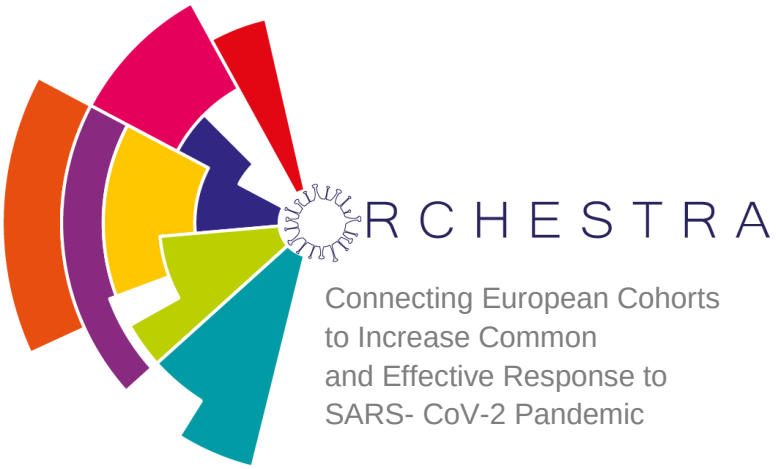

DELIVERABLE

WP8 D8.2

Report on estimates of intervention effects using individual-based models

Helmholtz Zentrum München – Deutsches Forschungzentrum Gesundheit Und Umwelt Gmbh (HMGU)

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Executive summary

As the global battle against SARS-CoV-2 continues, nations, states, and cities have implemented a range of interventions to curb its spread and prevent healthcare systems from becoming overwhelmed. In Deliverable 8.1, we consolidated information on the impact of non-pharmaceutical interventions, including voluntary physical distancing measures and mandatory shutdowns, such as school closures. Building on this, in this Deliverable we assessed the impact of pharmaceutical interventions, which became available relatively quickly.

Here we summarize the results of studies by HMGU and INSERM focusing on the impact of repeated vaccinations and, combined with infections, on the risk of breakthrough infections. Additionally, we investigated the potential of antivirals in studying the spread of SARS-CoV-2, particularly in reducing transmission risks within households. This deliverable provides a detailed analysis of datasets available in ORCHESTRA and the models developed based on these datasets.

Our model-based assessment of ORCHESTRA data revealed that the combination of vaccination and infection resulted in a broad spectrum of neutralizing antibodies. Following the Omicron wave, individuals previously vaccinated exhibited high antibody titers and a low risk of breakthrough infection. Predictions of antibody titers and cellular immunity levels suggest a significant dampening effect on subsequent waves. Furthermore, complementary modeling studies indicated that thorough use of antivirals within households with an index case could contribute to further controlling the spread of SARS-CoV-2. Administering antivirals upon detecting infection in a household member reduces the risk of transmission to other household members, effectively breaking the chain of transmission.

Overall, this deliverable emphasizes the crucial role of interventions, including vaccination and the strategic use of antivirals, in shaping the course of the pandemic. By employing individual-based models, we gain valuable insights into the potential impact of these interventions, informing effective strategies for mitigating the spread of SARS-CoV-2. The findings presented in this report contribute to our understanding of the pandemic's dynamics and can assist decision-makers in formulating evidence-based policies for public health protection.

Core content

This deliverable describes the datasets and computational models used for achieving the aforementioned results. In the first part we focus on the impact of vaccination and infection. In the second part we describe the work on antivirals. The methods described in the deliverable can be reused, and we are currently studying further datasets to confirm the already convincing results.

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1. Vaccinations and SARS-CoV-2 Omicron breakthrough infections

The most important pharmaceutical intervention used to counteract the SARS-CoV-2 pandemic was vaccination. Various studies showed that vaccinated individuals had a substantially reduced risk of a severe infection. Accordingly, for the assessment of potential future waves, we have to understand vaccination induced immunity. Nevertheless, the interplay of vaccination and natural infection is of key importance.

The emergence and dominance of the SARS-CoV-2 Omicron variant, in late 2021, resulted in high infection rates across populations in Europe with high vaccination coverage [Flechsler et al., 2022; Taylor et al., 2022]. For example, in Germany roughly 63% of the population was vaccinated by summer 2021 and then boosted in autumn/winter 2021 [Maier et al., 2022]. However, even triple-vaccinated individuals were insufficiently protected from SARS-CoV-2 Omicron infection, while the risk of severe disease was low in infected individuals [Petrone et al., 2023]. While parameters defining adaptive immunity to Omicron infection have not been fully established, these are likely comparable to those established in the pre-Omicron era; neutralizing antibody titers positively correlated with protection from SARS-CoV-2 infection during phase 3 efficiency vaccine trials [Gilbert et al., 2022; Feng et al., 2021] and pre-clinical vaccine studies [Corbett et al., 2021; Mercado et al., 2020]. Antibody transfer experiments using spike-specific IgG further established that antibodies alone are sufficient to mediate protection from disease in a preclinical infection model [Corbett et al., 2021].

In WP8 of the ORCHESTRA projects, we aimed to understand the interplay of vaccination and breakthrough infection, and its impact on protection levels within the populations. In the following, we present our core findings. The text is based on a manuscript draft currently in preparation. The title of the article is "*Evolution of protective SARS-CoV-2-specific B and T cell responses upon vaccination and Omicron breakthrough infection*" by Mohamed I.M. Ahmed, Sebastian Einhauser, Clemens Peiter, Antonia Senninger, Olga Baranov, Tabea M. Eser, Manuel Huth, Laura Olbrich, Noemi Castelletti, Raquel Rubio-Acero, Inge Kroidl, Kathrin Held, Andreas Wieser, Christian Janke, Michael Hoelscher, Jan Hasenauer, Ralf Wagner and Christof Geldmacher. The analysis and modeling presented here was mostly performed by the ORCHESTRA partner HMGU.

1.1. Summary

From 2021, vaccinations have been used worldwide to slow down the spread of SARS-CoV-2 and lower hospitalization numbers. More recently, breakthrough infections with the SARS-CoV-2 Omicron lineage have been largely observed. The protection provided by vaccines and mechanisms by which breakthrough infections protect against reinfection is still not fully understood.

To address this issue, we considered longitudinal data from Bavarian residents, which were collected by ORCHESTRA partners. These data provided information about humoral and cellular immune responses. Furthermore, neutralization capacity against several SARS-CoV-2 variants and frequency of virus-specific T cells were assessed.

Using an individual-based mathematical model, we estimated the protection from infection conveyed by both cellular and humoral immune responses. Post-vaccination Omicron BA.5 neutralization titers were most significantly associated with reduced hazard rate for SARS-

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CoV-2 infection also when accounting for spike-specific T-cell responses. However, 97% of triple vaccinees became SARS-CoV-2 infected, often shortly after the third vaccination. These breakthrough infections further boosted neutralization magnitude and breadth, broadened virus-specific T-cell responses to antigens not encoded by vaccines and protected from further infections.

