Interuniversity Institute for Biostatistics and statistical Bioinformatics

Deliverable 1

Study Protocol Benefit Risk contextualisation of COVID-19 vaccines.

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Section 1. Study protocol overview

The study protocol is organized as follows. In Section 2, we provide relevant background information concerning the topic of this proposal. In Section 3, we outline the various study goals and objectives addressed within this project. An assessment of the method for the primary risk-benefit contextualization is presented in Section 4. An overview of the proposed methodology for the quantification of the risk-benefit of COVID-19 vaccination in the European Union is discussed in detail in Section 5, with the construction of the composite measures described in Section 6. A proposal of the toolkit is shown in Section 7. Finally, a description of the deliverables and a summary of the way we will deal with data, outputs, publications (dissemination) are provided in Sections 8 to 11.

Section 2. Background

The ongoing SARS-CoV-2/COVID-19-pandemic, which caused the first patients with severe breathing problems to be hospitalized between December 2019 and January 2020 in Wuhan, China, rapidly became a world-wide health problem after the first reported case of this novel pneumonia. Moreover, it forced countries worldwide to take strong mitigation measures to prevent a collapse of health care systems and prevent excess COVID-19 related deaths. Despite these mitigation measures, the impact of the pandemic worldwide is overwhelming, with over 175 million officially registered SARS-CoV-2 infections and almost 3.8 million officially reported COVID-19 related deaths on June 13th, 2021 [1]. The true toll of the COVID-19 pandemic is arguably 3-4 times higher due to under-reporting of deaths in certain regions.

As the pandemic continued to bring health and economic hardship, keeping mortality as low as possible was the highest priority. Consequently, governments were forced to put in place measures, referred to as non-pharmaceutical interventions (NPIs), to mitigate the epidemic's impact, thereby minimizing the inevitable economic downturn [2]. While NPIs (e.g., social distancing, increased hygiene, face-and-mouth mask mandates, ...) control the pandemic with variable success, in part depending on the degree of adherence to these measures, vaccines against the SARS-CoV-2 virus were developed at an unprecedented speed, without compromising the required quality, safety and efficacy regulations [3]. This has led to several approved and licensed COVID-19 vaccines to date.

The European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC) jointly coordinate and oversee observational studies on monitoring the safety (i.e., by the EMA), and the effectiveness (ECDC) of these licensed vaccines. While interim reports of effectiveness indicate that vaccination against COVID-19 decreases the rate of infection with SARS-CoV-2 by at least 80%, reduces the viral load four-fold and reduces the risk of transmission [4], the real-life evidence shows vastly decreasing PCR-confirmed SARS-CoV-2 infections in many regions and especially in those age groups with a high vaccine uptake and completed (two-dose) vaccination schedule [5]. These early

results confirm the expectation of long-lasting stable control of the COVID-19 pandemic, which cannot be achieved with NPIs alone.

However, with the large-scale roll-out across the world of vaccination in the entire adult population, and in some cases large portions of the minor population (or at least within industrialized countries), close post-marketing monitoring thereof is required, similar to any marketed medication, in order to evaluate side effects, which cannot be observed in a highly selected experimental study population that is, however large, still limited in size relative to the post-marketing scale of the operation. Although, the majority of side effects following vaccination are transitory and non-severe in nature, potential rare life-threatening side effects can occur and should be documented, investigated and alerted timely. Currently, more than 2 billion doses of a COVID-19 vaccine are administered worldwide [1] and two safety signals have been further investigated by the EMA, concerning thromboembolic events [6, 7] on the one hand and myocarditis and pericarditis [8] on the other. These studies are key to generate adequate evidence to support continuous assessment and evaluation of the benefits of vaccines and health risks involved after vaccination. Next to that, these studies need to inform decision-making on the use of different vaccines in national or regional vaccination strategies among different populations.

The CenStat/I-BioStat team is delighted to contribute to EMA's important task to monitor these important safety signals by addressing three specific objectives introduced in more detail in the next section. To tackle these objectives, we bring in our longstanding expertise in (1) infectious diseases epidemiology, which includes extensive experience in mathematical modeling approaches including the development of deterministic and stochastic compartmental models, meta-population models, and individual-based models, and the estimation of epidemiological parameters, making use of information and methodology regarding observed incidence, (serial) serological and social contact data, (2) longitudinal data analysis, (3) Bayesian computational and inferential methods, (4) composite endpoints and (5) statistical programming, encompassing the development of R Shiny web applications and packages. The study goals and objectives are outlined in the next section. Our proposed methodological approach is outlined in Section 5.

Section 3. Study Goals and Objectives

In this section, we provide an overview of the different study goals and objectives.

3.1 Objective 1: Revised method

The **first objective** is to propose a valid method to quantify both the benefits and the risks related to COVID-19 vaccines given potential data limitations and reflecting uncertainty with regard to the various ingredients of the proposed risk-benefit measure.

3.2 Objective 2: Composite measures

The **second objective** is to explore the possibility of developing composite measures.

3.3 Objective 3: Toolkit

The **third objective** is to provide a toolkit to support the calculations and interpretation of the various outcomes.

Section 4. Assessment of method used for primary benefit risk contextualisation

The initial method used to evaluate the benefit-risk of COVID-19 vaccination was specifically tailored to thrombosis with thrombocytopenia syndrome (TTS) per age-gender subgroup, and defined the benefit of the vaccine as **prevented clinical events** of COVID-19 related hospitalisations, ICU admissions and deaths.

The **prevented clinical events** are estimated by multiplying the incidence of COVID-19 in the target population with the estimated proportion of events (i.e., hospitalizations, ICU admissions and deaths following SARS-CoV-2 infection) and with the effectiveness of the vaccine (i.e., in terms of severity and mortality). Data concerning the first two elements (i.e., the disease incidence and estimated probability of hospitalization and death) come directly from the member states and the ECDC, while data for the latter element is retrieved from observational or experimental (clinical) studies (and meta-analytic results of combining this information).

Moreover, the **TTS risk** is seen by contrasting observed and expected TTS events (background rates) by the number of (partially) vaccinated subjects (according to the two-dose vaccination scheme considered as a full vaccination scheme), where data for the latter comes directly from the EU member states and ECDC, data for the observed events from EudraVigilance and data for the expected events from EMA. However, there likely will be uncertainty related to incomplete or delayed reporting of clinical events and observed TTS events. In addition, there may be missing covariates of interest (age, gender, . . .) and uncertainty with regard to vaccine effectiveness estimates. Moreover, the level of uncertainty may differ between member states and reported clinical events within a subject may overlap (a COVID-19 related death at ICU).

