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Cécile Tran Kiem[1,2], Clément Massonnaud[3,4], Daniel Levy-Bruhl[5], Chiara Poletto[6], Vittoria Colizza[6], Paolo Bosetti[1], Arnaud Fontanet[7,8], Amélie Gabet[5], Valérie Olie[5], Laura Zanetti[9], Pierre-Yves Boëlle[6], Pascal Crépey[3], Simon Cauchemez[1]

1. Mathematical Modelling of Infectious Diseases Unit, Institut Pasteur, UMR2000, CNRS, Paris, France
2. Collège Doctoral, Sorbonne Université, Paris, France
3. Univ Rennes, EHESP, REPERES « Recherche en Pharmaco-Epidémiologie et Recours aux Soins » – EA 7449, Rennes, France
4. Centre Hospitalier Universitaire de Rouen, Département d'Informatique Médicale, D2IM, Rouen, France
5. Santé Publique France, Saint Maurice, France
6. Institut Pierre Louis d'Epidémiologie et de Santé Publique, Sorbonne Université, INSERM, Paris, France
7. Emerging Diseases Epidemiology Unit, Institut Pasteur, Paris, France
8. PACRI Unit, Conservatoire National des Arts et Métiers, Paris, France
9. Haute Autorité de Santé, Paris, France

Corresponding author:

Simon Cauchemez

Mathematical Modelling of Infectious Diseases Unit, Institut Pasteur,

25-28 rue du Dr Roux, 75015 Paris, France

simon.cauchemez@pasteur.fr

Abstract

Background

The roll-out of COVID-19 vaccines is a multi-faceted challenge whose performance depends on pace of vaccination, vaccine characteristics and heterogeneities in individual risks.

Methods

We developed a mathematical model accounting for the risk of severe disease by age and comorbidity and transmission dynamics. We compared vaccine prioritisation strategies in the early roll-out stage and quantified the extent to which measures could be relaxed as a function of the vaccine coverage achieved in France.

Findings

Prioritizing at-risk individuals reduces morbi-mortality the most if vaccines only reduce severity, but is of less importance if vaccines also substantially reduce infectivity or susceptibility. Age is the most important factor to consider for prioritization; additionally accounting for comorbidities increases the performance of the campaign in a context of scarce resources. Vaccinating 90% of ≥65 y.o. and 70% of 18-64 y.o. before the autumn 2021 with a vaccine that reduces severity by 90% and susceptibility by 80%, we find that control measures reducing transmission rates by 15-27% should be maintained to remain below 1,000 daily hospital admissions in France with a highly transmissible variant (basic reproduction number R_0=4). Assuming 90% of ≥65 y.o. are vaccinated, full relaxation of control measures might be achieved with a vaccine coverage of 89-100% in 18-64 y.o or 60-69% of 0-64 y.o.

Interpretation

Even in optimistic scenarios, current vaccination intentions in the French populations might not allow a complete relaxation of control measures. Vaccination of children, if possible, could help achieve this objective.

Funding

HAS.

Introduction

Over the last year, the COVID-19 pandemic has generated large numbers of hospitalisations and deaths. In addition, the drastic control measures implemented to contain disease spread have caused major social and economic disruptions. In most locations, immunity conferred by natural infection remains much lower than the one required for herd immunity.[1] In this context, the progressive roll-out of safe and effective COVID-19 vaccines provides a crucial pharmaceutical tool to exit the current crisis. It however comes with a number of challenges associated with availability, urgency and finally progressive phasing out of epidemic time.

It is important to further clarify how vaccines should be distributed when the number of vaccine doses is limited and one aims to minimize morbi-mortality and the stress on the healthcare system. This is crucial for countries that are still at an early stage of their campaign and for the many countries where vaccination has not started yet. For vaccines reducing the severity of the disease, vaccination strategies prioritized towards older individuals have been shown through modelling to substantially reduce the number of COVID-19 deaths[2–5] owing to the strong age dependence for severe infections.[6,7] It may also be relevant to consider comorbidities like obesity or diabetes in the prioritization scheme, as these are independent risk factors for mortality with an age-dependent effect.[8,9] As the extent of vaccine protection on the risk of infection is increasingly well characterized,[10,11] a renewed examination of the various prioritisation strategies combining age and comorbidities will be required.

To guide medium term strategic planning, it is essential to anticipate how vaccination might impact the course of the pandemic in the Autumn 2021. In a context where healthcare systems have been on the brink of saturation several times and economies have been devastated by restrictive control measures, we argue that vaccination could be considered successful if it allowed relaxing control measures while keeping COVID-19 stress on the healthcare system at a manageable level. It is therefore important to determine what combination of control measures and vaccine coverage in different age groups would ensure a small enough peak in COVID-19 hospital admissions after relaxation. Furthermore, examining how the vaccination of children might facilitate the control of the epidemic in the Autumn 2021 would be helpful in case vaccines were recommended in this age group.

Here, we developed a mathematical model to understand how vaccine characteristics, levels of vaccine coverage and heterogeneities in individual risks may affect the impact of vaccination in the short and medium term, using France as a case study. The model is used both to investigate the question of the relaxation of control measures in the autumn and that of prioritisation at the early stage of the campaign.

Methods

Epidemiological model and scenarios

We adapt an age-structured compartmental model describing the spread of SARS-CoV-2 in the general population in metropolitan France[6] (see Supplement) to capture the impact of comorbidities on the age-stratified risk of developing severe COVID-19. It accounts for the interaction between age and comorbidity on the risk of hospitalisation, as estimated by the Centers for Disease Control and Prevention based on the COVID-NET surveillance network

data[9] (see Supplement). We assume that children aged 0-9 years old (y.o.) and those aged 10-17 y.o. are respectively 50% and 25% less susceptible to infection than adults.[12,13]

In our baseline scenario, we assume that we will observe in 2021 a series of epidemic waves with the same magnitude as the one in the Autumn 2020 (501,000 COVID-19 hospitalisations and 102,000 hospital deaths during 2021 in the absence of vaccination) (Figure 1). In a sensitivity analysis, we assume that we will observe in 2021 a series of epidemic waves with a smaller magnitude than the one in the Autumn 2020 (330,000 hospitalisations and 66,000 hospital deaths during 2021 in the absence of vaccination) (Figure S1).

Model for the vaccination campaign

Nature of vaccine protection

The first clinical trials suggested that vaccines were 90% effective against severe outcomes (severity).[14–16] However, their impact on the risk of transmission (infectivity) or of infection (susceptibility) remained uncertain for several months. Recent data from vaccine field studies suggest that vaccines could reduce susceptibility by around 80%.[10,11,17,18] To investigate how changes in the understanding of vaccine characteristics can impact the assessment of vaccine strategies, we explored three different scenarios regarding the efficacy of vaccines: (i) a vaccine reducing the severity by 90%, without any impact on infectivity or susceptibility (vaccine *Severity*), (ii) a vaccine reducing the severity by 90% and the infectivity by 30%, that seemed a reasonable scenario in the absence of data regarding transmission (vaccine *Transmission*), (iii) a vaccine reducing the severity by 90% and the susceptibility by 80% (vaccine *Susceptibility*, see Supplement), the scenario that we now favor given current data. We assume that vaccine efficacy lasts until the end of the study period.

Vaccination campaign characteristics

We consider a two-doses distribution scheme, with vaccine efficacy acquired 15 days after the distribution of the first dose. We account for the constraints associated with the vaccine delivery schedule, the vaccination roll-out pace and the delay between doses. First doses are distributed when possible, always ensuring that a second dose will be available after a 21-day delay. We assume that the vaccination campaign starts on February 1st, 2021 under a roll-out pace of 200,000 doses per day, close to that in France throughout March 2021. The vaccine delivery schedule that we use is detailed in Table S1. As a sensitivity analysis, we also explore a scenario where vaccines are delivered under a roll-out pace of 450,000 doses per day.

Vaccination prioritisation strategies

We consider the following age- and comorbidities-groups: individuals (i) older than 75 y.o., (ii) aged 65-74 y.o. with 0, 1 or at least 2 conditions, (iii) aged 50-64 y.o. with 0, 1 or at least 2 conditions and (iv) aged 18-49 y.o. with 0, 1 or at least 2 underlying medical conditions. The size of these age groups in the French population are detailed in Table S2.

We first explore strategies targeted towards single age or comorbidity groups. We then explore prioritisation strategies, where a prioritisation order is defined. The vaccination starts within a group when 70% of vaccine coverages are reached in groups of higher priority. We consider

3 prioritisation strategies: (i) without prioritisation, where available doses are distributed at random in individuals older than 18 y.o. (*At random 18y+*), (ii) a prioritisation based on age (≥ 75 y.o. then 65-74 y.o. then 50-64 y.o. then 18-49 y.o.), (iii) a prioritisation based on age and comorbidities (≥ 75 y.o. then 65-74 y.o. with at least 2 conditions then with 1 condition then without any condition then 50-64 y.o. with at least 2 conditions and so on until reaching the 18-49 y.o. without any condition).

We assess the impact of each vaccination strategy on the proportion of deaths and hospital admissions averted during 2021.

Modelling the relaxation of control measures

We explore the extent to which control measures might be relaxed depending on vaccine coverage. For a range of vaccine coverages in individuals ≥65 y.o. and individuals aged 18-64 y.o., we derive the reductions in transmission rates in the general population that would remain necessary to ensure the peak in daily hospital admissions remains below 1,000 (an arbitrary threshold that is about 3 times lower than the values observed during the first two pandemic waves in France) between September 1st, 2021 and April 1st, 2022. This is done for different values of the basic reproduction number that characterizes a situation with complete relaxation of measures and no immunity: (i) R_0 of 2.5 and 3 (as estimated in several locations prior the implementation of control measures) (ii) R_0 of 4 (to explore the potential impact of more transmissible variants[19–21]). This assessment is performed for different proportions infected by September 1st, 2021 (30%, range 25-35%) (see Supplement). We also consider a scenario where vaccines have been demonstrated to be safe for children, have the same efficacy in children as in adults and where children are vaccinated.

Role of the funding source

Haute Autorité de Santé contributed to study design, data interpretation and commented on the manuscript. The corresponding author made the decision to submit the paper for publication.

Results

Our model can reproduce the dynamics of hospital and admissions in intensive care units (ICU) observed since the beginning of the pandemic in metropolitan France (Figure 1A, B). Accounting for the increased risk of developing a severe form of COVID-19 associated to identified comorbidities (Table S5), we derive estimates of the probability of hospitalisation given infection, the probability of ICU admission given hospitalisation and the probability of death given hospitalisation stratified by age-groups and number of comorbidities (Figure 1C-E). For instance, we estimate that individuals aged 70-74 y.o. have a probability of hospitalisation upon infection of 20.2% if they have at least 2 comorbidities and 9.6% if they have less than 2 comorbidities (Table S3).

We first evaluate the impact of vaccination strategies targeted towards specific age and comorbidity groups (Figure 2). When considering a vaccine that reduces the probability of severe outcomes among vaccinated individuals by 90% but has no impact on transmission and susceptibility (Vaccine *Severity*), the most efficient strategy to minimize hospitalisations and deaths is to allocate first doses to individuals older than 75 y.o. (8.5% reduction in deaths for the first 2 million doses, corresponding to the vaccination of 1 million individuals), followed by strategies targeting 65-74 y.o. (4.2% reduction) and 50-64 y.o. (2.1% reduction) with at least two comorbidities. Targeting individuals aged 18-49 y.o. has little impact (Figure 2A-B). When considering a vaccine that also induces a moderate 30% reduction on transmission (Vaccine *Transmission*), we find that the vaccination of those older than 75 y.o. remains the most efficient strategy to minimize deaths. Vaccinating individuals aged 18-49 y.o. without comorbidities enables larger reductions in deaths (3.1% for 2 million doses) compared to a vaccine that does not impact transmission (<0.05% for 2 million doses). Finally, if the vaccine reduces severity by 90% and susceptibility by 80% (Vaccine *Susceptibility*), vaccinating individuals aged 18-49 y.o. without comorbidities can induce a reduction in deaths (8.3% for 2 million doses) that is relatively similar to that obtained when vaccinating individuals older than 75 y.o. (11.2% for 2 million doses) (Figure 2E) and a reduction in hospitalisations even slightly higher (Figure 2F). For such a vaccine the largest reductions in hospitalisations are obtained by targeting those aged 50-64 y.o. with at least two comorbidities and the benefits associated with the vaccination of young individuals (that contribute substantially to transmission) increase as the reproduction number gets closer to 1 (Figure S2). Similar trends are observed when considering a vaccine with a lower efficacy (Figure S3) or a vaccine rolled-out at a faster pace (Figure S4).

