A structural epidemiological model for the optimal allocation of vaccines across countries

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Abstract

Description

Keywords: ...

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1 Introduction

... describe general SIR model, say that for biologists to remark compartmenst are different to biological compartments, thesis serves for both: epidemiologists inetrested in vaccine distribution but also for economcists or social scientists interested in compartment modleing

How it's currently done:

countries can decide to not take vaccine -> would be in our case assignment of zero vaccines

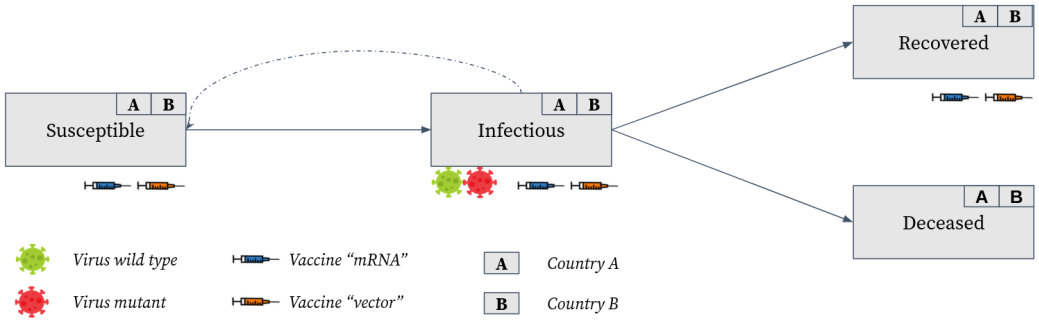
general model description: how do we deal with vaccines (most important), vaccination during infection, no vaccination during infection see here (US Center for Disease Control), no reinfections, no births and other deaths

The aim of a Stochastic Simulation algorithm (SSA) is to provide a computational model that allows for stochastic reactions. They can be classified as exact and approximate SSAs. Exact algorithms, like the Gillespie-Algorithm (Gillespie, 1977), do not group reactions together but model them one after another. Approximate algorithms, like $\tau-leaping$ (Gillespie, 2001), group reactions together and update the propensities within a larger interval τ. Thus, approximate algorithms might have an advantage when it comes to speed. However, by updating the propensities less often, we lose some accuracy.

2 Deterministic model

We subdivide the classic SIRD compartments, Susceptible (S), Infectious (I), Recovered (R) and Deceased (D), with sub-compartments allowing for heterogeneous areas of residence and vaccination states as well as infections by different virus types.

Figure 1 illustrates the general model. Individuals either live in country A or country B. They are non-vaccinated v_0, vaccinated with vaccine one v_1 or vaccinated with vaccine two v_2. We introduce two virus types. A wild type W that serves as baseline variant and a more infectious mutant variant M. To describe our model we denote every sub-group of individuals by a set $\mathcal{C}_t(F_n)$, where F_n is a placeholder for features that the individuals (elements) within the set $\mathcal{C}_t$ share and t denotes the time at which the set is evaluated. We illustrate the features F_n in the following with examples. Let X_i for $i \in \{S, I, R, D\}$ indicate to which general compartment an individual belongs, then, $\mathcal{C}_t(X_S)$ is the set of all susceptible individuals and $\mathcal{C}_t(X_I)$ is the set of all infectious individuals at t. If we want to distinguish not only between general compartments but additionally between countries of residence, we use the feature C_j for $j \in \{A, B\}$ to indicate that the country of residence is j. $\mathcal{C}_t(X_S, C_A)$ is the set of all susceptible individuals of country A and $\mathcal{C}_t(X_S, C_B)$ of



Note: Solid lines indicate transition paths and dashed lines indicate infections. Shots below a compartment indicate that individuals from this compartment are vaccinated. Viruses below a compartment indicate that this compartment is infectious. Each compartment is subdivided according to country of residence and vaccination status.

Figure 1: Model structure

country B. Note that the ordinary set operators apply, allowing us to us linkages such as $\mathcal{C}_t(X_S, C_A) \cup \mathcal{C}_t(X_S, C_B) = \mathcal{C}_t(x_S)$ or $\mathcal{C}_t(X_S) \cap \mathcal{C}_t(X_I) = \emptyset$. The negation operator $\neg$ is used to indicate that a certain feature applies for all but the specified compartment, e.g. $\mathcal{C}_t(\neg X_D)$ is the set of all alive individuals. The cardinality $|\cdot|$ represents the respective number of individuals in a set, e.g. $|\mathcal{C}_t(X_S)|$ equals the number of all susceptible individuals. To shorthand notation, we define $y_t(F_n) = |\mathcal{C}_t(F_n)|$ as the number of individuals within the set $\mathcal{C}_t(F_n)$.

By definition $\mathcal{C}_t() = \cup_{i \in \{S,I,R,D\}} \mathcal{C}_t(X_i)$ is the set of all individuals. An overview of all features is given in Table 1.

Table 1: Notation

Feature	Code	Indices	Explanaition
General compartment	X_i	$i \in \{S, I, R, D\}$	Individuals can either be Susceptible (S), Infectious (I), Recovered (R) or Deceasesd (D).
Country of residence	C_j	$j \in \{A, B\}$	Individuals can either live in country A or B. We exclude cross-border movements.
Virus Type	V_k	$k \in \{W, M\}$	An infection can either be caused by the wild type (W) or the mutant (M) virus. This feature has to be understood, depending on X_i, as *is* or *has been* infected with type k.
Vaccine Type	U_l	$l \in \{0, 1, 2\}$	An individual can either be vaccinated with vaccine 1 or 2 or being unvaccinated (U_0).
Placeholder	F_n	$n \in \mathbb{N}$	A placeholder that is used to address an arbitrary combination of features. $\mathcal{C}_t(F_n)$ should be read as the set of a fixed but arbitrary compartment. If we need to distinguish between two arbitrary compartments, we use F_1 and F_2.

We impose a set of assumptions to the compartments to rule out undesired cases within the model

Assumption 1. *For all* $t, r \in \mathbb{R}_+$, $k \in \{W, M\}$ *and* $s \in [-t, \infty)$ *let*

$$\mathcal{C}_t(X_I, V_k) \cap \mathcal{C}_{t+r}(X_S) = \emptyset \tag{1.1}$$

$$\mathcal{C}_t(U_1) \cap \mathcal{C}_{t+s}(U_2) = \emptyset \tag{1.2}$$

$$\mathcal{C}_t(C_A) \cap \mathcal{C}_{t+s}(C_B) = \emptyset \tag{1.3}$$

$$\mathcal{C}_t(X_S, V_k) = \emptyset. \tag{1.4}$$

Assumption 1.1 rules out reinfections such that an individual that has been infected once cannot become reinfected after it had recovered. According to Roy (2020), there is evidence that recovered individuals cannot become reinfected but reinfections cannot be ruled out fully. However, the number of reinfected individuals might be negligible and we therefore do not incorporate reinfections to keep our model parsimonious. Assumption 1.2 implies that an individual only receives one type of vaccine. Receiving one vaccination shot in our model implies that an individual is fully protected according to the vaccine properties making it unrealistic to assign a second shot to the same individual. Assumption 1.3 rules out permanent cross-country movements of individuals. This is of course unrealistic. However, permanent movements should not be a main driver of the pandemic and we therefore refrain from incorporating it to keep our model parsimonious. We incorporate cross-border infections by assigning a fraction of meetings to be a cross-border meeting. Assumption 1.4 rules out that susceptible individuals can be infected. We do so to ensure that an individual can only be infected with one virus type.

2.1 System of ordinary differential equations

Since we use a compartment SIRD model based on a system of ordinary differential equations (ODEs) and to make this thesis self-contained, we review how the dynamics of a chemical reaction network are modeled over time. We can limit ourselves to the case of irreversible reactions since recovered and deceased individuals cannot become infectious again and infectious individuals become recovered but not susceptible. Let $\mathcal{C}_t(F_1), \ldots, \mathcal{C}_t(F_n)$ be n pairwise disjoint sets. Every irreversible reaction R_j, for $j = 1, \ldots, m$, can be expressed as

$$\nu_{1j} y_t(F_1) + \ldots + \nu_{nj} y_t(F_n) \longrightarrow \mu_{1j} y_t(F_1) + \ldots + \mu_{nj} y_t(F_n), \tag{1}$$

where $\nu_{ij} \in \mathbb{N}_0$ and $\mu_{ij} \in \mathbb{N}_0$ are called stoichiometric coefficients. ν_{ij} describes how much of species $\mathcal{C}_t(F_i)$ is consumed and μ_{ij} how much is produced within reaction R_j. The difference $\mu_{ij} - \nu_{ij}$ is the total change of $y_t(F_i)$ due to one reaction R_j.