1.2. Description of the study population

Fifty study participants were recruited in Munich and surrounding regions in Bavaria, Germany by partners at the LMU Clinics Munich. The median age was 31 years (range 21 to 57 years) and 68% (34/50) were female. Out of 50 individuals, 18 were recruited before their first vaccination, 23 before administration of the second vaccination and an additional 9 participants were recruited after the second vaccination dose. A total of 34 subjects (indicated in the underlying data) were followed longitudinally over an extended period from the first quarter of 2021 until December 2022. 16 participants were followed only for a limited time or were lost to follow up before receiving a third vaccination. mRNA vaccines accounted for the majority of first immunizations, followed by adenoviral vector vaccines. Second and third booster vaccines were almost exclusively mRNA vaccines. Of these 34 vaccinated subjects, 33 experienced a breakthrough infection (BTI) with SARS-CoV-2 between November 2021 and December 2022 with a median time of 157.5 days after the last vaccination (Range in days: 10 – 406). 32 of 34 individuals received three vaccinations and were then infected, while two participants were infected after the second vaccination.

1.3 SARS-CoV-2 neutralizing antibody and T-cell response dynamics during vaccination

We assessed the dynamics of SARS-CoV-2 neutralizing activity against three clinically relevant variants of concern (VOCs), Wuhan, Delta and Omicron BA.5. The median and interquartile ranges of the neutralizing antibody titers (IC50) grouped by time bins are displayed in Figure 1.

The neutralizing antibody responses against the three variants followed a similar dynamic pattern, albeit at different levels. IC50 values for Wuhan neutralization were consistently higher as compared to Delta or Omicron BA.5, whereas Delta and Omicron BA.5 neutralization were comparable after vaccination. Beyond 150 days after the second vaccination titers had waned to that before the second vaccination, while the third vaccination boosted median IC50 titers 10-15-fold (depending on the tested variant) and remained significantly higher beyond 150 days as compared to the levels after the second vaccination for all tested variants ($p<0.001$, $n = 10$, excluding participants with BTI). We next wanted to assess neutralization breadth for different variants and combined single-variant data using a magnitude-breadth analysis approach (17, 18), in which areas under the curve (AUC) were determined for every single serum, based on the neutralization data against all three variants. A slight, but statistically significant increase in neutralization magnitude-breadth was observed after each vaccination, dwindling quickly (within 90 days, Figure 1D). Similar patterns as were observed for the neutralizing antibody titers could be observed for frequencies of Spike-specific CD4+ and CD8+ T cells.

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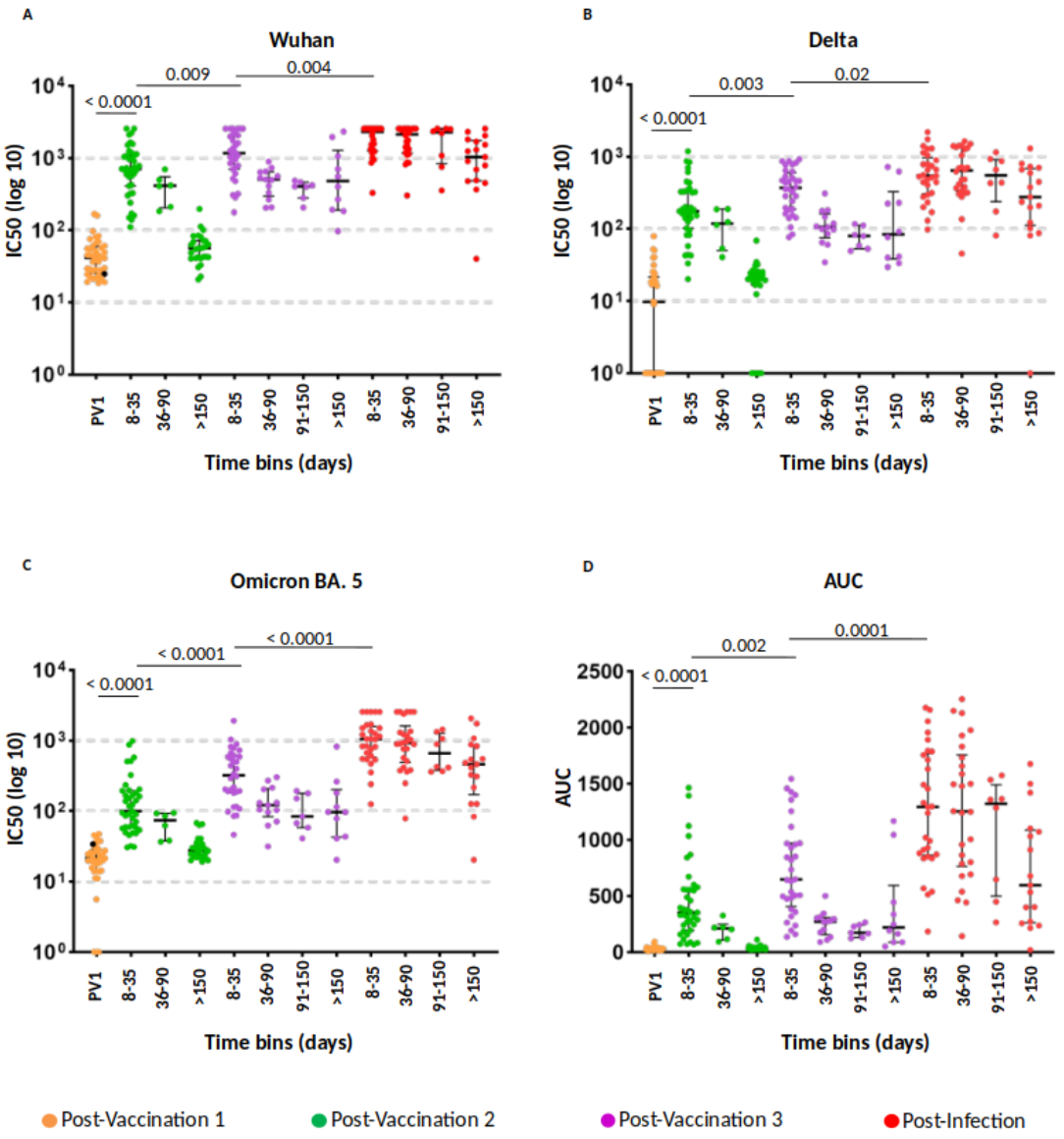

Figure 1. Dynamics of antibody neutralization during vaccination and after breakthrough infection. Neutralization was tested for original Wuhan (A), Delta (B) and Omicron BA.5 (C) strains using a lentiviral pseudovirus neutralization assay at post-vaccination 1 (PV1, orange), post-vaccination 2 (green), post-vaccination 3 (purple) and BTI (red). If multiple samples were available within one timeframe, the highest IC50 value was reported for the peak response at 8-35 days after vaccination or infection. For the other time points, a mean IC50 value was calculated if more than one data point was present. The upper limit of detection was an IC50 value of 2560, while the lower cutoff was 20. Statistical analyses were performed using the Mann-Whitney test. Median values, interquartile range and p-values below 0.05 are indicated.