We then evaluate several prioritisation strategies (Figure 3). For the vaccine *Severity*, prioritisation based on age or on age and comorbidities substantially outperforms distribution at random (Figure 3A-B). For example, assuming 9.4 million vaccinated individuals (i.e. the number of individuals who will have received a first dose by May 1st, 2021), 42.1-42.2% deaths would be averted under the prioritized strategies, whereas only 11.6% deaths would be averted in unprioritized strategy. Similar conclusions are drawn for a vaccine that also has a moderate impact on transmission, though the difference between the strategies shrinks (Figure 3C-D). For a vaccine that also substantially reduces susceptibility (Figure 3E-F), we find that the three strategies lead to similar reductions in deaths (51.4-51.4% for prioritized strategies and 50.8% for random distribution with 9.4 million vaccinated individuals). For this latter vaccine, the unprioritized strategy can outperform the prioritized ones if the reproduction number is closer to 1 (Figure S5). The rankings between the strategy remain unchanged if vaccines are distributed at a faster pace (Figure S6). Prioritization accounting for age and comorbidities is slightly better than a strategy solely based on age, with a gain that decreases as more doses are being distributed (Figure S7).

In Figure 4A, we show the expected peak in daily hospital admissions in the Autumn 2021 if control measures were to be completely relaxed on September 1st 2021, as a function of the vaccine coverage reached in those aged ≥65 y.o. and 18-64 y.o. This is done under the assumption that 25-35% of the population will have been infected by SARS-CoV-2 by September 1st 2021 and considering the vaccine *Susceptibility*. If the basic reproduction number R_0 of the dominant variant in the Autumn is similar to that measured in spring 2020 (R_0=3.0), a vaccine coverage of 90% in ≥65 y.o. and 70% in 18-64 y.o. (59% of the French population once we account for unvaccinated children) would result in a peak of 420-1,100

daily hospital admissions. If the circulation of more transmissible variants such as B.1.1.7 increased R_0 to 4, this would increase to 2,300-4,000 daily admissions at the peak, in between the peak values of the first (3,642) and second (2,791) waves in metropolitan France (Figure 4A).

To avoid reaching a peak of 1,000 daily admissions for a vaccine coverage of 90% in ≥65 y.o. and 70% in 18-64 y.o., control measures would need to reduce transmission rates in the general population by 0-2% for R_0=3.0 and 15-27% for R_0=4.0. The required effort would increase to 3-16% (R_0=3.0) and 27-37% (R_0=4.0) if we only managed to vaccinate 50% of 18-64 y.o. (Figure 4B). To put these reductions into context, control measures during the French strict lockdown in Spring 2020 and the softer lockdown in November 2020 reduced transmission rates by around 80% and 70%, respectively.

We then explore the combination of vaccine coverages in ≥65 y.o. and 18-64 y.o. that would ensure the peak in daily hospital admissions remains below 1,000 (Figure 4C). Assuming R_0=3.0, the vaccine coverage in 18-64 y.o. would need to be 62-84% and 54-73% for a vaccine coverage of 70% and 90% in ≥65 y.o, respectively. For R_0=4.0, complete relaxation would not be achievable for a vaccine coverage of 70% in ≥65 y.o.; if 90% of ≥65 y.o. were vaccinated, it would require a vaccination coverage of ≥89% in 18-64 y.o. If children were included in the campaign, complete relaxation of control measures might be possible with the vaccination of 60-69% of 0-64 y.o. if 90% of ≥65 y.o. were vaccinated (Figure 4D, S8). Vaccine coverages would need to be higher for vaccines that have a lesser impact on infectivity or susceptibility (Figure S8,S9) or that have lower efficacies (Figure S10). Lower vaccine coverages would be required if higher thresholds for the peak in daily hospital admissions were considered (Figure S11).

Discussion

We developed a mathematical model to investigate how vaccine characteristics, levels of vaccine coverage and heterogeneities in individual risks may affect the impact of SARS-CoV-2 vaccination strategies, both early on when prioritization may be necessary and at a later stage when relaxation of control measures may be considered.

We found that the impact of the vaccination campaign is strongly dependent on the nature of protection conferred by the vaccine, with important implications for campaign design. If the vaccine is protective against severe disease only, vaccination of those aged 18-49 y.o. is expected to have only limited impact on morbi-mortality as infections are mostly mild in this group. In this scenario, vaccination does not lead to a build up of herd immunity because vaccinated individuals can still get infected and transmit the virus. As a result, high levels of viral circulation may be observed even if vaccine coverage is high. In contrast, if the vaccine has an impact on transmission or susceptibility, the vaccination of younger individuals that play a key role in transmission can substantially reduce viral circulation and indirectly prevent the occurrence of severe forms of COVID-19. These results have important implications for the prioritisation of vaccines in the context of limited resources in the spring 2021. If vaccines only reduce disease severity with no impact on infectivity/susceptibility (direct effect only), prioritizing available doses to at-risk individuals largely outperforms strategies where vaccines are distributed at random (Figure 3A,B,G, H). As the indirect effect of vaccination becomes

larger (i.e. the vaccine also reduces infectivity and/or susceptibility), the gains achieved with age prioritisation decline (Figure 3C-F), with similar levels of reductions reached in the absence of prioritisation when vaccines substantially reduce susceptibility (Figure 3E).

Of the three possible effects of vaccines (i.e. reduction of severity, infectivity or susceptibility), the reduction in severity was the only one documented in early assessments of their impact.[14,16,22] In this context, prioritisation by age group and comorbidities was the most conservative approach to optimize allocation of first doses. Vaccine efficacy to reduce infectivity remains poorly characterized but there is increasing evidence that vaccines also substantially reduce susceptibility, at levels close to those considered in our vaccine *Susceptibility* scenario.[10,17,18] This information is crucial for the next stages of the vaccination campaign: while the vaccination of at-risk individuals needs to be maintained so that they benefit from the direct protection conferred by vaccines, it is also very important to achieve high vaccine coverages in younger age groups to benefit from the indirect effects of herd immunity. This is the only way to obtain an important relaxation of social distancing measures in the autumn.

Whether we can achieve full relaxation of control measures in the autumn will also depend on the transmission potential of the circulating viruses (usually characterized by the basic reproduction number R_0) at that time. If R_0 in the autumn 2021 was equal to 3 like in spring 2020,[6] we expect that a vaccine coverage of 90% in ≥65 y.o and 70% in 18-64 y.o. would be sufficient to maintain the peak in daily hospital admissions below 1,000. However, the variant B.1.1.7 that is now dominant in France is substantially more transmissible than historical lineages.[19–21] For R_0=4, and assuming a vaccine coverage of 90% in ≥65 y.o., vaccine coverage would need to increase to ≥89% in those aged 18-64 y.o. These levels are substantially higher than current vaccination intent in the French population (from 36% in 18-24 y.o. to 58% in 50-64 y.o. according to a survey performed in March 2021[23]). If such vaccine coverages cannot be achieved, some control of viral circulation may have to be maintained, potentially through Test-Trace-Isolate, protective measures (e.g. masks) or a certain level of social distancing. We would nonetheless expect these measures to be substantially less strict than those that have been necessary so far in the absence of vaccines (Figure 4). If vaccination is restricted to adults, high levels of viral circulation may be expected among children, contributing to the infection of unprotected parents and grandparents. If it is demonstrated that vaccines are safe in 0-17 y.o. and if they effectively reduce infectivity or susceptibility in this age group, full relaxation of control measures could be considered with a vaccine coverage of 60-69% in those aged 0-64 y.o. and 90% in ≥65 y.o. To illustrate the impact of the vaccination of children, we explored scenarios where all age groups below 18 y.o. were eligible for vaccination; but strategies restricted to older children might also be considered. Heterogeneities in the proportion of the population already infected by SARS-CoV-2 or in the levels of circulation of variants such as B.1.351 that partly escape protection conferred by the vaccine[24,25] also imply that the vaccine coverages required to go back to normal will differ across locations. Finally, the situation could be harder to control than anticipated here as we do not account for the increased severity reported for B.1.1.7.[25]

Compared to previous assessments of vaccination strategies, we explicitly accounted for how the probability to develop a severe form of COVID-19 increased with the number of comorbidities and for the interaction between the number of comorbidities and age. We could not consider the effect of comorbidities in those older than 75 y.o. due to insufficient data for this age group. However, our results show that the vaccination of individuals older than 75 y.o.

regardless of their number of comorbidities results in larger reductions in the number of deaths than the vaccination of younger age-groups (e.g. 65-74 y.o.) with at least 2 conditions. While prioritizing according to age and comorbidities optimally reduces the number of deaths and hospitalisations at the beginning of the program, accounting for comorbidities becomes less important when more doses are available. A limitation of our study is that the list of comorbidities we consider does not perfectly match the one used to characterize the association with severe outcome.[9] Nevertheless, the impact on our results should be limited, especially since we are considering relative risks associated to the number of conditions and not to specific pathologies individually.

Our modelling framework has been developed to describe the spread of SARS-CoV-2 in the community and is therefore not suited to describe epidemic dynamics in healthcare settings or elderly homes. As such, we do not account for the increased risks observed among healthcare workers and elderly homes' staff and residents. We may thus underestimate the impact of strategies prioritised towards the population older than 75 y.o., which implicitly takes into account the population of elderly homes.

Our modelling results highlight how understanding of vaccine characteristics, individual risks and vaccine coverages across groups is essential to optimize the design of the vaccination campaign and determine the level of relaxation of control measures that may be expected in the autumn.

Contributors: CTK and SC designed and planned the study. CTK, CM, PB, AG, VO and PC performed analyses. DLB, CP, VC, AF, LZ, PYB, SC critically commented on assumptions and model structure. CTK and SC wrote the first draft. All authors contributed to revisions of the manuscript.

Declaration of interests: PC reports consulting fees from Sanofi Pasteur for projects outside of the submitted work and unrelated to COVID-19. The other authors declare no competing interests.

