Designing impactful treatments against emerging SARS-CoV-2 variants

Charlotte Kern[1,2], Verena Schöning[1], Carlos Chaccour[3,4,5], Felix Hammann[1]

(1) Clinical Pharmacology and Toxicology, Department of General Internal Medicine, Inselspital, Bern University Hospital, Switzerland, (2) Graduate School for Health Sciences, University of Bern, Switzerland, (3) Department of Microbiology and Infectious Diseases, Clinica Universidad de Navarra, Pamplona, Spain, (4) Centro de Investigación Biomédica en Red de Enfermedades Infecciosas, Madrid, Spain, (5) ISGlobal, Hospital Clinic, University of Barcelona, Barcelona, Spain. Corresponding author: felix.hammann@insel.ch, presenting author: charlotte.kern@insel.ch

Background

- Despite abundant drug repurposing efforts, **no drug** has proved **effective;** only corticosteroids have (limited) benefits.
- Emerging **SARS-CoV-2 variants of concern** (VOCs) [1-2] have a **higher transmissibility** [3] and could prove more susceptible to specific drug therapy.
- **Molnupiravir** (Merck) is an **orally** bioavailable **prodrug**, inhibiting SARS-CoV-2 replication through **lethal mutagenesis**, as it is a nucleoside analog.
- Through **modeling** and **simulation** we explored the **effectiveness** of antiviral therapy with molnupiravir in SARS-CoV-2 with **different within-host reproduction numbers (R_0)**, as a proxy for altered within-host transmissibility.

Methods

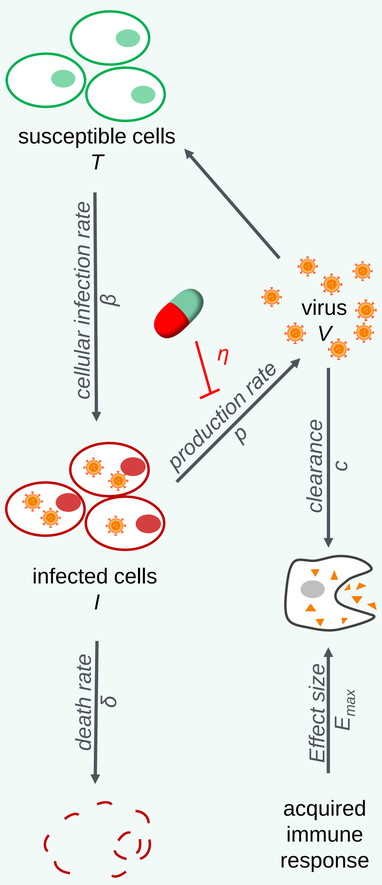
Viral kinetics model

- Viral loads were simulated from a **target-cell limited model** (Fig.1A) with dynamics of an **acquired immune response** 10 days post inoculation (dpi) [4]. **Highly transmissible variants** were set at 1.25-, 1.5-, 2-fold R_0, compared to wild type (R_0 = 3.79), whereas a putative co-adaptation variant (less transmissible) was 0.75-fold R_0.

Pharmacokinetic model and Pharmacodynamic effects

- Dosing: **molnupiravir 800 mg** every 12h for 5 days with an impulsive antiviral framework (Fig.1B) [4,5,6]. Treatment initiated 3 days before to 5 days after virus inoculation.
- NHC (active drug) inhibits viral production *in vitro* in Calu-3 cells (human lung epithelial cell line) with IC_{50} = 0.4146 µM [7].