The benefits and risks of COVID-19 vaccination are quantified based on different quantities that are inferred from different sources of data. However, a direct computation thereof relying on these estimates completely **ignores the uncertainty** with regard to the estimation of these ingredients. Moreover, some of the **quantities are already influenced by the**

presence and the extent of vaccination over time, for example, the disease incidence is affected by the prevention of severe disease, at least to some extent, hence, potentially leading to an underestimation of confirmed COVID-19 cases. Needless to say, such an underestimation of the disease incidence, as a consequence of COVID-19 vaccine uptake, already partially accommodates the benefit of vaccination in the population, hence a direct quantification of the benefits as **prevented clinical events** based on such incidence data **underestimates the benefit of vaccination**. For example, the prevented clinical events are obtained by multiplying the disease incidence with the estimated proportion of events (i.e., hospitalizations, ICU admissions and deaths). Given the underestimation in disease incidence, the number of clinical events are underestimated as well. Moreover, as vaccination coverage increases over time, the age- and time-specific probability of hospitalization given infection is influenced by the fact that COVID-19 vaccination impacts the severity of the disease, thereby leading to a lower case-hospitalization ratio. Needless to say, one could opt to estimate (and fix) these probabilities based on information prior to vaccination, albeit that **temporal differences exist in the rate of hospitalization, ICU admission and death** given chances in treatment, available hospital capacity (depending on the current epidemiological situation in a specific country), etc. Next to temporal aspects, **age of confirmed COVID-19 cases** (among other relevant factors such as the presence of (specific) comorbidities, information which is often not readily available) is of crucial importance with regard to, for example, the quantification of the probability of hospitalization, ICU admission and dying, as well as regarding the vaccine properties in case of persons being vaccinated.

Next to that, the **differential mix of vaccine uptake**, **mix of vaccine types** and a **differential ratio of non-vaccinated people**, **partially vaccinated persons** (single dose in the context of a two-dose scheme), or **fully vaccinated individuals across different countries** requires a tailored approach to quantify the benefits of vaccination. Needless to say, different vaccines have varying properties in terms of protection against infection, transmission, severe disease, hospitalization, and mortality. All these complexities, as well as uncertainty thereabout, should ideally be accounted for in the risk-benefit measure used. Such an approach would directly quantify the impact of vaccination, encompassing age- and time-specific SARS-CoV-2 dynamics and vaccination efforts in a given population, while relying on, for example, hospitalization data from the different countries.

Given the emergence of different variants of concern (VoCs) with different timings throughout different member states, the quantification of the benefits of vaccination has become even more challenging. Next to different vaccine effectiveness for different VoCs, these VoCs, like the alpha and delta VoC, are characterized by varying transmissibility and differential severity of disease, even for unvaccinated individuals, hence, preventing a straightforward computation of the **prevented clinical cases.** Such a quantification will heavily depend on the penetration (prevalence) of a specific SARS-CoV-2 type in the study

population. Consequently, the evolution of the prevalence of these emerging VoCs needs to be accounted for.

In the following section, we will specifically devote attention to our proposed methodology to improve the quantification of the risk-benefit ratio of COVID-19 vaccination in the different EU member states.

Section 5. Proposed method benefit risk calculation

Here, we provide details with regard to the proposed methodology for the risk-benefit quantification.

5.1 Addressing both benefits and risks

Benefits of COVID-19 vaccination

Flexible models that incorporate uncertainty about parameter estimates for relevant quantities and that allow for multiple benefits (and risks) are dynamic transmission models. These models have been recommended by the IMI-ADVANCE working group [9] and were also recently used in the Janssen thromboembolic benefit-risk assessment [10]. Both the societal perspective, via compartmental models, and the individual perspective, via individual-based models, belong to this family of dynamic transmission models. The models are informed by the same information as the initial method (see Section 4), but (parameter) uncertainty is naturally built in through the use of Bayesian (inferential) methodology. Moreover, when using a **stochastic compartmental model**, an additional layer of variability with regard to disease transmission can be incorporated. Additional compartments can be created to allow for indirect effects of vaccination and for subjects with mixed vaccines, but the flexibility of the models requires carefully balancing parsimony and general applicability, with sufficient granularity.

During the last year and in the face of the ongoing COVID-19 pandemic, an a**ge-structured discrete time stochastic compartmental model** was developed and tailored to the **Belgian context** [11]. More specifically, the model relies on daily incidence of new hospitalizations and deaths, and is further informed by serial serological data and social contact data. Next to the stochastic model an existing individual-based model (STRIDE), used in the past to describe measles dynamics, has been extended and perfected to accommodate COVID-19 related complexities such as superspreading in the transmission process [12]. Although both models have been used extensively to inform policy with regard to exit strategies, NPIs and mitigation measures in general, the latter model is more suited to study the impact of interventions on a more granular level whereas the stochastic model quantifies the impact of scenarios at the population level.

As both of these models have already been developed at UHasselt (SIMID group), we are convinced that the aforementioned models can be adapted for the quantification of the benefits of COVID-19 vaccination in the different member states. More specifically, the **prevented clinical cases** (hospitalizations, ICU admissions and deaths) as mentioned previously can be obtained directly from these transmission models by contrasting the number of observed clinical cases with those that would have been expected in case vaccination would not have taken place. Moreover, given the fact that key epidemiological parameters are either directly inferred from available incidence data or derived from literature allowing for the incorporation of uncertainty, the mathematical modeling approach allows for a direct quantification of uncertainty with regard to the **prevented clinical cases**.

In the next subsection, we provide a more detailed outline with regard to the refinements of the models to be applicable in the context of the different member states and relying on available data across countries.

Risks of COVID-19 vaccination

The potential risks of COVID-19 vaccination are not only subject to uncertainty, but may also depend on the specific vaccine administered or vaccine type (in particular, mRNA versus adenovirus-based vaccines, but also relative to alternative vaccine technology, depending on potential future approvals) as well as the background risk in different subpopulations (depending on gender, age, …).

Current information suggests that adenovirus-based vaccines may be more associated with thrombosis with thrombocytopenia syndrome (TTS), while mRNA vaccines are more associated with myo- and pericarditis.

The background risk to an adverse reaction to COVID-19 vaccination may differ between age groups or may be different in populations with comorbidities. Not only the probability of an adverse reaction to vaccination may differ in these subpopulations, but also the severity of the reaction may vary. Therefore, any risk evaluation of COVID-19 vaccination should allow for possible **stratification** by age, comorbidities, vaccine (type) and severity of adverse reaction. Importantly, the stratification used in the risk evaluation should be similar to the stratification in the evaluation of the benefits quantified using the proposed mathematical compartmental model (see detailed description below).

When relevant information on adverse reactions is **missing**, or risk events are **underreported** in Eudravigilance, information from other regions (i.e., from other member states for which the relation between vaccine uptake and the occurrence of specific adverse events is considered trustworthy) can be borrowed by means of the use of specifying (informative) priors in a Bayesian framework. Alternatively, (deterministic) sensitivity

analyses can be conducted with varying probabilities (according to the range of these probabilities as empirically observed across different member states). Finally, information on the background risk in the unvaccinated population (e.g., the background risk of TTS in unvaccinated COVID-19 infected or uninfected individuals) may be unavailable. Consequently, setting the background risk to zero under such circumstances will inevitably overestimate the risk of the adverse event under study as a result of vaccination. Again, a sensitivity analysis could yield insights in the risk-benefit measure depending on the input of the end user regarding the background risk, even and in particular when not readily available from literature.

