

Evulsheld hastens viral clearance in COVID-19 hospitalized patients: a modeling analysis of the randomized DisCoVeRy trial

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BACKGROUND

COVID-19 hospitalization

- SARS-CoV-2 responsible for large number of hospitalizations¹
- Mainly occurs on fragile population (unvaccinated, elderly, immuno-compromised)¹
- Antivirals and monoclonal antibodies (mAbs) can reduce the risk of severe form if administrated early^{2,3}

The use of mAbs against SARS-CoV-2

- Benefits of antivirals at later stage (i.e. hospitalization) is lower⁴
- Use of mAbs at hospitalization remains controversial
- Evusheld (AZD7442) is a cocktail of two humans mAbs, tixagevimab and cilgavimab⁵
- Marked loss of efficacy against Omicron variants⁶

Modeling for therapeutic evaluation

- High variability: variants, immune level, nature of mAbs, time treatment initiation
- Simple statistical approaches often fail to identify small treatment antiviral activity^{7,8}
- Our approach is to use mechanistic models to:
 - Reconstruct the neutralization activity after treatment
 - Integrate it into the individual viral load dynamics

DISCOVERY CLINICAL TRIAL

DisCoVeRy⁹: European, randomized, phase III, platform clinical trial (NCT 04315948)

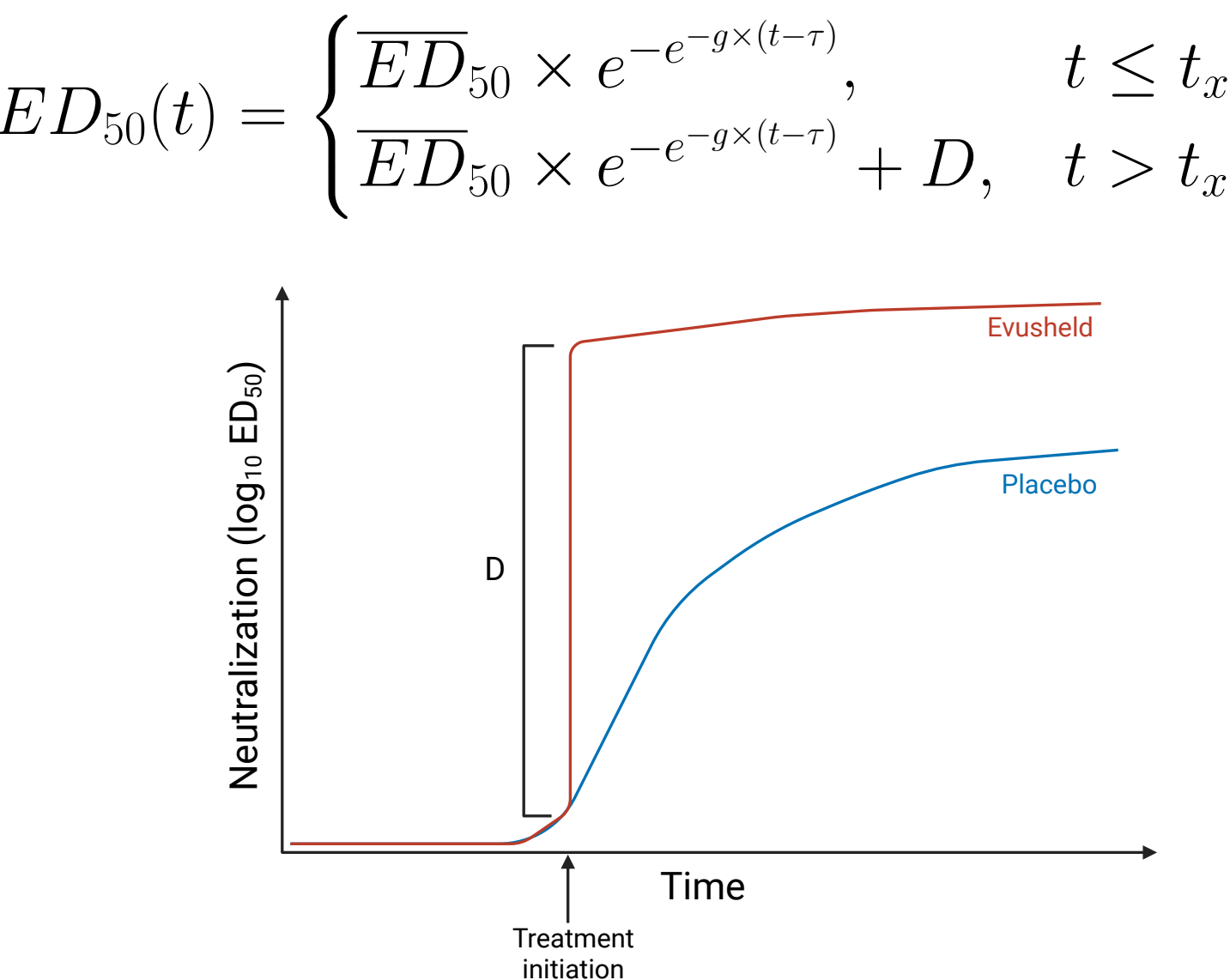
- 199 hospitalized patients were randomized between April 2021 and June 2022 either placebo or Evusheld arms
- Blood-neutralizing antibody titers against Delta, Omicron BA.1, and Omicron BA.2 variants and SARS-CoV-2 viral load were measured