In terms of our model we are not only interested in how one reaction (e.g. an infection, a vaccination, etc.) influences the state of the system but rather how often this happens within

an interval $[t, t+\tau]$, for $\tau \in \mathbb{R}_+$. For $\tau = 1$ the latter is described according to the law of mass action by

$$v_j = r_j \prod_{i=1}^{n} y_t(F_i)^{\mu_{ij}}, \tag{2}$$

where r_j is a reaction specific constant. The product is the number of combinations to assign individuals from different compartments, that have $\mu_{ij} \neq 0$, together. The change in the magnitude of $y_t(F_i)$, taking into account all m reactions, is given by

$$y_{t+\tau}(F_i) - y_t(F_i) = \sum_{j=1}^{m} (\mu_{ij} - \nu_{ij}) v_j \tau. \tag{3}$$

$(\mu_{ij} - \nu_{ij})$ is, as outlined above, the stoichiometry that specifies how one reaction influences the system, $v_j\tau$ is the number of times reaction R_j happens within the interval $[t, t+\tau]$, and therefore the product is the influence of R_j on $y_t(F_i)$ during this interval. Summed over all reactions yields the change of $y_t(F_i)$ within the system. We divide both sides of (3) by τ, let $\tau \to 0$ and plug in (2) to obtain the ordinary differential equation (ODE)

$$\dot{y}_t(F_i) = \sum_{j=1}^{m} \left[(\mu_{ij} - \nu_{ij}) r_j \prod_{i=1}^{n} y_t(F_i)^{\mu_{ij}} \right]. \tag{4}$$

We write down the equations for all compartments in matrix form to obtain a system of ODEs, which we use in subsequent chapters to ease notation.

$$\underbrace{\begin{pmatrix} \dot{y}_t(F_1) \\ \vdots \\ \dot{y}_t(F_n) \end{pmatrix}}_{Y(t)} = \underbrace{\begin{pmatrix} \mu_{11} - \nu_{11} & \dots & \mu_{1m} - \nu_{1m} \\ \vdots & \vdots & \vdots \\ \mu_{n1} - \nu_{n1} & \dots & \mu_{nm} - \nu_{nm} \end{pmatrix}}_{\mathbf{S}} \cdot \underbrace{\begin{pmatrix} v_1 \\ \vdots \\ v_m \end{pmatrix}}_{v} \tag{5}$$

Note that (5) is a linear mapping in v for which we can compute the kernel $\mathcal{K} = \{v \in \mathbb{R}^m | \mathbf{S} \cdot v = 0 \in \mathbb{R}^n\}$. Each element of the kernel represents a state where $Y(t) = 0$ and therefore the system is in a steady- state. If the pandemic reaches a state such that $v \in \mathcal{K}$, we would be stuck there. The trivial steady state is the state where all compartments are equal to zero $v = 0$. **write how the null space looks like in our model**

Since our model consists of over 100 reactions, we do not write down the ODE system explicitly. However, it can be constructed as stated within this section.

2.2 Reactions

We divide the reactions in three groups: (1) Infections, (2) Recoveries and Deaths and (3) Vaccinations. We group recoveries and deaths together, since their reactions have the same structure. For each reaction group, we first state the general reactions, defining the reactants, products and stoichiometric coefficients, subsequently specify the reaction constant, and state the reactions explicitly.

2.2.1 Infections

Every infection happens between an infectious individual $i_1 \in \mathcal{C}_t(x_I)$ and a susceptible individual $i_2 \in \mathcal{C}_t(x_S)$ and leads to two infectious individuals. Hence, the general form of the infection reactions is

$$y_t(x_I, F_1) + y_t(x_S, F_2) \longrightarrow y_t(X_I, F_1) + y_t(X_I, F_2), \tag{6}$$

where we use F_1, F_2 to indicate that the reactions differ with respect to not explicitly mentioned features, e.g. vaccinated individuals have a lower risk of becoming infected or transmitting the virus, the mutant virus is more infectious, and cross-border infections are scaled by a factor to make them comparatively rare events. The additional features represented by F_1 and F_2 are incorporated within the infection constants

$$\text{infection constant} = \text{contacts} \times \text{infectiousness} \times \text{vaccine modifier}$$

In the following we elaborate on how to define each component of the infection constants.

Infectiousness. Let $c \in R_+$ be the average number of contacts per individual and day and $\alpha \in [0, 1]$ be the proportion of susceptible individuals that become infected if they meet a wild type infected individual without any vaccination of both individuals. Let $\eta \in (1, 1/\alpha]$ be the factor with which the mutant is more infectious than the wild type. Then $\beta = \alpha c$ is the average number of individuals infected per day by i_1 if $i_1 \in \mathcal{C}_t(X_I, V_w, U_0)$. If $i_1 \in \mathcal{C}_t(X_I, V_M, U_0)$ the average infected number increases to $\eta\beta$.

Vaccine modifier. To account for the influence of vaccines on vaccinated susceptible individuals, we introduce the parameters $\delta_{k,l} \in [0, 1]$, where $k \in \{W, M\}$ indicates the virus type and $l \in \{1, 2\}$ the vaccine type. If $i_2 \in \mathcal{C}_t(X_S, U_l)$ for all individuals that $i_1 \in \mathcal{C}_t(X_I, V_k)$ meets, the average number of infected individuals is $1 - \delta_{k,l}$ times lower. Thus, the reaction constant in the respective reaction is multiplied by the factor. $\delta_{k,l}$ is interpreted as reduce in the probability of becoming infected while meeting an infectious individual.

Even while being infected, vaccinated individuals have a lower probability of trans-

mitting the virus (Harris et al., 2021). We account for this by introducing the parameter $\gamma \in [0,1]$ and multiplying the average number of infected individuals by $(1-\gamma)$ if $i_1 \in \mathcal{C}_t(X_I, U_1) \cup \mathcal{C}_t(X_I, U_2)$. γ is the reduction in the probability of not transmitting the virus after being vaccinated which we assume to be constant over time and across vaccines.

Contacts. We want to distinguish between how many of the average contacts per day c are within individuals from the same country and how many are within individuals from another country. We do so by defining probabilities that given a meeting occurs, it is with an individual from another country and multiply c with the respective probability to obtain the average number individuals infected by one individual in a certain country. We use the relative population number of a country as baseline probability and add a penalty term for cross-border meetings.

In the following we establish how we specify all meeting constants defining probabilities. We first define the (time dependent) probability that a randomly drawn living individual i_2 lives in country B

$$\mathbb{P}_t\left(i_2 \in \mathcal{C}_t(\neg X_D, C_B)\right) = y_t(\neg X_D, C_B)/y_t(\neg x_D). \tag{7}$$

Note that the probability depends on the state of the whole system $Y(t)$. To increase readability we omit conditioning on $Y(t)$ and directly define $\mathbb{P}_t$ to be conditioned on the state of the system $Y(t)$. Second, we define the conditional probability that given i_1 is from country A, i_2 is from country B by adding a multiplicative penalty term $b(\cdot)$ to reduce the probability of meeting individuals from other countries

$$\mathbb{P}_t(i_2 \in \mathcal{C}_t(\neg X_D, C_B) | i_1 \in \mathcal{C}_t(\neg X_D, C_A)) = \mathbb{P}_t\left(i_2 \in \mathcal{C}_t(\neg X_D, C_B)\right) \cdot b(d(A,B)), \tag{8}$$

where $d(A,B)$ is a distance between country A and country B and $b : \mathbb{R}_+ \to [0,1]$ is a function that maps the distance to the penalty value. By mapping the distance into the unit interval, we allow the probability of a cross-border meeting to be maximal as high as the relative population size. The distance can be interpreted as geographical distance but it could also serve to incorporate other factors, like favored holiday destinations, that encourage or discourage cross-border meetings. We impose three conditions on the function b

$$\lim_{b \to \infty} = 0 \tag{B.1}$$

$$b(0) = 1 \tag{B.2}$$

$$b(d_1) < b(d_2) \quad \text{if } d_1 > d_2. \tag{B.3}$$

Condition $(B.1)$ ensures that countries that a very large distance only have small influences onto each other, $(B.2)$ defines a rather theoretical case where cross-border meetings are as likely as within-country meetings, and $(B.3)$ ensures that countries that have a greater distance have a smaller influence onto each other. We define all possible conditional meeting probabilities depending on the countries of residence analogously. To increase readability when we define the reaction constants explicitly below, we collect them in a matrix $\mathbf{M} \in \mathbb{R}^{2\times 2}$, such that we can address them via m_{j_1,j_2} for $j_1, j_2 \in \{A, B\}$