5.2 Overview of proposed quantitative methodologies

5.2.1 Level of complexity/detail versus data availability

Needless to say, these mathematical models require a minimum of (incidence) data with minimum quality to be able to capture the disease dynamics, and to estimate and project past and future incidence rates in the absence or presence of vaccinations. A direct way of computing the effect of vaccination in terms of hospitalizations and deaths is through the use of a mathematical compartmental transmission model. A compartmental model subdivides the entire population in different compartments or disease states, thereby reflecting the disease process. The most famous compartmental model is the simple SIR model including a Susceptible, Infected, and Recovered compartment. Although a SIR model is frequently used to study disease dynamics and to investigate the impact of interventions, its applicability in the context of SARS-CoV-2 transmission is insufficient. Transmission of SARS-CoV-2 is characterized by an exposed period in which persons are infected, but not yet infectious, prior to moving to a pre-symptomatic stage in which infected individuals can transmit the disease. After some time, these individuals either develop symptoms or will remain asymptomatic throughout their entire infectious period. Upon displaying symptoms, infected individuals either recover or will require hospital care leading to hospitalization and/or intensive care unit (ICU) admission. Unfortunately, a non-negligible share of hospitalized individuals will eventually die due to SARS-CoV-2 infection. Next to the aforementioned complexities with regard to the infection dynamics, it has been shown that SARS-CoV-2 transmission is largely age-dependent. More specifically, the proportion of asymptomatic individuals, the probability of hospitalization and the mortality rates are shown to be age-dependent. Ignoring the dependence of these quantities on age, leads to a too simplistic reflection of the impact of COVID-19 on the population. Consequently, we advocate the use of a compartmental model that explicitly accounts for age-specific transition rates, at least to the extent possible which is mainly dependent on the availability of data to be able to inform those rates.

To be precise, we propose the use of a **compartmental model** including a susceptible, exposed, pre- and a/symptomatic state as well as hospital compartments following

symptomatic disease. Moreover, we include different age groups with age intervals determined by the resolution at which incidence data is available (preferably ten-year age groups). In order to develop such a compartmental model, we start from a simplification of the extended age-structured SEIR(-type) compartmental model which has been used to describe SARS-CoV-2 transmission in the Belgian population [11]. A schematic representation of the different disease states in the original model is graphically depicted in Figure 1.

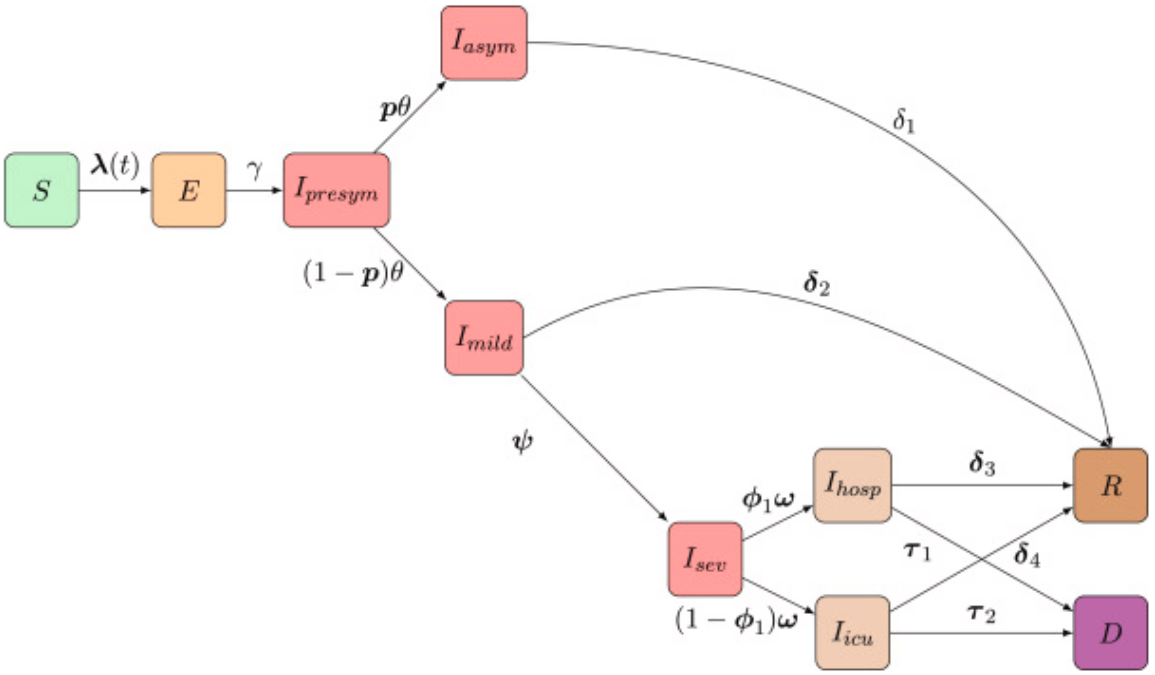

Figure 1: Schematic overview of the flows of individuals in the compartmental model: Following SARS-CoV-2/COVID-19 infection susceptible individuals (S) move to an exposed state (E) and after a latent period individuals further progress to a pre-symptomatic state (I_{presym}) in which they can infect others. Consequently, individuals stay either completely symptom-free (I_{asym}) or develop mild symptoms (I_{mild}). Asymptomatic individuals will recover over time. Upon having mild symptoms, persons either recover (R) or require hospitalization (going from I_{sev} to I_{hosp} or I_{icu}) prior to recovery (R) or death (D).

The stochastic discrete-time age-structured compartmental model by Abrams et al. [11] is calibrated on high-level hospitalization data, serial serological survey data, and Belgian mortality data. More specifically, the stochastic model generates (stochastic realisations of) the daily number of new hospitalizations per age group (i.e., 10 year age groups). In this model, individuals are susceptible to infection and after an effective contact (between a susceptible and infectious individual) the susceptible individual moves to an exposed state. After a latent period, the individual becomes infectious and moves to a pre-symptomatic state. Afterwards, individuals either develop symptoms or remain completely free of symptoms. Symptomatic infections are either very mild or severe such that individuals

require hospitalization. Hospitalized and critically ill patients admitted to the Intensive Care Unit (ICU) either recover or die. The model transitions are described based on a set of ordinary differential equations (ODEs) as follows:

$$\begin{aligned}
\frac{d\boldsymbol{S}(t)}{dt} &= -\boldsymbol{\lambda}(t)\,\boldsymbol{S}(t)\\
\frac{d\boldsymbol{E}(t)}{dt} &= \boldsymbol{\lambda}(t)\,\boldsymbol{S}(t) - \gamma\boldsymbol{E}(t)\\
\frac{d\boldsymbol{I}_{presym}(t)}{dt} &= \gamma\boldsymbol{E}(t) - \theta\boldsymbol{I}_{presym}(t)\\
\frac{d\boldsymbol{I}_{asym}(t)}{dt} &= \theta\boldsymbol{p}\boldsymbol{I}_{presym}(t) - \delta_1\boldsymbol{I}_{asym}(t)\\
\frac{d\boldsymbol{I}_{mild}(t)}{dt} &= \theta(1-\boldsymbol{p})\,\boldsymbol{I}_{presym}(t) - \{\boldsymbol{\psi}+\boldsymbol{\delta}_2\}\boldsymbol{I}_{mild}(t)\\
\frac{d\boldsymbol{I}_{sev}(t)}{dt} &= \boldsymbol{\psi}\boldsymbol{I}_{mild}(t) - \boldsymbol{\omega}\boldsymbol{I}_{sev}(t)\\
\frac{d\boldsymbol{I}_{hosp}(t)}{dt} &= \boldsymbol{\phi}_1\boldsymbol{\omega}\boldsymbol{I}_{sev}(t) - \{\boldsymbol{\delta}_3+\boldsymbol{\tau}_1\}\boldsymbol{I}_{hosp}(t)\\
\frac{d\boldsymbol{I}_{icu}(t)}{dt} &= (1-\boldsymbol{\phi}_1)\,\boldsymbol{\omega}\boldsymbol{I}_{sev}(t) - \{\boldsymbol{\delta}_4+\boldsymbol{\tau}_2\}\boldsymbol{I}_{icu}(t)\\
\frac{d\boldsymbol{D}(t)}{dt} &= \boldsymbol{\tau}_1\boldsymbol{I}_{hosp}(t) + \boldsymbol{\tau}_2\boldsymbol{I}_{icu}(t)\\
\frac{d\boldsymbol{R}(t)}{dt} &= \delta_1\boldsymbol{I}_{asym}(t) + \boldsymbol{\delta}_2\boldsymbol{I}_{mild}(t) + \boldsymbol{\delta}_3\boldsymbol{I}_{hosp}(t) + \boldsymbol{\delta}_4\boldsymbol{I}_{icu}(t)
\end{aligned}$$

Transmission of the disease is governed by an age- and time-dependent force of infection $\lambda(k,t)$, for age group $k = 1, \ldots, K$at calendar time t, i.e., the instantaneous rate at which a susceptible person in age group k acquires infection at time t. The transmission rate $\beta(k,k',t)$represents the average per capita rate at which an infectious individual in age group k' makes an effective contact with a susceptible individual in age group k, per unit of time, at calendar time t. Consequently, the force of infection is defined as

$$\lambda(k,t) = \sum_{k'=0}^{K} \beta(k,k',t)I(k',t),$$

where $I(k',t)$ denotes the total number of infectious individuals in age group k' at time t and $\beta(k,k',t)$ can be rendered as $\beta(k,k',t) = q(k,k',t)\times c(k,k',t)$, when relying on the so-called social contact hypothesis [13]. This hypothesis entails that $c(k,k',t)$ are the per capita rates at which an individual in age group $k$makes contact with an individual in age group k', per unit of time, at calendar time t and q is a proportionality factor capturing contextual and host- and disease-specific characteristics such as susceptibility to infection and infectiousness upon infection. In the absence of detailed social contact data for each of the member states, (age-dependent) transmission rates will be directly estimated by contrasting disease/hospitalization incidence with model-based output given specific values thereof, and potentially relying on a so-called Who-Acquires-Infection-From-Whom (WAIFW)

approach to allow for age-heterogenous transmission (see Hens et al. (2012) [14] for more details thereon).

Model parameters are estimated using a **Markov Chain Monte Carlo (MCMC) approach** with the model being implemented as a stochastic chain binomial model with transition probabilities being defined in Abrams et al. [11]. A two-phase method is considered in which the first phase consists of an adaptive Metropolis-within-Gibbs (AMWG) and/or adaptive mixture Metropolis–Hastings (AMM) algorithm to achieve stationary samples that seem to have converged to the target posterior distributions. In the second phase, a non-adaptive Random-Walk Metropolis (RWM) algorithm is used to draw final samples from the posterior distributions.

As an important goal of these compartmental models is the **quantification of the impact of vaccination**, specific vaccination compartments will be included as an extension of the model depicted in Figure 1, thereby reflecting first and second dose vaccine uptake and potential differential vaccine effectiveness following first and second dose, respectively. The final goal will be to estimate the number of hospitalizations, ICU admission and deaths in the absence of vaccination and to contrast this with observed values, to quantify the **prevented clinical events**. So far, we did not mention the **emergence and circulation of different variants of concern (VoCs)** and their potentially increased virulence and disease burden (both in terms of hospitalizations and deaths). Whereas the original compartmental model has been adapted to account for the alpha-variant B.1.1.7 as well as vaccination (see Figure 2); recent adaptations to include the delta-variant B.1.167.2 warrant the use of more detailed information that will become available during the next weeks and months. As novel VoCs are likely to emerge in the future, a generic way of introducing it in the modeling approach will be considered.

