

Mechanistic model of antibody response, SARS-CoV-2 viral loads and genetic mutation burden to optimise molnupiravir dosing



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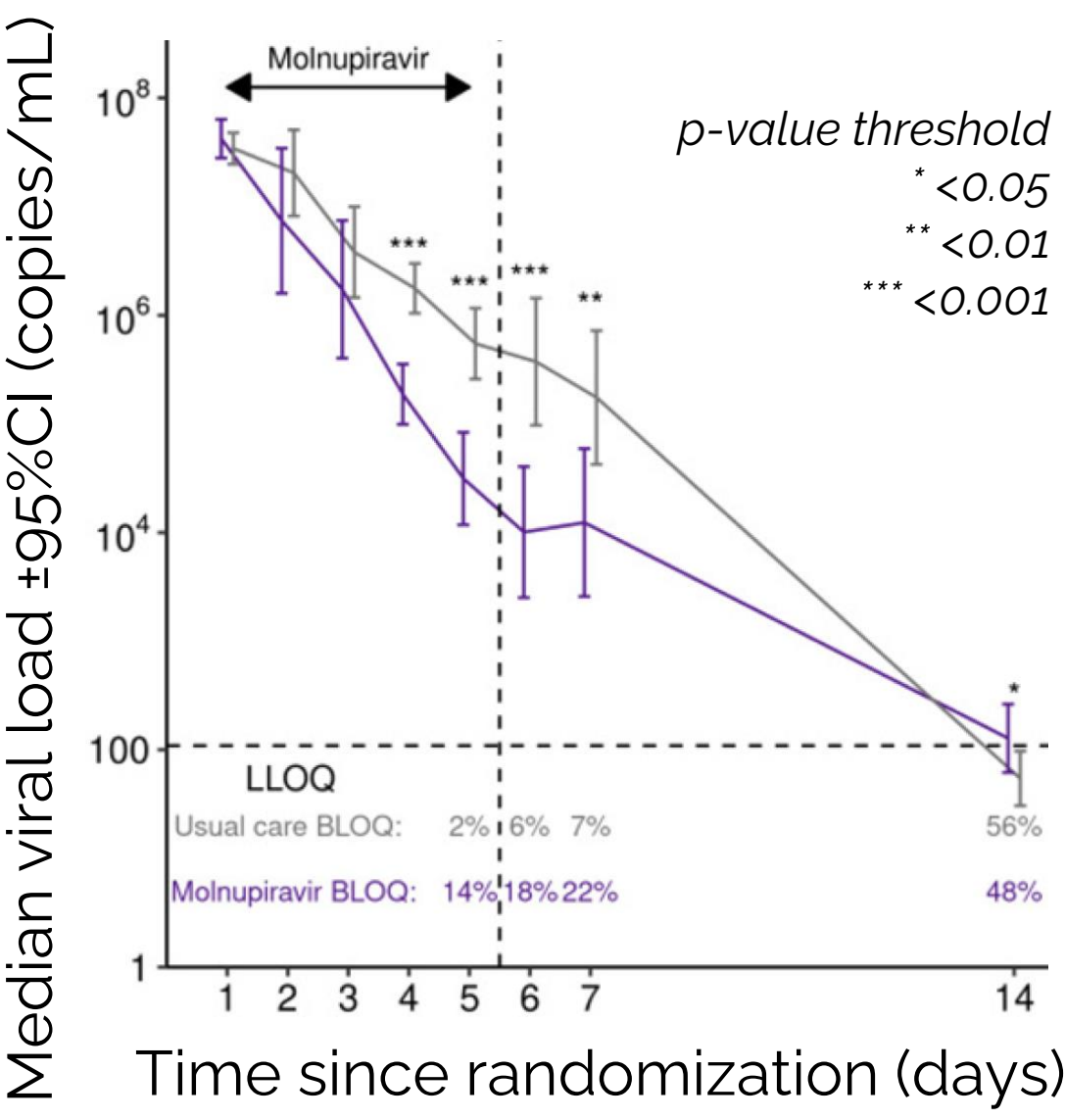