Patients characteristics	Global mod-mITT (N=199)	
	Evusheld (N=109)	Placebo (N=90)
Male gender	69 (63%)	65 (72%)
Age > 65 years	55 (50%)	52 (58%)
Fully or partially vaccinated	49 (45%)	44 (49%)
Clinical status (7-point ordinal scale)		
3 or 4	86 (79%)	78 (87%)
5	23 (21%)	12 (13%)
Variant of infection		
Pre-Omicron	66 (61%)	59 (66%)
Omicron BA.1	32 (29%)	20 (22%)
Omicron BA.2/5	11 (10%)	11 (12%)
Positive serology test at randomization	69 (63%)	59 (66%)
Viral load at randomization		
Missing data	7 (6%)	3 (3%)
Data below the LOD	6 (6%)	5 (6%)
Normalized viral load (log ₁₀ copies/10 ⁴ cells)	4.25 (3.02-5.23)	4.25 (3.45-5.40)
Neutralization against variant of infection at randomization		
Missing data	2 (2%)	2 (2%)
Data below the LOD	56 (52%)	48 (53%)
Neutralization activity (log ₁₀ ED ₅₀)	2.36 (2.03-2.92)	2.67 (2.19-3.08)
Time from symptom onset to hospitalization (days)	7.00 (6.00-9.00)	7.00 (5.00-9.00)
Duration of hospital stay (days)	8 (5-12)	8 (5-14)
Deaths at D90	15 (14%)	16 (18%)

Table 1. Patients characteristics, data are n (%) or median (IQR)

ASSOCIATION OF NEUTRALIZATION ACTIVITY WITH VIRAL LOAD DYNAMICS

Describe the neutralization activity dynamics with a sigmoid Gompertz model¹⁰:
$$ED_{50}(t) = \begin{cases} \overline{ED}_{50} \times e^{-e^{-g \times (t-\tau)}}, & t \leq t_x \\ \overline{ED}_{50} \times e^{-e^{-g \times (t-\tau)}} + D, & t > t_x \end{cases}$$



We tested the effect of patient characteristics on the estimated parameters of the neutralization and viral load dynamics models:

- Vaccinated patients had a higher level of neutralization than unvaccinated
- Variant of infection has a major impact on neutralization activity provided by Evusheld