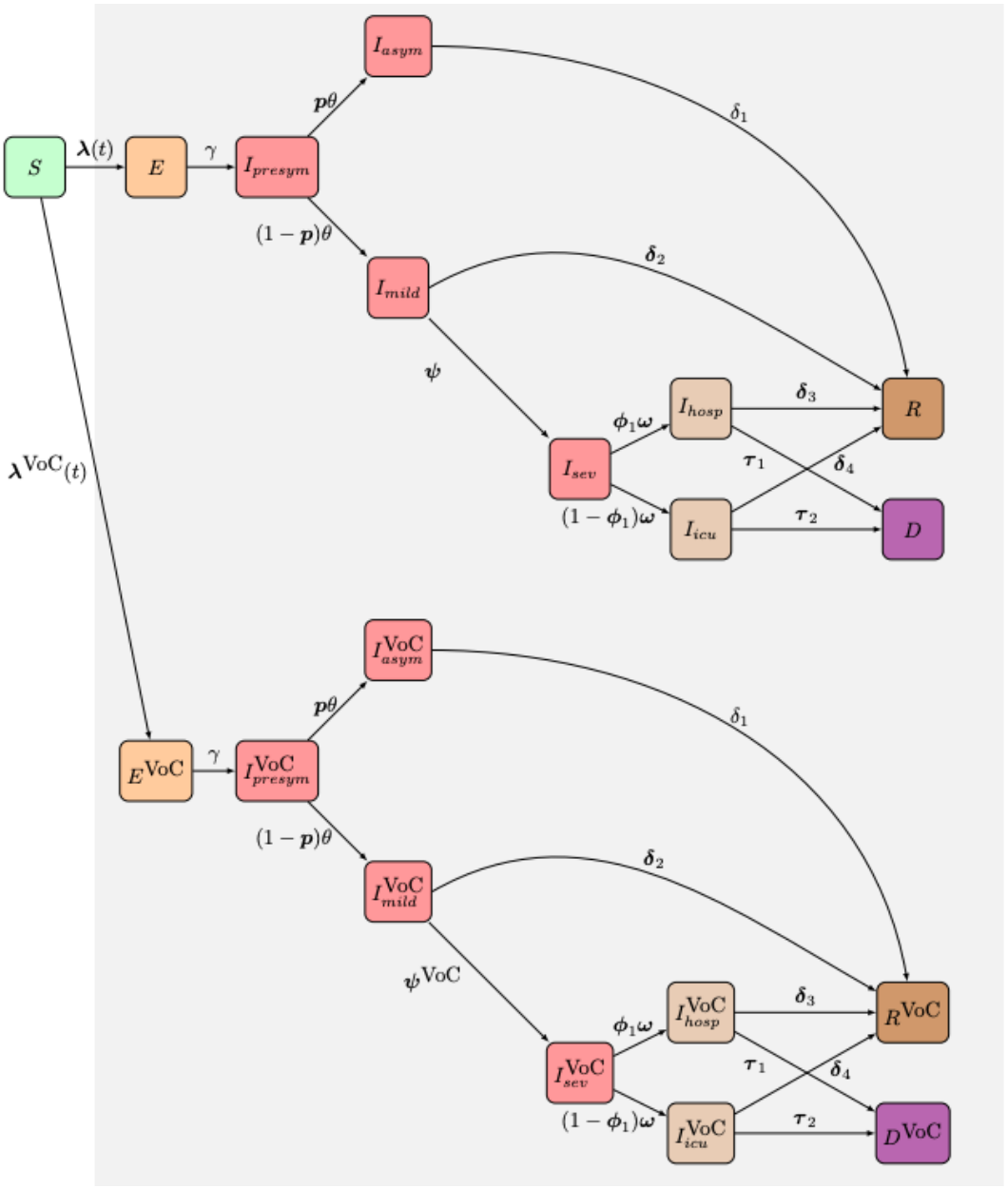

Figure 2: Schematic overview of the flows of individuals in the adapted version of the compartmental model.

The emergence of the alpha-variant was accommodated through the inclusion of additional infection states allowing disease features to be different for the alpha-variant as compared to the wild-type. Next to that, the increased transmissibility of the alpha-variant is estimated from Belgian genomic surveillance data. More specifically, the observed prevalence of the alpha-variant is contrasted with model-based predictions under a given transmissibility which is then inferred from the data.

Again, vaccination was accommodated by doubling the different disease states for vaccinated and unvaccinated individuals, in the presence of either the wild-type or VoC. Vaccinated individuals who acquire infection have a lower risk for COVID-19 related hospital

admission. Pending more evidence, we assume an overall reduction of 100% as shown in different vaccine trials [15]. Severe non-hospitalized cases are currently not separately modelled, hence the impact of vaccination on non-hospitalized severe cases, seen in primary care is not separately shown. Vaccine-induced immunity against infection is implemented as a step function with a switch from 0% to 75% protection against infection 21 days after the first dose. Vaccine-induced protection against hospital admission is implemented in the same way using the (higher) estimates reported above. We are able to include **differences between mRNA and adenovirus-based vaccines** in how they induce immunity and protection. An age-specific uptake scheme can be considered in the model based on available vaccination coverage information from the member states.

Given the complexity of creating a synthetic population for each of the different member states in an individual-based modeling approach, we limit our description to the development and application of a (sufficiently elaborate) compartmental model. In summary, we aim to develop a generic compartmental modeling approach to be applicable to the different member states and to be tailored to the differential availability of data in these countries. A minimum of input data is required to be able to reliably estimate the impact of vaccination in terms of hospital admissions and deaths averted. For more details about the methodology we refer to the description in Abrams et al. [11].

Note that as the compartmental model is used to describe the disease dynamics in the specific population under study, a change in the compartmentalization of the population will not be allowed for. Consequently, the model parameters governing the flows of individuals throughout the system cannot be changed by the member states. The benefit risk-analysis under a set of (plausible) scenarios, where the “epidemiological weather” of a certain point in time/period in time is used, together with key disease-specific factors can be considered. This is in line with our intention to 'borrow' certain conditional information from other countries should it not be available for the country under study. Or, a simpler approach without relying on social contact data could potentially be implemented to circumvent dependence there upon. Given that the most important game changers are VOCs and their characteristics on the one hand and characteristics of the vaccines on the other.

5.2.2 Deterministic versus probabilistic (parameter) constraints

Both deterministic as well as probabilistic parameter constraints will be considered in the modeling tool. In an initial phase, disease-specific model parameters (e.g., governing the mean latent period, mean infectious period, probability of asymptomatic infection, ...) are considered fixed (deterministic constraint) while (country-specific and age-dependent) transmission parameters (see model description) will be inferred from the available hospital

incidence data. Alternatively, probabilistic constraints in the form of informative priors can be specified for key epidemiological parameters. The R Shiny tool will allow for the specification of deterministic and probabilistic constraints for specific model parameters. Consequently, the proposed model accounts, through Bayesian MCMC methodology, for the uncertainty around quintessential estimates governing disease spread, while a deterministic sensitivity analysis can easily be performed by the end user.

Some disease-specific factors are well-studied to date (e.g., latent period, duration of the infectious period, etc.) while other (fixed) model parameters and data will require an update over time. Part of the model will be pre-compiled (e.g., the initialization of the model) and does not necessarily require an update, unless more detailed information concerning certain disease-, VoC and/or vaccine-related elements becomes available. In that case, the model should/could be recalibrated taking into account the updated information. Furthermore, it is difficult to predict how frequent updates should be performed in advance, especially when we are still in the midst of an epidemic (e.g., in non-pandemic times, for seasonal flu, it is pretty clear how frequent updates would be needed, but not now).

5.2.3 Challenges

5.2.3.1 Resources/runtime software

The implementation of the compartmental model will require a balance between complexity and (computational) feasibility. Therefore, the initial implementation of the model will focus on the estimation of a limited set of (age- and time-specific) transmission parameters (within the aforementioned WAIFW matrices) while other disease-specific characteristics or model parameters are either fixed to a specific value (see also Section 5.2.2).

5.2.3.2 Updating priors

Prior information will be specified in the toolkit using the selection of a parametric distribution from a set of standard distributions and the specification of corresponding distributional assumptions (e.g., normal distribution with mean and variance specified).

5.2.4. Advantages

5.2.4.1 Mixing and matching (currently emergenging)

Several small- and larger-scale studies are ongoing regarding the combination of vaccines belonging to different families. For example, it is of interest to gain both the immune response as well as the efficacy and effectiveness of combining an mRNA dose with an adeno dose or vice versa, rather than following a homologous scheme. It cannot merely be assumed that the benefits and/or the risks in such a heterologous administration can be inferred from risk-benefit knowledge of the underlying homologous schemes. Even though

EMA may not (yet) have approved such heterologous use of otherwise approved vaccines, member states may choose to allow or even routinely administer such an approach. Data should then be collected to gauge (rare) side effects as well as to study benefits. As long as use is limited, cross-national meta-analyses will be necessary to increase power. At the same time, risks identified from a dose common to a homologous and heterologous scheme can be combined in a single analysis.

5.2.4.2 Limitations/Uncertainties regarding data

The quality of the results depends not only on the methodology used but also on the quality of the input data. To this end, assessment of the data quality provided by the various data sources, nationally or internationally, is needed. Less reliable/more questionable data can be discounted by means of weighting techniques.

Should certain data components be missing, for example, because data is available at an aggregated level that is too high, disaggregation can be applied based on data (conditional distributions) coming from other sources. Such other sources can be data from neighbouring countries, for example, or from different regions within the same country. Especially in federal countries or with an otherwise articulated state form, it is possible that one federated entity carries data at a more refined level than another.

5.2.4.3 Reproducibility

All programs and data will be available so that every sufficiently knowledgeable end-user will be able to re-run the analyses. As some of the analyses are stochastic (Monte Carlo) in nature, provisions will be taken (e.g., by fixing seed values for random number generators) so that the exact same results can be obtained.

