatment type (ie, passive antibody *vs* small molecule therapies). The model used is based on the equation $y_{i,j} = \mu + u_i + \epsilon_{i,j}$ in which $y_{i,j}$ is the observed effect size (log of the RR) in the jth treatment group of the ith study, μ is the average effect size across all studies, $u_i \sim N(0, \tau^2)$ is the random effect for study i, and $\epsilon_{i,j} \sim N(0, v_{i,j})$ is the sampling error for treatment group j in study i, given the variance of the mean effect associated with the treatment group, $v_{i,j}$. To assess for evidence of a significant association between clinical efficacy and virological treatment effect, the same model was used with virological treatment effect at days 3, 5, or 7 added as a continuous covariate (and with no stratification by treatment type). We also considered a composite measure of the effect of treatment on viral load across all timepoints using a difference in the area under the curve (AUC) between treated and control individuals (AUC model). Random effects were used to account for study heterogeneity, which was quantified by the I^2 value. To assess whether the virological treatment effect measured on day 3 or day 5 was a better predictor of clinical effect, we fitted models with each covariate separately (using only those studies that reported data on both days) and compared these models using the Akaike information criterion (AIC).

In sensitivity analyses, we assessed the effect of other potential covariates on the relationship between virological treatment effect and efficacy—namely, treatment type (passive antibody or small molecule), timing of treatment relative to symptom onset, and SARS-CoV-2 variant, using both univariate and multivariate adjustments in the meta-regression. We also assessed potential publication bias using funnel plots and assessed the effect of studies with a high risk of bias by re-running our analysis with these studies excluded.

All correlations were assessed using a Pearson correlation. All statistical analyses were performed in R (version 4.2.1), with a threshold for statistical significance of 0·05.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We identified a total of 1718 unique records, of which 22 studies with a total of 16 684 participants were eligible for inclusion (figure 1; appendix pp 4–11).[1,11,17–36] During screening we found only two studies that assessed treatment in predominately vaccinated symptomatic outpatients[37,38] and so we excluded these studies and focused only on studies in primarily unvaccinated individuals (figure 1). The eligible studies included seven randomised controlled trials assessing small molecule antiviral therapies, and 15 assessing antibody treatments (14 monoclonals and one convalescent plasma). All 22 studies enrolled adult populations, with five of the studies also enrolling adolescents (aged ≥12 years) with risk factors for severe disease.[20,21,23,27,36] Most studies were entirely in unvaccinated individuals (20 of 22), with the remaining two studies including a total of

