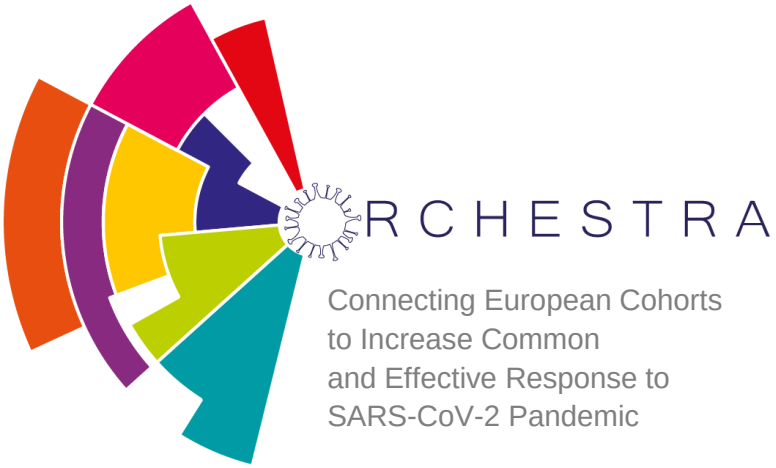

DELIVERABLE

WP8 Deliverable 8.6

Report on assessment of intra-host viral dynamics and immunity half-life

ORCHESTRA has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101016167

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0.1	01/10/2023	Hind Zaaraoui,Lulla Opatowski, Jérémie Guedj
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The document presents our results on intra-host dynamics and immunity. In part 1 we present how antibody dynamics is associated with different covariates; in part 2 we present how intra-host dynamics can be used to predict transmission and risk of severe disease in the context of nursing homes.

Part 1: Prediction of antibody response in COVID-19 vaccinated individuals using nonlinear mixed-effects modeling

An effective measure against infection is vaccination, which has been shown to provide strong protection against serious illness, hospitalization and death through production of anti-SARS-CoV-2 antibodies. However, the response to vaccination differs widely between individuals and effects of different covariates on the dynamics of the antibody response remain poorly understood. Moreover, predictions about waning antibody titers are vital for the prevention of viral spread and COVID-19-related deaths.

To this end, we employ two mathematical models of the antibody response in individuals that were vaccinated against COVID-19 [Clairon Q et al., 2023]. All reactions are expressed in a system of ordinary differential equations and the model is embedded in a nonlinear mixed-effects modeling framework to best capture the inter-individual heterogeneity. Most parameters of our model are unknown and need to be estimated from available data, which was obtained from partners in WP5 [Leomanni et al., 2023]. The data is used to calibrate our model, predict antibody responses after vaccination and analyze the effect of different covariates on the dynamics of the antibody response.

Thus, we provide a framework that can aid in furthering the mechanistic understanding of the antibody response following vaccination against SARS-CoV-2. Furthermore, it allows us to explain inter-individual heterogeneities that could lead to early waning of antibody titers and identify important factors influencing the immune response.

1.1 Neural posterior estimation for nonlinear mixed-effects models

The following section is based on a pre-print article by Arruda et al. [2023].

To facilitate scalable and flexible parameter estimation for NLME models, we developed and implemented an approach based on amortized machine learning. Established methods need a tractable likelihood and have high computational costs when the number of individuals is large. However, our machine learning approach allows inferring the parameters of nonlinear mixed-effects models with deterministic and stochastic mathematical models for a large number of individuals. Such models typically depend on unknown parameters ϕ such as reaction rates or initial concentrations, that need to be inferred from data. We assume that the underlying data generation process can be described via a mechanistic model $\mathcal{M}(\phi)$, incorporating dynamics, intrinsic sources of stochasticity, as well as measurement noise. In

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this work, individuals are modeled using ordinary differential equations (ODE). We consider a set of measurements for each individual *i*, for example, measurements of the antibody response in COVID-19 vaccinated individuals. To account for population heterogeneity, we assume that each individual can be described by an individual-specific set of parameters, which consist of fixed effects β shared across the population, and/or random effects *b(i)* specific to individuals. Taken together, this defines a non-linear mixed-effects (NLME) model, where the goal is to find the population parameters θ describing the fixed effects β and the distribution of the random effects *b(i)* in the population.

In this new machine learning approach, we employ neural posterior estimation to infer the population parameters from data, which occurs in three phases: (i) simulation using the mechanistic model $\mathcal{M}(\phi)$, (ii) training of an invertible neural network, and (iii) inference of the population parameters. In phase (i), samples are drawn from prior distributions of the parameters and simulated datasets are generated. Afterwards, the neural network is trained on a lower dimensional representation of the simulated data produced by a summary network that is simultaneously trained. After sufficiently long simulation and training phases with simulated data, we obtain a global approximation of the true posterior distribution from which we can efficiently draw samples conditioned on so far unseen data. In the amortized inference phase, we assume a population model and infer the population-level parameters θ using an approximation to the population likelihood.