Fig. 1: Viral kinetics model
A. Target-cell limited model



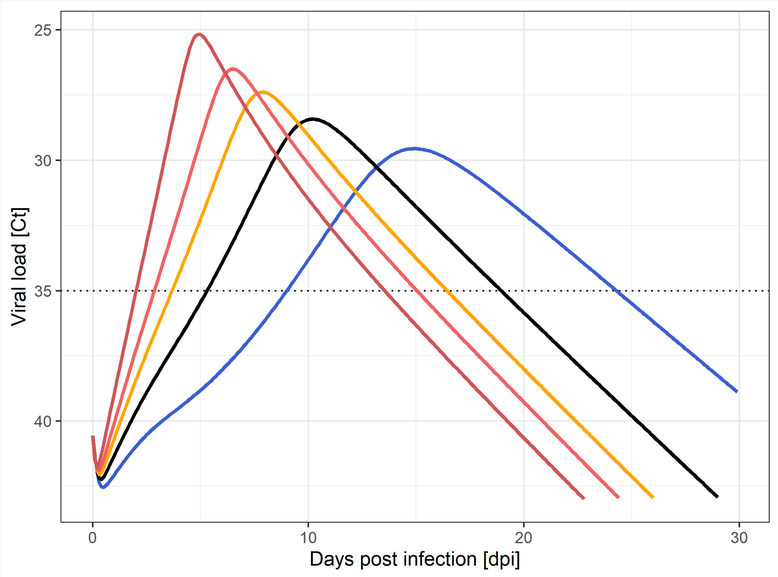
B. Ordinary Differential Equations system

$$\frac{dT}{dt} = -\beta TV \qquad \eta = \frac{E_{max} \times C(t)}{IC_{50} + C(t)}$$

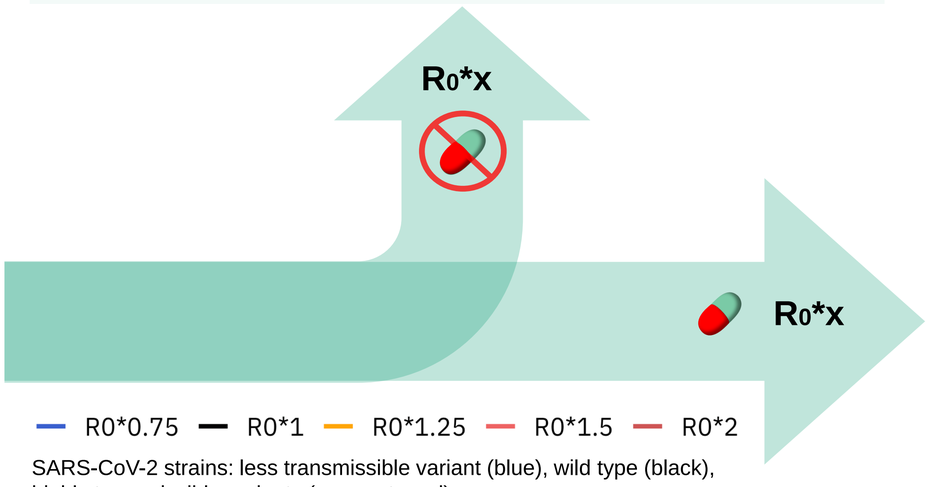
$$\frac{dI}{dt} = \beta TV - \delta I \qquad R_0 = \frac{p\beta T_0}{\delta(c+\beta T_0)}$$

$$\frac{dV}{dt} = (1-\eta)pI - c(1 + \varepsilon_{immunity})V$$

Fig. 2: Simulated viral load profiles by change in within-host infectivity (R_0) of VOCs

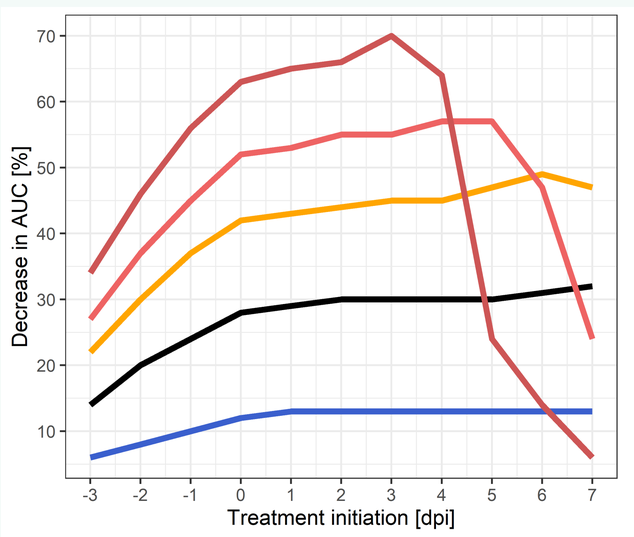


RT-PCR cycle threshold (Ct) values used as a measure of SARS-CoV-2 viral load. Limit of quantification: Ct = 35 (dotted line).