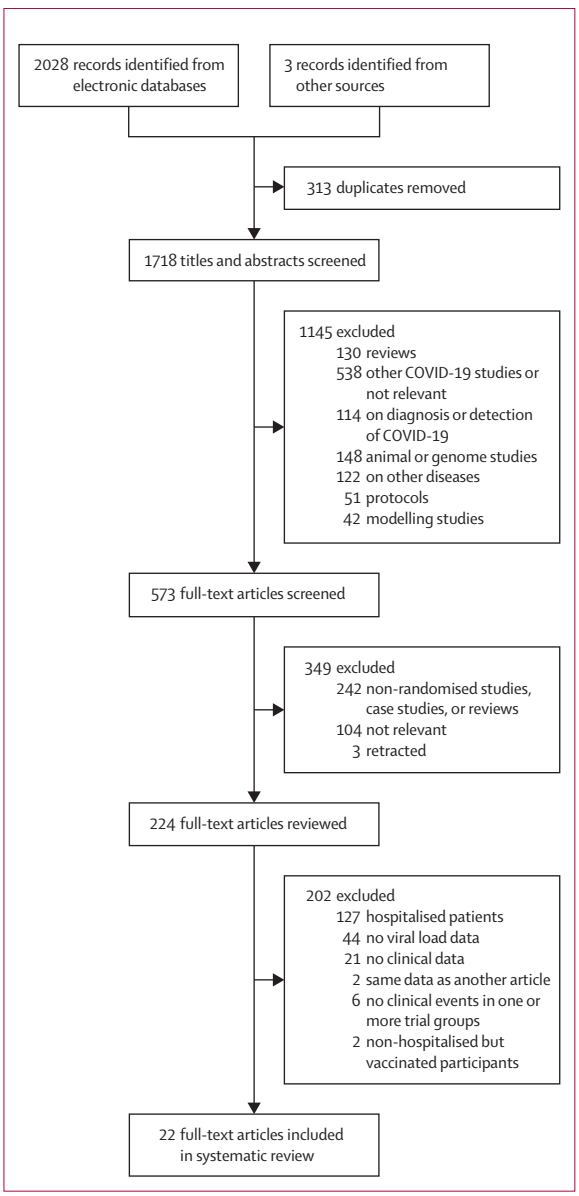

Figure 1: **PRISMA flow diagram for study inclusion**
Other sources: three studies were identified from the reference lists of other included studies or were identified because they cited an included study.

47 participants who had received one or two doses of vaccine. Of the 22 studies, seven excluded individuals with any previous confirmed infection,[11,19–22,27,34] four excluded individuals who had been previously hospitalised for COVID-19,[1,23,29,30] one excluded individuals with a known history of positive antibody serology,[36] and ten had no exclusion criteria based on previous infection.[17,18,24–26,28,31–33,35] 12 of 22 studies had no criteria for inclusion of study participants that were based on risk factors for severe COVID-19. Of the remaining ten studies, seven studies selected only individuals with at least one existing risk factor for severe disease, two studies required either moderate disease or at least one risk factor if mild disease was recorded at enrolment, and one study only enrolled individuals with no risk factors.

The clinical endpoint reported across all studies was the RR of hospitalisation or death within 28 days following treatment, in the treated group compared with the control group. The proportion of participants who had disease progression to hospitalisation or death in the placebo group ranged from 2% (two of 128) to 14% (23 of 167) across all 22 studies, with a tendency for lower rates of disease progression in studies with participants at lower risk. 19 of 22 studies were assessed as having a low risk of bias for clinical outcomes, with three studies being assessed as having some risk of bias (appendix p 19). The reported efficacy ranged from –51% (95% CI –550 to 74) to 89% (72 to 96). The overall efficacy of all therapies was assessed using a linear mixed effect meta-regression. Overall efficacy was 61% (95% CI 50 to 70), with evidence of moderate study heterogeneity (I^2=45%, 95% CI 11 to 74). Stratifying by treatment type (antibody *vs* small molecule therapies) gave similar results: efficacy was 63% (95% CI 53 to 70) for antibody therapies (n=15) and 60% (22 to 79) for small molecule therapies (n=7; figure 2).

Viral load samples were obtained from nasopharyngeal swabs in 19 of 22 studies, nasopharyngeal or nasal swabs in one study, mid-turbinate nasal swabs in one study, and saliva samples in the remaining study. In all studies, and in both treatment and placebo groups, viral loads were at or near the peak at baseline and only declined thereafter (figure 3). Thus, viral load decline occurred even without treatment, and the goal of this study was to assess the extent to which treatment accelerated the rate of viral clearance (above that observed in the placebo group). Relative to the day of treatment (day 1), viral load data were available at various different timepoints, with day 3 being the most common (17 of 22 studies), followed by day 7 (13 of 22) and day 5 (11 of 22; appendix p 21). The risk of bias in virological outcomes was assessed as high in half of the studies (11 of 22), primarily due to missing data and reporting of the reasons for missing data (appendix p 20). All but one of the remaining studies were assessed as having some risk of bias. We found a significant correlation between the virological treatment effect (excess drop in $\log_{10}$ copies per mL from baseline in treated groups *vs* placebo groups) measured at day 3 and day 5 (r=0·71; p=0·013) and day 3 and day 7 (r=0·87; p<0·0001), but not day 5 and day 7 (r=0·44; p=0·27; appendix p 22). Further, for studies in which a virological treatment effect was seen and in which data were available for any timepoint after day 7 (18 of 22), the maximum observed virological treatment effect occurred on or before day 7 in all except two studies (ie, 16 of 18).[17,34] Together, these findings indicate that the largest observed virological treatment effect tends to occur on or before day 7.