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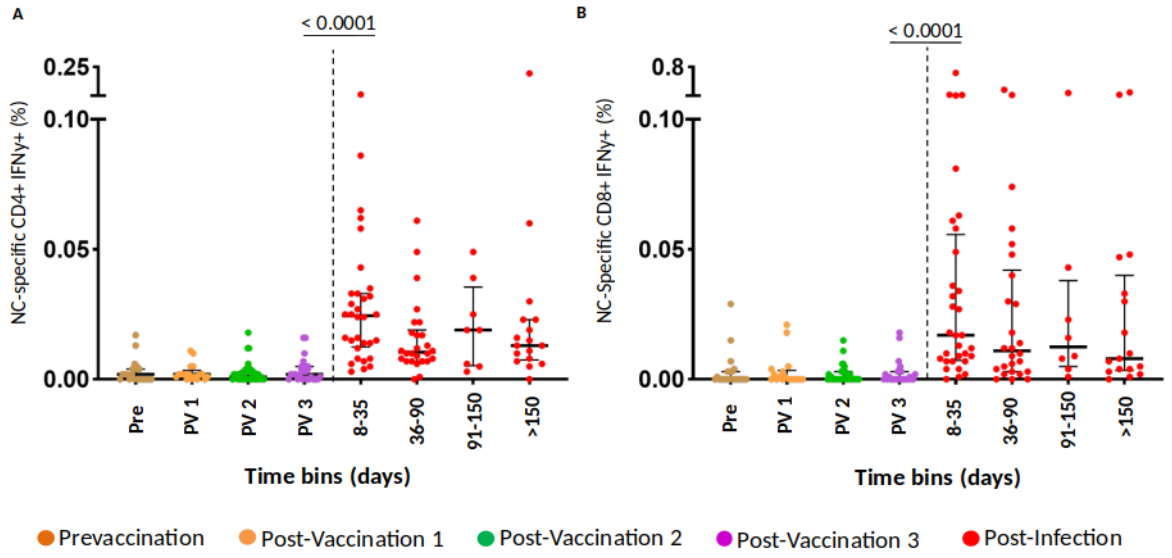

Figure 2. Frequency of nucleocapsid-specific IFNɣ+ CD4+ (**A**) and CD8+ (**B**) T cells before vaccination (Pre, brown), post-vaccination 1 (PV1, orange), post-vaccination 2 (PV2, green), post-vaccination 3 (PV3, purple) and after breakthrough infection (red). The time bins after each vaccination and breakthrough infection are shown on the x-axis. The median and quartiles enclosing 50% of the datapoints are shown, whiskers extend up to the last point inside 1.5*(IQ3 - IQ1) range (Tukey definition). The Mann-Whitney test was used for statistical analyses. p-values below 0.05 are indicated.

Looking at neutralizing antibody titers and T-cell frequencies after BTI, we could observe an induction of high levels of long-lasting cross-neutralizing antibody and T-cell responses to viral structural proteins. Even beyond 150 days after BTI, median IC50 neutralization values were comparable to peak levels directly after the third vaccination for all three tested variants. Omicron BTI also boosted spike-specific CD4+ and CD8+ T-cell populations (Figure 2), which persisted beyond 150 days at several-fold higher median levels compared to pre-vaccination. Furthermore, BTI induced CD4+ and CD8+ T-cell responses targeting the non-vaccine-encoded Nucleocapsid protein of SARS-CoV-2 even beyond 150 days after BTI.

1.3. Breakthrough infection analysis

Considering only triple-vaccinated individuals, we examined infection times after third vaccination of each individual. In order to determine the protective effect of T-cell responses, as well as neutralizing antibodies from infection with SARS-CoV-2 Omicron, Cox-regression was performed. As covariates in our model, we used a binary variable indicating high or low neutralizing antibody titers or T-cell frequencies at peak (8 to 35 days post third vaccination) for each study participant. Then, we estimated hazard ratios for each group (Figure 3).

As can be seen in Figure 3, Omicron BA.5 neutralization IC50 values above 400 were most significantly associated with a reduced hazard for Omicron infection (HR [95% CI]) = 0.27 [0.1-0.7], p=0.007). Other variables, such as frequencies of T cells or neutralization titers against other SARS-CoV-2 variants, were not associated with a reduction in hazard.

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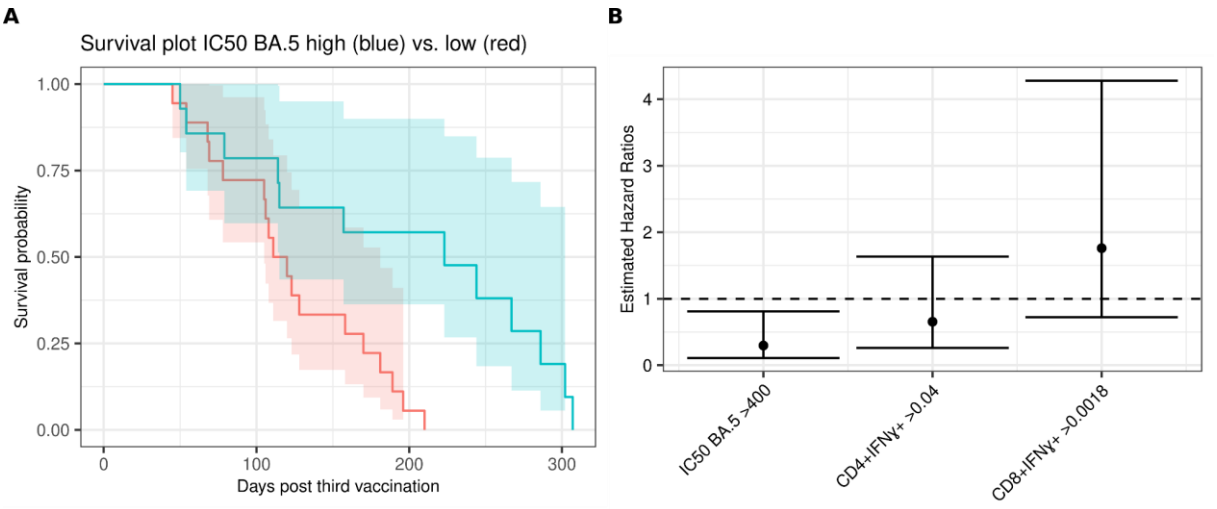

Figure 3. Survival analysis example for triple-vaccinated study participants after third vaccination. Kaplan-Meier plot showing infection events (solid line) and estimated survival confidence intervals (light-shaded area) are shown on the left. The participants were separated into two groups, one with high early neutralizing antibody titer and one with low titer. On the right, estimated hazard ratios with 95% confidence intervals for participants with neutralizing antibody titers and Spike-specific T-cell frequencies above a given threshold are displayed.

1.4. Hazard rate reduction through neutralizing antibodies

Additionally, we utilized a mathematical model describing a time-dependent hazard rate that could be used to estimate the reduced infection risk conveyed by the presence of neutralizing antibodies against Omicron BA.5. A schematic representation of this model can be seen in Figure 4A. The time-dependent hazard rate is parameterized by the corresponding seven-day incidence in Munich (Figure 4B, left) and the level of neutralizing antibodies of the individual (Figure 4B, right). The incidence is connected to the base infection risk $\beta 0$ (for which different values were taken from literature: Dandekar et al. (2020), Volz et al. (2021) SAGE (2021), Ito et al. (2022)), whereas the effect of the antibodies is captured by $\beta 1$. Larger values of $\beta 1$ lead to a reduction in hazard, whereas values close to zero have the opposite effect.