1.2 Antibody response model

To describe the dynamics of the antibody response after vaccination against COVID-19, we employ an ordinary differential equation (ODE) model described in Clairon et al. [2023]. Shortly, injection of the vaccine V triggers the production of memory cells M at rate k_M. These can further differentiate to antibody secreting cells S at rate $k_S^{act}\ V$, which produce antibody Ab at rate k_{Ab}^{prod}. V, S, and Ab degrade at rates k_V^{deg}, k_S^{deg}, and k_{Ab}^{deg}:

$$dV/dt = -k_V^{deg} V$$

$$dM/dt = k_M V - k_S^{act} V M$$

$$dS/dt = k_S^{act} V M - k_S^{deg} S$$

$$dAb/dt = k_{Ab}^{prod} S - k_{Ab}^{deg} Ab$$

Since measuring only the antibodies leads to non-identifiability of the model [Clairon et al.], we derived a smaller identifiable model by rescaling the model for $\bar{S} = S/(k_S^{act} V_0 \bar{M}_1)$ and assuming that M can be replaced by its steady-state value $\bar{M}_k$ for the k-th vaccination. The model can then be formulated as

$$d\bar{S}/dt = f_{\bar{M}_k} exp(-k_V^{deg}(t - t_k)) - k_S^{deg} S$$

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$$dAb/dt = k_{Ab}^{prod} \bar{S} - k_{Ab}^{deg} Ab.$$

$f_{\bar{M}_k} = \bar{M}_k/\bar{M}_1$ is the fold-change for steady-state memory compartment after the k-th vaccination. In this work, we assumed all rate parameters to be unknown and estimated them using the available data by neural posterior estimation. The initial concentrations for $\bar{S}$ and Ab are 0, given that individuals were not infected before receiving a first vaccine dose.

1.3 Available data and model fit

Using the smaller model by Clairon et al. [2023], we fit the model to the available data using the amortized inference approach. In contrast to this model, we estimate all parameters and also allow for random effects on all parameters.

Figure 7 shows the obtained model fit and data for five representative individuals. In total, there were 822 individuals of which 51 were infected before being vaccinated and 12 became infected within the observation period. 77% of the study population was female and 23% male with a median age of 48 (IQR: 37-56). Any individual that became infected was excluded from further analysis. For each individual four measurements of the antibody response were taken and most measurement time-points fall between the second and third vaccination. Antibody levels after the third vaccination often lie at or above the upper limit of detection.

Given these data the model produced an appropriate fit to the data (Figure 7). The prediction interval shown here was produced by simulating the model with parameter sets sampled from the individual-specific posterior distributions. A time of larger uncertainty can be observed following the third vaccination, likely due to the limited amount of data and detection threshold. Furthermore, the neural posterior estimation already produced sufficiently good fits to the data, as can be seen when comparing the posterior median and empirical bayes estimate fits in Figure 7 and other fits not shown here.

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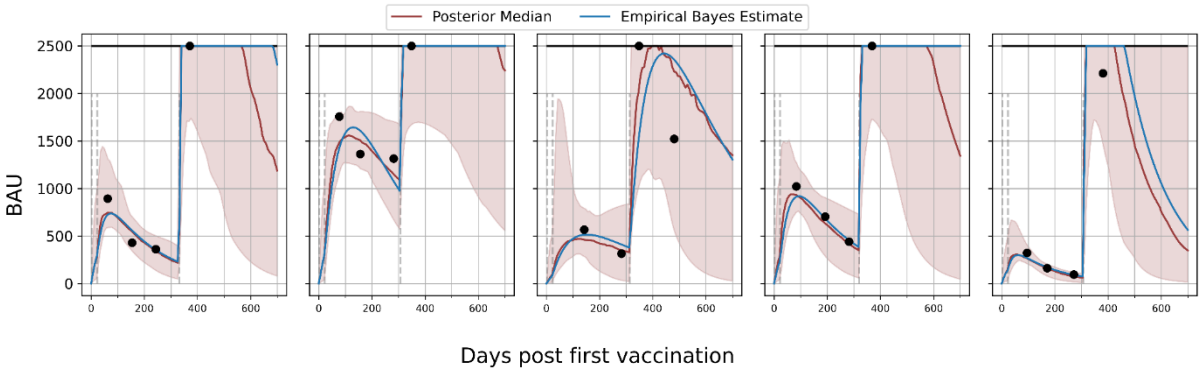

Figure 7. Exemplary model fit for five representative individuals. The red line and red shaded area indicate fits obtained solely using the neural posterior estimation method. The shaded area indicates the 95% credible interval. In addition, we estimated the optimal parameters for each individual given the population parameters obtained in the inference phase and displayed the optimal parameters in blue (Empirical Bayes Estimates). Solid black lines indicate the upper limit of detection and dashed grey lines indicate the time of vaccination.

1.4 Effects of covariates on the dynamics of the antibody response

Following the assessment of the model fit, we used the obtained Empirical Bayes Estimates to identify relationships between parameters and different covariates. In Figure 8, we display the optimal parameters for a subset of the entire study population in relation to different covariates. Given the trendline shown, we can observe minor increases of the parameters determining the steady state fold-change after second and third vaccination (f_{M_2} and f_{M_3}) with an increase in age. On the other hand, a negative relationship between age and the parameter determining the antibody production rate can be seen. Otherwise, we could identify strong relationships between the different covariates and parameters of the smaller model by Clairon et al. [2023].