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Figure 1

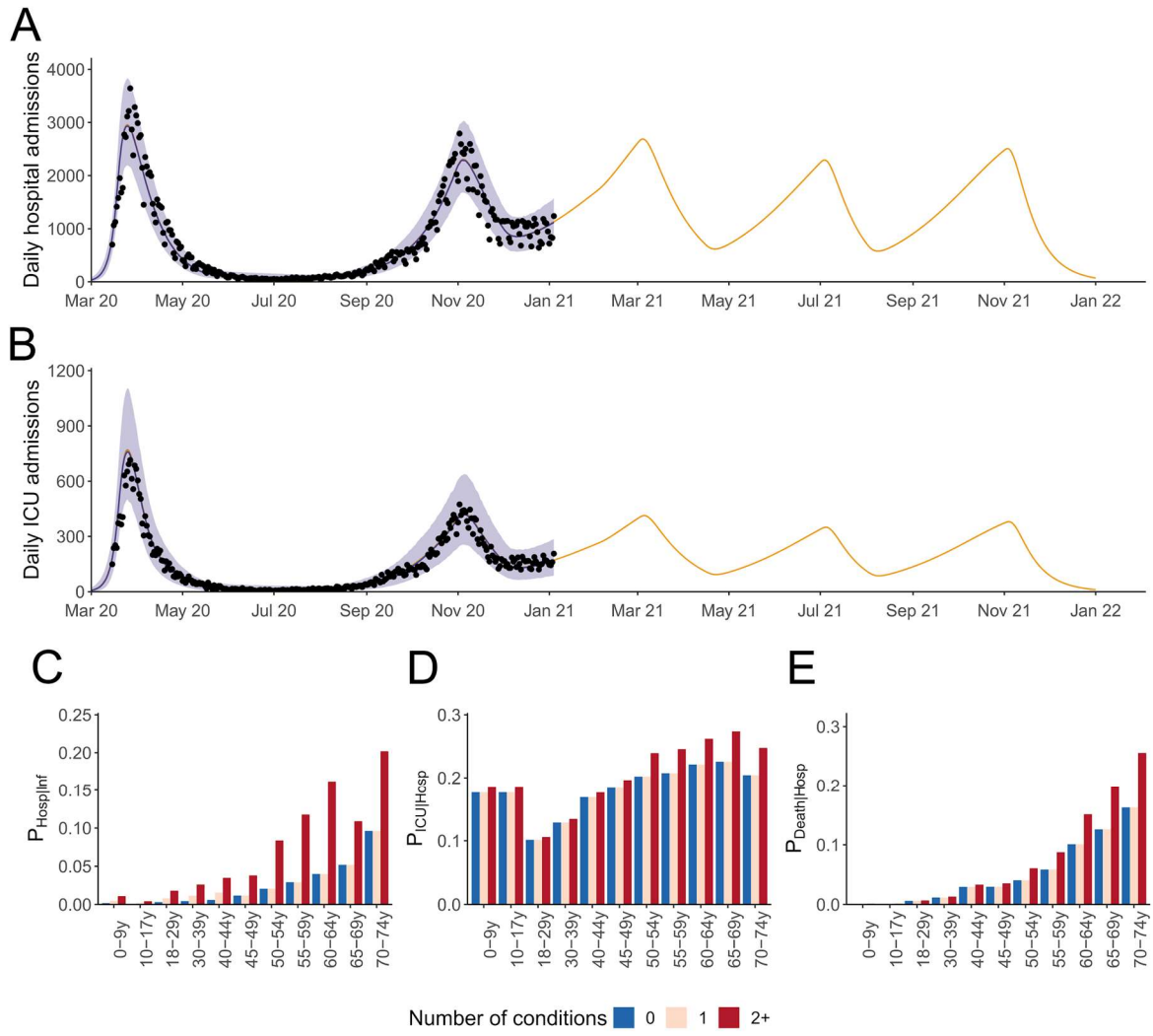

Figure 1: Daily **(A)** ICU and **(B)** hospital admissions in metropolitan France in our baseline epidemiological scenario. **(C)** Probability of hospitalisation given infection, **(D)** probability of ICU admission given hospitalisation and **(E)** death given hospitalisation stratified by age group and number of conditions.

Figure 2

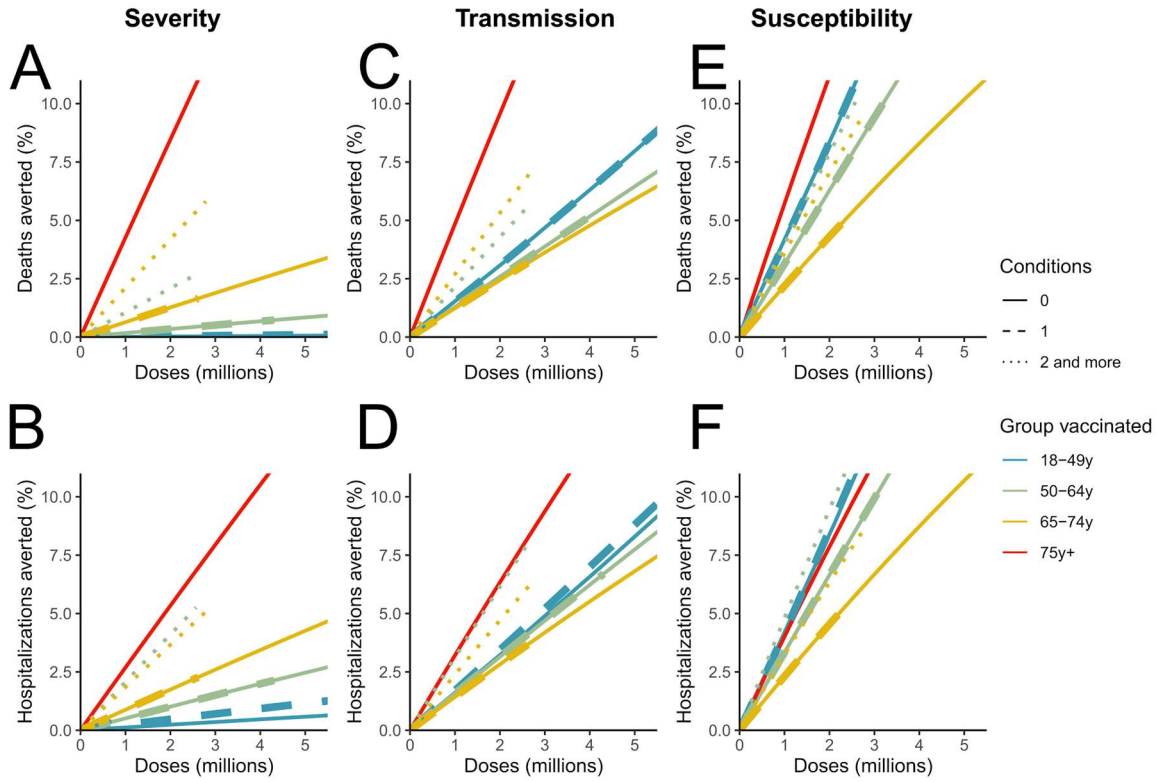

Figure 2: Impact of vaccination strategies targeted at different age and comorbidity groups. (A) Deaths and **(B)** hospitalisations averted for the vaccine *Severity* that reduces severity by 90% **(C)** Deaths and **(D)** hospitalisations averted for the vaccine *Transmission* that reduces severity by 90% and infectivity by 30% **(E)** Deaths and **(F)** hospitalisations averted for the vaccine *Susceptibility* that reduces severity by 90% and susceptibility by 90%.

Figure 3

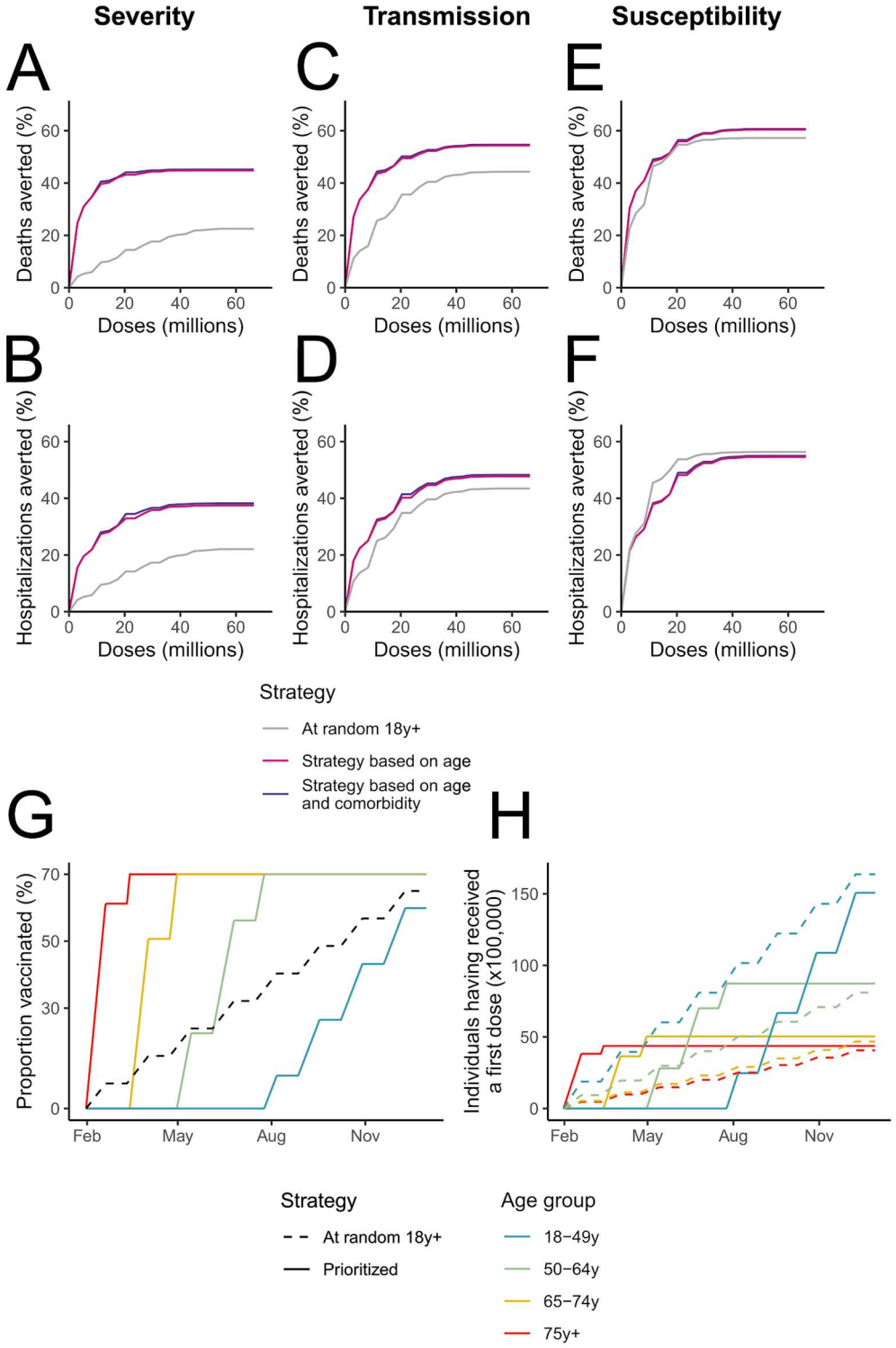

Figure 3: Impact of different vaccine prioritisation strategies. (A) Deaths and **(B)** hospitalisations averted **(A)** for the vaccine *Severity* that reduces severity by 90% **(C)** Deaths and **(D)** hospitalisations averted for the vaccine *Transmission* that reduces severity by 90% and infectivity by 30%. **(E)** Deaths and **(F)** hospitalisations averted for the vaccine *Susceptibility* that reduces severity by 90% and susceptibility by 90%. **(G)** Proportion of the population and **(H)** number of individuals having received a first dose throughout 2021 in the different age groups by prioritisation strategy.

