RCHESTRA

Connecting European Cohorts
to Increase Common
and Effective Response to
SARS- CoV-2 Pandemic

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In silico model of vaccination strategies

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

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Executive summary

Vaccines have proven to be one of the most powerful tools in fighting pandemics. When, however, vaccine supply cannot suffice to meet its demand, efficient measures against the pandemic require policymakers to allocate available vaccine doses according to appropriate distribution schemes. The requirements on these schemes are manifold. On the individual level, conditions due to old age and frequent on-the-job exposure contribute to the risk of becoming infected. On a geographical scale, mutated variants with varying rates of infectiousness and vaccine resistances pose increased threats to certain regions. The mutated variants are transmitted by travelers to other regions so that policymakers must take travel dynamics into account to come up with efficient distribution schemes. Could it be beneficial under certain conditions to forego vaccine doses such that they can be used by adjacent areas or is it always beneficial to keep vaccines within the country?

This deliverable provides a simulation analysis of a multi-country model investigating the effects of optimized vaccine-allocation schemes using different types of vaccines with varying efficacies within one model. To understand the influence of the distribution of different virus mutants on optimal strategies, varying initial virus distributions are considered. Furthermore, the deliverable provides a description of the established modeling pipeline and the results of its application to a two-country model based on COVID-19 parameters.

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Core content

Vaccinations are used worldwide to slow down the spread of SARS-CoV-2 and lower hospitalization numbers. The European Union has mainly allocated vaccines according to a population-size-based allocation scheme. However, this allocation scheme does not account for the distribution of variants with different infectiousness nor for the type of vaccine used.

To address this issue, we conducted simulations showing that an optimized vaccination strategy can improve over the population-based vaccination strategy. In particular, we show that Pareto improvements can be achieved, meaning that every country experiences fewer deaths as with the population-size-based strategy.

1. Description of the established model-based analysis pipeline

In the first two months, we focused on building the compartment model and established a reusable simulation and optimization pipeline. The pipeline minimizes the total number of deaths, potentially with additional Pareto constraints. In sections 1.1 and 1.2 the different components of the pipeline are described, while in section 1.3 we report the results of the application to a two-country model based on COVID-19 parameters.

1.1. Formulation of the mathematical model

We developed a compartmental model of SARS-CoV2 transmission within and between countries using a system of ordinary differential equations (ODEs). The rough structure of the model is illustrated in Figure 1.

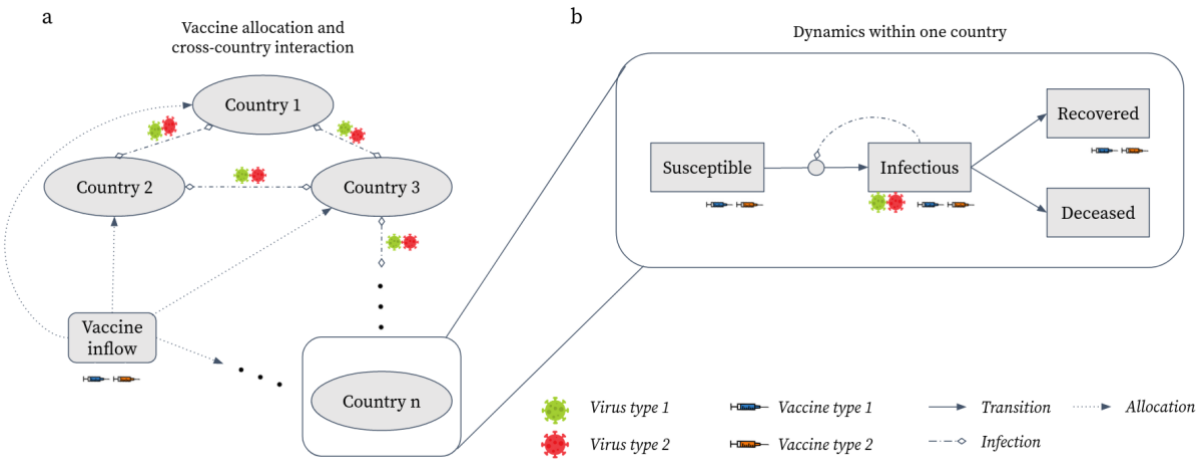

Figure 1: (a) In-between country interactions and (b) SARS-CoV-2 infection stages

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To model the vaccination process, each compartment that is eligible for vaccination (Susceptible, Infectious, and Recovered) is duplicated by the number of distinct vaccines explored within the model. Policymakers can influence the transition rate by adjusting for all vaccine types the vaccine doses allocated to a country. The transmission rates within a country depend on the fraction of vaccinated individuals and the strength of non-pharmaceutical interventions (NPI. Country specific and time-varying NPI parameters control for non-pharmaceutical interventions influencing optimal vaccine allocations. The transmission rate between compartments of two countries is controlled by a parameter encoding the frequency of encounters between individuals from different countries.