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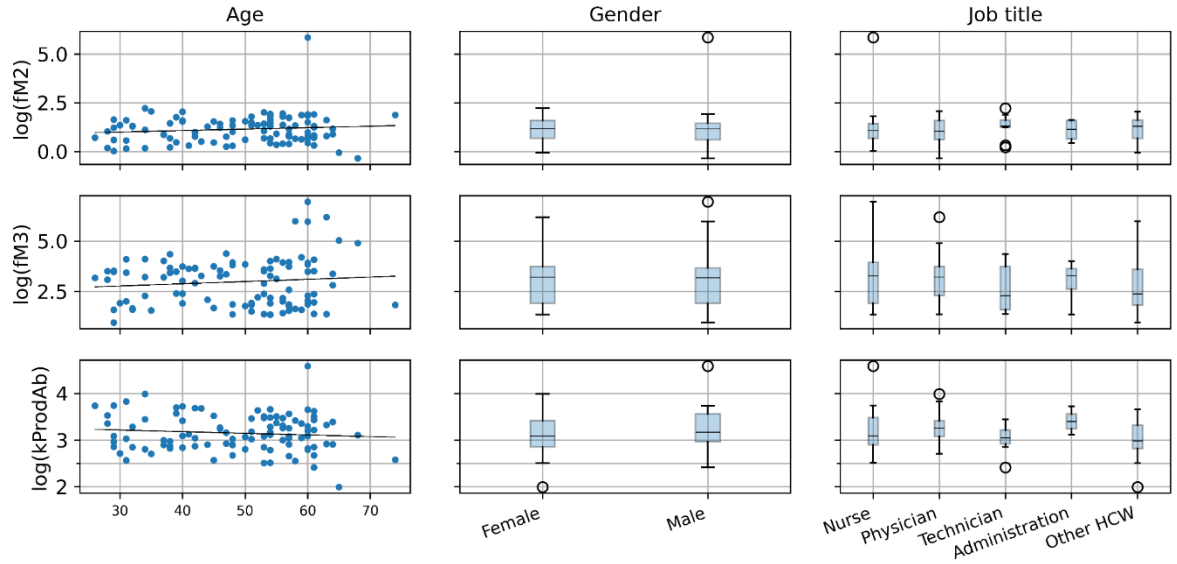

Figure 8. Relationship between parameters and covariates for 100 randomly drawn individuals and three parameters. The individuals were randomly drawn from the study population that did not experience an infection before being vaccinated. Parameter values are on log-scale. The solid black line in the age column shows a linear trendline.

1.5 Discussion

In this work, we aim to gain insights into the dynamics of the antibody response after vaccination against COVID-19. More specifically, we aim to identify key differences in the dynamics between individuals based on several features. Additionally, we want to showcase a novel method for parameter estimation in nonlinear mixed-effects modeling. As a basis for our analysis, we used an ODE model described by Clairon et al. [2023]. To describe inter-individual heterogeneity, we employ nonlinear mixed-effects modeling and use a novel approach introduced by Arruda et al. [2023] for parameter estimation.

The calibrated model could capture different dynamics of the individuals well and allowed us to observe relationships between covariates and the parameters of the model. These trends that were observed need to be further validated by incorporating them into the model and estimating their effect on the dynamics. Using the new parameter estimation approach, testing different covariate models can be done more efficiently compared to established methods like SAEM [Kuhn and Lavielle, 2005] or FOCEI [Wang, 2008]. As long as the underlying model does not change significantly, many different parameter-covariate relationships can be tested quickly with a comparatively low computational cost.

Furthermore, to describe more scenarios and obtain a more holistic view of the vaccination process, additional complexity should be incorporated into the model, such as individuals who have experienced an infection before becoming vaccinated. These individuals could be characterized by an already existing antibody secreting cell population, which translates into an initial value for S that is nonzero. This would also allow us to assess whether a pre-vaccine infection changes more than only the initial state of the system, but also affects dynamics

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through other parameters meaningfully. Additionally, until this point, we did not consider differences between vaccination compounds in the model or even infections that happen between two vaccination time points. The type of vaccination could play a major role in the dynamics.

This work can aid in furthering the mechanisms governing the dynamics of the antibody response against COVID-19 and could allow informed decisions for vaccination strategies. Additionally, it may provide a dynamic vaccination model for other diseases.

While vaccination is an effective strategy to protect from severe illness, some individuals may, for example, not respond to vaccination and therefore still be at risk. Other risk factors, such as advanced age, may also play a role, as the majority of severe COVID-19 cases occurred in elderly individuals. In this population, antiviral treatment is an important component to reduce the risk of infection and severe disease. In the following we present a novel model to predict the efficacy of antiviral treatment, in terms of reduction of infection and severe disease within nursing homes.

Part 2: Treatment strategies to avoid residents' isolation in nursing homes: modeling analysis

Nursing homes are at risk of being afflicted by epidemics of respiratory viruses such as COVID-19 [Smith et al., 2020, Smith et al., 2022]. In 2020, three out of four nursing homes had at least one resident infected by COVID-19, and 44% of deaths caused by COVID-19 are represented by nursing home residents. During the epidemic, in order to avoid virus transmission, nursing homes applied different aggressive isolation strategies, where symptomatic residents were isolated for long periods [Worcel et al., 2021] or all the residents were isolated when a symptomatic is detected [Bernadou et al., 2021]. However, these strategies had a high impact on physical and cognitive health for residents [Simard et al., 2020]

Antiviral treatments may reduce incidence (and therefore transmission), risk of having severe disease within nursing homes [Cohen et al., 2021] as a pre- or post-exposure prophylaxis, with the additional benefit of reducing the need of isolation. 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].