Figure 4

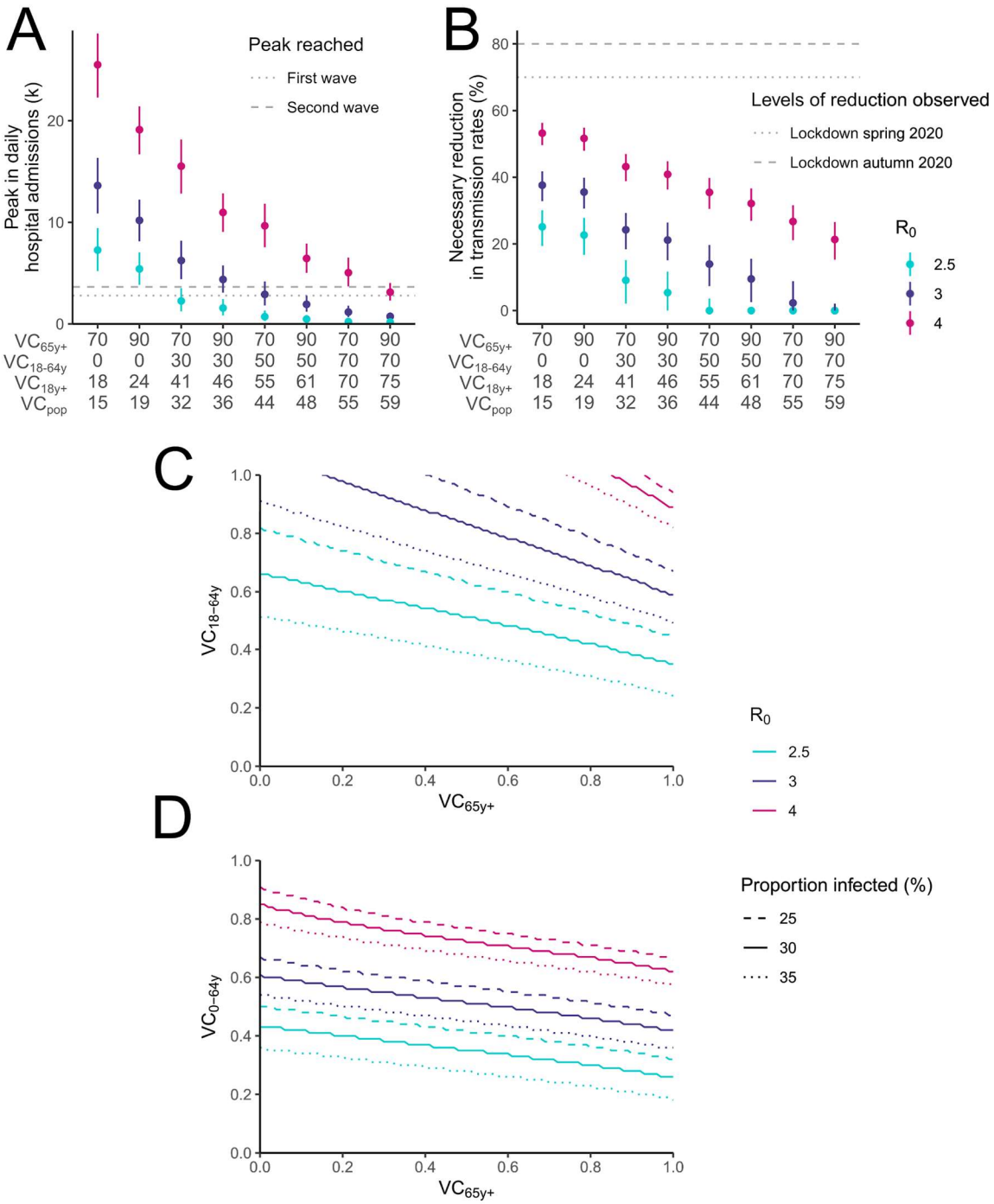

Figure 4: Manageable relaxation of measures by levels of vaccine coverage. (A) Peak in daily hospital admissions for different combinations of vaccine coverages in 18-64 y.o. ($VC_{18\text{-}64y}$) and ≥65 y.o. (VC_{65y+}). **(B)** Reduction in transmission rates necessary to avoid reaching 1,000 daily hospital admissions. **(C)** Combinations of vaccine coverages in 18-64 y.o. and ≥65 y.o. and in **(D)** 0-64 y.o. and ≥65 y.o. necessary to avoid reaching 1,000 daily hospital admissions. Different values of the basic reproduction number R_0 assuming complete relaxation are explored. The reductions computed in (A-B) assume a proportion infected of 30% (range 25%-35%) upon relaxation on September 1st 2021. Results are reported for the vaccine *Susceptibility* that reduces severity by 90% and susceptibility by 80%. For each

combination of vaccine coverage in 18-64 y.o. and ≥65 y.o., we report the corresponding vaccine coverage in those older than 18 y.o. (VC_{18y+}) and in the general population (VC_{pop}).

Supplementary materials

Data sources

Hospitalisation data

We use hospitalisation data stemming from the SI-VIC database, a national surveillance system maintained by the ANS (Agence du Numérique en Santé) and providing real-time information about COVID-19 patients hospitalized in French public and private hospitals. Data, including age, region, date and type of hospitalisation, are sent daily to Santé Publique France, the French national public health agency. Each COVID-19 case is either biologically confirmed or present with a tomographic image which is highly suggestive of SARS-CoV-2 infection. We consider events (e.g. hospitalisations or admission in ICU) by date of occurrence (and not date of reporting) and we correct data for reporting delays.[6] In our analyses, we consider patients admitted in general wards (*Hospitalisation conventionnelle*) and intensive care units (*Hospitalisation réanimatoire: réanimation, soins intensifs et unité de surveillance continue*). We discard patients hospitalized in psychiatric care units (*Hospitalisation psychiatrique*), in emergency care units (*Soins d'urgence*) and in long-term and rehabilitation units (*Soins de suite et réadaptation*).

Estimation of the prevalence of comorbidities of interest in the French population using the Esteban survey (2014-2016)

We derive estimates of the prevalence of comorbidities accounted for in the model using the Esteban survey, a cross-sectional national health study, carried out in France between 2014 and 2016, on a representative sample of the French adult population.[26] This survey describes a sample of 2,105 individuals aged between 18 and 74 y.o. A three-stage geographic sampling based on the selection of urban units, households, and individuals within each household was carried out. In this study, data collection was achieved using face-to-face questionnaires, a self questionnaire and a medical examination. Individual data were then matched with the Système National des Données de Santé (SNDS: National System of Health Data, the French national healthcare system database). Estimated prevalences were weighted to take into account survey design and non-response. The study was registered in the French National Agency for Medicines and Health Products Safety (No. 2012-A00456-34) and was approved by the Advisory Committee for Protection of Persons in Biomedical Research.

The comorbidities of interest are those identified by the Haute Autorité de Santé as being associated with an increased risk of severe outcome after a detailed literature review: complicated hypertension, heart failure, active cancers, chronic obstructive pulmonary disease or respiratory failure, diabetes, chronic kidney disease and obesity. We defined complicated hypertension as high blood pressure during the medical examination and/or antihypertensive treatment delivery associated with at least one of the following complications: diabetes, chronic kidney disease (CKD) as defined below, or declared cardiovascular pathology. Obesity was defined when measured body mass index was ≥30 kg/m^2. Diabetes was defined if people self-reported diabetes, if they were currently using anti-diabetic treatment (oral agents or injections), or if fasting blood glucose was ≥7 mmol/L during medical examination. Chronic kidney disease (CKD) stage 3-5 is defined as a glomerular filtration rate estimated with MDRD equation < 60 mL/min/1.73m^2 (MDRD: Modification of Diet in Renal

Disease). The prevalence of chronic obstructive pulmonary disease (COPD) is estimated using declared data from individuals included in the survey. Active cancers were identified by a hospitalisation on year n or a long-term disease status with a cancer diagnosis (for cancer starting on year n, n-1 or n-2). Because of missing hospitalisation data for year n-1 and n-2, we likely underestimate the prevalence of active cancers. Heart failures were identified by self declaration of patients, hospitalisations with a diagnosis of heart failure on year n or a long-term disease status with heart failure diagnosis in the year prior to the medical examination). The estimated prevalences are detailed in Table S4.

Model details

Model parametrization

The model is informed by data describing the age pyramid of the French population as well as the way individuals from different age groups interact with each other.[27] The age groups being considered are: [0-10), [10-18), [18-30), [30-40), [40-45), [45-50), [50-55), [55-60), [60-65), [65-70), [70-75), [75-80), ≥ 80. Furthermore, we make the assumption that children aged 0 to 9 y.o. and those aged 10 to 17 y.o. are respectively 50% and 25% less susceptible to infection than adults.[12,13] The model accounts for age-specific mixing patterns described by contact matrices. These contact matrices have been modified to capture changes associated with control measures (lockdown, telework). We assume that in 2021, contacts outside the household will be reduced by 30% compared to a non-epidemic period.[27] The model diagram is depicted in Figure S12.

Upon infection, susceptible individuals (S compartment) enter a latent state that lasts on average 4 days (E_1 compartment). They subsequently move to a second exposed compartment (E_2), in which the average length of stay is 1.0 day and in which they become infectious. They then move to another compartment (compartment I^{mild}/I^{hosp}), upon entry of which a fraction of them will develop symptoms. A fraction of infected individuals will develop a severe form of COVID-19 (trajectory starting from I^{hosp}), requiring an admission into hospital and/or into ICU. We consider that patients are admitted to hospital on average 6 days after symptoms onset if they will require an admission in ICU and 7 days otherwise. Patients are admitted into ICU on average 1.5 days after being hospitalized.[6] Age-specific probabilities of hospitalisation given infection are estimated from the joint analyses of serological and hospitalisation data collected during the first pandemic wave in Île-de-France and Grand Est, the two regions most affected by COVID-19 during that wave.[28–30] The age specific probabilities of death given hospitalisation are estimated using the proportion of deaths among patients admitted in hospitals between November 1st, 2020 and January 1st, 2021.

Accounting for changes in the probability of ICU admission through time

The proportion of patients admitted in ICU upon hospitalisation evolved throughout the epidemic.[31] We use the same approach as in[6] to account for these changes. We assume that the probability of being admitted in ICU after hospitalisation changed following a linear trend from ${p_{ICU}}^{baseline}$ to $\alpha_1 \cdot {p_{ICU}}^{baseline}$ between March 20th, 2020 and April 7th, 2020. We assume that this probability remained constant until July 7th, 2020, where it changed from

$\alpha_1 \cdot {p_{ICU}}^{baseline}$ to $\alpha_2 \cdot {p_{ICU}}^{baseline}$ on October 1st, 2020 following a linear trend. We then assume a further change in this probability between October 1st, 2020 and December 1st, 2020 to reach $\alpha_3 \cdot {p_{ICU}}^{baseline}$. The parameters α_1,α_2 and $\alpha_3$are estimated. ${p_{ICU}}^{baseline}$ is derived to ensure the mean probability of ICU admission given hospitalisation used in the model matches the one observed during the first wave.[6] The average age-specific probabilities of ICU admission between March 20th, 2020 and April 7th, 2020 are estimated using the proportion of patients admitted to ICU during this time period in the different age groups.

Statistical framework

The model is calibrated on the daily number of ICU and hospital admissions between 15 March 2020 and 4 January 2021 reported in the SI-VIC database. Model parameters are estimated using a bayesian Markov Chain Monte Carlo framework. We implement a Metropolis-Hastings algorithm with lognormal proposals and uniform priors. Chains are run for 10,000 iterations ; we remove 2,000 iterations of burn-in.

Let $H^{pred}(t)$ and $H^{obs}(t)$ denote respectively the predicted and observed number of hospital admissions on day t. Let $ICU^{pred}(t)$ and $ICU^{obs}(t)$ denote respectively the predicted and observed number of ICU admissions on day t. We define the likelihood function as:

$$L = \prod_{t = 15\ Marc\ \ 2020}^{4\ January\ 2021} g(H^{pred}(t) \mid H^{obs}(t)\ ) \cdot g(ICU^{pred}(t) \mid ICU^{obs}(t)\ )$$

where $g(\cdot\ |X)$ is a negative binomial distribution of mean X and overdispersion parameter X^{δ}, with δ a parameter to be estimated. Parameters estimates are reported along 95% credible intervals in Table S6.

Stratification by age and comorbidity

In our model, we explicitly account for the fact that the probability to develop severe clinical signs depends on the number of comorbidities (0, 1 or at least 2) and that the effect may vary with age. We consider comorbidities identified by the Haute Autorité de Santé as being associated with an increased risk of severe outcome. The age-specific prevalence of individuals with 0, 1 or at least 2 comorbidities has been estimated from the Esteban survey[26] (Table S4). The probabilities of hospital admission following infection are adjusted by age and by number of comorbidities, using the relative risk of hospital admission following infection by age and comorbidity estimated in the US study COVID-NET when they are statistically significant[9,32] (Table S5).