Data from the same triple-vaccinated participants as before were used to estimate the effect of the neutralizing antibodies on the hazard rate. The parameter $\beta 1$ was optimized for different base infection risks and fits of the model to the data were found to be similar (one model fit is shown in Figure 4D). The reduction in hazard through the presence of neutralizing antibodies can be observed in Figure 4C (on the left for one exemplary base infection risk and on the right for different base infection risks plotted against the IC50 BA.5 value). Additionally, we used this model to predict another infection after the breakthrough infection for the same participants (Figure 4D). In our simulation, we observed fewer infections after breakthrough infection compared to the observed infections after the third vaccination of the study participants. Conversely, no additional infections were found in study participants after breakthrough infection, arguing for additional protection through cellular immune responses.

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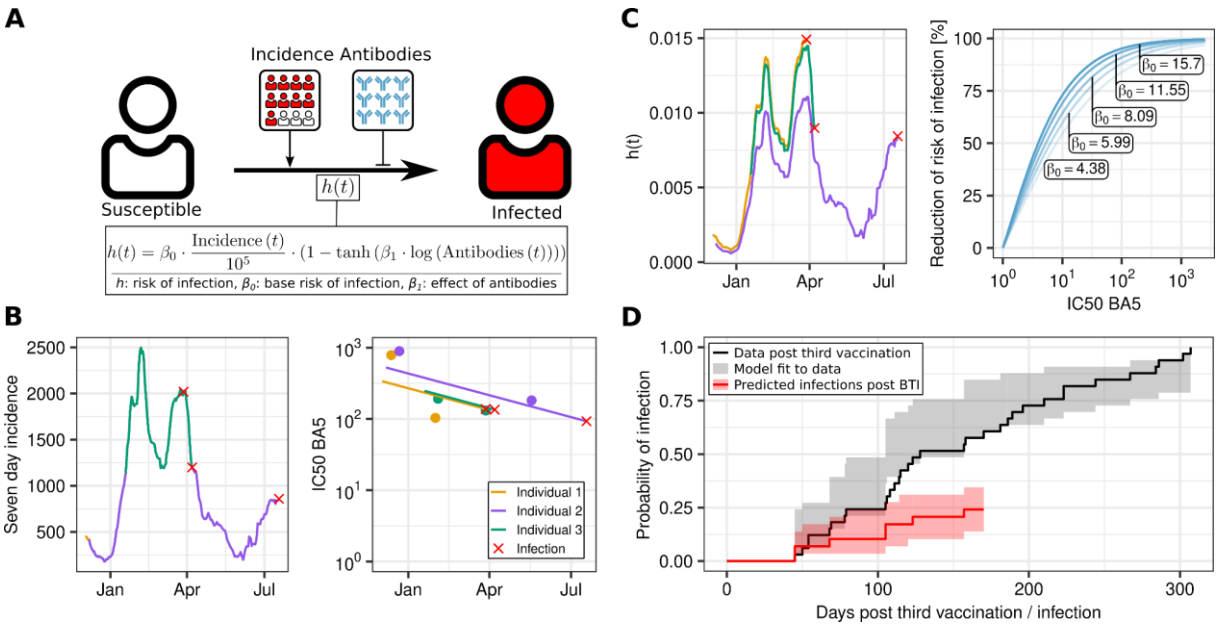

Figure 4. A schematic representation of the model with a susceptible person (S) that becomes infected (I) is shown in (A). This model shows the risk of infection (h(t)), which is dependent on the seven-day incidence per 100,000 inhabitants in Munich (Incidence(t)) and the neutralizing antibody titers (Antibodies(t)), where a high incidence increases the infection risk (h(t)) and vice versa for the antibodies. Different parameter values for the Omicron variant base infection risk β0 were obtained from literature [Dandekar et al., 2020; Volz et al., 2021; SAGE, 2021; Ito et al., 2022]. The effect of the antibodies is represented by β1 and was estimated from the data of this study. The current seven-day incidence in Munich (B, left panel) and IC50 neutralizing antibody titers (B, right panel) are shown for three individuals after their third vaccination until the time of infection. The antibody level is estimated from a linear mixed effects model. Furthermore, the hazard rate for the different individuals is shown in C (left panel) for β0 ≈ 11.55 and β1 ≈ 0.36. Different base infection risk parameters were utilized to present the reduction in the infection risk via the IC50 antibody neutralizing titers (C, right panel). In D we show the infections from this study (black) and results of a simulation study in which individuals become infected after their BTI. Given our estimate of β0 and β1 from C (left panel), seven-day incidence in Munich and measurements of antibody levels after BTI, samples were drawn from the estimated cumulative distribution function after BTI up to 180 days after infection (limit of reported incidence at time of writing).

1.5. Reduction of upper airway viral load upon reinfection with SARS-CoV-2

To estimate the effect of SARS-CoV-2-specific T cells on the upper airway viral load (UA-VL) during a hypothetical second infection with a completely neutralization resistant virus variant, we employed a linear mixed-effects model previously described by Eser et al. (2022). A schematic comparison of estimated viral load levels within 7 days after secondary infection between a patient with or without pre-existing memory SARS-CoV-2 nucleocapsid-specific CD4+ T cells is shown in Figure 5A. For individuals with BTI, we estimated the frequency of pre-existing nucleocapsid-specific T cells from measurements at the time point of second infection at 180 days after initial BTI (Figure 5B). Assuming that no expansion of pre-existing nucleocapsid-specific T cells occurred upon second infection (i.e., the fold expansion is equal to one), a reduction of UA-VL between 7.3% and 23.0% can be observed (Figure 5C). Highly variable expansion of pre-existing Influenza membrane- and nucleocapsid-specific T cells with an average of tenfold at day seven was observed during human Influenza challenge experiments [Wilkinson et al., 2012]. Using the previously described linear mixed-effects model

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and an estimated 10-fold expansion of nucleocapsid-specific CD4+ T cells, acute infection UA-VL could be reduced by 77.5% (53.0%-92.7%) on average compared to previously non-exposed individuals (Figure 5C). In summary, pre-existing nucleocapsid-specific CD4+ IFNɣ+ T cells induced by a first BTI are likely to associate with a multi-fold reduction of acute phase viral load upon a second re-infection compared to first infection.

1.6 Discussion

We investigated the evolution of SARS-CoV-2-specific antibody and T-cell responses in a longitudinal Bavarian cohort from early 2021 to December 2022, during vaccination and upon subsequent breakthrough infection. Peak Omicron BA.5 neutralization IC50 titers after the third vaccination correlated most strongly with transient protection from Omicron infection, while spike-specific CD4+ and CD8+ T-cell frequencies did not correlate with a reduced infection risk. 42% of vaccinated individuals with peak BA.5-IC50 values above 400 (and likely higher IC50s for BA.1/2) became infected within 120 days after the third vaccination in early 2022 [Cheng et al., 2022].