To understand the impact of antiviral treatment, a multiscale model that accounts for the effect of treatment at within host and between hosts scales, and also the individual contact behavior within nursing homes is required [Duval et al., 2018]

In order to clarify an optimal strategy to reduce residents' isolation, transmission and risk of severe disease in nursing homes by administering antiviral treatment, we developed a multi-scale model integrating the evolution of viral load within infected individuals, a function to

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compute to risk of severe disease or hospitalization and the risk of virus transmission that takes into account contact matrices within nursing homes.

2.1 Viral Dynamic, Risk of severe disease and Transmission models

In our previous work we have defined the viral dynamic model, and the transmission model within households as a function of the viral load (please see Deliverable 8.2). In this ongoing work we take similar models where we added the reduction immunity for the residents in the viral load dynamic, and a contact matrix in transmission to have a more realistic contacts behavior between individuals:

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 infected viral cells. 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:

$$dT/dt = -\beta\, TV_1$$
$$dI_1/dt = \beta\, TV - k\, I_1$$
$$dI_2/dt = k\, I_1 - \delta I_2 - \phi \frac{F}{F+\theta} I_2$$
$$dV_I/dt = \mu(1 - \epsilon I_{t\geq t_x})pI_2 - cV_{NI}$$
$$dV_{NI}/dt = (1-\mu)(1 - \epsilon I_{t\geq t_x})pI_2 - cV_{NI}$$
$$dF/dt = I_2 - d_f F$$

As for residents we need to include the age and other risk factors that impact the viral clearance time, we suppose a 40% drop in immune system for residents, which is equivalent to reducing the viral load parameter $\phi\ to\ \phi \times 0.6$ for only the residents which is equivalent to approximately 10 days delay of viral clearance time compared to the staff.

The risk of severe disease is computed with the exponential survival model which is a function of the viral load and of the individual characteristic (staff or resident) to take into account the age and comorbidities effect of older individuals that are the residents:

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$$S_j(t) = e^{-\int_0^t \ h_j(\psi_j)du}$$

With $h_j(\psi_j) = \lambda e^{\gamma \times 1_{resident} + \nu \times (V_j(u))}$. The median risk of severe disease of symptomatic patients is fixed to 25% and hence $\lambda, \gamma \ and \ \nu$ are calibrated to this purpose.

The transmission mechanism for a risky punctual contact of 5 minutes, 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, $\boldsymbol{p(t) = 1 - exp(-m\ V(t)^h)}$. 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.

To take into account the contact behavior within nursing home in the transmission, we compute the probability that individual i infects j, upon a contact ending at time t, including the duration of the contact $C_{i,j}(t)$ [Duval et al., 2018] (saturated after 30 min of one contact) as following:

$$P_{i,j}(t) = 1 - \prod_{u=1}^{C_{i,j}(t)} (1 - p_i(u))$$

2.2 Measuring impact of antiviral treatment

Outbreak severity can be measured by a function of infected residents within a nursing home, once all transmission chains have been exhausted, by the average risk of severe disease and by the average isolation duration within nursing homes. Transmission can occur to any other non-infected individuals in the nursing home if there is contact, and we assume that an individual can be infected only once during an outbreak (no reinfection).

The impact of the treatment on the instantaneous transmission probability is shown in Figure 2.1.A: if the treatment is initiated before symptoms (if an individual is a contact case) the transmission probability is highly impacted (green curves) compared to the transmission probability for the treated symptomatic individuals (orange curves). The attack rate computed as the proportion of the residents infected within nursing homes is the transmission endpoint. The risk of severe disease is averaged over all the infected patients using $S_j(t)$. In Figure 2.1.B we show the impact of the treatment in case of pre and post-symptom onset.It can be observed that treatment after symptom onset enhances the survival to 80% compared to not treating, while treating before symptom onset increases the treatment effect to 90% for avoiding severe disease. Finally, we suppose that if residents or staff are isolated, each individual is isolated 10 days after symptom onset.

Different intervention strategies are studied in this work (Figure 2):

1) No intervention: there is no isolation and no treatment within nursing home
2) Only symptomatic individuals are isolated: when a symptomatic individual is detected, the resident is isolated 0 to 3 days after symptom onset,

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3) Only symptomatic individuals are isolated and treated: when a symptomatic individual is detected, the resident is isolated and treated 0 to 3 days after symptom onset,
4) Contacts treated if positive: when a symptomatic individual is detected, they are treated and isolated 0 to 3 days after symptom onset and their 5 days contacts with positive test (PCR or Antigen test (Ang)) are treated.
5) All contacts are treated: when a symptomatic individual is detected, they are treated and isolated 0 to 3 days after symptom onset and all their 5 days contacts are treated whether they are infected or not
6) All residents are isolated: when a symptomatic individual is detected, all the residents are isolated. Isolation ends 10 days after the last symptomatic case detection.