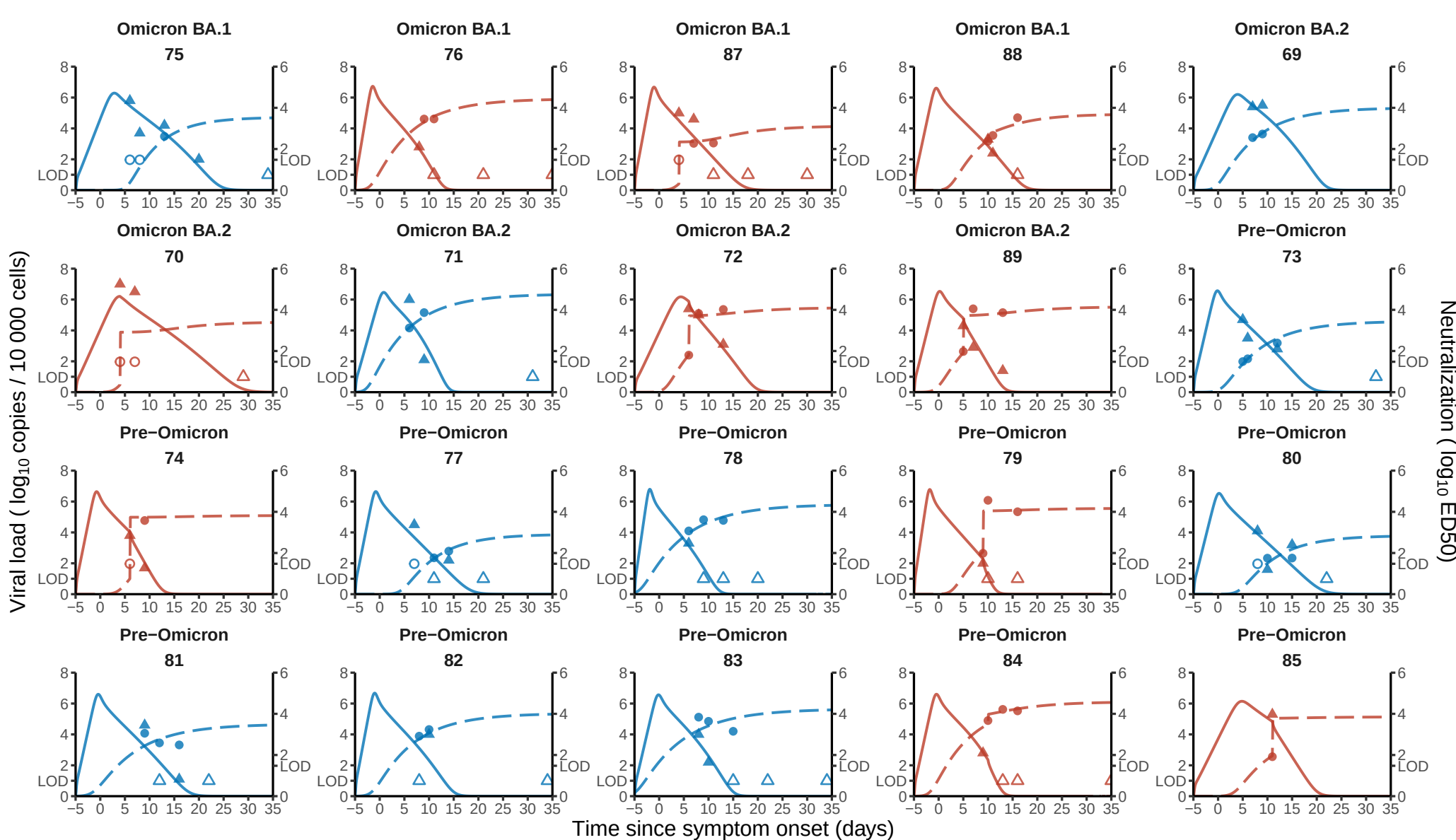


Figure 1. Individual fits of viral load (solid lines) and neutralization activity (dashed lines). Triangles are observed viral load and dots are observed ED₅₀, empty shapes are observations below the LOD

RESULTS

- Based on estimated population parameters, we simulated 5,000 in silico Evusheld-treated profiles
- For each simulated profile, we:
 - reconstructed the viral kinetics with and without treatment (assuming $D = 0$)
 - calculated the gain in viral load decline
 - calculated the time to reach an undetectable viral load (TTU)