In addition, we use parameters from the literature to exogenously specify all vaccine, virus, and country-related parameters, see Figure 2.

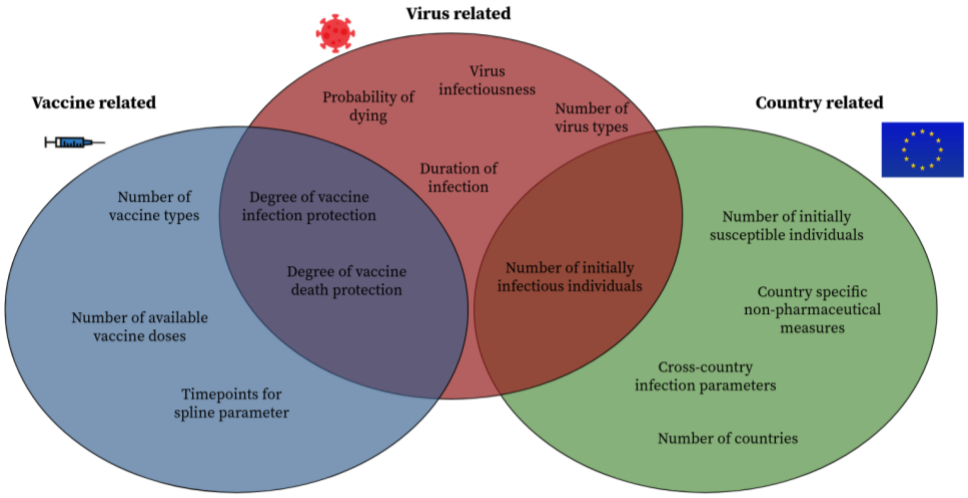

Figure 2: Exogenous model parameters

1.2. Computational modeling pipeline

We established a reusable computation pipeline to automate model building, simulation, and optimization. This will facilitate the continuous update with new model parameters throughout the duration of ORCHESTRA.

The compartment model is encoded in the Systems Biology Markup language (SBML) (Bornstein et al., 2008), a widely used standard in the systems biology community. This standard facilitates the reproduction of the results in various different tools and adds to the reusability. The processed model is simulated within Python 3.8 using the module AMICI (Fröhlich et al., 2021) interfacing with the Sundials solver CVODES (Hindmarsh et al., 2021).

The policymaker's minimization problem is formally an optimal control problem with all possible vaccine allocation pathways as controls. Solving this problem would require optimizing over the function space of all functions that take time as input and the fractions assigned to each country as output. Since this is computationally infeasible, we postulate a functional form of the vaccination pathways, as standard in computationally optimal control. Our choices are logistically transformed splines converting the optimization task to a nonlinear minimization problem which we can solve using standard numerical methods.

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The numerical minimization problem of finding the best vaccine allocation is solved using optimizers from the Python Parameter Estimation Toolbox (pyPESTO) and estimagic (Gabler, 2001). We use the multi-objective optimization package pymoo (Blank et al., 2020). This tool offers the possibility to compute the Pareto front showing the trade-off of deaths between countries induced by different vaccine allocations.