Let C_0 denote the event : 'Having no comorbidity'. Let C_1 denote the event 'Having one comorbidity'. Let C_2 denote the event: 'Having two comorbidities'. Let C_3 denote the event: 'Having at least three comorbidities'. Let ${RR_j}^{H}(a)$ denote the relative risk of hospitalisation given infection among individuals of age group a. Let $p_H(a)$ denote the mean probability of hospitalisation given infection among individuals of age group a. We derive the probability of hospitalisation given infection among individuals of age group a by levels of comorbidity using the following expression:

$$P[Hosp \mid Inf, C_j, a] = \frac{RR_j^H(a) \cdot p_H(a)}{\sum_{k=0}^{3} RR_k(a) \cdot P[C_k|a]}, \; j = 0,1,2,3$$

For $k < 3$, $P[C_k|a]$ corresponds to the proportion of individuals having k comorbidities in age group a. $P[C_3|a]$ corresponds to the proportion of individuals having at least 3 comorbidities in age groupe a.

The same type of adjustment is applied on the probabilities of ICU admission and death following hospitalisation using relative risks (that were not stratified by age) estimated from the same US based surveillance network.[33]

Parametrization for the vaccine that has a moderate effect on transmission

We detail how we built the scenario for the vaccine *Transmission*. In this scenario, we assume that the vaccine reduces the risk of developing symptoms upon infection, which results in a reduction of the average infectivity of vaccinated individuals. Let $VE_{severity}$denote the efficacy of the vaccine on the severity of the infection. We assume that the vaccination reduces by $VE_{severity}$the probability of developing symptoms upon infection or a severe form of COVID-19 requiring hospital care.

$$\begin{aligned} &P[Hosp \mid Infection, Vaccination] \\ &= (1 - VE_{severity}) \cdot P[Hosp \mid Inf, No\ vaccination] P[Symptoms \mid Infection, Vaccination] \\ &= (1 - VE_{severity}) \cdot P[Symptoms \mid Inf, No\ vaccination] \end{aligned}$$

Several analyses have suggested that individuals developing symptoms be more infectious than infected individuals who remain asymptomatic.[34] Let p^{sympto}denote the proportion of infected individuals who will develop symptoms. Let β denote the average transmission rate in the population, β^{sympto} denote the average transmission rate of individuals infected by SARS-CoV-2 developing symptoms and $\beta^{asympto}$ the average transmission of infected individuals remaining asymptomatic. Let $\theta^{asympto}$denote the relative reduction of the transmission rate in asymptomatic compared to symptomatic individuals:$\beta^{asympto} = \theta^{asympto} . \beta^{sympto}$

The average transmission rate can be derived as:

$$\beta = \beta^{sympto} \cdot [p^{sympto} \cdot (1 - \theta^{asympto}) + \theta^{asympto}]$$

Amongst vaccinated individuals, the mean transmission rate $\beta_V$verifies:

$$\beta_V = \beta^{sympto} \cdot [(1 - VE_{severity}) \cdot (1 - \theta^{asympto}) \cdot p^{sympto} + \theta^{asympto}]$$

We define the efficacy of the vaccine on transmission $VE_{transmission}$ by:

$$VE_{transmission} = 1 - \beta_V / \beta = VE_{severity} \cdot \frac{p^{sympto} \cdot (1 - \theta^{asympto})}{p^{sympto} \cdot (1 - \theta^{asympto}) + 1}$$

We assume that the transmission rate of asymptomatic individuals is 55% that of symptomatic individuals[34] and that 60% of SARS-CoV-2 infected individuals will develop symptoms.[35] This allows us to derive hypotheses regarding the efficacy for a vaccine that has a moderate impact on transmission.

$VE_{severity}$	$VE_{transmission}$
90%	29.6%
70%	23.0%

Parametrization for the vaccine that reduces the susceptibility to the infection

We explore scenarios where vaccines reduce the susceptibility to the infection of vaccinated individuals ($VE_{susceptibility}$) as well as the severity of the infection of vaccinated individuals that will eventually be infected ($VE_{severity}$). The overall vaccine efficacy VE_{tot} on the risk of developing a severe form of the disease is a combination of these two effects and can be derived as:

$$1 - VE_{tot} = (1 - VE_{susceptibility}) \cdot (1 - VE_{severity})$$

Setting $VE_{severity}$ to 50%, we obtain the following parametrization for VE_{tot} of 90% or 70%:

VE_{tot}	$VE_{severity}$	$VE_{susceptibility}$
90%	50%	80%
70%	50%	40%

Modelling relaxation of control measures

To explore the extent to which control measures might be relaxed, we explore a range of scenarios, where the relaxation of control measures is defined by the effective reproduction number upon measures relaxation on September 1st, 2021. This allows us to determine the highest effective reproduction number ensuring the peak in daily hospital admissions stays below a specific threshold, as a function of the vaccine coverage reached in individuals ≥65 y.o. and individuals aged 18-64 y.o. Simulations are run until April 1st, 2022. From this value, we derive the reductions in transmission rates in the general population that remain necessary, exploring different values of the basic reproduction number that characterizes a situation with complete relaxation of measures and no immunity as well as different values for the proportion of the population that might have already been infected upon relaxation of measures. To estimate the impact that would have a change in the proportion infected on the transmission rate, we use the next-generation matrix approach[36] and assume that the increase or decrease in new infections compared to the baseline scenario is distributed proportionally to the number of susceptible individuals across age groups. Examples of epidemiological trajectories upon measures relaxation in the absence of vaccination are presented in Figure S13.

Model equations

Model equations are detailed below. The indices a and a' are used to denote the different age groups (n_a age groups). The indices c and c' are used to denote the different comorbidity levels (n_c comorbidity levels). The superscript V corresponds to vaccinated compartments. Let $c_{a,a'}$ denote the average daily number of contacts that an individual in age group a has with individuals within the age group a'. Let $1/g_1$ denote the average length of the latent state E_1. $D = 1/g_2 + 1/g_3$ is the mean infectious period. The transmission rate β can be derived from the basic reproduction number R_0 using the next-generation matrix approach:[36]

$\beta = R_0 / (D \cdot \rho[(c_{a,a'})])$ where $\rho[(c_{a,a'})]$ is the maximum eigenvalue of the matrix $(c_{a,a'})_{a,a'}$.

Let ${p_{a,c}}^{hosp}$ and ${p_{a,c}}^{ICU}$ denote respectively the probability of hospitalisation given infection and the probability of ICU admission given hospitalisation for individuals of age group a and comorbidity levels c. Let $V_{a,c}(t)$ denote the number of individuals belonging to age group a with comorbidity level c that are vaccinated at time t following the vaccination schedule. ${N^{NV}}_{a,c}$ corresponds to the number of individuals belonging to age group a with comorbidity level c that are not vaccinated. Let N_a denote the number of individuals belonging to age group a regardless of their comorbidity level. $1/g_3 + 1/g^{to\ hosp}$corresponds to the average delay between disease onset and hospitalisation for individuals that will not require an ICU admission, $1/g_3 + 1/g^{to\ hosp\ ICU}$ to the average delay between disease onset and hospitalisation for individuals that will require an hospitalisation in ICU, $1/g^{to\ ICU}$ to the average length of stay in general wards prior ICU admission, $2/g^{out\ hosp}$to the average length of stay in general wards for patients that are not admitted to ICU and $2/g^{out\ ICU}$to the average length of stay in ICU. $VE_{severity}$is the efficacy of the vaccine on the reduction of the probability of hospitalisation upon infection, $VE_{infectivity}$is the efficacy of the vaccine on the reduction of the infectiousness of vaccinated individuals and $VE_{susceptibility}$ the efficacy of the vaccine on the reduction of the probability of becoming infected upon contact with an infectious individual for vaccinated individuals.

$$\frac{dS_{a,c}}{dt} = -\beta S_{a,c} \sum_{a'=1}^{n_a} \sum_{c'=1}^{n_c} \left(c_{a,a'} \cdot \frac{I^{mild}_{a',c'} + I^{hosp}_{a',c'} + E_{2a',c'} + (1 - VE_{infectivity}) \cdot (I^{V\,mild}_{a',c'} + I^{V\,hosp}_{a',c'} + E^{V}_{2a',c'})}{N_{a'}} \right) - V_{a,c}(t) \cdot \frac{S_{a,c}}{N^{NV}_{a,c}}$$

$$\frac{dE_{1a,c}}{dt} = \beta S_{a,c} \sum_{a'=1}^{n_a} \sum_{c'=1}^{n_c} \left(c_{a,a'} \cdot \frac{I^{mild}_{a',c'} + I^{hosp}_{a',c'} + E_{2a',c'} + (1 - VE_{infectivity}) \cdot (I^{V\,mild}_{a',c'} + I^{V\,hosp}_{a',c'} + E^{V}_{2a',c'})}{N_{a'}} \right) - g_1 E_{1a,c} + V_{a,c}(t) \cdot \frac{E_{1a,c}}{N^{NV}_{a,c}}$$

$$\frac{dE_{2a,c}}{dt} = g_1 E_{1a,c} - g_2 E_{2a,c} - V_{a,c}(t) \cdot \frac{E_{2a,c}}{N^{NV}_{a,c}}$$

$$\frac{dI^{mild}_{a,c}}{dt} = g_2(1 - p^{hosp}_{a,c}) E_{2a,c} - g_3 I^{mild}_{a,c} - V_{a,c}(t) \cdot \frac{I^{mild}_{a,c}}{N^{NV}_{a,c}}$$

$$\frac{dI^{hosp}_{a,c}}{dt} = g_2 p^{hosp}_{a,c} E_{2a,c} - g_3 I^{hosp}_{a,c} - V_{a,c}(t) \cdot \frac{I^{hosp}_{a,c}}{N^{NV}_{a,c}}$$

$$\frac{dI^{\bar{ICU}}_{a,c}}{dt} = g_3 p^{ICU}_{a,c} I^{hosp}_{a,c} - g^{to\,hosp} I^{\bar{ICU}}_{a,c} - V_{a,c}(t) \cdot \frac{I^{\bar{ICU}}_{a,c}}{N^{NV}_{a,c}}$$

$$\frac{dI^{non\bar{}ICU}_{a,c}}{dt} = g_3(1 - p^{ICU}_{a,c}) I^{hosp}_{a,c} - g^{to\,hosp\,non\,ICU} I^{non\bar{}ICU}_{a,c} - V_{a,c}(t) \cdot \frac{I^{non\bar{}ICU}_{a,c}}{N^{NV}_{a,c}}$$

$$\frac{dH_{1a,c}}{dt} = g^{to\,hosp\,non\,ICU} I^{non\bar{}ICU}_{a,c} - g^{out\,hosp} H_{1a,c} - V_{a,c}(t) \cdot \frac{H_{1a,c}}{N^{NV}_{a,c}}$$

$$\frac{dH_{2a,c}}{dt} = g^{out\,hosp} H_{1a,c} - g^{out\,hosp} H_{2a,c} - V_{a,c}(t) \cdot \frac{H_{2a,c}}{N^{NV}_{a,c}}$$

$$\frac{dH_{ICU\,a,c}}{dt} = g^{to\,hosp} I^{\bar{ICU}}_{a,c} - g^{ICU} H_{ICU\,a,c} - V_{a,c}(t) \cdot \frac{H_{ICU\,a,c}}{N^{NV}_{a,c}}$$

$$\frac{dICU_{1a,c}}{dt} = g^{ICU} H_{ICU\,a,c} - g^{out\,ICU} ICU_{1a,c} - V_{a,c}(t) \cdot \frac{ICU_{1a,c}}{N^{NV}_{a,c}}$$

$$\frac{dICU_{2a,c}}{dt} = g^{out} ICU_{1a,c} - g^{out\,ICU} ICU_{2a,c} - V_{a,c}(t) \cdot \frac{ICU_{2a,c}}{N^{NV}_{a,c}}$$