GREAT ORMOND STREET
INSTITUTE OF CHILD HEALTH

BACKGROUND

PANORAMIC trial

Standing et al, Nat Commun, 2024



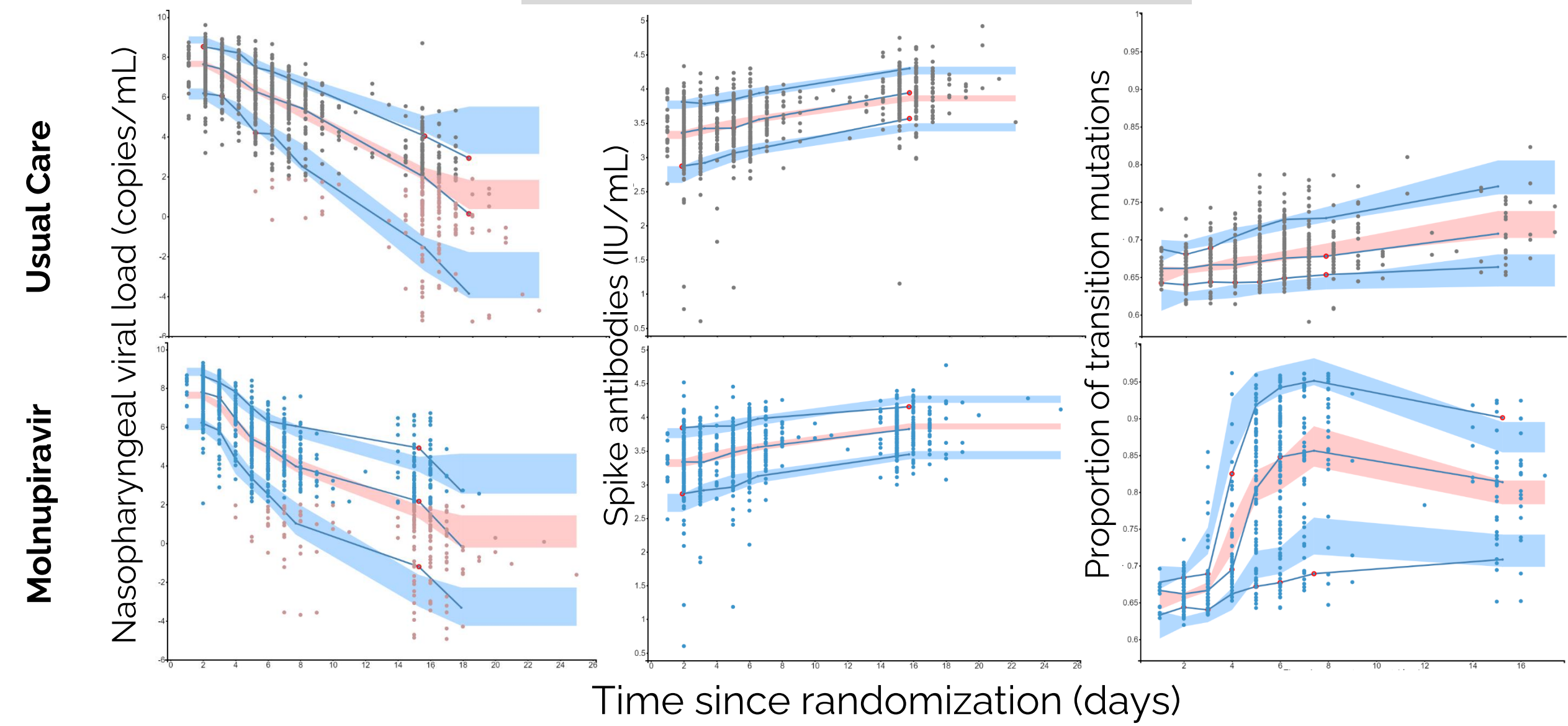
- The virological efficacy of molnupiravir has not yet been clearly quantified.
- Suboptimal antiviral efficacy & virological rebound following 5-day administration probably result from unadapted treatment duration.
- Mutation types maybe associated with virologic response.