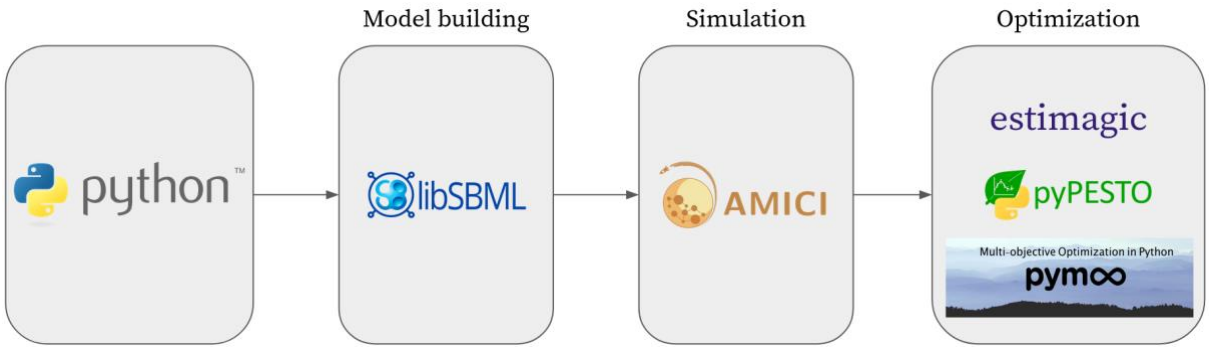

Figure 3: Computational modeling pipeline

1.3. Results for the computational modeling pipeline

For a first application of the pipeline, we consider a two-country model with initially equal-sized populations which are fully unvaccinated at the beginning of the simulation. We incorporate two virus types: A wild type serving as a baseline variant and a mutant virus. The mutant is roughly twice as infectious. Cross immunity is perfect and no immune escape is assumed. Susceptible and infectious individuals are eligible to become vaccinated with one of two available vaccines. Vaccinations initially start at the beginning of the simulation and the vaccine doses inflow is constant over time with 30,000 doses per week for both vaccines. The splines used to parameterize the vaccine allocation pathways are defined on a uniform grid with a spacing of two weeks. We consider an unequal initial virus distribution across countries. Country A is initially exposed to ten wild-type-infected individuals, whereas country B is initially exposed to ten mutant-infected individuals. The two vaccine types have asymmetric efficacies against the two virus types. This can be exploited by policymakers to reduce the number of deaths. Vaccine 1 is around 34% more efficient than vaccine two in preventing an infection with the wild type. Vice versa, vaccine 2 is roughly 34% more efficient in preventing an infection with the mutant virus.

A graphic representation is used to present our preliminary results. As can be seen in Figure 3, both optimized strategies (unconstrained and Pareto-optimal) yield a reduction in the total number of deaths. However, if the unrestricted optimal strategy is applied country B would be worse off than with the population-size-based strategy and thus unlikely to agree to that strategy given knowledge of the model. As shown in Figure 4, policymakers have to decide on a trade-off between deaths in country A and deaths in country B and the space of possible solutions for the Pareto optimal strategy is restricted to the intersection of the set of all Paretom improvements and the Pareto front. Figure 5 depicts that optimized vaccination strategies differ highly from the population-size-based allocation.

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In the future, we will extend the analysis to a multi-country framework studying optimal vaccine allocations during the COVID-19 pandemic.