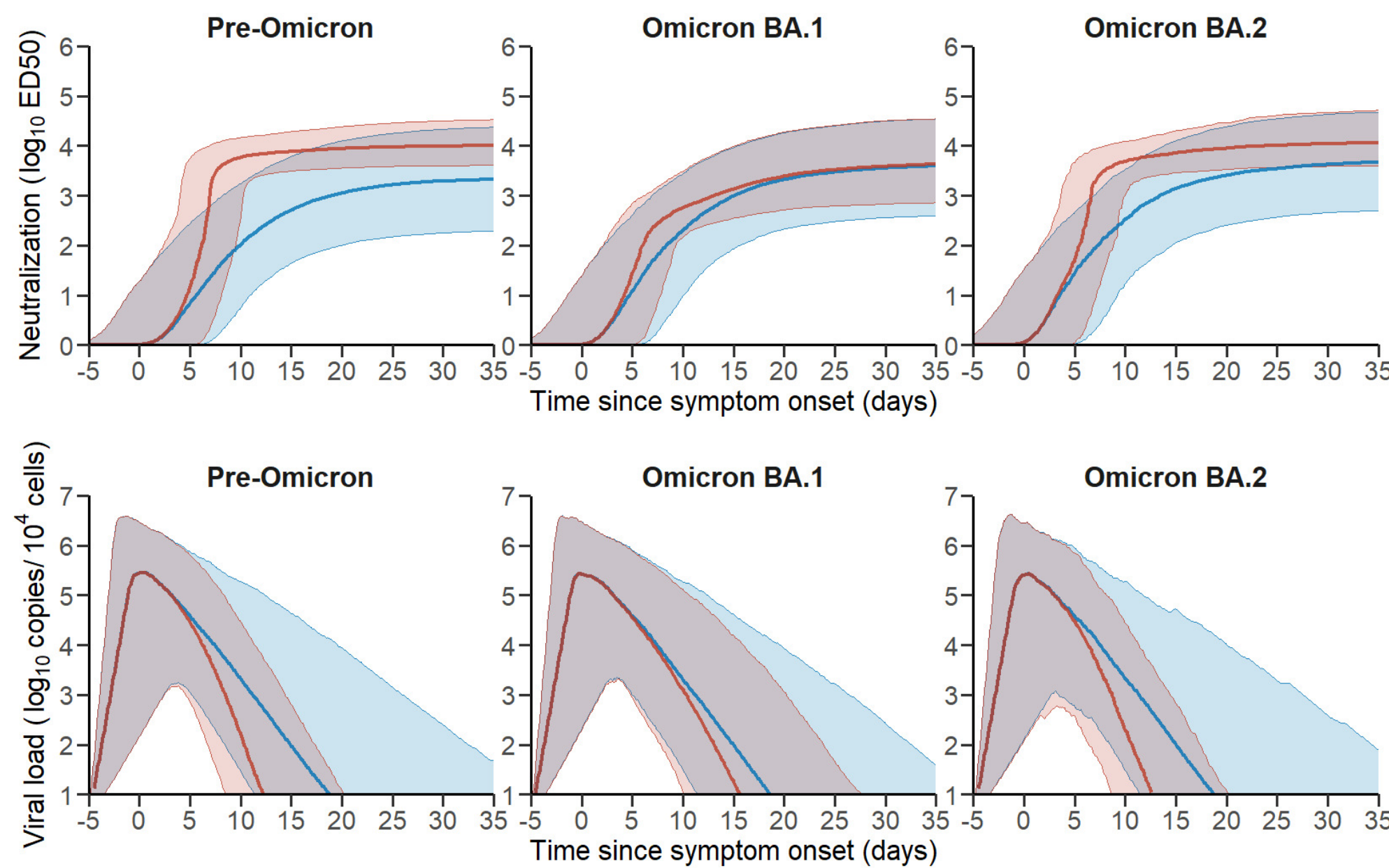


Figure 2. Median (PI 10-90) prediction of viral load and neutralization dynamics of the 5000 treated (red) and non-treated (blue) simulated profiles, stratified by variant of infection

- Evusheld injection led to a substantial increase in the neutralization activity against pre-Omicron and Omicron BA.2 variants
- Evusheld only slightly increases neutralization activity against Omicron BA.1 variant
- These higher levels of neutralization activity induced by Evusheld led to a more rapid viral decline