$$\begin{aligned}\mathbf{M} &= \begin{pmatrix} m_{A,A} & m_{A,B} \\ m_{B,A} & m_{B,B} \end{pmatrix} \\ &= \begin{pmatrix} \mathbb{P}(i_1 \in \mathcal{C}_t(\neg X_D, C_A) | i_1 \in \mathcal{C}_t(\neg X_D, C_A)) & \mathbb{P}(i_1 \in \mathcal{C}_t(\neg X_D, C_A) | i_2 \in \mathcal{C}_t(\neg X_D, C_B)) \\ \mathbb{P}(i_2 \in \mathcal{C}_t(\neg X_D, C_B) | i_1 \in \mathcal{C}_t(\neg X_D, C_A)) & \mathbb{P}(i_2 \in \mathcal{C}_t(\neg X_D, C_B) | i_2 \in \mathcal{C}_t(\neg X_D, C_B)) \end{pmatrix} \\ &= \begin{pmatrix} 1 - y_t(\neg X_D, C_B)/y_t(\neg X_D) & y_t(\neg X_D, C_A)/y_t(\neg X_D) \\ y_t(\neg X_D, C_B)/y_t(\neg X_D) & 1 - y_t(\neg X_D, c_A)/y_t(\neg X_D) \end{pmatrix} \cdot b\left(\mathrm{d}(a_1, a_2)\right). \end{aligned} \tag{9}$$

We show subsequently how we define the average number of contacts for concrete F_1 and F_2 from (6). We set $i_2 \in \mathcal{C}_t(X_S, C_B, U_0)$ and $i_1 \in \mathcal{C}_t(X_I, V_W, C_A, U_0)$. We are interested in the conditional probability $\mathbb{P}_t(i_2 \in \mathcal{C}_t(X_S, X_B, U_0) | i_1 \in \mathcal{C}_t(X_I, V_W, C_A, u_0))$. This to say, the probability that the individual that can be infected (i_2) is susceptible, unvaccinated and from area two given that individual i_1 is infected with the wild type, unvaccinated and from area one. We facilitate our model and assume that the vaccination status as well as the type of virus infection of individual i_1 are independent of the features of i_2. Assuming independence of the vaccination status implies that an unvaccinated individual i_1 does not change her contact habits, given a certain number of meetings, compared to her counterfactual vaccinated self. Note that this does not mean that we assume that vaccinated and unvaccinated individuals have the same average number of contacts since the probabilities are defined on *conditioned a meeting occurs*. Differences in the average number of contacts between vaccinated and unvaccinated individuals can be incorporated implicitly via the vaccination parameter $\delta_{k,l}$.

Furthermore, we assume that the probability is dependend on whether an individual is alive but not on the exact general compartment S, I or R. Making use of these assumptions, we can omit conditioning on V_w and U_0 and change X_I to $\neg X_D$ such that the exercise facilitates to defining $\mathbb{P}_t(i_2 \in \mathcal{C}_t(X_S, C_B, U_0) | i_1 \in \mathcal{C}_t(\neg X_D, C_A))$. Using Bayes' formula we

can rewrite this as

$$\begin{aligned}\mathbb{P}_t(i_2 \in \mathcal{C}_t(X_S, C_B, U_0) | i_1 \in \mathcal{C}_t(\neg X_D, C_A)) &= \mathbb{P}_t(i_2 \in \mathcal{C}_t(\neg X_D, C_B) | i_1 \in \mathcal{C}_t(\neg X_D, C_A)) \\ &\quad \cdot \mathbb{P}_t(i_2 \in \mathcal{C}_t(X_S, U_0) | i_1 \in \mathcal{C}_t(\neg X_D, C_A), i_2 \in \mathcal{C}_t(\neg X_D, C_B)) \\ &= \mathbb{P}_t(i_2 \in \mathcal{C}_t(\neg X_D, C_B) | i_1 \in \mathcal{C}_t(\neg X_D, C_A)) \\ &\quad \cdot \mathbb{P}_t(i_2 \in \mathcal{C}_t(X_S, V_0) | i_2 \in \mathcal{C}_t(\neg X_D, C_B)) \\ &= \mathbb{P}_t(i_2 \in \mathcal{C}_t(\neg X_D, C_B) | i_1 \in \mathcal{C}_t(\neg X_D, C_A)) \\ &\quad \cdot \mathbb{P}_t(i_2 \in \mathcal{C}_t(X_S, C_B, V_0)) \end{aligned} \tag{10}$$

The conditional probability is therefore the product of the probability that i_2 is from country B given that i_1 is from country A and the probability that i_2 is a susceptible, unvaccinated individual from country B. Using equations (9) and (10) we obtain

$$\mathbb{P}_t(i_2 \in \mathcal{C}_t(X_S, C_B, U_0) | i_1 \in \mathcal{C}_t(X_I, V_W, C_A, U_0)) = m_{B,A} \cdot y_t(X_S, C_B, U_0)/y_t(\neg X_D, C_B). \tag{11}$$

Note that if we were not to distinguish between countries, such that $d(A, B) = 0$, we would end up with the relative number of individuals living in country B.

Explicit reactions. With the derived probabilities we are able to specify the compartment specific infection constants. We illustrate this by two examples.

The first example deals with the compartments $\mathcal{C}_t(X_I, C_A, V_W, U_0)$ and $\mathcal{C}_t(X_S, C_B, U_0)$. The corresponding reaction is

$$y_t(X_I, C_A, V_W, U_0) + y_t(X_S, C_B, U_0) \xrightarrow{r_{j_1}} y_t(X_I, C_A, V_W, U_0) + y_t(X_I, C_B, V_W, U_0), \tag{12}$$

where r_j denotes the reaction rate. By assumption, every individual $i_1 \in \mathcal{C}_t(X_I, C_A, V_W, U_0)$ has on average c contacts per day. Equation (11) defines the fraction of contacts which are between the two compartments of interest. Since both compartments are non-vaccinated compartments and $i_1 \in \mathcal{C}_t(V_W)$, the fraction of infectious contacts is α. Thus, i_1 infects on average $\beta m_{B,A} \cdot y_t(X_S, C_B, V_0)/y_t(\neg X_D, C_B)$ susceptible, unvaccinated individuals from country B. Both individuals are non-vaccinated and therefore the vaccine modifier is simply one. The respective infection constant is given by

$$r_{j_1} = \frac{\beta \cdot m_{B,A}}{y_t(\neg X_D, C_B)} \tag{13}$$

For the second example, we consider vaccinated and mutant infected compartments $\mathcal{C}_t(X_I, C_A, V_M, U_1)$ and $\mathcal{C}_t(X_S, C_B, U_2)$ to showcase the influence of the vaccine and the mutant

modifier.

$$y_t(X_I, C_A, V_M, U_1) + y_t(X_S, C_B, U_2) \xrightarrow{r_{j_2}} y_t(X_I, C_A, V_M, U_1) + y_t(X_I, C_B, V_M, U_2). \tag{14}$$

We derive the infection constant analogously to the previous example. Using the vaccine modifiers γ, $\delta_{M,2}$ and the increase in infectiousness of the mutant η

$$r_{j_2} = \frac{(1-\delta_{M,2})(1-\gamma)\eta\beta \cdot m_{B,A}}{y_t(\neg x_D, c_B)}. \tag{15}$$

Technically we multiply α by $(1-\delta_{M,2})(1-\gamma)$ to reduce the degree of infectiousness accounting for vaccinations and increase it by multiplying it by η, to account for the more infectious mutant.

To ensure readability we refrain from writing down all exact infection rules. They are defined for all possible combinations of features F_1 and F_2. Their infection constants can be derived analogously to what we have showcased.

2.2.2 Recoveries and deaths

The transition from the infectious state to the recovered or deceased state is independent of any other compartments, meaning that infectious individuals will transmit, independent of the numbers in the other compartments. The general reactions are

$$\begin{aligned} \mathcal{C}_t(X_I, F_1) &\longrightarrow \mathcal{C}_t(X_D, F_1) \\ \mathcal{C}_t(X_I, F_2) &\longrightarrow \mathcal{C}_t(X_R, F_2). \end{aligned} \tag{16}$$

Defining the reaction constants, depends on the state of the product (deceased or recovered) and on the vaccination status, since vaccinated individuals have a much lower probability of having a severe course of disease (Tenforde, 2021; Voysey et al., 2021).