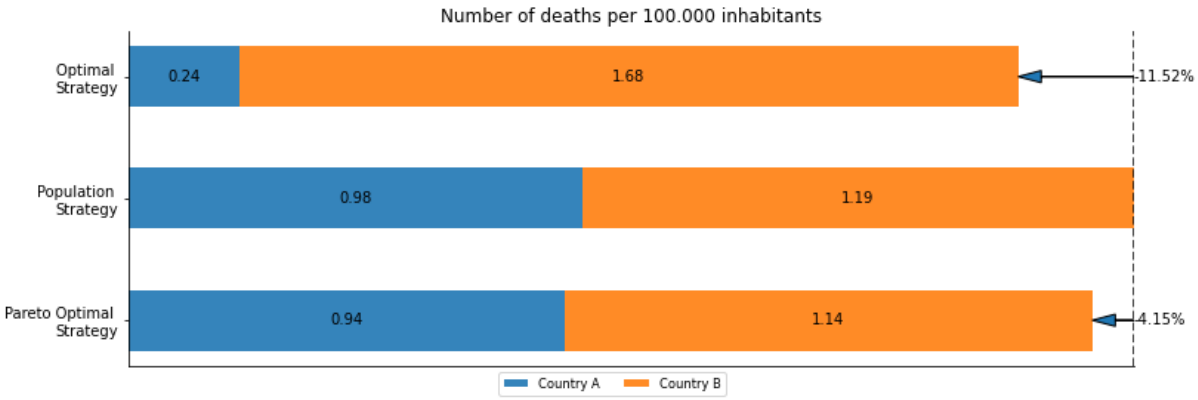

Figure 3: Number of deaths according to strategy and country

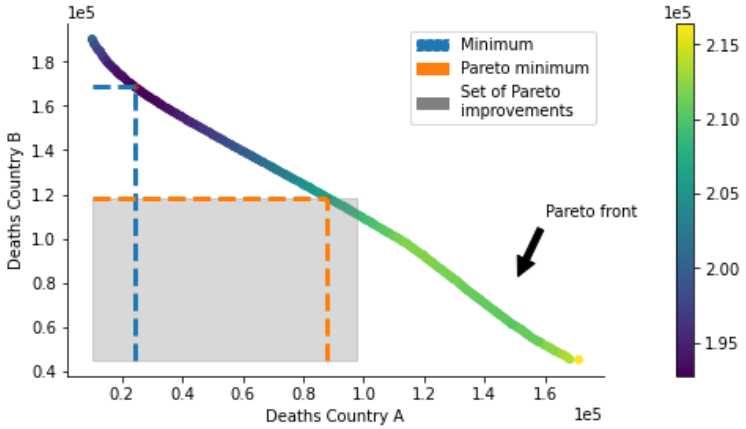

Figure 4: Pareto front and set of Pareto improvements

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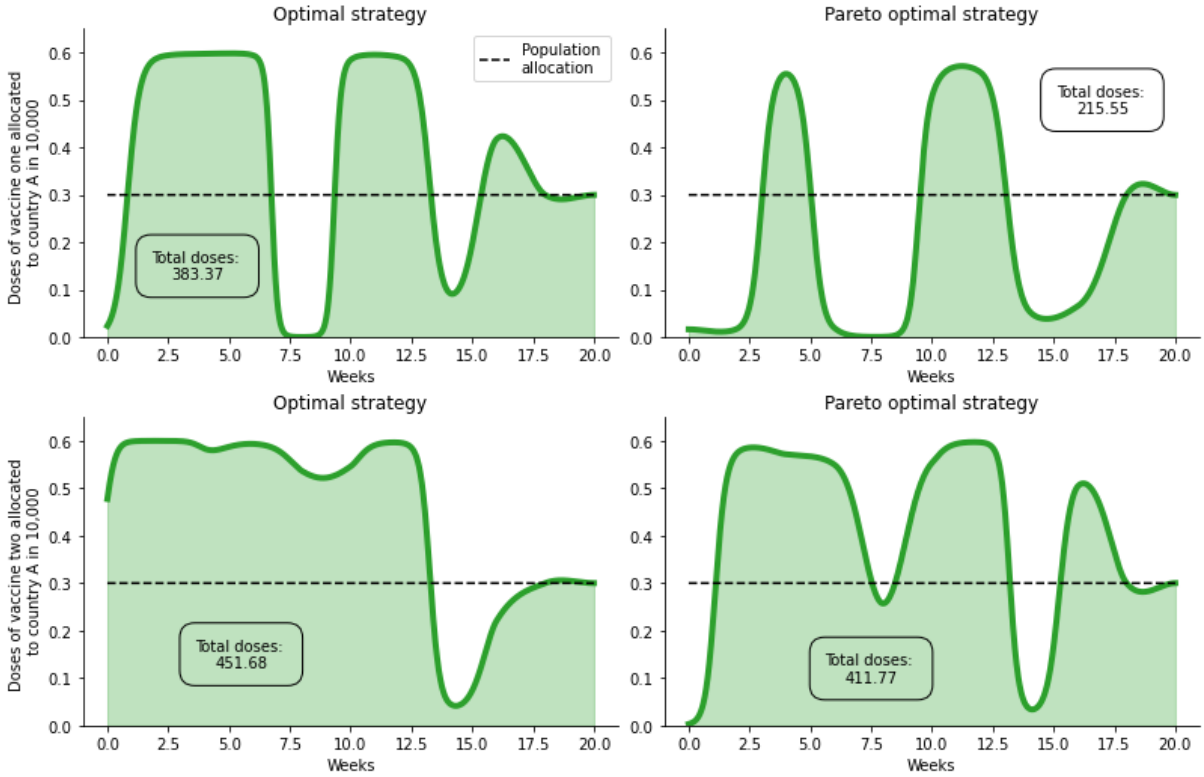

Figure 5: Vaccination pathways dependent on strategy

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