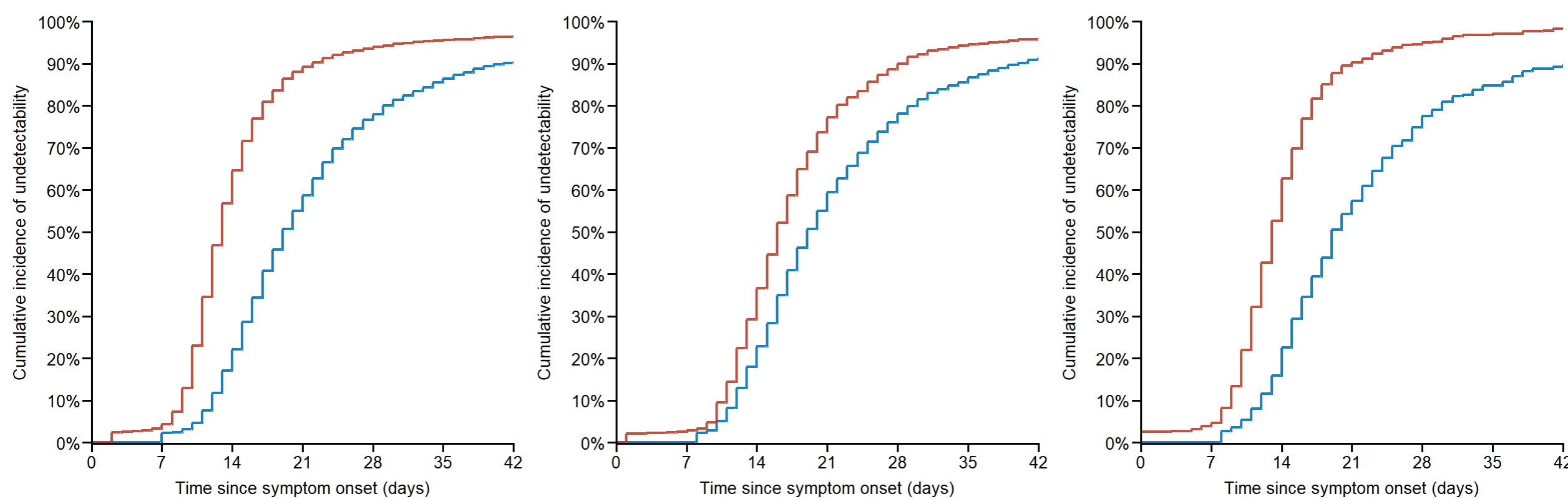


Figure 3. Cumulative incidence of TTU of the simulated 5000 treated (red) and non-treated (blue) profiles, stratified by variant of infection

- Evusheld hastens the viral clearance by more than 5 days in patients infected by pre-Omicron (median: 5.9; IQR: 3.5-9.2) or Omicron BA.2 (median: 5.4; IQR: 3.4-8.95)
- The effect was more modest in patients infected by the Omicron BA.1 variant, reducing the time to viral clearance by 2 days (median: 2.2; IQR: 1.0-4.7)

CONCLUSION

- Evusheld hastens viral clearance in COVID-19 hospitalized patients
- First study to identify a virological effect of a mAb in hospitalized patients
- Prerequisites to observe a clinical benefit of an antiviral^{8,12}
- No data in the early phase of the disease → high uncertainty in early phase parameters
- Mathematical modeling is critical to identify an antiviral treatment effect in COVID-19 hospitalized patients

¹ Kirwan et al. *Nature Communication* 2022; ² Najjar-Debbiny et al. *Clinical Infectious Diseases* 2023; ³ Abani et al. *The Lancet* 2022; ⁴ Lingas et al. *Journal of Antimicrobial Chemotherapy* 2022; ⁵ Hobbs et al. *Infectious Diseases and Therapy* 2023; ⁶ Bruel et al. *Nature Medicine* 2022; ⁷ Jittamala et al. *Journal of Infectious Diseases* 2023; ⁸ Parienti and Grooth *Journal of Antimicrobial Chemotherapy* 2022; ⁹ Hites et al. *Journal of Infection* 2024; ¹⁰ Tjorve and Tjorve *PLOS ONE* 2017; ¹¹ Phan et al. *PLOS Pathogens* 2024; ¹² Mitjà et al. *Clinical Infectious Diseases* 2021;