5.3 Data Requirement

5.3.1 Required input parameters risks and benefits

Benefits

Based on the proposed method as described in Section 5, we will use several data sources which are made available by EMA or upon request from the ECDC. A summary of the different data sources is given below:

1. **The incidence dataset**
   This dataset is obtained from both the EMA as well as the ECDC database. It contains information from 18 countries reporting case-based data between January until the end of March 2021 by 10-year age categories (<10, 10-19, ...) (and potentially gender) for the incidence of confirmed COVID-19 cases, hospitalizations, ICU

admissions, and COVID-19 related deaths. Note that these data are not available for each of the member states. In order to calibrate the mathematical model properly, we need access to (daily) incidence data, ideally from the start of the country-specific epidemics, which will be requested from the ECDC.

2. **Vaccination coverage dataset**
   The data in this dataset comes from the European Union/European Economic Area (EU/EEA) countries' Vaccine Tracker submissions to ECDC via the European Surveillance System (TESSy). It contains data on the COVID-19 vaccine rollout, with each row containing the corresponding data for each targeted study vaccine (Pfizer, AstraZeneca, Moderna, and Janssen) for a specific week and country. The data is stratified by several age categories (0-4, 5-9, 10-14, …) with information regarding the number of doses received (first/second dose) and age-specific population for the country are available.

3. **Data on vaccine effectiveness**
   Literature reviews (e.g., by Bernal et al. (2021) [16] and Vasileiou et al. (2021) [17]) can be used to determine the efficacy of various vaccines against symptomatic disease, COVID-19 hospitalization, COVID-19 ICU admission, and COVID-19 death.

4. **Data on Variance of Concerns (VoCs)**
   The dataset contains data on the volume of COVID-19 sequencing, as well as the number and percentage of variants of concern (VoCs) distributed by week and country (30 countries included) that was submitted to the GISAID EpiCoV database and TESSy since the beginning of September 2020. The dataset also included several VoCs (such as Alpha and Delta), the number of variant detections reported, and the variant percentage.

Risks

The potential risks of COVID-19 vaccination are similar as in the initial EMA methodology defined as a difference in probability of the risk event in the vaccinated population and the unvaccinated population.

$risk = R_v - R_0$, with R_0 the probability of a risk before and R_v after vaccination

The **observed events after vaccination** are recorded by EudraVigilance and the patients exposed to the vaccine under study can be retrieved directly from Member States by EMA and ECDC. The ratio of the observed events and patients exposed to vaccine results in an estimate for the **probability of the risk after vaccination**. The probability of risk in the unvaccinated population or background risk can be retrieved through background rates

provided (or estimated) by EMA or, in case no information is available for a specific adverse event, it can be set to zero.

5.3.2 Covariates

Additional benefits and risks can be added to the model, as well as additional covariates such as comorbidities and additional compartments for vaccines or mixed vaccines. When covariate data is missing, data augmentation could be used, although it may not be trivial to do so.

5.3.3 Vaccine effectiveness

Vaccine effectiveness will be estimated from available observational and experimental data.

5.4 Software requirements (for recalculating prior)

The model will be implemented in the statistical software package R. The toolkit will be made available through an interactive online R Shiny web application.

5.5 Data management

Data needs to be structured in a well-documented format, of which a clear description will be given, such that it is straightforward for the end user to upload and use the relevant data.

5.6 Sensitivity Analysis/Simulation

Uncertainty of input variables can be incorporated into priors into the Bayesian analysis. Alternatively, sensitivity analysis can be performed by repeating the analysis with varying input values. The latter is a deterministic sensitivity analysis. For example when underreporting of risk events is suspected.

5.7 Quality Control

Scientific & computational risks: The project shows a natural overlap with core research activities of the team (See Section 2). Specific methodological focus of individual tasks are aligned with the expertise of researchers. The team has access to and ample experience with supercomputing infrastructure of the (VSC) in case computing complexity would require so (e.g., to calibrate the compartmental model for different member states).

Reproducibility: All necessary parameters to fully reproduce results will be saved and included in the deliverable: e.g., R (incl. R packages) and (R2)OpenBUGS versions, seeds for

random number generation (used in simulation studies & statistical methods using random number generators), etc.

Deliverables: The service manager coordinates the scientific content of the project, checks confidentiality and security issues, and guarantees high quality protocols, reports and tools as deliverables. THe GVP Module VIII1, section VIII.B.4.3.2. will be followed as format for the study report (D2).

Code review: The R code written by the main researcher to analyse and model the data, will undergo an independent check by a backup researcher in the same profile. Best practices for writing code will be used throughout, such as relevant commenting and structuring the code and use consistent naming.

User friendliness of the tool and manuals/tutorials: The team will give special attention to the user friendliness of the tool and supporting manuals. In the tutorial, we will guide the user through the steps required to load the data and to perform and interpret different kinds of analyses. The R Shiny web application will be user-friendly and accompanied with the required explanation on how to use it. It will be easy to install, update and does not need commercial third-party software. The interface will be reliable, intuitive to use, well-organized and easy to locate different tools and options. Internal review as well as feedback from EMA will be taken into account to optimize these aspects.

Warranties: We would like to clarify that The Flemish Codex Higher Education limits the capacity of universities to provide warranties. UHasselt can assume liability regarding the execution of the research, but we cannot provide any warranties on the usability or suitability of the results for a particular purpose. We will provide services in accordance with all applicable law and to our best effort.

5.8 Other aspects

Not applicable

Section 6. Construction of composite measures

6.1. Available methodologies (literature review)

The “Accelerated development of vaccine benefit-risk collaboration in Europe” (ADVANCE) project funded by the Innovative Medicines Initiative (IMI), recently reviewed existing benefit-risk methodology specifically for vaccines [9]. The **IMI-ADVANCE project** was launched in October 2013 and consisted of 200 researchers from more than 30 institutions, including the European Centre for Disease Prevention and Control (ECDC), the EMA, vaccine manufacturers, academics, regulators, public health institutes and authorities and small and medium enterprises (SMEs).

Benefit-risk measures can be divided into three groups: (1) Number Needed to Treat (NNT) or Harm (NNH) and variants thereof, (2) measures based on differences in benefit and risk, and (3) measures based on ratios of benefit and risk.

The **NNT or NNH** is the reciprocal of a difference in probabilities, which results in undesirable statistical and mathematical properties [18], implying that NNT, and all its variants taking the reciprocal of differences, is not a good measure to reflect uncertainty [9]. Variants without a reciprocal of differences have been proposed, such as PIN-ER-t [19] , but they are limited to only one event for clinical benefit and one risk event.

Of the benefit-risk measures based on differences in benefit and risk, the **Incremental Net Health Benefit (INHB)** is often used in Health Technology Assessments [9]. The net health benefit (NHB) is the difference between the sum of the benefits and the sum of the risks of vaccination, with all outcomes expressed using the same metric. The INHB is then the, possibly weighted, difference between the NHB in the vaccinated population and the unvaccinated population:

$$INHB = \sum_{i=1}^{k} w_i(E_{vi} - E_{0i}) - \sum_{j=1}^{l} w_j(R_{vj} - R_{0j}),$$

with *k* and *l* the number of benefit and risk outcomes, E_0 the benefits before and E_v after vaccination, and similarly for the risks (R_0 and R_v). The weights w_i and w_j are all positive and reflect the relative severity of the health outcomes. If the weights are all equal to 1, all benefit and risk outcomes are considered equally important.