For $\lambda \in \mathbb{R}_+$ we assume that on average an individual stays $1/\lambda$ days in the infectious state before it transmits either to the recovered or the deceased state. Thus, on average λ individuals transmit out of each infectious compartment every day. We assume that a fraction $p \in [0,1]$ of these unvaccinated individuals transmits to the deceased state and $(1-p)$ to the recovered state. Note that the assumption that deceasing and recovering individuals have the same average infection duration might not hold in reality, since deceasing individuals might have more severe cases with more viral load. However, incorporating this would raise the need for more compartments and since we allow for vaccinations of recovered and infectious individuals, assuming the same infection duration should not influence the vaccination rates

anyways. We therefore we assume that the influence on our model results are negligible.

p can be interpreted as the probability of dying after becoming infected. Note that p does not depend on the virus type. The virus type therefore only influences the number of infections but not the probability of dying for infected individuals. According to Davies et al. (2021) this assumption might be violated. We do so however, since we difference is rather low and we want to keep our model simple.

The explicit reactions for unvaccinated individuals are for $i \in \{A, B\}$ and $k \in \{W, M\}$

$$\begin{aligned} \mathcal{C}_t(X_I, C_j, V_W, U_0) &\xrightarrow{p\lambda} \mathcal{C}_t(X_D, C_j, V_w, U_0) \\ \mathcal{C}_t(X_I, C_j, V_w, U_0) &\xrightarrow{(1-p)\lambda} \mathcal{C}_t(X_R, C_j, V_w, U_0) \end{aligned} \tag{17}$$

We introduce the parameters $\omega_{k,l} \in [0, 1]$, for $k \in \{W, M\}$ and $l \in \{1, 2\}$, to account for the reduce in the probability of dying after being vaccinated. We use $p\omega_{k,l}$ as new probability of dying due to being infected with virus k after being vaccinated with vaccine l. $\omega_{k,l}$ is thus the reduction in the probability of dying. The corresponding reactions for vaccinated individuals are for $i \in \{A, B\}, k \in \{W, M\}$ and $l \in \{1, 2\}$

$$\begin{aligned} \mathcal{C}_t(X_I, C_j, V_k, U_l) &\xrightarrow{p\omega_{k,l}\lambda} \mathcal{C}_t(X_D, C_j, V_k, U_l) \\ \mathcal{C}_t(X_I, C_j, V_k, U_l) &\xrightarrow{(1-p\omega_{k,l})\lambda} \mathcal{C}_t(X_R, C_j, V_k, U_l) \end{aligned} \tag{18}$$

2.2.3 Vaccination

The general setting of vaccination reactions is the same as for recoveries and deaths in (16). Besides susceptible individuals, we allow for vaccinations of infectious and recovered individuals as well. We do the former to account for vaccinations of asymptomatic individuals, which has been reported to be around 17% (Byambasuren et al., 2020) and the latter to account for vaccination shots that are assigned to recovered individuals, which are vaccinated to increase their degree of immunity (Skelly et al., 2021). Let $\phi_{t,l,j} \in \mathbb{R}_+$ be the vaccination constant of vaccine l in country j at time t. The vaccination constant of one vaccine is assumed to be equal for all vaccination subcompartments of S, I, R within one country, which is to say, that the decision of vaccinating an individual is independent whether it is susceptible, infectious or recovered. The corresponding reactions are $j \in \{A, B\}$, $k \in \{W, M\}$

and $l \in \{1, 2\}$

$$\begin{aligned} \mathcal{C}_t(X_S, C_j, U_0) &\xrightarrow{\phi_{l,j}} \mathcal{C}_t(X_S, C_j, U_l) \\ \mathcal{C}_t(X_I, C_j, V_k, U_0) &\xrightarrow{\phi_{l,j}} \mathcal{C}_t(X_I, C_j, V_k, U_l) \\ \mathcal{C}_t(X_R, C_j, V_k, U_0) &\xrightarrow{\phi_{l,j}} \mathcal{C}_t(X_R, C_j, V_k, U_l). \end{aligned} \tag{19}$$

Since the vaccination constant is determined by the optimal policy, we explain in greater detail how the vaccination constant is derived in Chapter 3.

3 Optimal vaccine allocation

We denote the number of vaccination shots of type U_l available at time t in country j by $W_{l,j}(t)$ and the total number number of available vaccine l shots by $W_l(t) = W_{l,A}(t) + W_{l,B}(t)$. $W_{l,j}(t)$ is exogenous in our model and based on the true number of COVID-19 vaccine doses allocated to the EU. We assume that all doses of vaccines are immediately vaccinated. Thus, it must hold that

$$W_{l,j}(t) = \phi_{l,j} \cdot y_t(\neg X_D, C_j, U_0). \tag{20}$$

Which is to say that the total number of vaccine l at t must equal the number of individuals vaccinated with l at t.

We do not directly optimize the vaccination rates but rather the fraction of vaccines that are allocated to a certain country. Let $f_l(\theta_l; t)$, with $f_l : \mathbb{R}^z \times [0, \tau] \to [0, 1]$, be the function that defines the fraction of vaccine l allocated to country A. The fraction depends on the time t and a parameter vector $\theta_l \in \mathbb{R}^z$ that defines the form of $f_l(\theta_l; t)$. The fractions enter the model through the vaccination rates. The total number of doses of vaccine l assigned to country j equals the total number of doses times the fraction of vaccine l allocated to country j $W_{l,A}(t) = f_l(\theta_l; t) W_l(t)$ and $W_{l,B}(t) = [1 - f_l(\theta_l; t)]\, W_l(t)$. Combining this with Equation (20) yields for the vaccination rates

$$\begin{aligned} \phi_{l,A} &= \frac{f_l(\theta_l; t) W_l(t)}{y_t(\neg X_D, C_A, U_0)} \\ \phi_{l,B} &= \frac{[1 - f_l(\theta_l; t)]\, W_l(t)}{y_t(\neg X_D, C_B, U_0)}. \end{aligned}$$

Given a specific functional form of f_l, a specific $\bar{\theta}_l \in \mathbb{R}^z$ is called a *strategy* for vaccine l. A *vaccination strategy* $\bar{\Theta} = \begin{pmatrix} \bar{\theta}_1 \\ \bar{\theta}_2 \end{pmatrix}$ is a collection of strategies defined for both vaccines l.

We label the strategy Θ_{EU} assigning the fraction of the population in country A to be the fraction of vaccines assigned to country A, such that

$$f_l(\theta_{EU}, t) = \frac{y_t(\neg X_D, C_A)}{y_t(\neg X_D)}, \tag{21}$$

current EU strategy or *current strategy*. We denote the number of deceased individuals in country A, conditioned on the current strategy, by $y_T(X_D, C_A; \Theta_{EU})$ and the corresponding number in country B by $y_T(X_D, C_B; \Theta_{EU})$. We use this strategy as baseline case to examine how we can improve using an optimal strategy. An optimal strategy Θ^* is the solution to the minimization problem using constraints $C.1 - C.6$

$$\begin{aligned}
&\underset{\Theta \in \mathbb{R}^{2z}}{\arg\min} && y_T(X_D) \\
&\text{subject to} && \phi_{l,A} = \frac{f_l(\theta_l; t) W_l(t)}{y_t(\neg X_D, C_A, U_0)} && \text{for } l \in \{1, 2\}, && \text{(C.1)} \\
& && \phi_{l,B} = \frac{[1 - f_l(\theta_l; t)]\, W_l(t)}{y_t(\neg X_D, C_B, U_0)} && \text{for } l \in \{1, 2\}, && \text{(C.2)} \\
& && W_l(t) = w_l(t) && \text{for } l \in \{1, 2\}, && \text{(C.3)} \\
& && Y(0) = Y_0, && && \text{(C.4)} \\
& && \Theta = \begin{pmatrix} \theta_1 \\ \theta_2 \end{pmatrix}, && && \text{(C.5)} \\
& && \beta, \eta, \gamma, \delta_{k,l}, \omega_{k,l}, \mathbf{M}, && && \text{(C.6)} \\
& && y_T(X_D, C_A) < y_T(X_D, C_A; \Theta_{EU}), && && \text{(C.7)} \\
& && y_T(X_D, C_B) < y_T(X_D, C_B; \Theta_{EU}) && && \text{(C.8)}
\end{aligned}$$

and we call it *optimal vaccination strategy* with respect to the given minimization problem. If additionally constraints $C.7$ and $C.8$ are satisfied, the optimal strategy is Pareto optimal and we call it *Pareto optimal vaccination strategy*.