To investigate the relationship between clinical and virological outcomes, we tested whether virological treatment effect was a significant covariate in our random effects linear meta-regression model. We compared this relationship using virological treatment effect assessed at days 3, 5, and 7,

separately (figure 4). The models using data at day 3 (17 of 22 studies) and at day 5 (11 of 22) produced broadly consistent results, with both showing a significant relationship between clinical and virological outcomes (appendix p 12). Each $\log_{10}$ copies per mL of additional viral clearance in treated individuals compared with control individuals was associated with a reduced risk of disease progression (day 3: RR 0·12 [95% CI 0·04–0·34], p<0·0001; day 5: RR 0·20 [0·08–0·50], p=0·0006). The model using data from day 7 (13 of 22) showed a flatter association between virological and clinical effects of treatment (RR 0·53 [0·30–0·94]; p=0·030), and a significantly non-zero intercept (ie, efficacy was estimated as 47% [95% CI 20–65] when the virological treatment effect was zero). Study heterogeneity was low in all models once accounting for the virological effect size of different treatments (I^2=0% [95% CI 0–53] on day 3, 0% [0–71] on day 5, and 0% [0–43] on day 7).

We assessed the robustness of these associations in a series of sensitivity analyses. In univariate and multivariate analyses we tested the effect of other potential confounders (ie, treatment type, timing of treatment relative to symptom onset, and SARS-CoV-2 variant) and found none of these factors was significant (appendix pp 13–15). In the multivariate analysis, after adding these covariates, the association between viral load and efficacy was no longer significant for the day 7 timepoint, but remained significant for day 3 and day 5. Further, we found no strong signal of publication bias (using funnel plots; appendix p 23). Finally, excluding studies with a high risk of bias in our meta-regression did not alter our conclusions for the day 3 and day 5 models, but the association at day 7 was no longer significant (appendix p 16).

To assess whether the virological treatment effect measured on day 3 or day 5 was a better predictor of clinical effect, we compared the model fits obtained using only those studies that reported data on both days (ten of 22). We found that the virological treatment effect at day 3 and day 5 were similarly predictive of efficacy with no clear evidence of one covariate providing a better explanation of the data than the other (AIC 23·8 for day 3 *vs* 24·7 for day 5). Finally, we also considered a composite measure of the effect of treatment on viral load across all timepoints (difference in the AUC between treated and control individuals [AUC model]). This composite measure has the advantage that it uses information across multiple virological samples and can be calculated for studies that used slightly different virological sampling times. We found that the AUC model also showed a significant correlation between virological effect and clinical effect (appendix pp 17, 24).