OBJECTIVES

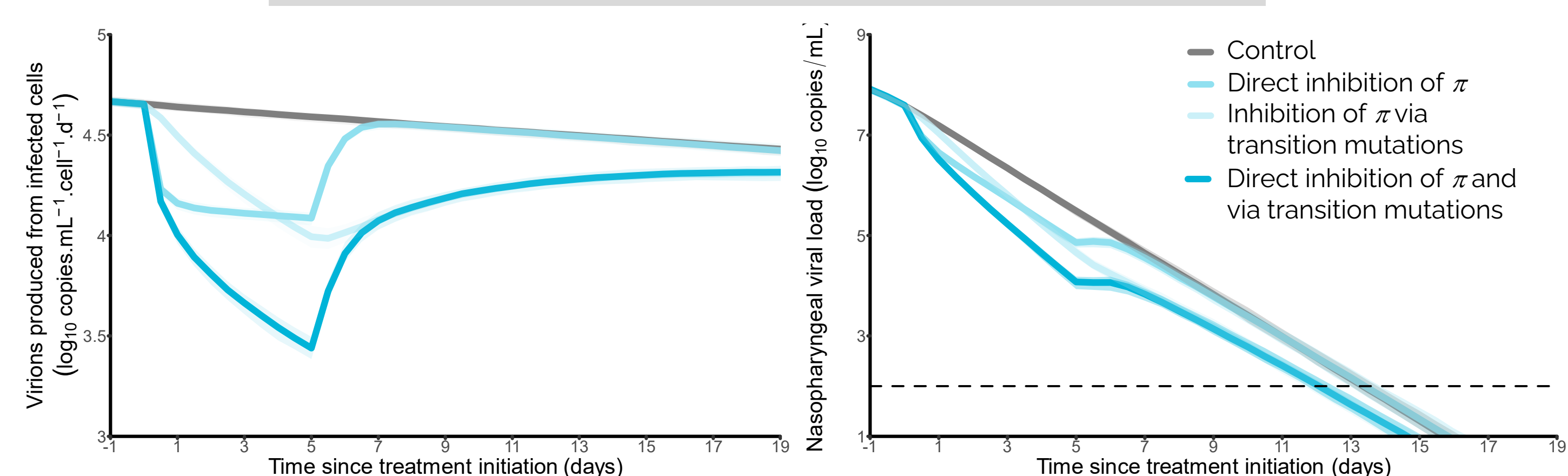
- To disentangle host immune & drug effect on viral load, spike antibodies and proportion of transition mutations.
- To evaluate longer treatment courses on virological response.