The benefits and risks usually are expressed in QALYs or derivations thereof [20], which are not readily available for the COVID-19 vaccines. Recently, in a simulation study on rotavirus vaccination, rates per life years were used [21], which have the disadvantage of interpretation. Indeed, the INHB value, based on rates per life years, will be continuous, unlimited and depends on the number of events or risks. Consequently, the advantage or disadvantage of vaccination is not clearly available from the INHB value, especially in comparison between vaccines with a different number of events or risks.

Finally, the **incremental risk-benefit ratio (IRBR**) is the ratio of the difference in risk to the difference in benefit and is analogous to the incremental cost-effectiveness ratio (ICER) used in Health Technology Assessment. The IRBR however shares the undesirable statistical and mathematical properties of a ratio, similar to NNT and ICER.

The composite benefit-risk measure, recommended by the IMI-ADVANCE is the Incremental Net Health Benefit (INHB) [9].

Recently, a class of **Generalized Pairwise Comparison (GPC) statistics** [22] has been suggested as a benefit-risk measure [23]. The GPC statistics are based on comparing outcomes for each possible pair of subjects and assigning a winner in the pair. In the GPC methodology, outcomes can be ranked according to preference, where usually the most severe is ranked first, and allows for the combination of any type and number of outcomes. Both absolute (net benefit [24]) and relative (win odds [25], win ratio [26]) measures have been proposed, with a relatively straightforward interpretation. Benefit-risk measures, based on aggregates, have been criticized to ignore correlation between benefit and risk. **Prioritized benefit-risk assessment** with GPC has been suggested in oncology trials [23], which accounts for correlation between benefit and risk. However, treating the risk as the lowest ranked outcome would not fully evaluate the risk. Moreover, the method **requires subject-specific data**, which is not available for the vaccine evaluation.

6.2. Assessment of feasibility to create composite measures for the purpose of this exercise

We propose a net benefit (NB) statistic, based on non-prioritized GPC, which is very similar in spirit to the INHB.

Within the GPC framework, outcomes can also be evaluated in a **non-prioritized** way [22, 27, 28], which would allow for full evaluation of benefits and risks, while preference weights can be incorporated. The correlation between benefits and risks will not be displayed in the size of the statistic, but in the context of COVID-19 vaccine evaluation this correlation may be less important.

Although the GPC statistics are based on comparing outcomes for each possible pair of subjects, which would require subject-specific data and may create computational difficulties with the size of subjects in this proposal, when binary outcomes are used, an analytic calculation based on **probabilities of an event** is possible [29]. To exclude overlapping events within subjects, conditional probabilities of the clinical events derived from the compartmental model can be used.

Computationally, the **net benefit (NB) statistic**, based on non-prioritized GPC, is very similar in spirit to the INHB (likewise for the win ratio statistic and the IRBR). We propose to divide the net benefit statistic with the number of benefits and risks, so the statistic will have values between -1 and 1, which makes it comparable between vaccine evaluations:

$$NB = \{ \sum_{i=1}^{k} w_i (P_{0i} - P_{vi}) + \sum_{j=1}^{l} w_j (R_{0j} - R_{vj}) \} / (k + l),$$

with *k* and *l* the number of benefit and risk outcomes, P_0 the probability of an event in the benefit evaluation before and P_v after vaccination, and similarly for the probability of a risk event (R_0 and R_v). The weights w_i and w_j are all positive and reflect the relative severity of the health outcomes. If the weights are all equal to 1, all benefit and risk outcomes are considered equally important.

Considering all probabilities as independent variables, it is straightforward to construct a 95% confidence interval for the proposed statistic. The GPC framework offers thus interesting possibilities for the construction of composite endpoints in a benefit-risk assessment.

Section 7. Proposal toolkit

A user-friendly, interactive dashboard will be constructed in a Shiny R app, where the user can enter relevant or updated estimates on the clinical events and risks. Error messages will be prompted if these input values are incorrectly provided (a proportion above 100%). A menu with point and select functions will allow the user to flexibly choose the covariates, and benefit and risk measures in the benefit risk assessment. Both single and multiple benefits and risks can be integrated. Several dashboards have been created by UHasselt in the last year concerning COVID [30], including an interactive dashboard [31].

The generated output will display the estimated benefits and risks per covariate selected. If multiple benefits and risks have been selected, the benefit-risk assessment will be displayed per benefit-risk combination in a figure. All figures, each with one benefit-risk combination will be shown in one screen. Per benefit-risk figure, the benefit-risk assessment will be displayed for all categories of a covariate, where benefits are displayed on the left of the covariates and risks to the right, similar as in Winton Centre Cambridge [32]. Uncertainty about the benefit-risk estimates will be incorporated in the values of the figures, making the interpretation of the values for the users easier. The interactivity allows the user to perform a deterministic sensitivity analysis by entering several estimates for a single input variable.

Section 8. Summary of Deliverables

DL 1 Initial Toolkit (what will be delivered)

The initial interactive dashboard will allow the user to select multiple benefits and risks and covariates such as age class, gender or comorbidities.

DL 3 Updated Toolkit

In collaboration with EMA, additional features can be added to the dashboard, such as a split of the results by low/high incidences, per vaccine, or by allowing the selection of a time period or VoC. Additionally, comparative figures from other member states can be added to give a European perspective to the country-specific benefit-risk assessment.

Manual to support the use of the dashboard

The manual will include a Getting Started section, where the link to the dashboard and a description of the general screen will be provided. In a subsequent section the detailed use of the different parts of the application will be explained. This section contains several subsections, such as entering country-specific estimates, selecting benefits, risks and covariates, interpretation of the output and additional features. The final section will provide details of the methodology.

Section 9. Storing and Archiving of Data/Outputs.

Google Drive's controlled and collaborative document management strategy makes it easy to collaborate on documents directly, write comments, assign tasks, receive feedback and see changes taking place in real time. All data and documents (draft reports, R code, minutes of weekly meetings, etc.) related to the project will be treated as confidential, access will only be granted to members of the project team. The Google Cloud platform provides a backup system with a 30-day guaranteed backup system (in practice over 1 year). The Google Cloud platform used by UHasselt is encrypted and data storage only happens on servers within the European Economic Area. Version control and encryption of data on the GCP is a default. A separate Google shared drive would be created to store and share all the data within this project. The data and information that is included, is only accessible by the project team.

Transfer of data and deliverables between EMA and the UHasselt project team will take place via email or via EUDRALINK whenever requested by EMA.

Section 10. Plans for disseminating and communicating study results

Where applicable, publication, dissemination, or use in teaching will be sought of the methodology and other results developed, in full compliance with the contract with EMA, which stipulates that EMA acquires ownership, but with art. I.14 stating that materials can be used in teaching and for publication in the peer-reviewed literature. In line with the contract, EMA will be given a chance to review and give feedback, prior to submission or use in teaching.