During the early phase 3 efficiency trials, even peak Wuhan-strain IC50 values above 100 associated with protective efficiency of above 90% [Maier et al., 2022; Petrone et al., 2023]. Lower protective IC50 in our study may be explained by the fact that phase 3 vaccine trial participants, at that time, encountered a more homologous-to-the-vaccine virus strain. In addition, extraordinarily high numbers of virus encounters during the Omicron BA.1/2 wave likely contributed to these infections in the presence of high neutralizing antibody titers. It should be noted that our mathematical model suggested that Omicron BA.5 IC50 titers above 400 reduces the infection risk by more than 90% against Omicron BA.5 infection, which is in the similar range as described for the phase 3 vaccine trials of the pre-Omicron era. One additional reason behind the difference in our results compared to the clinical trials could therefore be the high incidence in Bavaria in early 2022, which was multi-fold higher as compared to July 2020 to March 2021, when these trials were conducted [Baden et al., 2021; Falsey et al., 2021; Logunov et al., 2021; Polack et al., 2020; Sadoff et al., 2021]. Protection from SARS-CoV-2 Omicron infection in Bavaria early 2022 therefore likely required higher titers of neutralizing antibodies as compared to the pre-Omicron era. Some methodological variability such as different amounts of input virus used in the neutralization assay may also contribute to these differences in protective titers.

Breakthrough infection with Omicron further increased neutralization against the three tested variants significantly. Our mathematical model further confirmed that high neutralizing antibody titers after Omicron BTI contribute to protection from subsequent reinfection. Of note, the protection in our cohort was higher than predicted by our model considering only the antibody levels reached after a BTI, arguing for a protective role of cell-mediated immunity against reinfection. Even long after breakthrough infection, we observed broad memory T-cell recognition against the three tested virus antigens S, M and N, similar to what was observed in non-BTI Wuhan infection [Cantoni et al., 2022; Wyllie et al., 2021] and possibly contributing to the high level of protection observed in our cohort after BTI. Indeed, pre-existing T cell responses, in particular those targeting the N protein, have been associated with protection from SARS-CoV-2 infection [Jay et al., 2023; Kundu et al., 2022; Swadling et al., 2022]. Moreover, N-specific T-cell responses are also associated with control of SARS-CoV-2 in the

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upper airways and reduced systemic inflammation [Eser et al., 2022]. The effect of pre-existing T cells on virus control and early T cell expansion was studied after controlled Influenza challenge of human volunteers [Wilkinson et al., 2012]. Key results from the Eser and Wilkinson studies were therefore utilized to estimate the effect of pre-existing SARS-CoV-2-specific memory T cells on upper airway viral load upon a hypothetical reinfection with a neutralization resistant SARS-CoV-2 variant. If SARS-CoV-2 reinfection and the host T-cell expansion behave similarly to Influenza infection and the effect of T cells on virus clearance is similar to what was observed during primary infection, individuals with circulating SARS-CoV-2-specific T cells, in particular those targeting N, probably often control the neutralization resistant virus quite efficiently. This likely depends on the level of pre-existing virus-specific memory T cells and should reduce onward transmission and may even abort infection early [Swadling et al., 2022].

In conclusion, our results show that Omicron BTI induced a state of hybrid immunity that is characterized by higher cross-reactive, more persistent neutralizing antibody responses and broader SARS-CoV-2-specific T-cell responses. These characteristics aligned with a high level of protection from further reinfection, likely reflecting events on a population basis in Bavaria. It should be noted that Omicron waves occurred until October 2022 in the Bavarian population but waned thereafter despite the onset of the winter season. These data therefore suggest that BTI-induced hybrid immunity was an important contributor to the reduced virus transmission observed in the early winter of 2022.

2. Antiviral treatment strategies to prevent household transmission of acute respiratory viruses

One of the most important setting of disease transmission from acute respiratory viruses occurs within households. For example, the household attack rate was close to 40% for SARS-CoV-2 before the advent of the Omicron variant [Layan et al., 2022; Madewell et al., 2020; Jing et al., 2020]. In the Omicron era, household attack rates as high as 80% have been reported [López-Muñoz et al., 2022]. Studies on viruses such as Influenza and the Omicron variant of SARS-CoV-2 are known to have large variability in reporting the influence of household size, household composition and social habits that affect the fraction of members infected after the index infection. Finding correct preventative measures within households is key to stopping the proliferation of the respiratory virus within the larger community, and circumvent unsustainable economic or social practices, such as curfews or social distancing. This is achieved by reducing the spread of these respiratory viruses by reducing transmission chains within households.

One still underexplored intervention for the prevention of SARS-CoV-2 spread is the use of antiviral therapy such as monoclonal antibody therapy. These treatments can be highly effective, reducing the risk of severe disease by 70-90% when administered within the first week of symptom onset [Iwanami et al., 2021; Focosi et al., 2022]. The use of this strategy for the SARS-CoV-2 pandemic has so far been limited by supply and the intravenous nature of the treatment, but also from a lack of understanding of the optimal time period to apply the antiviral treatment. This intervention strategy greatly affects the virus transmission rate and the timing of treatment administration, and thereby affects the spread of disease within households especially. It is therefore necessary to identify the conditions required for a deployment of antivirals in households, and to quantify the expected effectiveness.

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The following report is based on the manuscript draft of the paper titled “Modelling the effectiveness of antiviral treatment strategies to prevent household transmission of acute respiratory viruses” by Hind Zaaraoui, Xavier Duval, Bruno Hoen, Lulla Opatowski and Jérémie Guedj. The analysis and modeling presented here was mostly performed by the ORCHESTRA partner INSERM.

We note that the results presented in the following are located at the interface of Tasks 8.1 and 8.5.