The pareto optimality conditions ensure that every country is better off than with the current strategy. Taking the perspective that both countries can veto against strategies, Pareto optimal strategies are the only implementable strategies since no country would agree to deviate from the current strategy if it experiences more deceased individuals with the new strategy.

The problem is specified through the vaccination rates $(C.1)/(C.2)$, the exogenous inflow of vaccines $(C.3)$, the initial conditions of the ODE system $(C.4)$, and the fixed parameters introduced in Chapter 2 $(C.6)$. Note that our objective is the total number of deceased

individuals. Other objectives, like the total number of infectious individuals or some combination of both, could be considered as well. We decided to choose the total number of deaths such that the death protection parameters $\omega_{k,l}$ influence the solution. However, we include sensitivity checks using the total number of infectious individuals as objective function.

In this paper we examine three different functional forms of f_l. Each form is parameterized via θ_l.

1. f_l is a stepwise function
2. f_l is a logistically transformed third order spline function
3. f_l is a neural network

To define the functional forms, we subdivide the interval $[0, T]$ into a partition $0 = t_0 < t_1 < \cdots < t_z = T$. Let $\mathcal{T}_i = [t_{i-1}, t_i)$, for $i = 1, \ldots, z$, be the corresponding intervals of the tagged partition. We label $\mathcal{T}$ as the i-th decision period.

Stepwise. The functional form of f_l is a stepwise function. In this world, policy makers determine a fraction that is allocated to country A for a fixed decision period $\mathcal{T}_i$, evaluate, and then adjust before the next decision period T_{i+1} begins. We subdivide $\theta_l = \begin{pmatrix} \theta_{l,1} & \theta_{l,2} & \ldots & \theta_{l,z} \end{pmatrix}'$ such that $\theta_{l,i} \in [0, 1]$ is the fraction of vaccine l that is assigned to country A if $t \in \mathcal{T}_i$. The resulting stepwise functions are determined by

$$f_l(t) = \theta_{l,i} \quad \forall t \in \mathcal{T}_i$$

In Figure 2 we show an exemplary vaccination strategy for vaccine l. Note that the COVID-19 vaccine allocation is a special case of a step function, where $\theta_{l;1} = \theta_{l,2} = \ldots = \theta_{l,z} = y_0(\neg X_D, C_l)/y_0(\neg X_D)$, assuming that the allocations are not adjusted for small changes in the population sizes over the course of the pandemic.

Splines. Policy makers decide on a flexible fraction, which is depending on t, assigned to each country. By using polynomials, rather than constant functions in the stepwise approach, we allow for more complex policy decisions within one decision period $\mathcal{T}_i$. However, one should note that this exercise is rather theoretical and aims to show what strategies could be achieved theoretically.

Figure 3 shows an exemplary spline and how it is shrinked into the unit interval via the logistic function. f_l follows a spline $S(t)$ of order three that is transformed via the logistic function $\sigma(x)$ to obtain values between zero and one. Within the sensitivity analysis we use the hyperbolic tangent function $\tanh(x)$ to examine if the functional choice of the

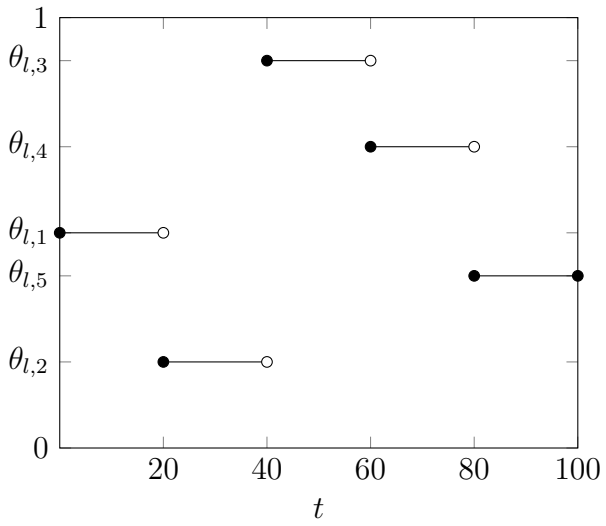


Figure 2: Example for a stepwise vaccination strategy of vaccine l

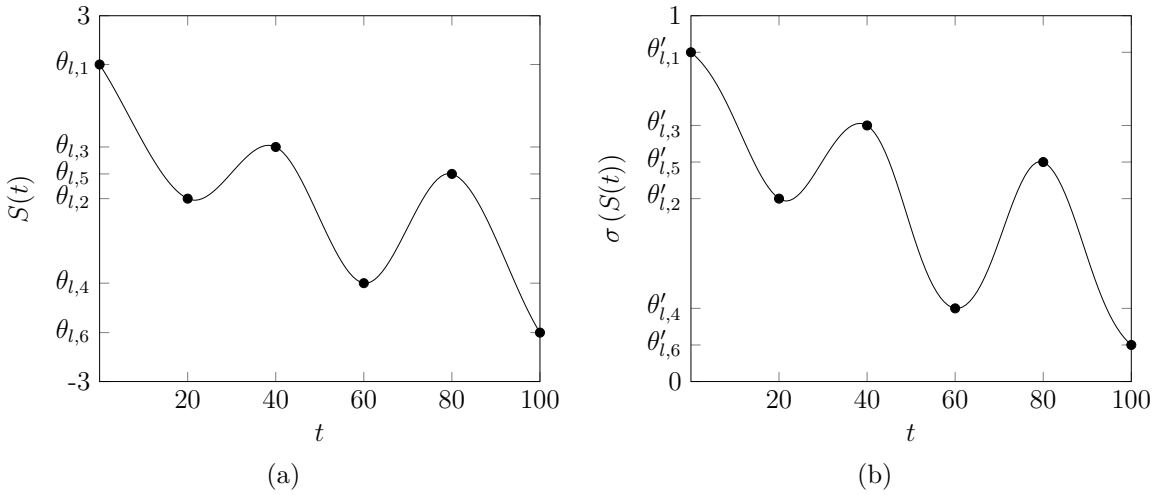


Figure 3: Exemplary spline (a) and the logistically transformed spline (b)

transformation changes our results.

$$f_l(\theta; t) = \frac{1}{1 + \exp\left(-P_{l,i}(t)\right)} \quad \forall t \in \mathcal{T}_i. \tag{23}$$

$P_{l,i}(t) \in \mathbb{R}_3(t)$ is a polynomial from the third order polynomial ring over the real numbers. We chose $P_{l,i}(t)$ to be in cubic hermite form, such that we can parameterize it by specifying the polynomial values at the boundaries

$$\begin{aligned} P_{l,i}(t_{i-1}) &= \theta_{l,i-1} \\ P_{l,i}(t_i) &= \theta_{l,i} \end{aligned} \tag{24}$$

and using finite differences as approximations of the derivatives $P'_{l,i}(t)$. To compute the approximations, we use central finite differences and forward as well as backward finite differences at the respective boundaries t_0 and t_z

$$\begin{aligned} P'_{l,1}(t_0) &\approx \frac{P_{l,1}(t_1) - P_{l,1}(t_0)}{t_1 - t_0} \\ P'_{l,i}(t_{i-1}) &\approx \frac{1}{2}\left[\frac{P_{l,i}(t_i) - P_{l,i}(t_{i-1})}{t_i - t_{i-1}} + \frac{P_{l,i-1}(t_{i-1}) - P_{l,i-1}(t_{i-2})}{t_{i-1} - t_{i-2}}\right] \\ P'_{l,z}(t_z) &\approx \frac{P_{l,z}(t_z) - P_{l,z}(t_{z-1})}{t_z - t_{z-1}} \end{aligned} \tag{25}$$

Let $t' = (t - t_{i-1})/(t_i - t_{i-1})$. The polynomial $P_{l,i}(t)$ is given as a linear combination of four basis polynomials $B_1(t), B_2(t), B_3(t), B_4(t) \in \mathbb{R}_3(t)$ with the boundary values of the polynomial and its derivative

$$\begin{aligned} P_{l,i}(t) = B_1(t')\overbrace{P_{l,i}(t_{i-1})}^{\theta_{l,i-1}} + B_2(t')(t_i - t_{i-1})P'_{l,i}(t_{i-1}) \\ + B_3(t')\underbrace{P_{l,i}(t_i)}_{\theta_{l,i}} + B_4(t')(t_i - t_{i-1})P'_{l,i}(t_i) \quad \forall t \in \mathcal{T}_i. \end{aligned} \tag{26}$$

The scalars are dependent on the parameter vector θ_l through (24) and (25). The basis polynomials are defined by$B_1(t) = 2t^3 - 3t^2 + 1, B_2(t) = t^3 - 2t^2 + t, B_3(t) = -2t^3 + 3t^2$ and $B_4(t) = t^3 - t^2$. We show subsequently that they indeed form a basis of $\mathbb{R}_3(t)$. Showing the basis property proves that the four polynomials span $\mathbb{R}_3(t)$ and we therefore do not exclude any polynomials from the space of policies that could be implemented.

