Predicting the Efficacy of Passive Antibody Treatment of COVID-19

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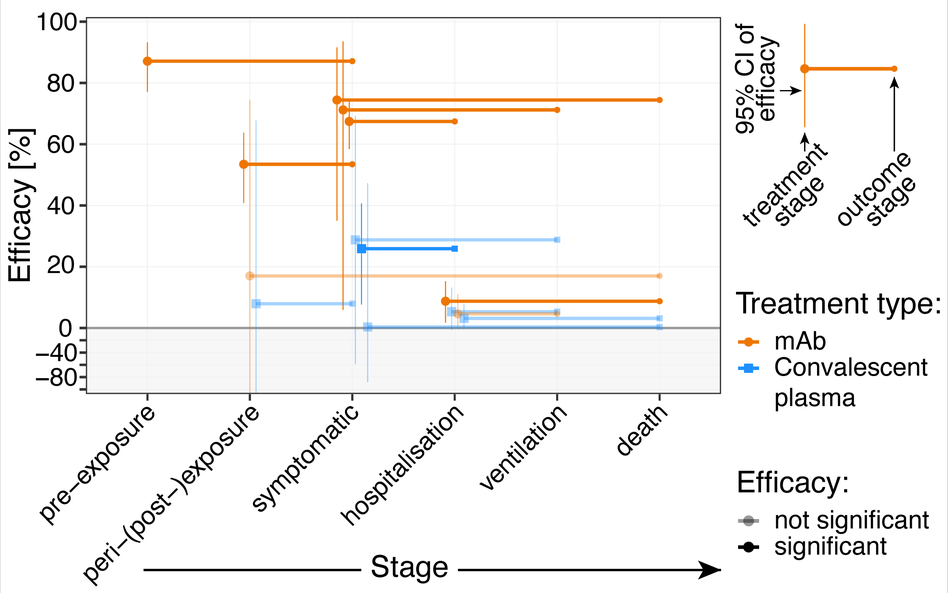
Introduction

- A range of passively administered antibody (Ab) therapies and prophylaxis have been tested in randomised controlled trials, including
  - Monoclonal antibodies (mAbs)
  - Convalescent plasma
  - Hyperimmune globulin
- These showed highly variable efficacy (some ineffective and some highly effective).
- **We test whether <u>timing and dose administered predict efficacy?</u>**
- **We also establish a tool for <u>using *in vitro* data to predicting efficacy</u> of new mAb and against new variants.**

Methods

- We performed a systematic search of the literature and identified 58 RCTs assessing antibody-based treatments/prophylaxis for COVID-19.
- We used a mixed-effects log-binomial model to analyse aggregated data.
- We estimated the (geometric mean) IC50 for each mAb-variant combination and for the convalescent neutralization titer using a mixed-effects model including inter study and assay variability and data from the Stanford University Coronavirus Antiviral & Resistance Database.
- We estimated a dose-response relationship by fitting a logistic model to the efficacy reported in each RCT against the administered dose.
- The dose-response relationship is used to predict the efficacy of Ab's against variants and in a population with various levels of immunity.
- 95% Confidence intervals were computed using parametric bootstrapping of model parameters (n = 100,000) and computing the 2.5th and 97.5th quantile.