$$\frac{dRD_{a,c}}{dt} = g_3 I^{non\,hosp}_{a,c} + g^{out\,hosp} H_{2a,c} + g^{out\,ICU} ICU_{2a,c} - V_{a,c}(t) \cdot \frac{RD_{a,c}}{N^{NV}_{a,c}}$$

$$\frac{dS^{V}_{a,c}}{dt} = -\beta \cdot (1 - VE_{susceptibility}) \cdot S^{V}_{a,c} \cdot \sum_{a'=1}^{n_a} \sum_{c'=1}^{n_c} \left(c_{a,a'} \cdot \frac{I^{mild}_{a',c'} + I^{hosp}_{a',c'} + E_{2a',c'} + (1 - VE_{infectivity}) \cdot (I^{V\,mild}_{a',c'} + I^{V\,hosp}_{a',c'} + E^{V}_{2a',c'})}{N_{a'}} \right)$$
$$+ V_{a,c}(t) \cdot \frac{S_{a,c}}{N^{NV}_{a,c}}$$

$$\frac{dE^{V}_{1a,c}}{dt} = \beta \cdot (1 - VE_{susceptibility}) \cdot S^{V}_{a,c} \cdot \sum_{a'=1}^{n_a} \sum_{c'=1}^{n_c} \left(c_{a,a'} \cdot \frac{I^{mild}_{a',c'} + I^{hosp}_{a',c'} + E_{2a',c'} + (1 - VE_{infectivity}) \cdot (I^{V\,mild}_{a',c'} + I^{V\,hosp}_{a',c'} + E^{V}_{2a',c'})}{N_{a'}} \right)$$
$$- g_1 E^{V}_{1a,c} + V_{a,c}(t) \cdot \frac{E_{1a,c}}{N^{NV}_{a,c}}$$

$$\frac{dE^{V}_{2a,c}}{dt} = g_1 E^{V}_{1a,c} - g_2 E^{V}_{2a,c} + V_{a,c}(t) \cdot \frac{E_{2a,c}}{N^{NV}_{a,c}}$$

$$\frac{dI^{V\,mild}_{a,c}}{dt} = g_2(1 - \cdot(1 - VE_{severity}) \cdot p^{hosp}_{a,c}) E^{V}_{2a,c} - g_3 I^{V\,mild}_{a,c} + V_{a,c}(t) \cdot \frac{I^{mild}_{a,c}}{N^{NV}_{a,c}}$$

$$\frac{dI^{V\,hosp}_{a,c}}{dt} = g_2 \cdot (1 - VE_{severity}) \cdot p^{hosp}_{a,c} E^{V}_{2a,c} - g_3 I^{V\,hosp}_{a,c} + V_{a,c}(t) \cdot \frac{I^{hosp}_{a,c}}{N^{NV}_{a,c}}$$

$$\frac{dI^{V\,\bar{ICU}}_{a,c}}{dt} = g_3 p^{ICU}_{a,c} I^{V\,hosp}_{a,c} - g^{to\,hosp} I^{V\,\bar{ICU}}_{a,c} + V_{a,c}(t) \cdot \frac{I^{\bar{ICU}}_{a,c}}{N^{NV}_{a,c}}$$

$$\frac{dI^{V\,non\bar{}ICU}_{a,c}}{dt} = g_3(1 - p^{ICU}_{a,c}) I^{V\,hosp}_{a,c} - g^{to\,hosp\,non\,ICU} I^{V\,non\bar{}ICU}_{a,c} + V_{a,c}(t) \cdot \frac{I^{\bar{hosp}}_{a,c}}{N^{NV}_{a,c}}$$

$$\frac{dH^{V}_{1a,c}}{dt} = g^{to\,hosp\,non\,ICU} I^{V\,non\bar{}ICU}_{a,c} - g^{out\,hosp} H^{V}_{1a,c} + V_{a,c}(t) \cdot \frac{H_{1a,c}}{N^{NV}_{a,c}}$$

$$\frac{dH^{V}_{2a,c}}{dt} = g^{out\,hosp} H^{V}_{1a,c} - g^{out\,hosp} H^{V}_{2a,c} + V_{a,c}(t) \cdot \frac{H_{2a,c}}{N^{NV}_{a,c}}$$

$$\frac{dH^{V}_{ICU\,a,c}}{dt} = g^{to\,hosp} I^{V\,\bar{ICU}}_{a,c} - g^{ICU} H^{V}_{ICU\,a,c} + V_{a,c}(t) \cdot \frac{H_{ICU\,a,c}}{N^{NV}_{a,c}}$$

$$\frac{dICU^{V}_{1a,c}}{dt} = g^{ICU} H^{V}_{ICU\,a,c} - g^{out\,ICU} ICU^{V}_{1a,c} + V_{a,c}(t) \cdot \frac{ICU_{1a,c}}{N^{NV}_{a,c}}$$

$$\frac{dICU^{V}_{2a,c}}{dt} = g^{out} ICU^{V}_{1a,c} - g^{out\,ICU} ICU^{V}_{2a,c} + V_{a,c}(t) \cdot \frac{ICU_{2a,c}}{N^{NV}_{a,c}}$$

$$\frac{dRD^{V}_{a,c}}{dt} = g_3 I^{V\,non\,hosp}_{a,c} + g^{out\,hosp} H^{V}_{2a,c} + g^{out\,ICU} ICU^{V}_{2a,c} + V_{a,c}(t) \cdot \frac{RD_{a,c}}{N^{NV}_{a,c}}$$

Figure S1

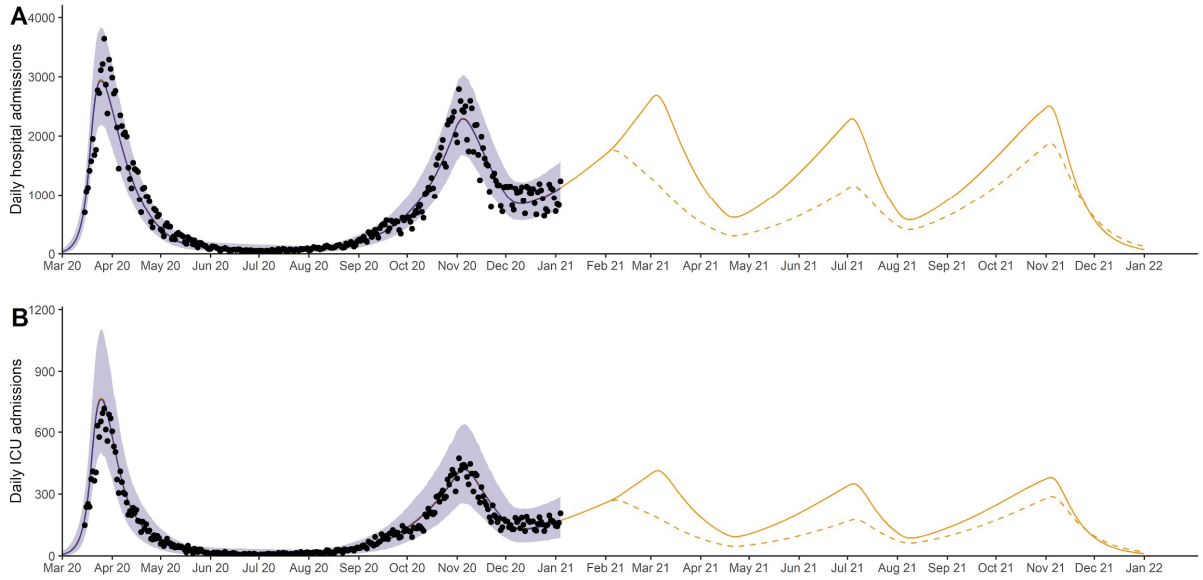

Figure S1: Epidemiological scenarios for 2021. Daily **(A)** hospital and **(B)** ICU admissions in the baseline scenario used for 2021 (solid line) and the scenario with a more controlled epidemic (dashed line) used as a sensitivity analysis.

Figure S2

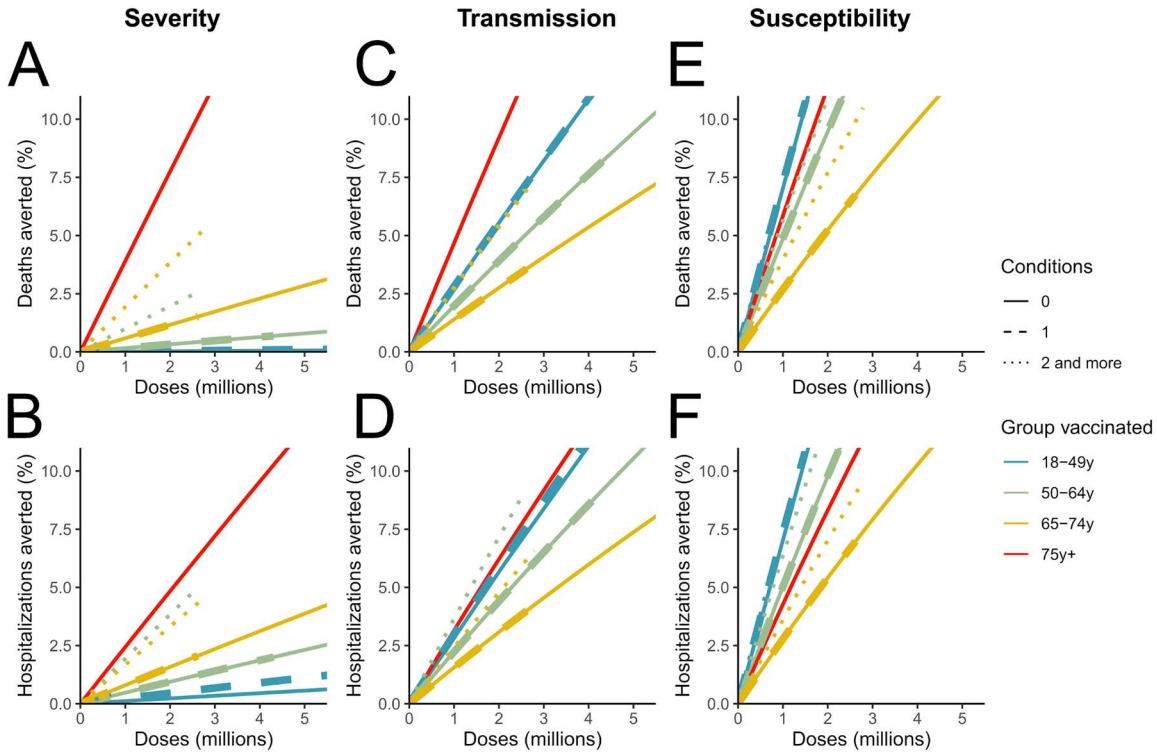

Figure S2: Sensitivity analysis changing the epidemiological scenario. (A) Deaths and **(B)** hospitalisation averted for a vaccine reducing the severity of the infection by 90%. **(C)** Deaths and **(D)** hospitalisation averted for a vaccine reducing the severity of the infection by 90% with a moderate impact on transmission (30%). **(E)** Deaths and **(F)** hospitalisation averted for a vaccine reducing the susceptibility to SARS-CoV-2 infection (80%) and the severity of the infection by 90%. Results are reported in our baseline epidemiological scenario describing a more controlled epidemic. Results are reported in the epidemiological scenario describing a more controlled epidemic.