Theorem 1. *$B_1(t), B_2(t), B_3(t), B_4(t) \in \mathbb{R}_3(t)$ form a polynomial basis of $\mathbb{R}_3(t)$.*

Proof. We need to show that the four polynomials are linearly independent. We do so by writing the polynomials in vector form, collect them in a matrix and show that this matrix has full rank.

$$\begin{pmatrix} 2 & 1 & -2 & 1 \\ -3 & -2 & 3 & -1 \\ 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix} \Leftrightarrow \begin{pmatrix} 0 & 0 & -2 & 1 \\ 0 & 0 & 1 & -1 \\ 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix} \Leftrightarrow \begin{pmatrix} 0 & 0 & 0 & -1 \\ 0 & 0 & 1 & -1 \\ 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix} \Leftrightarrow \begin{pmatrix} 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix}$$

Since $B_1(t), B_2(t), B_3(t), B_4(t)$ are four linearly independent polynomials of degree 3, they form a basis of $\mathbb{R}_3(t)$. □

Neural network.

4 Stochastic model

Within the deterministic model, we have assumed that for each reaction R_j, the number of times the reaction happens within one unit of time is deterministic, see Equation (2). However, it is more likely the these events occur random over time. To account for this, we test our deterministically derived optimal vaccination strategy and test it in a stochastic set-up.

τ-leaping. We impose an arbitrary order to all subcompartments. We do so by using n features $F_1, \dots F_n$, such that $\cup_{i=1}^{n} \mathcal{C}_t(F_i) = \mathcal{C}_t()$ and $\mathcal{C}_t(F_1), \dots, \mathcal{C}_t(F_n)$ are mutually disjoint. We specify the state of the system in terms of the subcompartments $Y(t) = \begin{pmatrix} y_t(F_1) & y_t(F_2) & \dots & y_t(F_n) \end{pmatrix}'$. Recall that $\mathbf{S} \in \mathbb{R}^{n \times m}$ is the stoichiometric matrix, as defined in (5), with coefficients s_{ij} and columns $s_{\cdot j}$ and R_j, for $j = 1, \dots, m$, is the j-th reaction. Let $V_{t,j}$ the random variable counting the number of times R_j will fire within the interval $[t, t+\tau)$, for $\tau \in \mathbb{R}_+$. We denote by V_j the random vector collecting the random variables. Dividing the whole period of interest $[0, T]$ in intervals of length τ, the leaping is an iterative update of the discretizised system's state.

$$Y(t+\tau) = Y(t) + \mathbf{S}V_t. \tag{27}$$

This equation is similar to equation (3). Only the number of reactions within a given interval is in (27) random.

The change in the system's state $\Delta Y(t) = Y(t+\tau) - Y(t) =$ can be written in terms of a linear combination of the columns of $\mathbf{S}$ with random scalars $K_{t,j}$

$$\Delta Y(t) = \sum_{j=1}^{m} K_{t,j} \cdot s_{\cdot j}. \tag{28}$$

$s_{\cdot j}$ consists of the magnitudes of the mass actions for each compartment i according to reaction R_j and therefore indicates how the state of the system changes if reaction R_j happens. $K_{t,j}$ is the number of occurences of reaction R_j. Thus, the product is the system's change due to R_j. Aggregating over all reactions yields the total change of the system R_j, similar to the deterministic equation (3).

So far we have not specified the distribution of K_t. We are interested in the conditional joint probability distribution $\mathbb{P}_t(K_{t,1} = k_{t,1}, \dots, K_{t,m} = k_{t,m} | \tau)$ of the random vector $K_t = \begin{pmatrix} K_{t,1}, \dots, K_{t,m} \end{pmatrix}'$ conditioned on the state of the system and a fixed interval size. Recall that we have defined $\mathbb{P}_t$ to be the conditional distribution with respect to the state of the system and we therefore omit to write it explicitly in the condition statement. Assuming

independence, we bring the problem down to specifying the margins. Let $a_j(y)$ be the propensity function $\mathbb{P}_t(K_{t,j} = 1|\tau = 1)$ of the j-th reaction with respect to the state of the system $Y(t) = y$. We assume that for infinitesimal small dt

$$\mathbb{P}_t(K_{t,j} = 1|\tau = dt) = a_j(y) \cdot dt, \tag{29}$$

is the probability that R_j fires once within the interval $[t, t + dt)$ and $(K_{t,j}|Y(t), \tau = dt)$ is Bernoulli $\text{Ber}(a_j(y) \cdot dt)$ distributed. The Bernoulli assumption is justified by choosing dt infinitesimal small, such that R_j fires at most once almost surely.

If we assume that $a_j(y)$ is constant within $[t, t + \tau)$, we can partition the interval in $\frac{\tau}{dt}$ subintervals with length dt. Note that for simplicitly we assume that $\frac{\tau}{dt}$ is an integer. In each of these subintervals $(K_{t+s\cdot dt,j}|Y(t), \tau = dt)$, for $s = 0, 1, \ldots, \frac{\tau}{dt} - 1$, is Bernoulli $\text{Ber}(a_j(y)\cdot dt)$ distributed and thus the sum

$$\sum_{s=0}^{\frac{\tau}{dt}-1} (K_{t+s\cdot dt,j}|Y(t), \tau = dt) \sim \text{B}\left(\frac{\tau}{dt}, a_j(y) \cdot dt\right)$$

follows a binomial distribution. The practical problem of this Binomial distribution is that sampling from it requires to define a value for dt. By definition dt is infinitesimal small, such that we actually aim for $dt \to 0$. The literature has found a solution to circumvent by breaking the problem down to draw from a Poisson random variable that can be specified by τ and $a_j(y)$.

Theorem 2. *$B\left(\frac{\tau}{dt}, a_j(y) \cdot dt\right) \xrightarrow{d} Po(a_j(y) \cdot \tau)$ if $dt \to 0$.*

Proof. Let p_n be a sequence with $\lim_{n\to\infty} p_n = 0$. We first show that if $\lambda' = n \cdot p_n$ is constant, $n \to \infty$ and $p_n \to 0$, a general Binomial random variable $\text{B}(n, p_n)$ converges in distribution to a Poisson random variable $\text{Po}(\lambda')$. Note that this proof is in essence just a restatement of the Poisson limit theorem of Poisson (1835).

$$\begin{aligned}
\lim_{n\to\infty} \binom{n'}{k} p_n^k (1 - p_n)^{n-k} &= \lim_{n\to\infty} \frac{n \cdot (n-1) \cdot \ldots \cdot (n-k+1)}{k!} \left(\frac{\lambda'}{n}\right)^k \left(1 - \frac{\lambda'}{n}\right)^{n-k} \\
&= \lim_{n\to\infty} \frac{n^k + O(n^{k-1})}{k!} \left(\frac{\lambda'}{n}\right)^k \left(1 - \frac{\lambda'}{n}\right)^{n-k} \\
&= \frac{(\lambda')^k}{k!} \exp(-\lambda')
\end{aligned}$$

Note that by definition τ is fixed and by assumption $a_i(y)$ is constant within $[t, t+\tau)$. Thus, $\lim_{dt\to 0} \frac{\tau}{dt} = \infty$, $\lim_{dt\to 0} a_i(y) \cdot dt = 0$ and $\frac{\tau}{dt} \cdot a_i(y) \cdot dt = \tau \cdot a_i(y)$. Using the convergence property mentioned above yields the result. □

The τ- leaping algorithm we use is the stochastic Euler algorithm with fixed step-size

since we use a fixed step-size within the deterministic model.

Algorithm 1: Stochastic Euler algorithm

Result: $Y(t) \quad \forall t \in [0, T]$

Initialize $Y(0) = Y_0, t = 0$, and set fixed $\tau, \mathbf{S}$;

while $t < T$ **do**

  Set y = Y(t);

  Draw $K_{t,j} \sim \text{Po}(a_j(y)\tau)$ for all $j = 1, \ldots, m$;

  Compute $Y(t + \tau) = Y(t) + \mathbf{S}K_t$;

  Store $Y(t + \tau)$;

  Update $a_j = a_j(Y(t + \tau))$ for all $j = 1, \ldots, m$;

  Update $t = t + \tau$;

end

5 Simulation and optimization

We use Python and mainly its libraries libSBML (Bornstein et al., 2008) and AMICI (Fröhlich et al., 2021) to implement our models. pyPESTO (Schälte et al., 2021) is our main tool for optimization. To minimize the optimization problem, we use the L-BFGS-B algorithm (Zhu et al., 1997) for which pyPESTO uses Scipy's (Virtanen et al., 2020) implementation. For each optimization we run a muli-start using 50 starts and choose the corresponding vaccination strategy that minimizes the objective. For each start, we draw uncorrelated $\theta_{l,i} \sim \mathcal{U}(0, 1)$. In the case of Pareto optimal constraints, we only accept a starting vector Θ if the Pareto constraints $C.7$ and $C.8$ are satisfied. Otherwise we reject it and draw a new sample until 50 starts are reached.