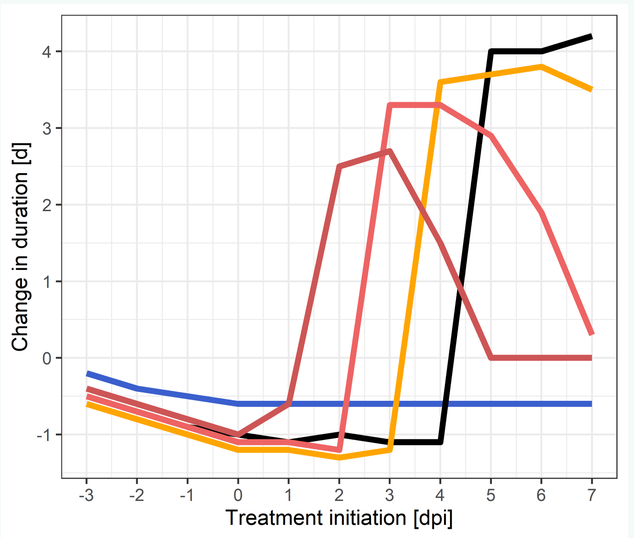
SARS-CoV-2 strains: less transmissible variant (blue), wild type (black), highly transmissible variants (orange to red).

Fig. 3: Molnupiravir treatment effect in VOCs
A. Decrease in total viral exposure



Total viral load is determined by the area under the viral load curve (AUC).

B. Change in duration of viral shedding



Results

- Viral load dynamics of wild type SARS-CoV-2 (Fig.2): positivity reached at 5.4 dpi and maintained for 13.5 days, viral load peaks of 28.4 Ct_{min} at 8.1 dpi.
- An **increased R_0** results in **earlier positivity** (2.1–3.7 dpi), **higher viral load peaks** (25.2–27.4 Ct_{min}) and **increased total viral load** (152-402%), whereas **decreased R_0** has the **opposite effect**.
- **Treatment** with molnupiravir leads to a reduced viral load (51-30%) in the **highly transmissible variants,** but only if **treatment** is **started** in the **first 1–3 days** post inoculation (Fig.3).
- Duration was less sensitive to changes in R_0, with a tendency towards prolonged positivity with increasing R_0 (R_0*1.25: 16.5 vs. 12.7 days untreated, R_0*2: 14.1 vs. 11.4 days untreated). In less transmissible variants, treatment effects are less pronounced.

Conclusion

- **Higher transmissibility** of VOCs leads to a **quicker infection** of all target cells, which can be seen as steep ascent**.**
- Molnupiravir treatment was **correlated** with **R_0**, making **highly transmissible VOCs more sensitive to antiviral therapy.**
- **Antiviral treatment** for SARS-CoV-2 needs to **be initiated early.** This effect is accentuated in VOCs with higher within-host transmissibility.
- Results are **in line with trial results** reported by Merck, where earlier outpatient treatment (MOVe-OUT trial) was superior to late initiation in in-patients (MOVe-IN trial).
- Pre-emptive **pre- or post-exposure prophylaxis** appears to be the most effective intervention strategy.

References: [1] Rambaut et al., (2020); [2] Tegally et al., doi:10.1101/2020.12.21.20248640 (2020); [3] Baric et al., doi:10.1056/NEJMcibr2032888 (2020); [4] Painter et al., doi:10.1128/aac.02428-20 (2021); [5] Kern et al., doi:10.3389/fphar.2021.625678 (2021); [6] Schöning et al., doi: 10.3389/fphar.2022.816429 (2022); [7] Rosenke et al., doi:10.1038/s41467-021-22580-8 (2021)