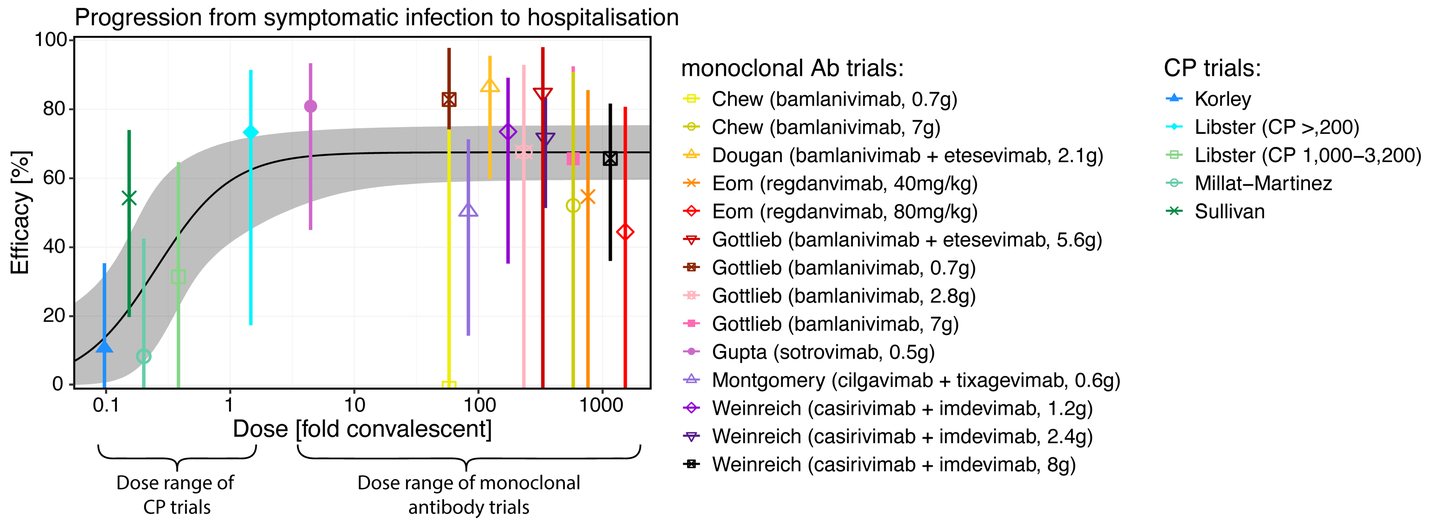
Timing of treatment



Treatment at earlier stages has a significantly higher efficacy.

Dose-response curve

- There is a significant relationship between the administered dose of neutralizing antibodies and the efficacy of treating symptomatic infection to prevent hospitalization (relative risk change per $\log_{10}$-dose: 0.77, 95% CI: 0.70-0.86, p<0.0001).
- Thus, we estimate a dose-response curve:

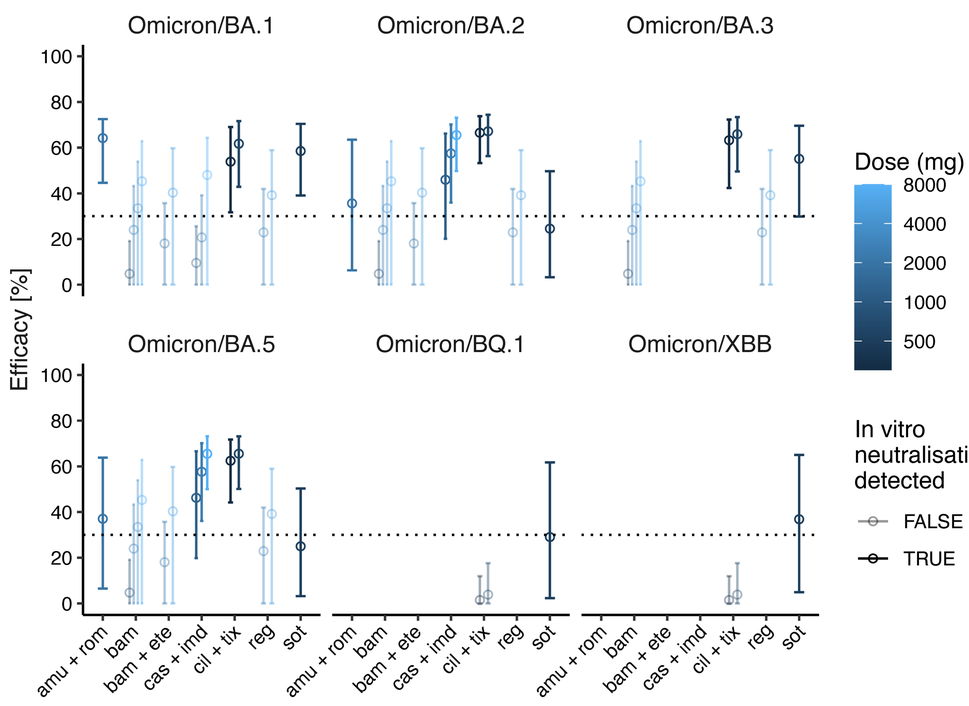


There is a correlation between the administered dose of Ab and efficacy.

- From the dose-response curve, we estimate:
  - Maximal efficacy of passive Abs: 67.5% (95% CI: 59.6 – 75.4%)
  - Dose for 50% of maximal protection: 0.25-fold convalescent (95% CI: 0.11 – 0.61)
  - Dose for 50% protection: 0.53-fold convalescent (95% CI: 0.19 – 2.52)
  - Dose for 90% of maximal protection: 1.18-fold conv. (95% CI: 0.29 – 20.19)
- The administered mAb doses were between 4.4- and 1,524-fold convalescent. Thus, the actually administered doses are 3.8- to more than 1,000-fold higher than doses required to provide 90% of the maximal protection.

The dose-response curve provides a tool for predicting the efficacy in preventing hospitalizations of passive Abs.

Efficacy against variants



Method.

The above dose response allows us to predict the loss of efficacy to new variants.

E.g., when an Ab is 10-fold less active against a new variant, we assume it is equivalent to administering 10-fold less antibody.

No mAb is expected to maintain >30% clinical efficacy against Omicron BQ.1 or XBB.

Summary

We provide the first quantitative tool for <u>predicting efficacy of new monoclonal antibodies</u> and against novel variants, <u>based on *in vitro* data</u> of potency.

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Links to our preprints (Lancet Microbe in press):