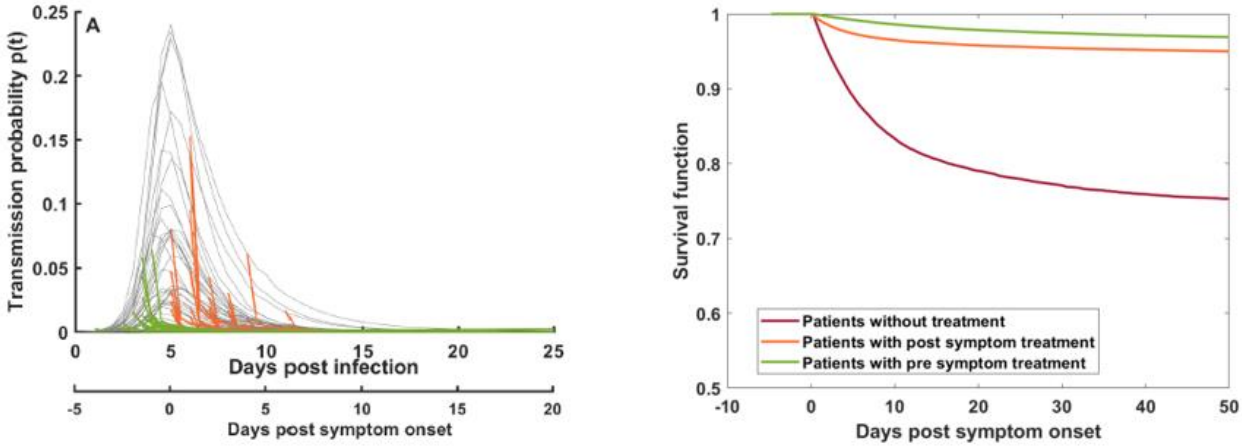

Figure 2.1. Treatment impact on transmission and risk of severe disease **A.** Top: Instantaneous transmission probability for 30 individuals without treatment (gray), in the case of treatment before symptom onset (green) and after symptom onset (orange). **B.** Avoiding severe disease function in time for residents in case of no treatment (red), treated before symptom (green) and treated after symptom (orange).

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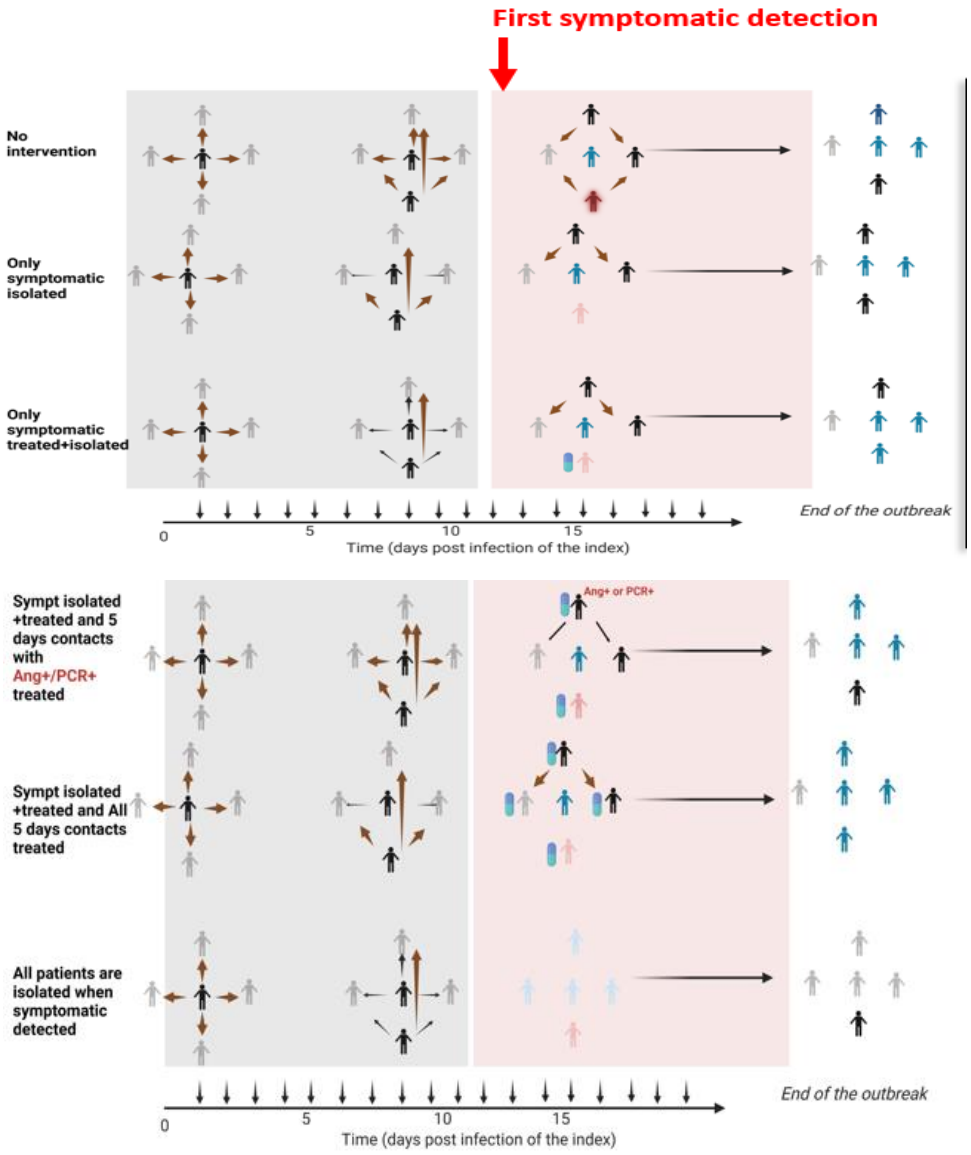

Figure 2.2. Different type of intervention in nursing homes from top to bottom: 1/ No intervention, 2/ Only symptomatic are isolated, 3/ Only symptomatic are treated and isolated 0 to 3, 4/ Treating symptomatic and isolated + treating their contacts with PCR positive or Ang positive, 5/ Treating symptomatic and isolated + treating all their contacts, 6/ all residents are isolated.