Section 11. Confidentiality of handling data

The confidentiality of the data used will be maintained, in agreement with the contract and the laws applicable.

Section 12. References

[1] World Health Organization. *WHO Coronavirus (COVID-19) Dashboard*, 2021. https://covid19. who.int/.

[2] N. Hens, P. Vranckx, and G. Molenberghs. The COVID-19 epidemic, its mortality, and the role of non-pharmaceutical interventions. *European Heart Journal: Acute Cardiovascular Care*, 9(3):204–208, 2020.

[3] G. Molenberghs, M. Buyse, S. Abrams, N. Hens, P. Beutels, C. Faes, and others. Infectious diseases epidemiology, quantitative methodology, and clinical research in the midst of the COVID-19 pandemic: Perspective from a European country. *Contemporary clinical trials*, 99:106189, 2020.

[4] European Centre for Disease Prevention and Control. *Risk of SARS-CoV2 transmission from newly infected individuals with documented previous infection or vaccination.*, 2021. https://www.ecdc.europa.eu/en/publications-data/
sars-cov-2-transmission-newly-infected-individuals-previous-infection.

[5] European Centre for Disease Prevention and Control. *Weekly COVID-19 country overview.*, 2021. https://covid19-country-overviews.ecdc.europa.eu/.

[6] European Medicines Agency. *AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets*, 2021. https://www.ema.europa.eu/en/news/
astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood.

[7] European Medicines Agency. *COVID-19 Vaccine Janssen: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets.*, 2021. https://www.ema.europa.eu/en/news/
covid-19-vaccine-janssen-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood.

[8] European Medicines Agency. *COVID-19 vaccines: update on ongoing evaluation of myocarditis and pericarditis.*, 2021. https://www.ema.europa.eu/en/news/covid-19-vaccines-update-ongoing-evaluation-myocarditis-pericarditis.

[9] Innovative Medicines Initiative. *Accelerated development of vaccine benefit-risk collaboration in Europe*, 2021. https://www.imi.europa.eu/projects-results/project-factsheets/advance.

[10] Centres for Disease Control and Prevention. *Population-Level Risk-Benefit Analysis, 2021*. https: //www.cdc.gov/vaccines/covid-19/info-by-product/janssen/risk-benefit-analysis. html.

[11] S. Abrams, J. Wambua, E. Santermans, L. Willem, E. Kuylen, P. Coletti, and others. Modeling the early phase of the Belgian COVID-19 epidemic using a stochastic compartmental model and studying its implied future trajectories. *Epidemics*, 35:100449, 2021.

[12] L. Willem, S. Abrams, P. Libin, P. Coletti, E. Kuylen, O. Petrof, and others. The impact of contact tracing and household bubbles on deconfinement strategies for COVID-19: an individual-based modelling study. *Nature Communications*, 12:1524, 2021.

[13] Wallinga, J., Teunis, P., & Kretzschmar, M. (2006). Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents. *American journal of epidemiology*, *164*(10), 936-944.

[14] Hens, N., Shkedy, Z., Aerts, M., Faes, C., Van Damme, P., & Beutels, P. (2012). Who Acquires Infection from Whom? The Traditional Approach. In *Modeling Infectious Disease Parameters Based on Serological and Social Contact Data* (pp. 219-232). Springer, New York, NY. https://doi.org/10.1007/978-1-4614-4072-7_14

[15] Creech, C. B., Walker, S. C., & Samuels, R. J. (2021). SARS-CoV-2 vaccines. *JAMA*, *325*(13), 1318-1320.

[16] Lopez Bernal, J., Andrews, N., Gower, C., Gallagher, E., Simmons, R., Thelwall, S., ... & Ramsay, M. (2021). Effectiveness of Covid-19 vaccines against the B. 1.617. 2 (Delta) variant. *New England Journal of Medicine*, *385*(7), 585-594.

[17] Vasileiou, E., Simpson, C. R., Robertson, C., Shi, T., Kerr, S., Agrawal, U., ... & Sheikh, A. (2021). Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people.

[18] Lesaffre, E., & Pledger, G. (1999). A note on the number needed to treat. *Controlled Clinical Trials*, *20*(5), 439-447.

[19] Heller, R. F., Buchan, I., Edwards, R., Lyratzopoulos, G., McElduff, P., & St Leger, S. (2003). Communicating risks at the population level: application of population impact numbers. *Bmj*, *327*(7424), 1162-1165.

[20] LD. Lynd, M. Najafzadeh, L. Colley, MF. Byrne, AR. Willan, MJ. Sculpher, et al. Using the incremental net benefit framework for quantitative benefit-risk analysis in regulatory decision-making–a case study of alosetron in irritable bowel syndrome. *Value Health*, 13(4):411–7, 2010. 23

[21] Bollaerts, K., De Smedt, T., Donegan, K., Titievsky, L., & Bauchau, V. (2018). Benefit–Risk Monitoring of Vaccines Using an Interactive Dashboard: A Methodological Proposal from the ADVANCE Project. Drug safety, 41(8), 775-786.

[22] J. Verbeeck, E. Spitzer, T. de Vries, G. van Es, W. Anderson, N. Van Mieghem, et al. Generalized pairwise comparison methods to analyze (non)prioritized composite endpoints. *Stat Med*, 38:5641–5656, 2019.

[23] Buyse, M., Saad, E. D., Peron, J., Chiem, J. C., De Backer, M., Cantagallo, E., & Ciani, O. (2021). The Net Benefit of a treatment should take the correlation between benefits and harms into account. *Journal of Clinical Epidemiology*, *137*, 148-158.

[24] M. Buyse. Generalized pairwise comparisons of prioritized outcomes in the two-sample problem. *Stat Med*, 29:3245–3257, 2010.

[25] E. Brunner, M. Vandemeulebroecke, and T. Mütze. Win odds: An adaptation of the win ratio to include ties. *Stat Med*, 40:3367– 3384, 2021.

[26] S. Pocock, C. Ariti, T. Collier, and others. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J*, 33:176–182, 2012.

[27] R. Ramchandani, D. Schoenfeld, and D. Finkelstein. Global rank tests for multiple, possibly censored, outcomes. *Biometrics*, 72:926–935, 2016.

[28] S. Yang and J. Troendle. Event-specific win ratios and testing with terminal and non-terminal events. *Clinical Trials*, 18:180–187, 2021.

[29] G. Rauch, A. Jahn-Eimermacher, W. Brannath, and M. Kieser. Opportunities and challenges of combined effect measures based on prioritized outcomes. *Stat Med*, 33:1104–1120, 2014.

[30] P. Beutels, N Hens, T. Neyens, K. Pepermans, and P. Van Damme. *Corona Study*, 2020. https: //corona-studie.shinyapps.io/corona-studie/.

[31] SIMID Group and S. Funk. *Social Contact Rates (SOCRATES) Data Tool*, 2020. http://www. socialcontactdata.org/socrates/.

[32] Winton Centre Cambridge. *News - Communicating the potential benefits and harms of the Astra-Zeneca COVID-19 vaccine*, 2021. https://wintoncentre.maths.cam.ac.uk/news/communicating-potential-benefits-and-harms-astra-zeneca-covid-19-vaccine/.