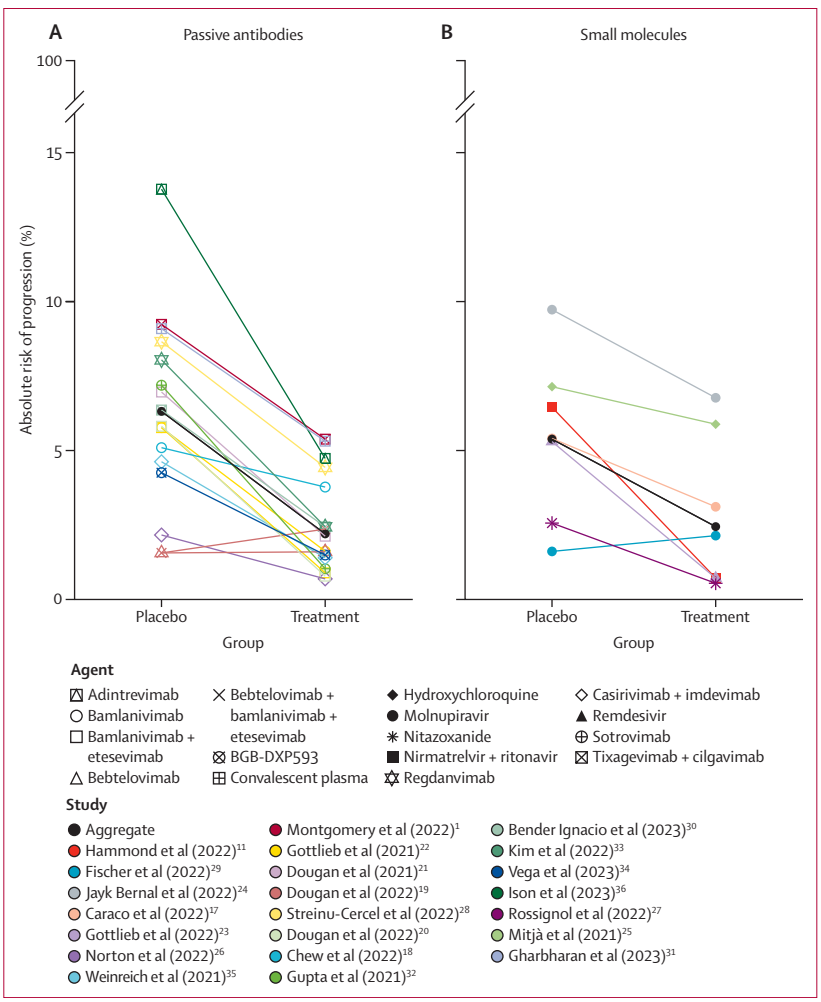

Figure 2: **Absolute risk of progression to hospitalisation or death within 28 days for treatment and placebo groups, for each included study, stratified by treatment type**
(A) Passive antibody treatment. (B) Small molecule treatment. The aggregated estimate of absolute risk for treated and untreated groups across all included studies is also shown (black line).

Discussion

Our analysis suggests that the effects of treatment on viral loads measured on day 3 or day 5 are similarly and robustly associated with treatment efficacy, and could be useful predictors of therapeutic efficacy. A much flatter association was observed between clinical outcomes and virological effect at day 7, and this association was not significant with the inclusion of other potential covariates or when excluding studies with a high risk of bias. This work is consistent with an earlier study that combined viral load data collected between day 5 and day 8 after treatment and also found viral loads might be predictive of clinical outcome.[10] Thus, virological clearance, measured at appropriate timepoints, represents a potential surrogate of clinical efficacy, and could have value in early-stage clinical trials.

Despite the association between virological and clinical efficacy observed here, it is also plausible that some novel treatments might affect clinical outcomes without affecting virological outcomes in upper respiratory tract samples. This possibility might be especially true for host-targeted therapies aimed, for example, at reducing pathogenic immune responses, which are not included in this analysis. In this case, the relationship between virological outcomes and clinical outcomes presented here should be interpreted as predicting a minimum expected efficacy for a given