RESULTS

VPC plots for the final model

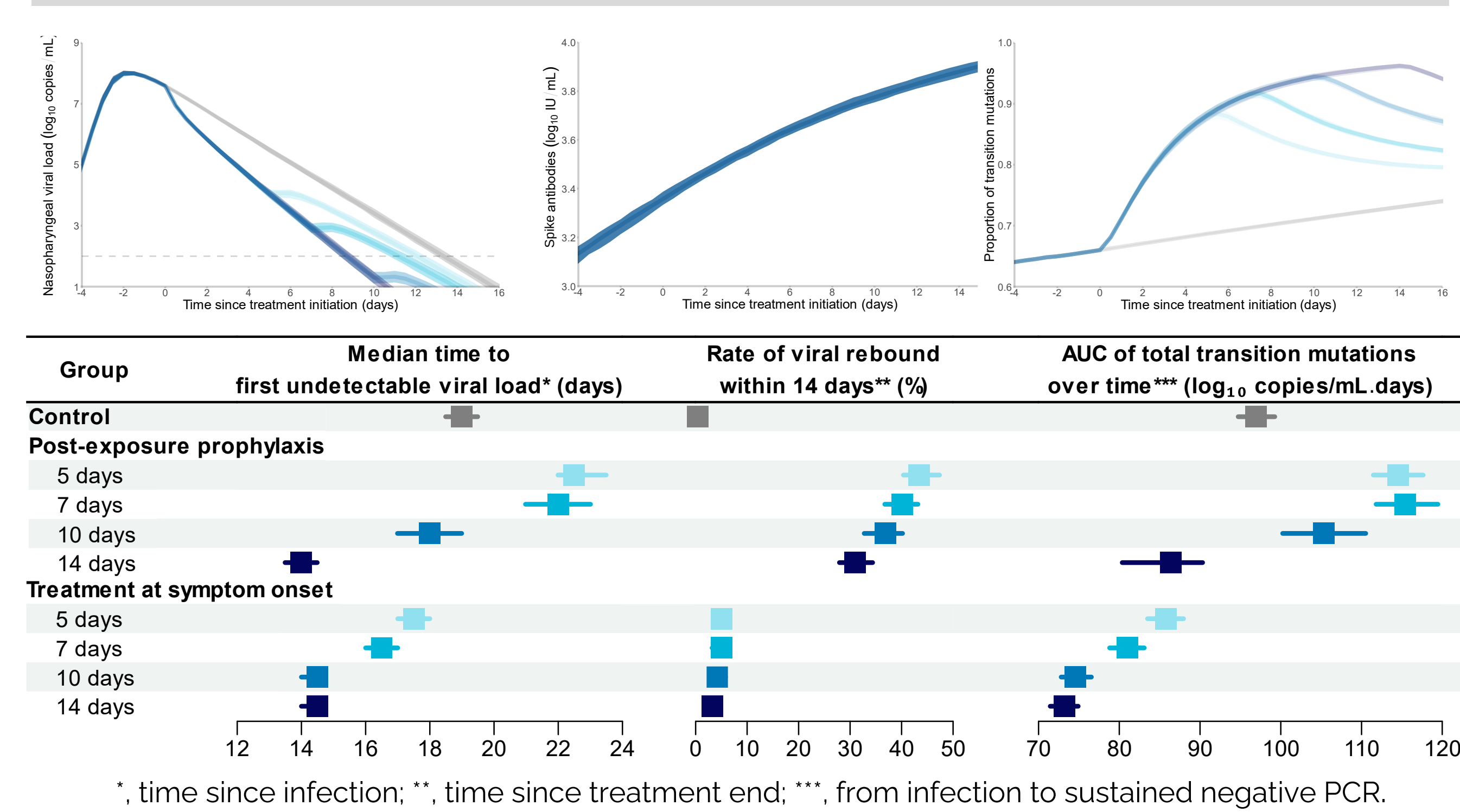


Antiviral effect via different mechanisms of action



- Antibody effect on eliminating infected cells: $EC_{50} = 1.7 \times 10^4$ IU/mL, $\epsilon_A = +108\%$.
- Molnupiravir effect on viral production by maximum 69% via direct inhibition, 76% via transition mutations, and 93% with both mechanisms.

Predicted outcomes for different treatment durations with molnupiravir



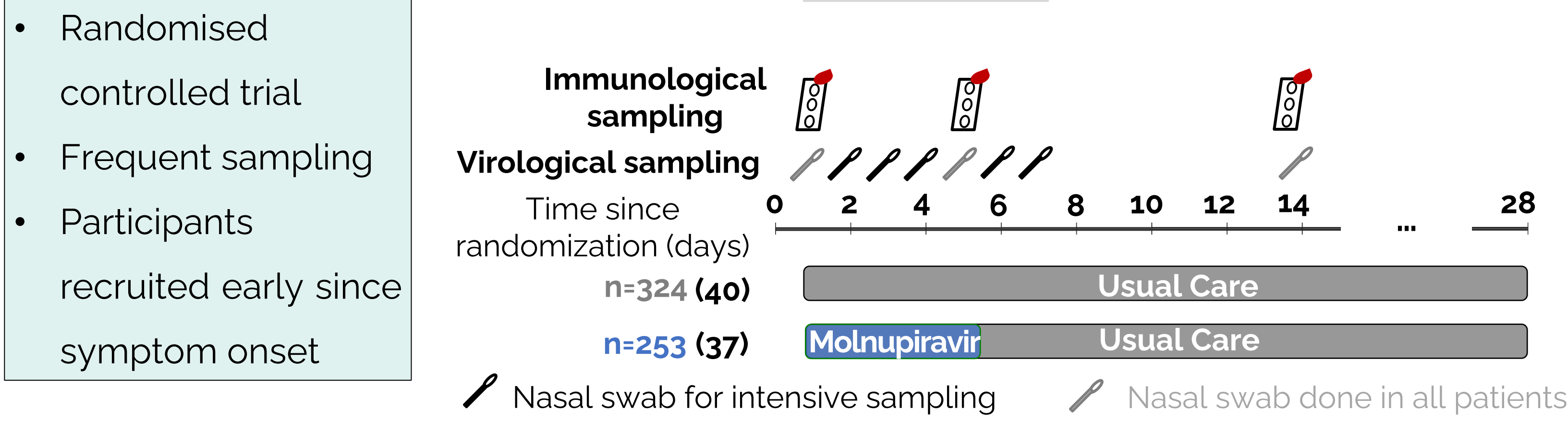
Treatment durations necessary for optimised virological outcomes:

- 14 days for prophylaxis to minimised transition mutation load & rebound rates
- 10 days for therapeutic use