Figure S3

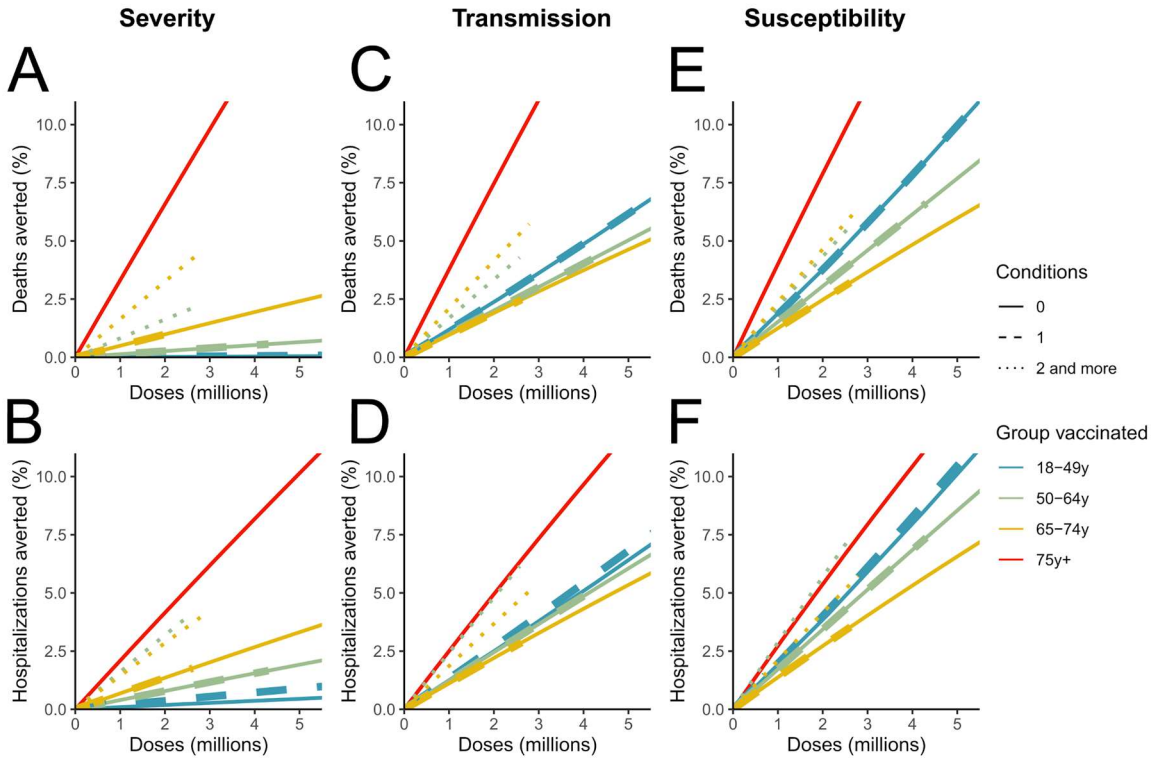

Figure S3: Sensitivity analysis changing the vaccine efficacy. (A) Deaths and **(B)** hospitalisation averted for a vaccine reducing the severity of the infection by 70%. **(C)** Deaths and **(D)** hospitalisation averted for a vaccine reducing the severity of the infection by 70% with a moderate impact on transmission (30%). **(E)** Deaths and **(F)** hospitalisation averted for a vaccine reducing the susceptibility to SARS-CoV-2 infection (40%) and the severity of the infection by 70%. Results are reported in our baseline epidemiological scenario describing a more controlled epidemic. In the absence of vaccination, such a scenario would result in 330,000 COVID-19 hospitalisations and 66,000 hospital deaths. In the absence of vaccination, such a scenario would result in 501,000 COVID-19 hospitalisations and 102,000 hospital deaths.

Figure S4

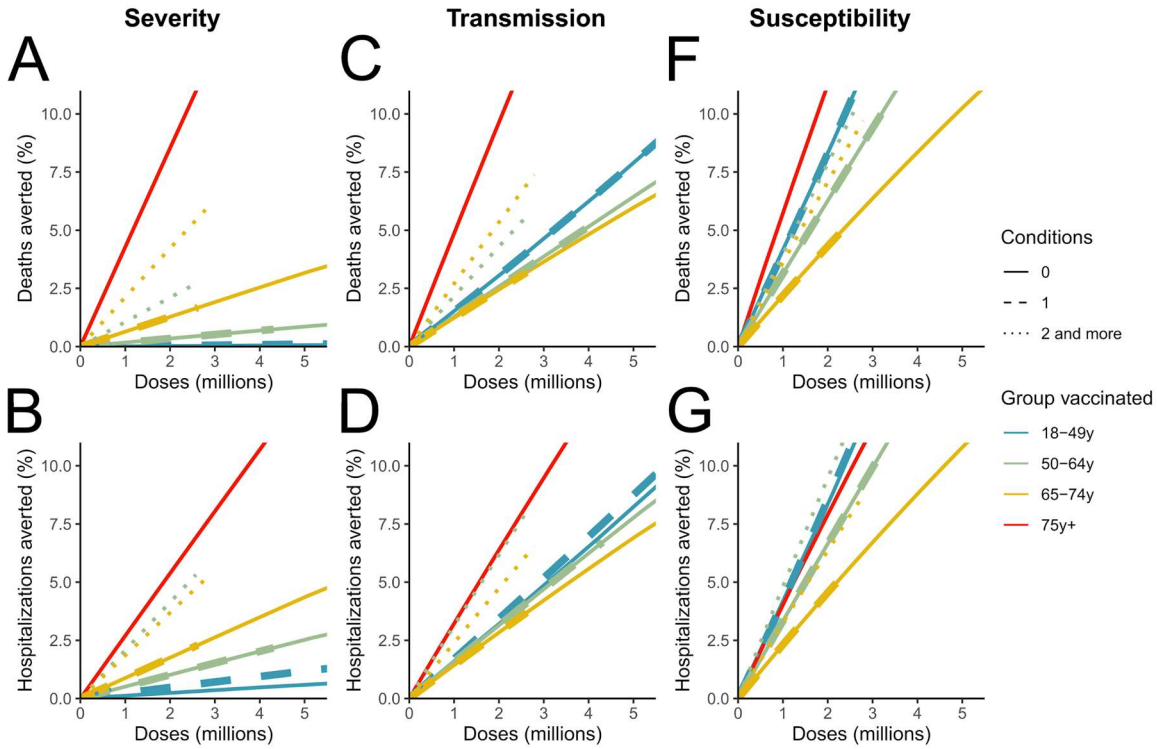

Figure S4: Sensitivity analysis changing the vaccine roll-out pace. (A) Deaths and **(B)** hospitalisation averted for a vaccine reducing the severity of the infection by 90%. **(C)** Deaths and **(D)** hospitalisation averted for a vaccine reducing the severity of the infection by 90% with a moderate impact on transmission (30%). **(E)** Deaths and **(F)** hospitalisation averted for a vaccine reducing the susceptibility to SARS-CoV-2 infection (80%) and the severity of the infection by 90%. Results are reported in our baseline epidemiological scenario describing a more controlled epidemic. In the absence of vaccination, such a scenario would result in 330,000 COVID-19 hospitalisations and 66,000 hospital deaths. In the absence of vaccination, such a scenario would result in 501,000 COVID-19 hospitalisations and 102,000 hospital deaths. Results are reported for a roll-out pace of 450,000 doses per day.

Figure S5

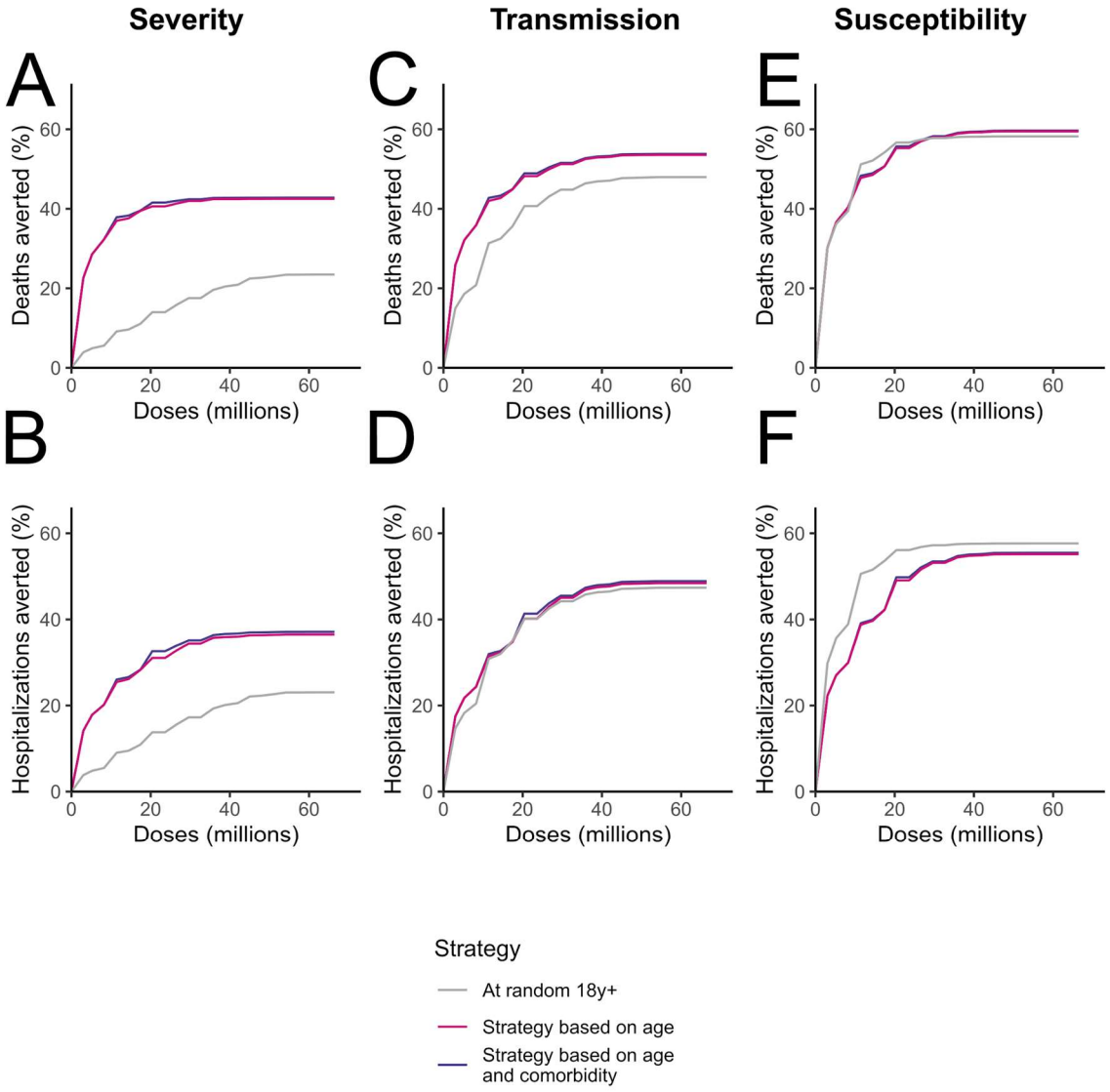

Figure S5: Sensitivity analysis changing the epidemiological scenario. (A) Deaths and **(B)** hospitalisations averted **(A)** for a vaccine reducing the severity of the infection (90%). **(C)** deaths and **(D)** hospitalisations averted for a vaccine reducing the severity of the infection (90%) with a moderate impact on transmission (30%). **(E)** Deaths and **(F)** hospitalisations averted for a vaccine reducing the susceptibility to SARS-CoV-2 infection (80%) and reducing the severity by 90%. In the absence of vaccination, such a scenario would result in 330,000 COVID-19 hospitalisations and 66,000 hospital deaths.