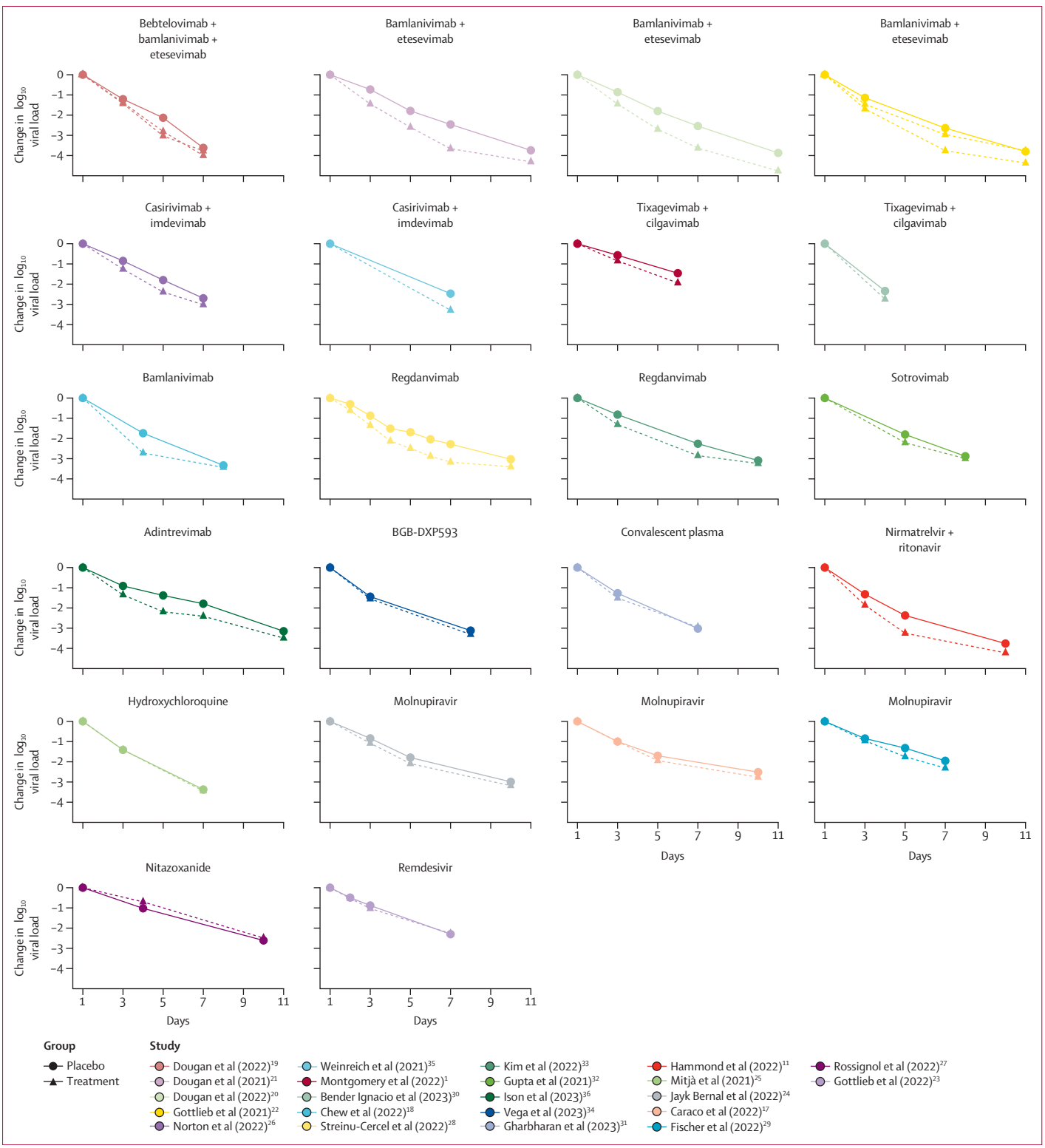

Figure 3: **Change in viral load over time for each study, in the treatment (dashed line) and placebo (solid line) groups**
Gottlieb et al (2021)[22] had two treatment groups (one received bamlanivimab alone, the other received bamlanivimab and etesevimab), and Dougan et al (2022)[19] had two treatment groups (one received bebtelovimab alone, the other received bebtelovimab together with bamlanivimab and etesevimab).