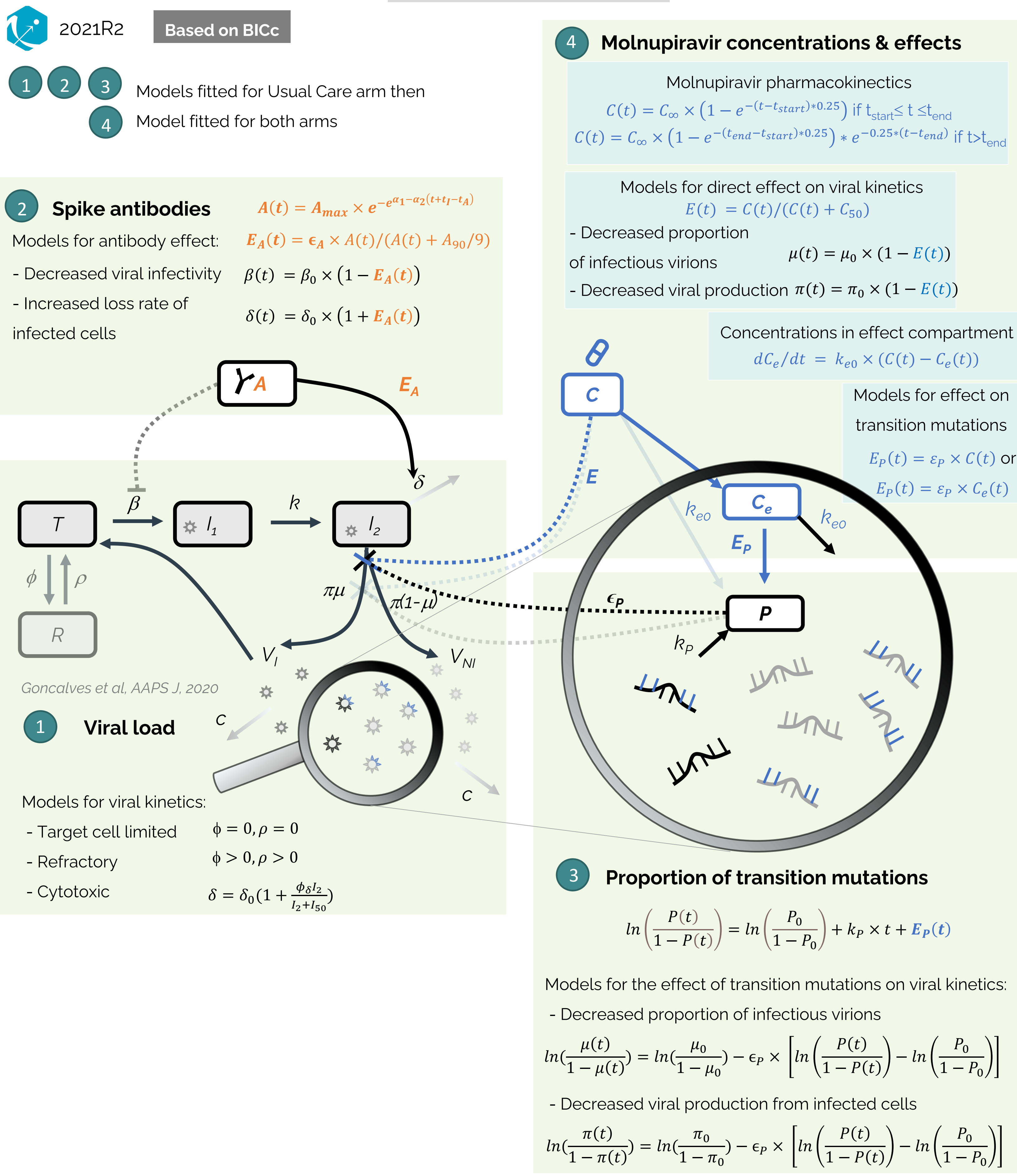
MATERIALS AND METHODS

Study design

Butler et al, The Lancet, 2023



Model building strategy



CONCLUSION

- Our model estimated that on average, molnupiravir would directly reduce viral production by maximum 69%.
- By increasing mutation load by 1.3 times, molnupiravir would further inhibit viral production by 76% on average at treatment completion.
- Insufficient treatment duration was identified as the main driver of virological rebound observed in participants treated with molnupiravir.
- Molnupiravir administered for at least 10 days should adequately limit the risk of virological rebound.

AFFILIATIONS

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