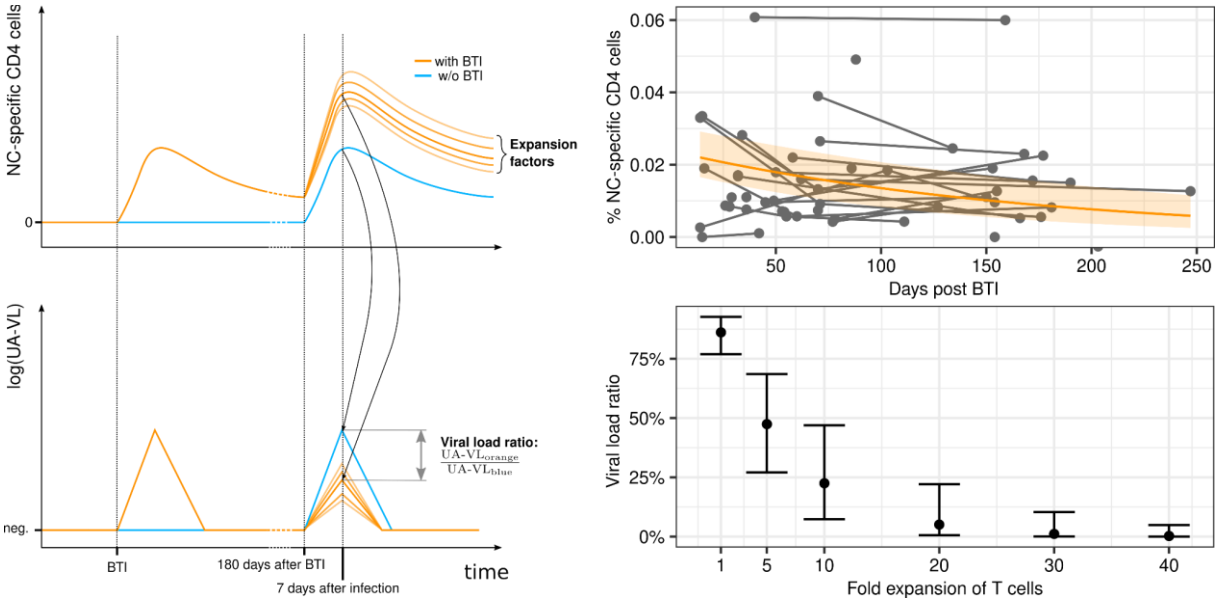

Figure 5. Possible reduction of upper airway viral load through pre-existing nucleocapsid-specific CD4+IFNɣ+ T cells. **A** shows theoretical trajectories of nucleocapsid-specific CD4+IFNɣ+ T cells and upper airway viral (UA-VL) load after breakthrough infection (BTI) and after an additional infection at 180 days after BTI. Orange curves show the trajectory of an individual who experienced a BTI, whereas blue curves show the trajectory of an individual who has not experienced the BTI and is infected for the first time at time point 180 days after BTI. Measurements of nucleocapsid CD4+IFNɣ+ T cells after BTI with a fitted exponential decay model are displayed in (**B**, red). The orange-shaded area represents the 95% confidence interval for the estimated fixed effect parameters. Using the level of nucleocapsid-specific CD4+IFNɣ+ T cells at 180 days after BTI and different cell expansion factors, we can estimate the approximate T cell level at 7 days after secondary infection and compare it to measurements from individuals without any previous infection. Then, a linear mixed-effects model from Eser et al. (2022) allows us to estimate the difference (displayed as a ratio) in viral load of individuals with and without pre-existing T cells (**C**).

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2.1. Summary

In order to clarify an optimal strategy in timing in administering antiviral treatment, we develop a multi-scale model integrating both the evolution of viral load within infected individuals and the risk of virus transmission within households. The model reproduces the kinetics observed with SARS-CoV-2, with a time to peak viral load that coincides with the incubation duration and is equal to 5 days on average, albeit with a large inter-subject variability. We find that the window for therapeutic administration depends on the time between the peak viral load and the duration of incubation period, and if we focus on households with pre-symptomatic indexes, antiviral interventions have a very high effectiveness in reducing both transmission and viral burden.

2.2. Viral Dynamic and Transmission Model

The viral dynamic model builds on previous Influenza and SARS-CoV-2 literature [Smith & Perelson, 2011; Néant et al. 2020; Baccam et al., 2006], characterizing the changes in viral load levels over time with treatment initiated at a given time which thereby reduces the production of virions. The model includes three types of cell populations: uninfected susceptible target cells (***T***), infected cells in an eclipse phase (I_1), and productively infected cells (I_2). A fraction μ of the viral particles was assumed to come from infectious virus V_I, and the remaining viral particles $(1-\mu)$ were assumed to come from noninfectious virus V_{NI}. Viral load at time ***t*** post infection, ***V(t)***, is measured in RNA copies and is the sum of infectious and non-infectious viral particles. When an individual is exposed to antivirals, the dynamics of viral particles is altered. Assuming treatment is initiated at time, we modeled drug action through a reduction of the production of viruses by infected cells, with an efficacy noted ϵ, beginning at a given time, t_x. The following set of nonlinear ordinary differential equations define the viral dynamic model:

$$
\begin{aligned}
dT/dt &= -\beta\, TV_1 \\
dI_1/dt &= \beta\, TV - k\, I_1 \\
dI_2/dt &= k\, I_1 - \delta I_2 - \phi \frac{F}{F+\theta} I_2 \\
dV_I/dt &= \mu(1-\epsilon I_{t\geq t_x}) p I_2 - cV_{NI} \\
dV_{NI}/dt &= (1-\mu)(1-\epsilon I_{t\geq t_x}) p I_2 - cV_{NI} \\
dF/dt &= I_2 - d_f F
\end{aligned}
$$

The transmission mechanism is defined by a Power-law model that is used to relate the non-linear relationship between the viral load ***V(t)*** to the risk of transmission to another individual, $p(t) = 1 - exp(-m\, V(t)^h)$. The strength between the viral load and the overall disease transmission is denoted by the dimensionless parameter, ***m***, whereas ***h*** specific the steepness of this relationship.

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2.3. Measuring impact of antiviral treatment

Outbreak severity can be measured as a function of infected individuals within a household, once all transmission chains have been exhausted. Transmission can occur to any other non-infected individuals in the household, and we assume that an individual can be infected only once during an outbreak (no reinfection). Figure 6A gives an illustrative example of a transmission chain for a household of size 6. The First Attack Rate, $FAR = (C-1)/(S-1)$ defined here as the proportion of infected individuals in a household after infection of the infected index. We define the Secondary Attack Rate, **SAR**, as the mean of the cumulative probability of transmission, $P(t) = 1 - \Pi(1 - p(u))$. Figure 6B displays the relationship between SAR and FAR percentage for varying household sizes. In households of size 2 or 3, the FAR increases linearly with SAR, consistent with the fact that most transmission events originate from the index case. However, in households of size greater than 4, the FAR increases in a non-linear fashion with SAR, reflecting the multiple chains of transmission that can exist in large households.

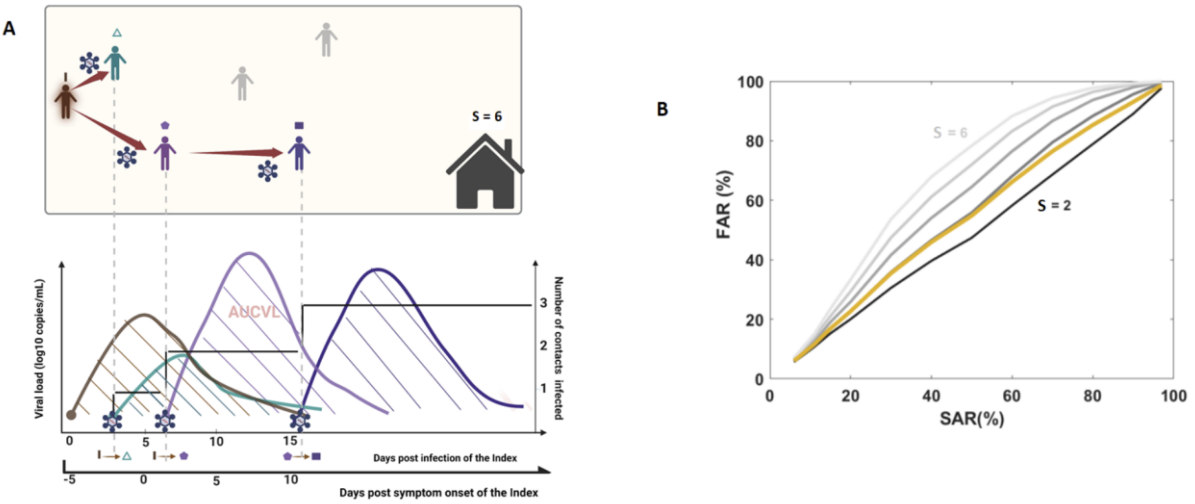

Figure 6. Transmission chains in households **A.** Top: Illustrative schematic of a transmission chain in a household; bottom: temporal profile of the virological burden. The dashed area represents the cumulative area under the curve of the viral load in the household. **B.** Model based prediction of the relationship between the Final Attack rate (FAR) and SAR, for household sizes ranging from 2 to 6. The yellow line represents the average FAR when sampling in the household size distribution in France.