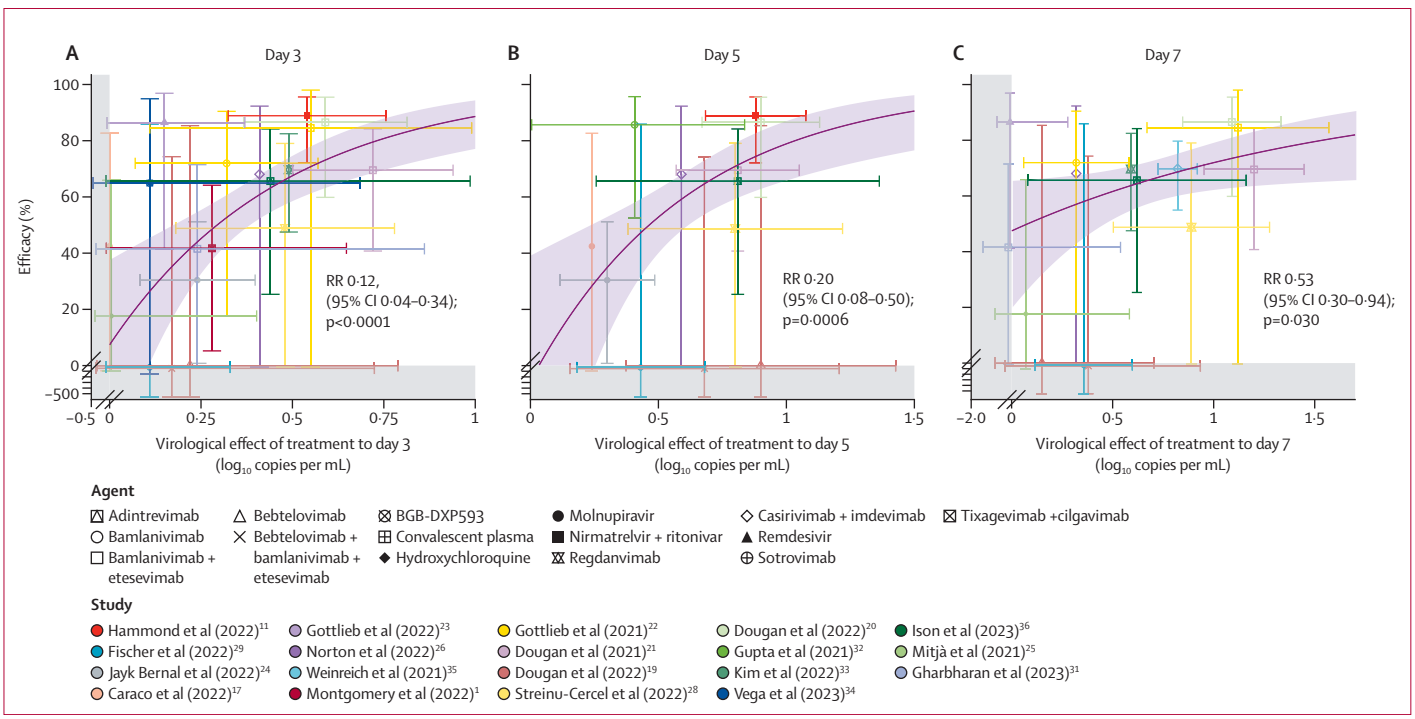

Figure 4: **Correlation between virological effect and clinical efficacy in primarily unvaccinated outpatients with COVID-19 treated with small molecule antivirals, convalescent plasma, or monoclonal antibodies**

Virological effect of treatment was the change in viral load from baseline to day 3 (A), day 5 (B), and day 7 (C). Clinical efficacy was 1 minus the relative risk of hospitalisation or death within 28 days with versus without treatment, converted to a percentage. Error bars of each datapoint indicate 95% CI. Points without horizontal error bars are studies for which it was not possible to calculate a 95% CI from the published data on the spread of virological treatment effect. The solid lines indicate the fitted regression models with 95% confidence regions indicated by shading. Grey shaded regions highlight a change in the scale of the axes. RR=relative risk.

observed virological effect (appendix p 25). For example, if a study aimed to have high confidence that a therapy was at least 50% effective at preventing hospitalisation, the study should aim for at least an extra 0·38 log_{10} copies per mL drop in viral load by day 3 compared with placebo (appendix p 25). Since we have not yet been able to determine the optimal timing for measuring a virological effect, we suggest that in future phase 1 and 2 clinical trials aiming to provide an indication of eventual clinical efficacy of a treatment, virological outcomes should be measured on at least day 1 (ie, on the day of first treatment), day 3, and day 5. Ideally, these data could be used to construct a composite measure, or to determine whether a virological treatment effect is observed at both day 3 and day 5. If it can be shown that the virological effect of treatment is similar in both populations at low risk and at high risk of poor COVID-19-related outcomes, placebo-controlled trials in individuals at low risk might represent a means of predicting efficacy for individuals at higher risk without needing to run a placebo-controlled trial in the most susceptible populations.