5.1 Calibration

Vaccine parameter. Within our model there only exist two vaccines U_1 and U_2. Whereas in the EU, as of July 2021, 4 vaccines are approved and two are in the development phase (European Commission, 2021). To establish the link from our theoretical model to the real-world COVID-19 vaccines, we use data based on the four approved vaccines to calibrate our model. Vaccine U_1 represents the messenger ribonucleic acid (mRNA) vaccines and vaccine U_2 represent the vector vaccines. In contrast to conventional vaccines, mRNA vaccines do not contain viral proteins themselves. They only contain the information human cells need to produce a virus trait that triggers the desired immune response (Biontech, 2021).

The mRNA vaccines currently approved are Comirnaty, also known as BNT162b2,

from Pfizer-BioNTech and Spikevax, also known as mRNA-1273, from Moderna. The corresponding vector vaccines are Vaxzevria from Oxford-Astra Zeneca and Janssen, also known as Johnson & Johnson COVID-19 vaccine, from Janssen Vaccines.

We use efficacy values reported within the literature to calibrate the vaccine specific parameters $\delta_{k,l}$ and $\omega_{k,l}$. Efficacy describes the effect with respect to perfect conditions whereas effectiveness measures the effect under real-world clinical settings (Gartlehner et al., 2006). Therefore, real-world effectiveness could be lower than the numbers reported in Table 2. We account for this within our sensitivity analysis by lowering the magnitudes of $\delta_{k,l}$ and $\omega_{k,l}$.

We use data from the early alpha virus type to calibrate the wild type parameters and data from the lately spreading delta variant to calibrate the mutant parameters.

Vaccine	Efficacy		Sources
	alpha	delta	
Comirnaty	94%-95%	87%-95%	Callaway (2021), Nasreen et al. (2021), Polack et al. (2020), Prüβ (2021), Sheikh et al. (2021)
Spikevax	94%	-	Oliver (2021b), Prüβ (2021)
Vaxzevria	66%-73%	60%-71%	Callaway (2021), Emary et al. (2021), Prüβ (2021), Stowe et al. (2021)
Janssen	66%	-	Oliver (2021a), Sadoff et al. (2021)

Note: Efficacy is measured as protection against an infection after 14 days of the second vaccine shot.

Table 2: Vaccine efficacy

Due to the recent spread of the delta variant, data is still limited and we did not find reliable sources for the delta efficacy of Spikevax and Janssen. For the latter a recent study of Jongeneelen et al. (2021) reports that even though real world effectiveness has been shown, they found no efficacy for the Janssen vaccine against the delta variant. Since their study only included 8 individuals and we therefore refrain from using the study to calibrate our model.

With respect to Table 2, we decide to set the protection of the mRNA vaccines against the alpha variant (wild type) to be $\delta_{1,W} = 0.94$ and against the delta variant (mutant) to be $\delta_{1,M} = 0.9$. We set the protection of the vector vaccines against the alpha variant to $\delta_{2,W} = 0.7$ and to $\delta_{2,M} = 0.65$ against the delta variant.

Abu-Raddad et al. (2021) report Comirnaty to protect from hospitalization by 97.4%. Tenforde (2021) find that Comirnaty and Spikevax yield 94% protection against hospitalization within the the age group of ≥ 65 aged individuals. Voysey et al. (2021) report a 100%

efficacy against hospitalization regarding Vaxzevria and the alpha variant. We generalize the empirical results and set the value against death protection $\omega_{k,l}$ to 99% for all vaccines.

Harris et al. (2021) found that in a study using more than 365,000 British households, mixed with vaccinated and unvaccinated individuals, that full vaccination with Comirnaty or Vaxzevria reduces the transmission probability by 40%-60%. We therefore set $\delta = 0.5$.

Basic reproduction number. The basic reproduction number R_l of virus type l is the average number of individuals infected by one infectious individual. Translated to our model, this yields the following equations

$$\begin{aligned} R_W &= \frac{\beta}{\lambda} \\ R_M &= \frac{\eta\beta}{\lambda}, \end{aligned} \tag{30}$$

Recall that $1/\lambda$ is the average time an individual is infected and β, or $\eta\beta$, is the average number of individuals infected by one infectious individual per day. The German Robert Koch Institut (2021) reports the basic reproduction number to be between 2.8 and 3.8. Moreover, they state that an individual is around 10 days infectious for which we do not account in our model. However, individuals with severe cases might be infectious even longer. We use $\lambda = 0.1, R_W = 3$ and $R_M = 3.6$, yielding $\beta = 0.3$ and $\eta = 1.2$. Note that this numbers do not take non-pharmaceutical measures, like testing and social distancing, into account. We incorporate lower R_l values within the sensitivity analysis to account for non-pharmaceutical policy measures against the pandemic.

Death rate. Baud et al. (2020) find a death rate of 5.7% for symptomatic cases. However, this number might be overestimated due to undetected asymptomatic cases. Wu and McGoogan (2020) account for asymptomatic cases and find estimates to be between 2%-3%. We therefore use $p = 2.5\%$ for our simulations.

Start conditions. In our first set-up, we set the initial population of susceptible individuals in both countries to $y_0(X_S, C_A) = y_0(X_S, C_B) = 80$ million, a country size similar to Germany. Country A starts with one wild type infectious individual $y_0(X_I, C_A, V_W) = 10$ and country B with one mutant type infected individual $y_0(X_I, C_B, V_M) = 10$. All other compartments are set to zero at $t = 0$.

Distance. To specify the cross-border meeting modifier $b(d(A, B))$, we use tourism data from Germany and France. We use France since it is populationwise the largest country

with a border to Germany. In 2016, $1,725,854$ individuals from France traveled to Germany and stayed on average for two days (Statistisches Bundesamt, 2017). We divide this number by 366 to get an estimate of the average number of French individuals in Germany at each day in 2016 and scale it by $\frac{80}{67}$ to adjust that our second country has a population size of 80 million but France has around 67 million inhabitants $\frac{2 \cdot 1,725,854}{366} \cdot \frac{80}{67} \approx 11,261$. Assuming that the same number of French individuals have been in Germany every day and using equation (8) with a constant proportion $y_t(\neg X_D, C_B)/y_t(\neg X_D)$ yields

$$b(d(A,B)) = \frac{11,261}{80,000,000} \approx 0.0002$$

Note that this estimate is rather conservative since we do not take commuters and unregistered visits, such as shopping trips, into account.

Length of decision periods. We set the length of the whole decision period to $T = 140$ and subdivide the length of each decision interval $\mathcal{T}_i$ to 14 days.

Vaccine inflow. The daily vaccine inflow $W_l(t)$ is computed using EU data of the vaccine inflow taken from the open source data bank of the European Centre for Disease Prevention and Control (2021). The data reports the weekly inflow of vaccines for all countries within the EU. We accumulate the numbers of Corminarty and Spikevax to compute the total numbers of mRNA vaccines and accumulate the total numbers of Vaxzevria and Janssen to compute the total numbers of vector vaccines per week. We scale this number down to our model's population size by dividing it through the total number of EU habitants and multiplictae it by the number of individuals in our model. We subsequently accumulate the vaccines within each 14-day interval $\mathcal{T}_i$ and divide this number by 14 to get the average number of vaccine doses inflow per vaccine and day. Thus, the inflow per day of each vaccine is constant within each interval $\mathcal{T}_i$ but varies across intervals and vaccines.