2.4. Results

We studied the multi-scale model using numerical simulation. The model reproduces the kinetics observed with SARS-CoV-2, with a time to peak viral load that coincides with the incubation duration(5 days on average), albeit with a large inter-subject variability (Figure 7). In this context, initiating a treatment after symptom onset (i.e., after peak viral load) has only a minimal effect on viral dynamics and shedding. Conversely, initiating a treatment before symptom onset can have a dramatic effect on viral load, reducing the duration of viral shedding.

Figure 8 displays the impact of different intervention strategies across SAR percentages. Because most index cases are already in the clearance phase of the virus when treatment is initiated, the strategy of treating only the symptomatic index patient has only a minimal effect

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in both reducing the number of infected individuals and the virological burden, regardless of SAR and household size. A more aggressive strategy where all household members are treated upon diagnosis of the symptomatic index, regardless of their infection status, is more effective in this case. Although most transmission events originating from the index case have already occurred when index case initiates treatment, this strategy allows to initiate treatment early in contact individuals, thereby acting as a pre- or post-exposure prophylaxis, reducing both the risk of further transmission events and the virological burden in secondary infected individuals.

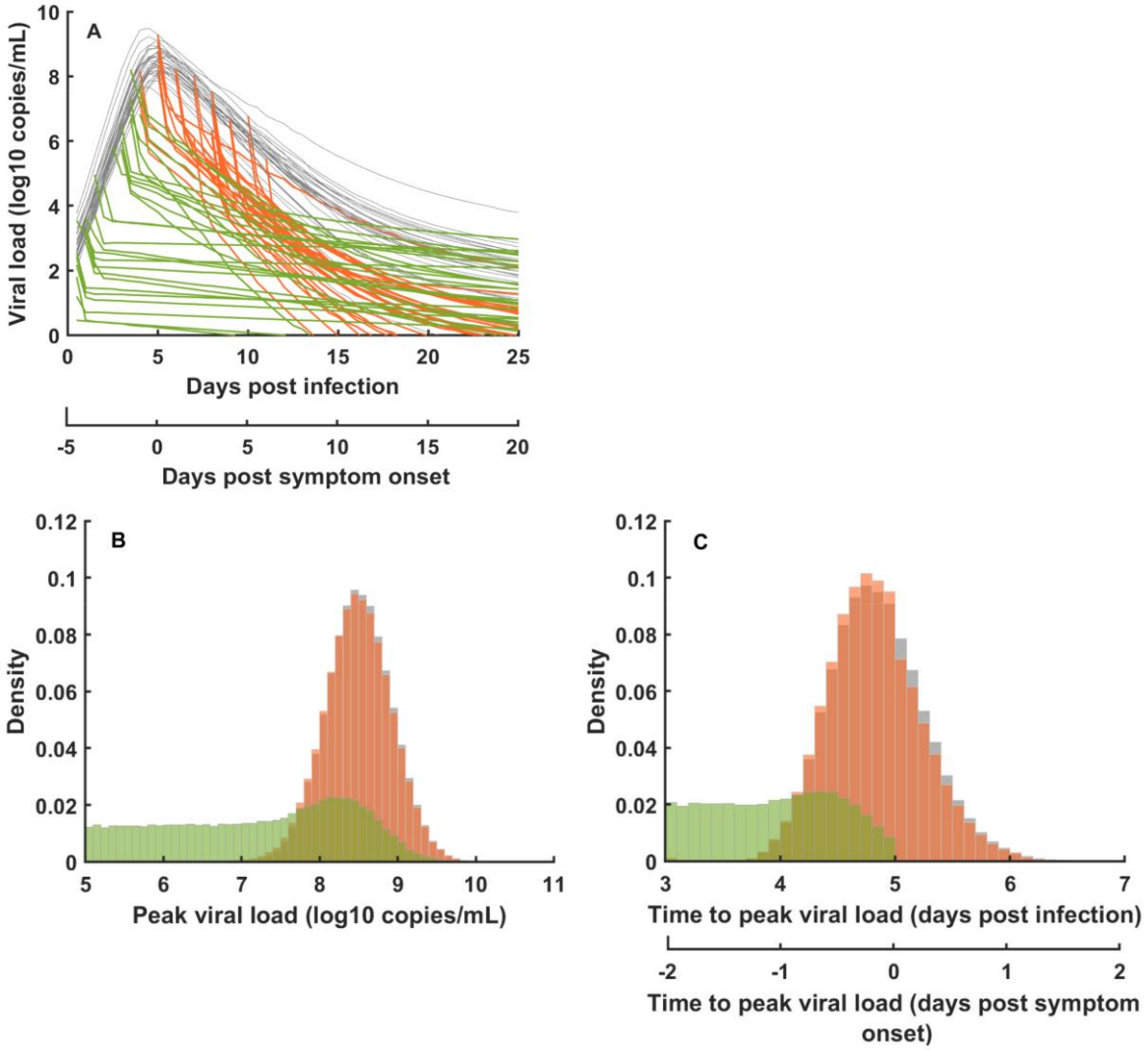

Figure 7. Viral dynamics and antiviral treatment. **A.** Individual viral dynamic profiles predicted by the model in 30 individuals that are either left untreated (grey), treated within 5 days after symptom onset (orange), or treated within 5 days after infection (green), and the model assumes that a mean incubation period of 5 days, and a mean treatment antiviral efficacy of 99%. **B.** Distribution of the peak viral load predicted by the model. **C.** Distribution of the time to peak viral load predicted by the model. The peak viral load occurs at day 5 post infection on average, and coincides with the onset of symptom. Post-exposure prophylaxis (green) can dramatically reduce both peak viral load and time to peak, in the other hand treatment initiation after symptom onset (orange) has not much effect on peak viral load.

Within Figure 9, an incubation period of 3 days is considered, with a varying time to peak viral load occurring at 1, 3, 5 and 7 days after infection. When the index case is already symptomatic

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and peak viral load occurs before or at symptom onset, the effectiveness on reducing transmission remains low in all cases considered. The effectiveness of treating the index case gradually increases with the time to peak viral load, with values ranging 25-50% when the peak viral load occurs 2 days after symptom onset and 50-75% when the peak viral load occurs 4 days after symptom onset. In all these scenarios, the effectiveness decreases with SAR and we observe a limited additional benefit of treating all household members.