2.3 Results

We studied the multi-scale model using numerical simulation. This revealed that 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 (Figure 2.3). In this context, initiating a treatment after symptom onset,

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hence after peak viral load in general, has only a minimal effect on viral dynamics and shedding. Conversely, initiating a treatment before symptom onset, which is in general the case of individual contact cases, can have a dramatic effect on viral load, reducing peak viral load and the duration of viral shedding.

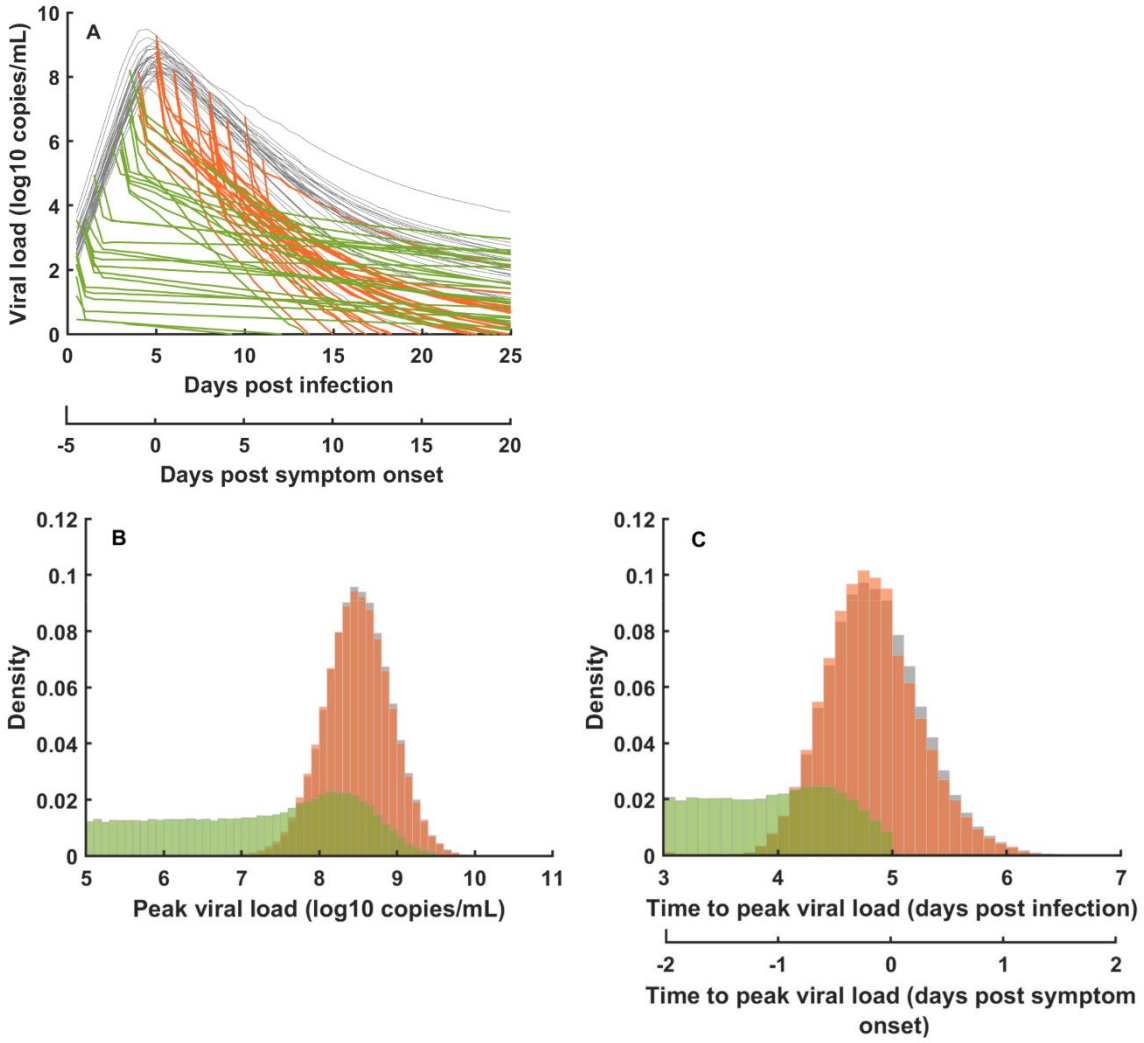

Figure 2.3. Viral dynamics and antiviral treatment. **A.** Individual viral dynamic profiles predicted by the model in 30 individuals that are either left untreated (grey), treated within 5 days after symptom onset (orange), or treated within 5 days after infection (green), and the model assumes that 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.

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We simulate 1000 nursing homes of size 200 of which 100 are residents and 100 are staff. The initial R0 is fixed to a value of 4 independent of the intervention strategy. We assumed that 50% of all nursing home residents and staff remain asymptomatic throughout the course of the infection.