5.2 Simulations

same for unrestricted waterfall plots for both; 4 best strategies for both

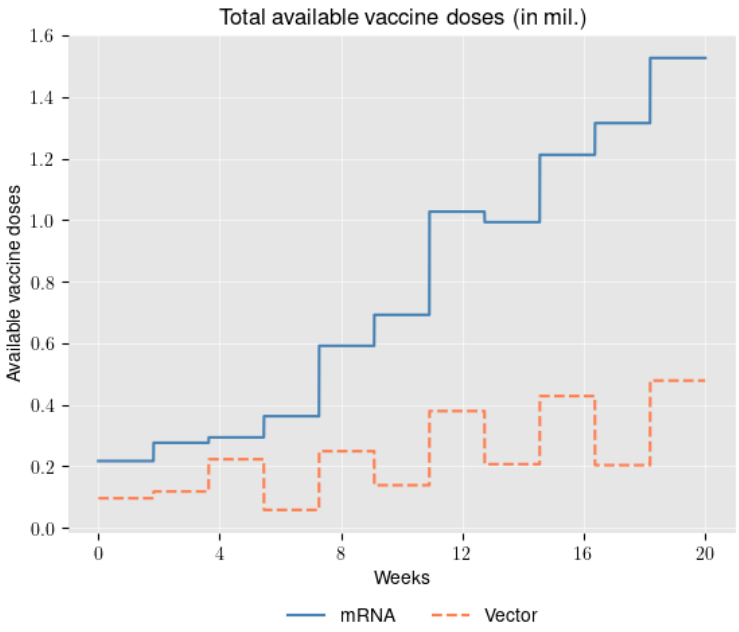
table comparing three variants (see orchestra presentation)

optimal results splines fractions in appendix

same for infectious individuals

waterfall

table comparing three variants (see orchestra presentation);



Note:

Figure 4: Vaccines

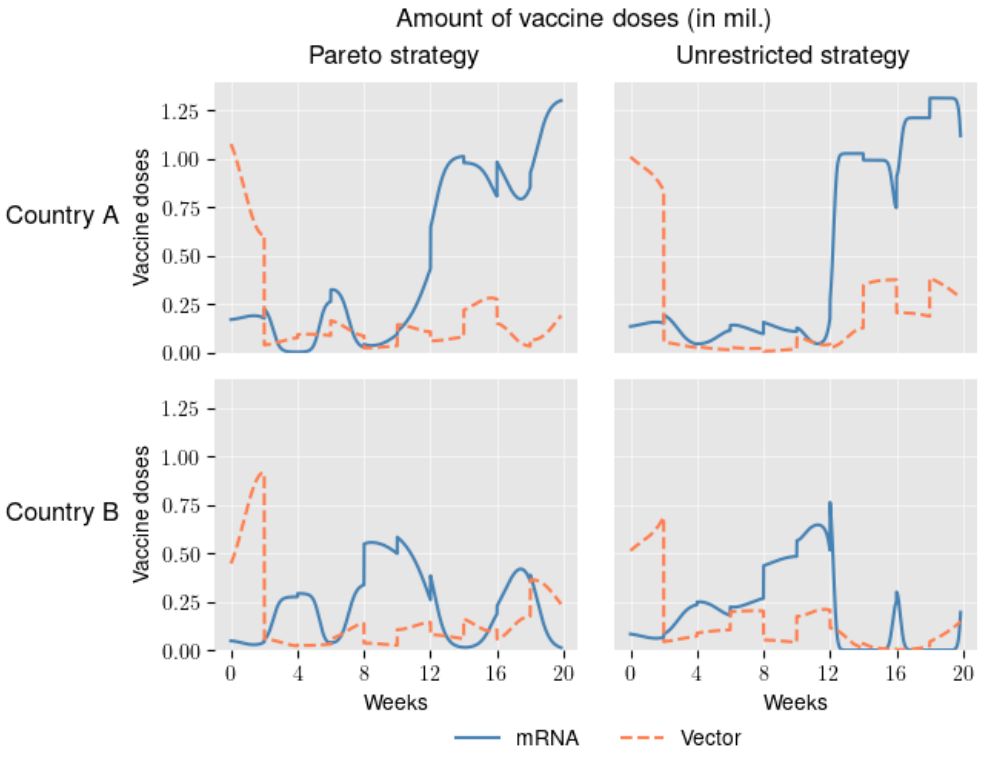
	Strategies		
	Current	Pareto optimal	Unrestricted optimal
Comirnaty	94%-95%	87%-95%	Callaway (2021), Nasreen et al. (2021), Polack et al. (2020), Prüβ (2021), Sheikh et al. (2021)
Spikevax	94%	-	Oliver (2021b), Prüβ (2021)
Vaxzevria	66%-73%	60%-71%	Callaway (2021), Emary et al. (2021), Prüβ (2021), Stowe et al. (2021)
Janssen	66%	-	Oliver (2021a), Sadoff et al. (2021)

Note:

Table 3: Number of deceased individuals depending on the vaccination strategy.

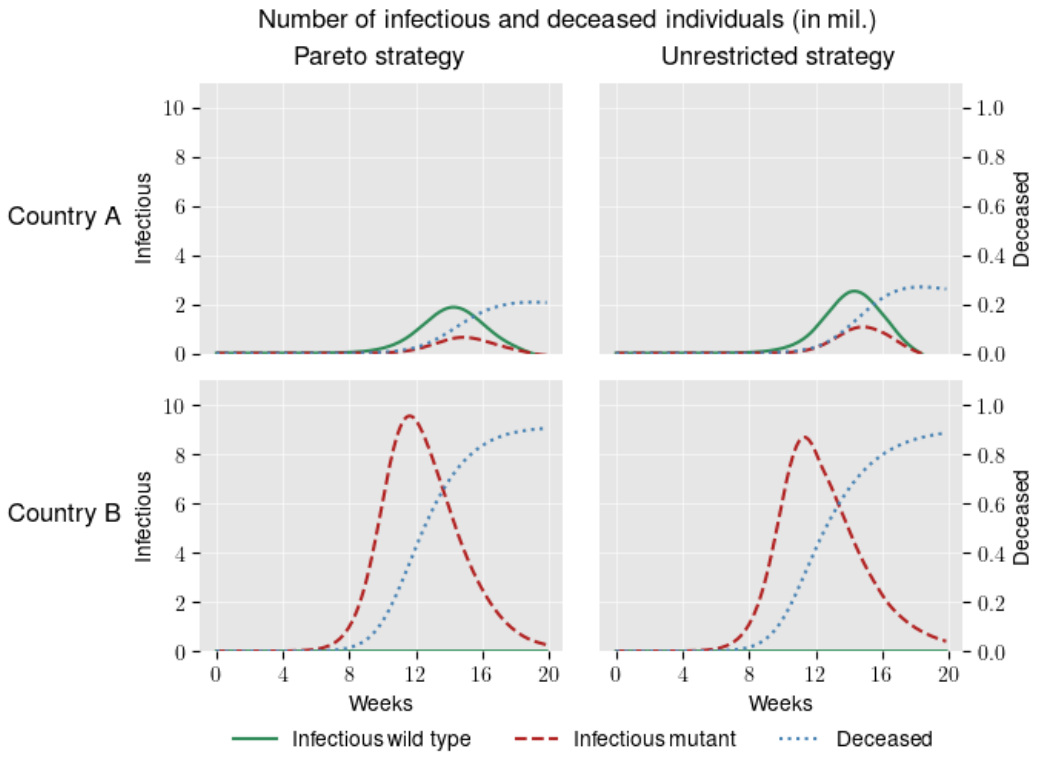
5.2.1 Test with stochastic set-up

6 Sensitivity analysis



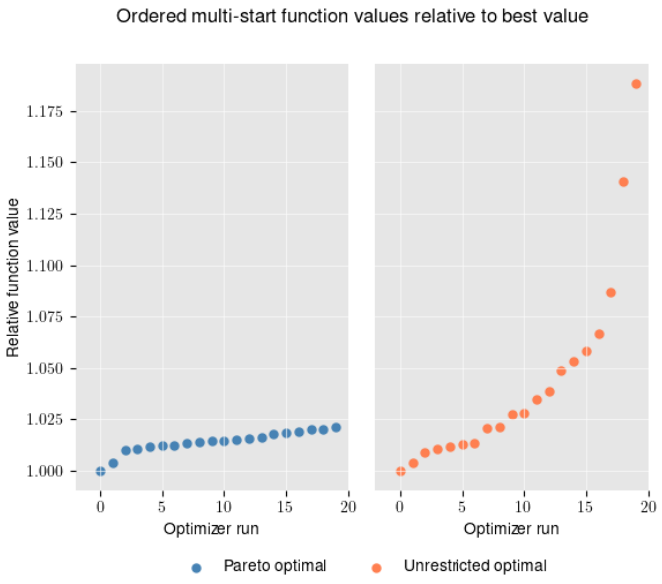
Note:

Figure 5: Vaccines



Note:

Figure 6: Vaccines



Note:

Figure 7: Vaccines

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