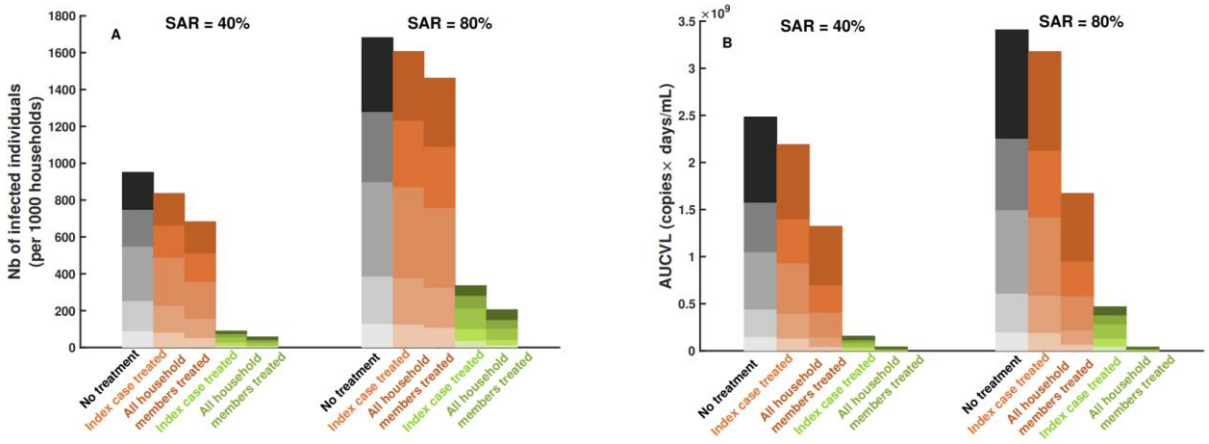

Figure 8. Impact of different treatment strategies on transmission and virological burden for SAR of 40% (left) and 80% (right). **A.** Number of infected individuals per 1000 households, assuming no treatment (black), treatment initiated when the index case is symptomatic (orange), or treatment initiated when the index case is pre-symptomatic (green). Results are broken down by household sizes, ranging from S=2 (darkest color) to S=6 (lightest color), and the distribution of household sizes is sampled from the distribution observed in the French population. **B.** Same results on the average of virological burden (mean AUCVL) over each household size.

2.5. Discussion

The evaluation of acute respiratory viruses is challenging because the risk of transmission is not constant and changes very rapidly over a short period of time, reflecting the dynamic evolution of viral replication. In this work, we developed a multi-scale modeling approach that follows viral dynamics at the individual level and relates it to the risk of transmission within households. In utilizing this model, we could predict the effectiveness of antiviral strategies according to key factors, in particular the virus Secondary Attack Rate (SAR), household size, incubation period, time to peak viral load, antiviral efficacy and timing of treatment initiation.

Our results suggest that in the typical conditions of SARS-CoV-2 pre-Omicron Variants, i.e., a peak viral load that coincides with symptom onset and occurs about five days after infection, treatment strategies targeting a symptomatic index case will be poorly effective at reducing both the number of secondary infections and the virological burden. In general, our results show that when the index case is symptomatic, there is a large benefit in treating all household members, regardless of their infection status. This strategy can achieve effectiveness greater than 50% on either the virological or the clinical endpoint when SAR is greater than 20% and peak viral load occurs two days or more after symptom onset, as observed for Influenza or SARS-CoV-2 Omicron variant. The effectiveness of strategies targeting individuals when they

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are exposed to contact cases, i.e., the index case is treated before symptom onset, is unambiguously better, with effectiveness larger than 50% in all cases considered. We find that the additional benefit of treating all household members is limited. Identifying and treating index cases before symptoms is challenging but not out of reach. Our results show that strategies targeting the index case are key to achieve a high effectiveness and could be utilized for public health measures to reduce the burden of disease, protect most at-risk individuals and accordingly reduce the duration of isolation of high risk contacts.

In conclusion, our model can be used to quantify and anticipate the clinical effectiveness of antiviral treatment strategies against acute respiratory viruses in households. It provides a novel understanding on the conditions that need to be met, at the pharmacological, virological and behavioral levels, for an antiviral treatment to be effective, and can guide interventions aiming to reduce disease burden during a viral pandemic.

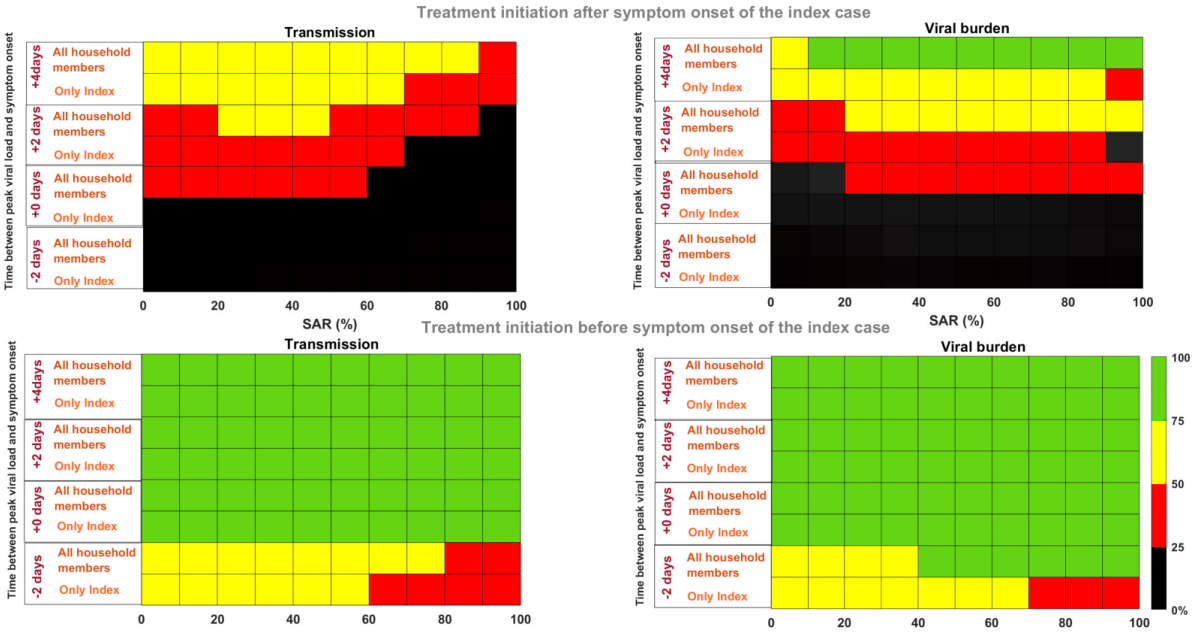

Figure 9. Effectiveness of antiviral treatment strategies according to the delay between symptom onset and time to peak viral load. Left: effectiveness on virus transmission; right: effectiveness on virological burden. Up: treatment initiated after symptom onset of the index case; bottom: treatment initiated before symptom onset of the index case. A positive value means that peak viral load appears on average after symptom onset, while a negative value means that peak viral load precedes on average symptom onset. “Only index” gives the relative effectiveness of treated the index vs no treatment, while “All household members” gives the relative effectiveness of treating all household members vs no treatment.

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