Figure 2.4 depicts the attack rates in residents considering different intervention strategies displayed in Figure 2.2. With an R0 fixed to a value of 4, the equivalent attack rate in the nursing home for the residents is 39%. When only the symptomatic are isolated, this attack rate is not highly impacted (intervention effectiveness =11% compared to no intervention) as most of transmission has already occurred before the time of symptom onset. Similar results can be observed for the strategy of treating symptomatic individuals as in our study we have supposed that for all intervention strategies, we isolated all the symptomatic cases independent of whether they were treated or not. So, the treatment does not have any effect on the transmission for this strategy. However, treating symptomatic cases impacts the average risk of severe disease within nursing homes as observed in Figure 5. The intervention effectiveness on risk of severe disease including the symptomatic treatment is approximately 48% compared to 11% if no treatment has been allocated.

Considering more aggressive intervention strategies where also the 5 days contacts of the symptomatic are treated, three testing strategies are studied: Ang test (Antigen test), PCR test, no test where even not infected are treated in prophylaxis.

As the PCR test is more sensitive than the antigen test, we can detect infected individuals contacts earlier (before their viral peak time) than for Ang test which induces a treatment effectiveness on transmission of 66% compared to 52% for Ang testing strategy. Treatment effectiveness on risk of severe disease for both these strategies are respectively 76% and 90% (Figure 5). The average risk of severe disease is highly impacted as the treatment not only reduces the risk of hospitalization of the infected individuals but also avoids new infections and hence new individuals having risk of severe disease.

Treating all the contacts, whether they are infected or not, increases treatment effectiveness on transmission to 75% (Figure 4) as some of these individuals are treated prophylactically, which improves the effectiveness on risk of hospitalization to 94% (Figure 5). An effectiveness on transmission of 85% can be achieved for the strategy of isolating all the residents as soon as symptomatic cases are detected. However, this latter strategy induces a high impact on residents' isolation (Figure 6): an average of 37 days of isolation over the 1000 nursing homes of is computed compared to less than 1 to 3 days for any other intervention strategy, with minimal isolation duration for the strategies where contacts are treated (less than 1 day), which leads to an effectiveness of 95% on isolation duration relative to total isolation.

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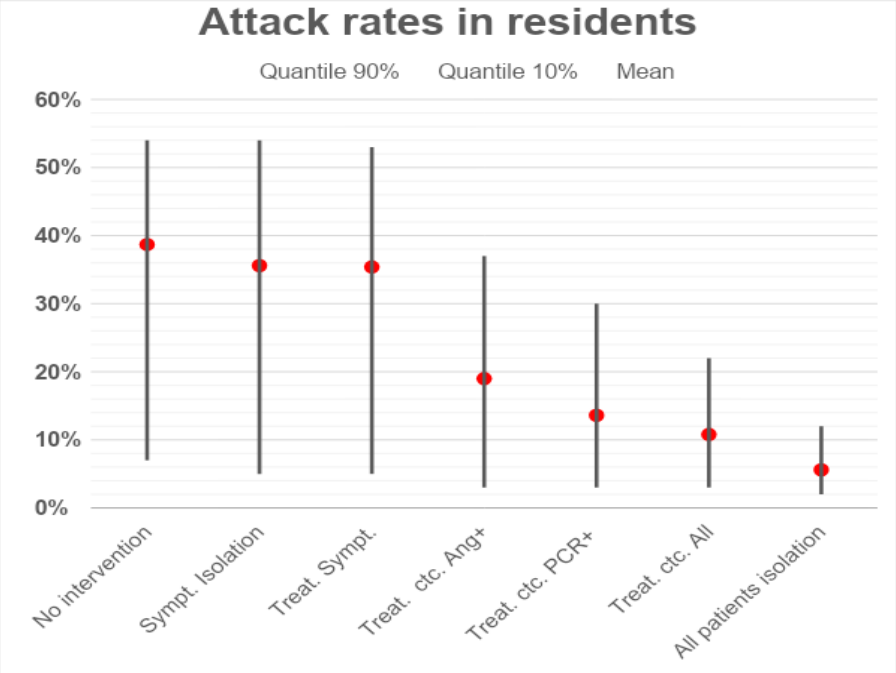

Figure 2.4. Impact of different intervention strategies on the transmission: attack rates in residents