An important limitation of this study is that our analysis has only considered studies of COVID-19 therapeutics in primarily unvaccinated individuals who had not previously been infected with SARS-CoV-2, and (largely) immunocompetent populations, whereas these drugs are currently most commonly being used in vaccinated individuals or people with immunosuppression. Although this is a substantial limitation of our study and of the use of a virological surrogate, it is also a broader issue for the field, since treatments are still being administered in populations for which efficacy has not been directly shown. Conflicting evidence exists as to treatment efficacy in vaccinated populations. The PANORAMIC trial[37] studied the effects of molnupiravir in a largely (97%) vaccinated population and found no statistically significant protection from hospitalisation or death, in contrast to the original studies in unvaccinated participants.[17,24] However, an observational study showed no effect of vaccination status on the efficacy of nirmatrelvir–ritonavir[39] (although lower overall efficacy was observed than in the original phase 3 trial of nirmatrelvir–ritonavir[11]). Studies of therapeutic efficacy in partially immune populations are more difficult to power than in immunologically naive populations, given the lower risk of progression to severe outcomes that has been observed in recent waves than at the start of the pandemic.[37] Even so, more studies of therapies in vaccinated or previously infected populations are needed to validate viral clearance as a surrogate of therapeutic efficacy in these populations.

An additional limitation is that our study might be affected by publication bias or underlying bias in the included studies. Fortunately, we observed no obvious evidence of publication bias (appendix p 23), and results were robust to

the exclusion of studies that were assessed as having a high risk of bias (although the results for day 7 were no longer significant; appendix p 16). We were also unable to account for the potential effect of previous infection in 14 studies in which seropositivity or other methods were not used to exclude people with previous infection. Finally, there were also methodological differences between the trials, such as the definition of severe outcomes, criteria for hospital admission, and timing and site of swab collection for viral load measurement (appendix pp 4–11), which could not be accounted for in our analysis.

Importantly, we have not shown that the correlation between a virological treatment effect and improved clinical outcomes described here is the causal mechanism of protection of these therapies. However, this assumption seems highly plausible given links between higher viral load and disease severity.[20] Also, we did not see an effect of treatment type (small molecule *vs* antibody) on the relationship between virological and clinical effects (appendix pp 13–15). However, in aggregating multiple classes of antiviral and monoclonal antibody therapies, we have ignored differences in pharmacokinetics and pharmacodynamics or mechanism of action. For example, these compounds can differ in terms of time to achieve therapeutic concentrations, tissue penetration, persistence, and activity (many of which are not known). It is possible that different relationships between viral clearance and efficacy will exist for different treatment types and we simply did not have sufficient power to identify these differences.

Future studies should look to validate the observed associations in this study, potentially using individual-level data, to study an association between viral load clearance and risk of hospitalisation. Additionally, future studies should consider other clinical outcomes, such as time to symptom alleviation, as another potential surrogate of therapeutic efficacy to prevent severe outcomes. However, care should be taken to conduct such studies with standard definitions of symptoms and symptom alleviation.

Overall, this work provides an evidence base to accelerate drug discovery and approval using viral outcomes as a potential surrogate of efficacy during early-stage clinical trials, for COVID-19 and potentially other viruses of the upper respiratory tract.

Contributors

All authors contributed to study conceptualisation. KME, SRK, TT, MPD, and DSK contributed to the design of the systematic literature search. KME, SRK, ES, TES, MPD, and DSK contributed to data curation, methodology, formal analysis, and visualisation. KME, SRK, and DSK accessed and verified the underlying data. All authors contributed to writing the manuscript, reviewed and approved the final report, had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Declaration of interests

MNP declares receiving provision of drugs for clinical trials from CSL Behring, Takeda, Grifols, Emergent Biosciences, and Gilead. DSK has received access to unpublished data via collaboration with employees of Merck & Co for research purposes on an unrelated pharmaceutical product. All other authors declare no competing interests.

Data sharing

Extracted data and codes for analysis are available on GitHub at https://github.com/iap-sydney/COVID19-treatment-in-unvaccinated.

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