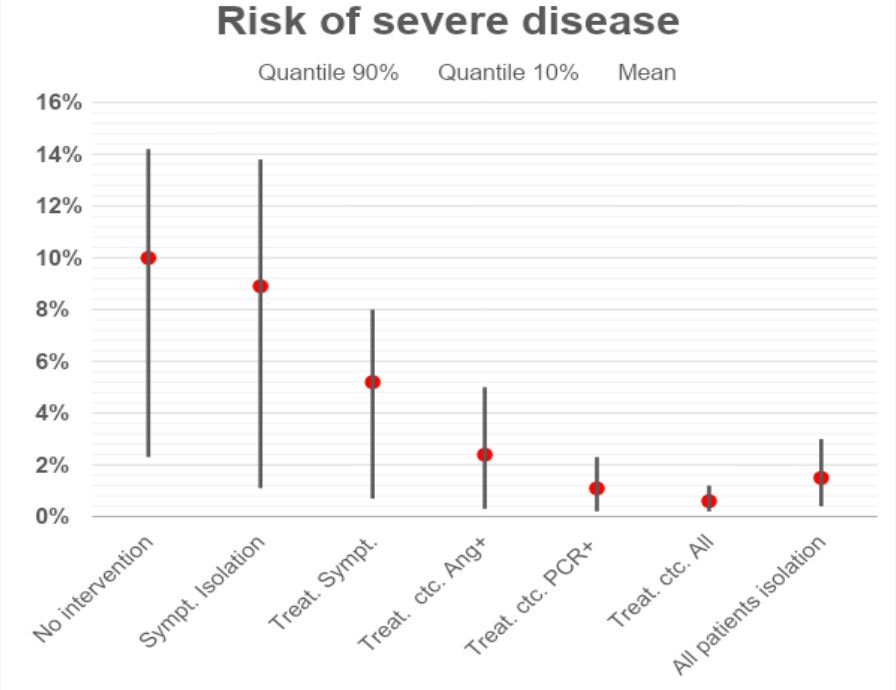

Figure 2.5. Impact of different intervention strategies on risk of severe disease in residents

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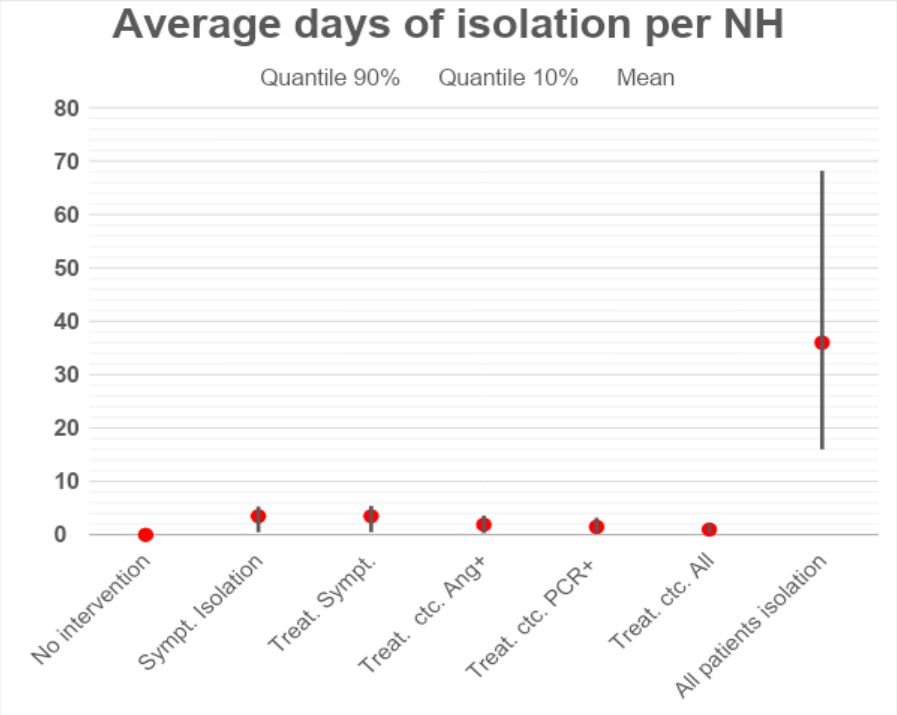

Figure 2.6. Impact of different intervention strategies on isolation duration average

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2.4 Discussion

High transmission rates of acute respiratory viruses are a major issue in nursing homes as the risk of severe disease and death are much higher than that of the general population. This has led to drastic isolation interventions of nursing home inhabitants. In our previous work, we have developed a multi-scale modeling approach that follows viral dynamics at the individual level and relates it to the risk of transmission within nursing homes. In this work we have integrated a more realistic contact behavior between individuals in the transmission model, and a survival model to describe the risk of having a severe disease taking into account the viral load dynamic. In utilizing these models, we could predict the effectiveness of antiviral strategies according to key factors, in particular the virus contagiousness level (R0 value), the nursing homes size (number of residents and staff), contact behavior modification…

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 transmission but may lead to an effectiveness on risk of severe disease of approximately 50%. In general, our results show that when symptomatic cases are detected, there is a large benefit in treating all their contacts, regardless of their infection status. This strategy can achieve effectiveness of 75% on transmission and 94% on risk of severe disease. We also find that the effectiveness on transmission and risk of severe disease for the strategy of treating all the symptomatic contacts positive to PCR or Ang show high efficacy that are quite similar to treating all the contacts without testing. All the results with PCR and Ang are almost equivalent to the strategy of all the contacts being treated, even the not infected individuals. Isolating all the residents as soon as symptomatic individuals are detected could be an appropriate intervention strategy both to prevent transmission and risk of severe disease. However, it may negatively impact physical and cognitive health of the residents. Treating symptomatic and their PCR positive contacts could be a reasonable strategy to reduce 95% of average isolation duration relative to all patients' isolation strategy.

In conclusion, our model can be used to quantify and anticipate the clinical effectiveness of antiviral treatment strategies against acute respiratory viruses in nursing homes. It provides a novel understanding on the conditions that need to be met, at the pharmacological, virological and behavioral level and can guide interventions aiming to reduce disease burden during a viral pandemic and avoid drastic interventions such as long-term isolation of residents.

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