Figure S6

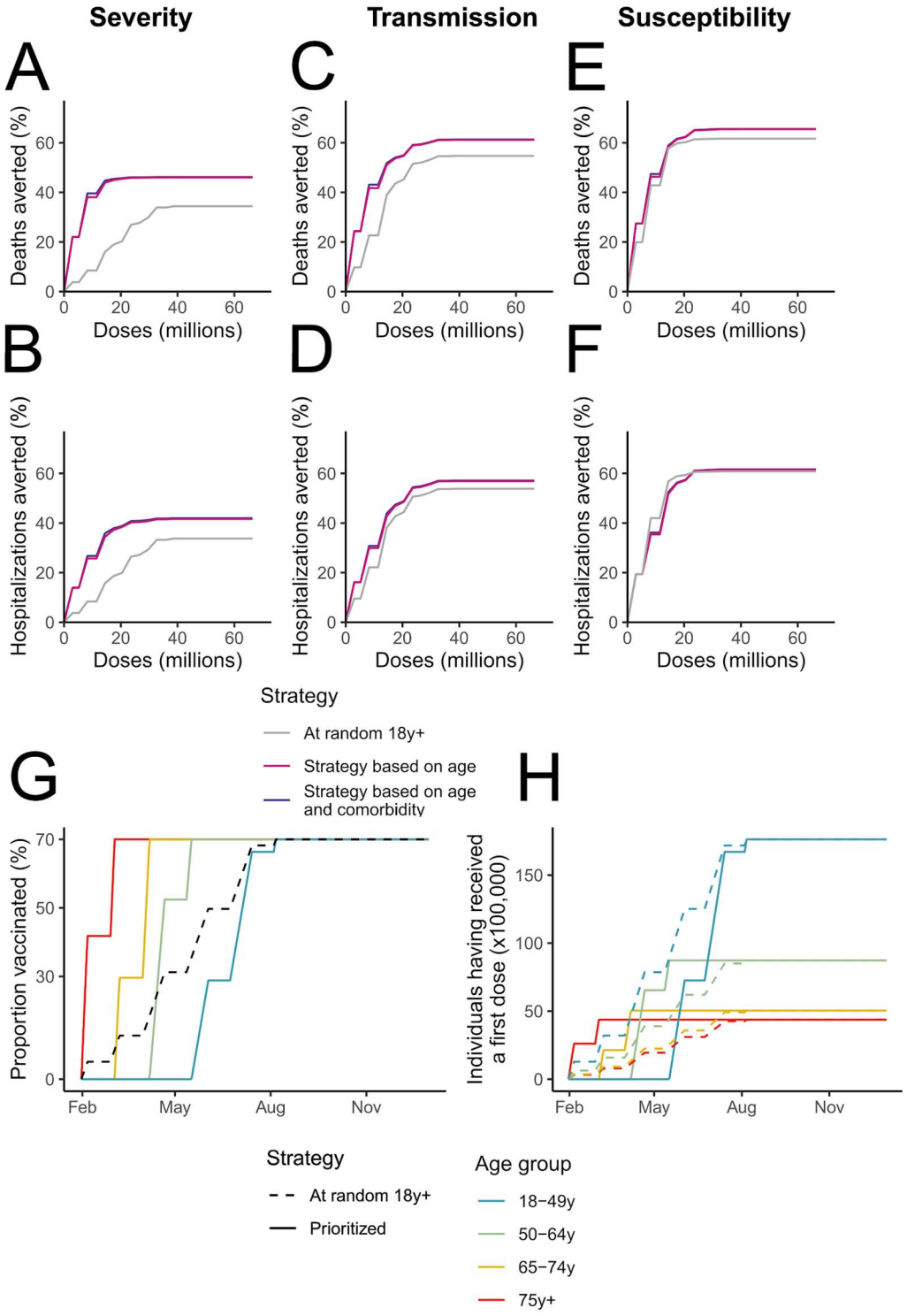

Figure S6: Sensitivity analysis changing the vaccine roll-out pace (450,000 doses per day). (A) Deaths and **(B)** hospitalisations averted **(A)** for the vaccine *Severity*. **(C)** Deaths and **(D)** hospitalisations averted for the vaccine *Transmission*. **(E)** Deaths and **(F)** hospitalisations averted for the vaccine *Susceptibility*. **(G)** Proportion of the population and **(H)** number of individuals having received a first dose throughout 2021 in the different age groups by prioritisation strategy.

Figure S7

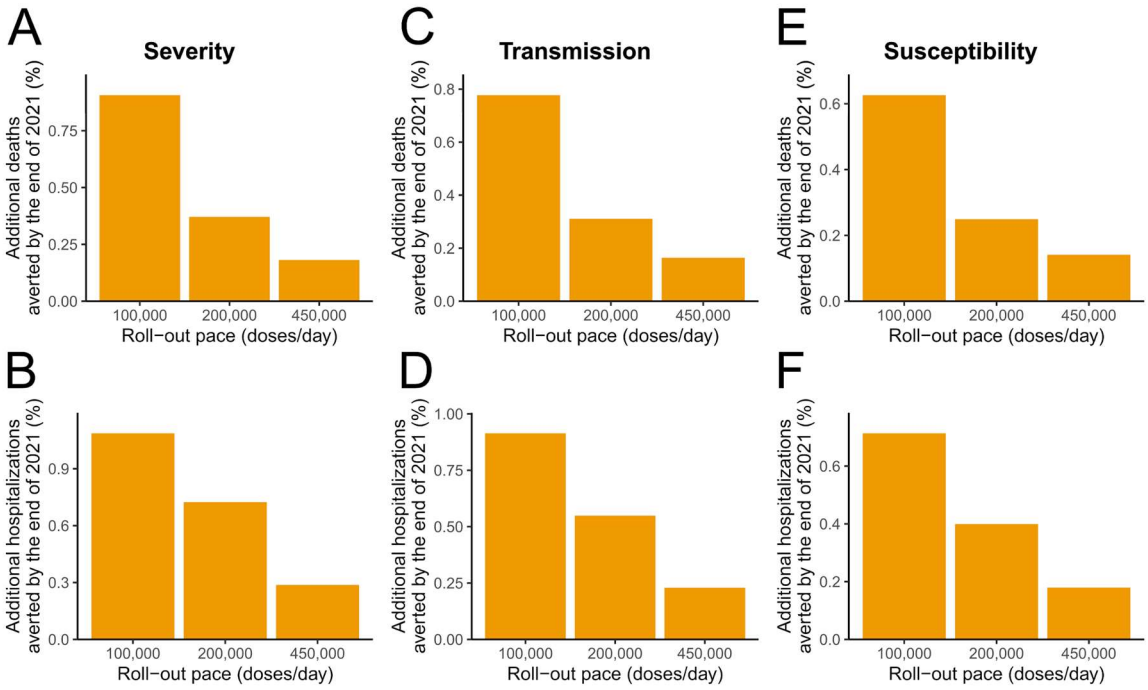

Figure S7: Comparison of the prioritization strategy based on age and comorbidities and the prioritization strategy based on age solely. Difference between the **(A)** proportion of deaths and the **(B)** proportion of hospitalisations averted in the prioritization strategy based on age and comorbidities and the prioritization strategy based on age for the vaccine *Severity*. Difference between the **(C)** proportion of deaths and the **(D)** proportion of hospitalisations averted in the prioritization strategy based on age and comorbidities and the prioritization strategy based on age for the vaccine *Transmission*. Difference between the **(E)** proportion of deaths and the **(F)** proportion of hospitalisations averted in the prioritization strategy based on age and comorbidities and the prioritization strategy based on age for the vaccine *Susceptibility*. Different roll-out paces are explored.

Figure S8

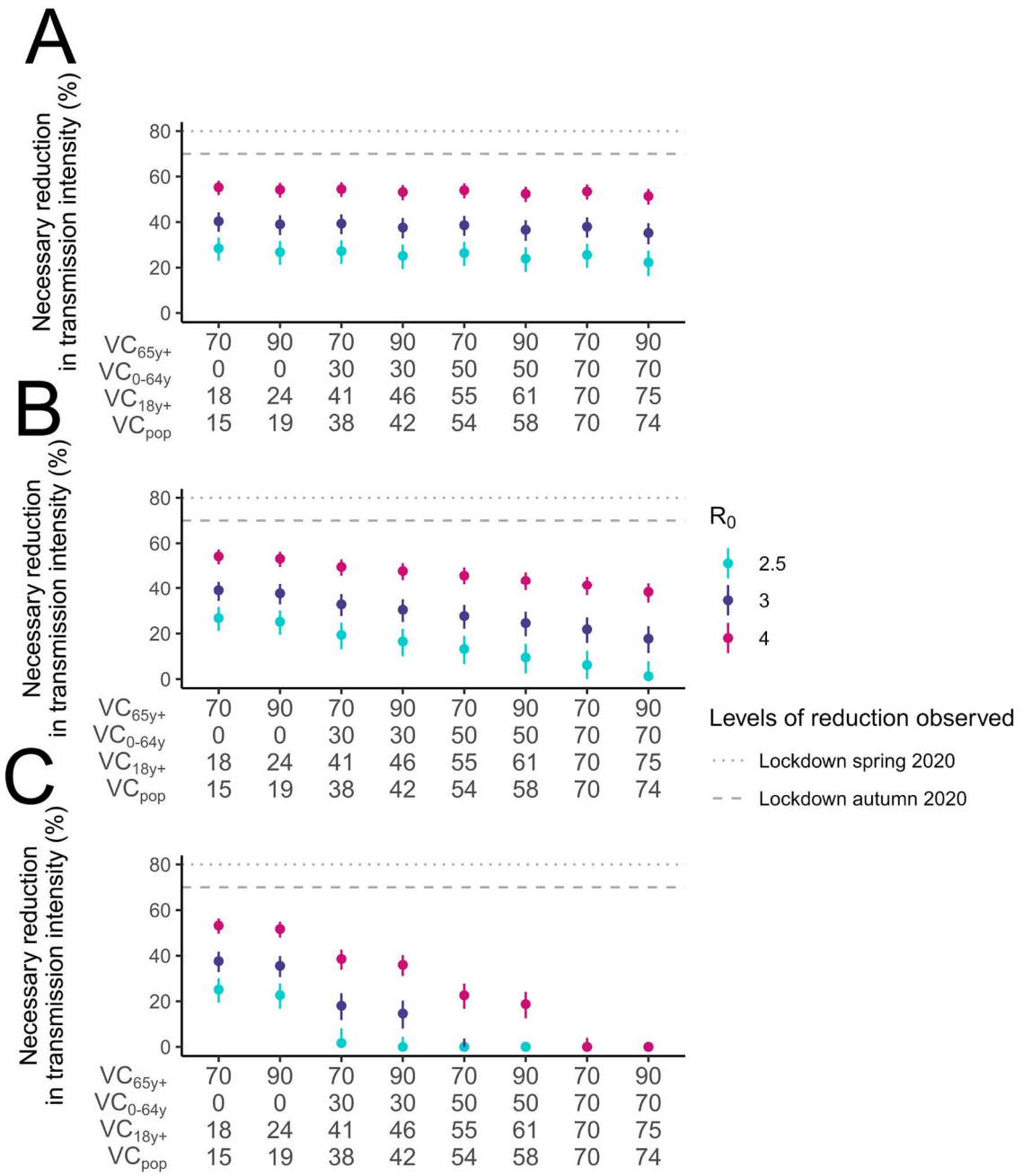

Figure S8: Sensitivity analysis with vaccination of 0-17 y.o. - Manageable relaxation of measures by levels of vaccine coverage ensuring the peak in daily hospital admissions remains below 1,000. Reductions in transmission that remain necessary in September **(A)** for the vaccine *Severity*, **(B)** for the vaccine *Transmission*, **(C)** for the vaccine *Susceptibility*. Different levels of vaccine coverage in 0-64 y.o. ($VC_{0\text{-}64y}$) and in ≥65 y.o. (VC_{65y+}) (in %) and values of the basic reproduction number R_0 assuming complete relaxation are explored. The reductions are computed assuming a proportion infected upon relaxation of 30% (range 25%-35%). For each combination of vaccine coverage in 18-64 y.o. and ≥65 y.o., we report the corresponding vaccine coverage in those older than 18 y.o. (VC_{18y+}) and in the general population (VC_{pop}).

Figure S9

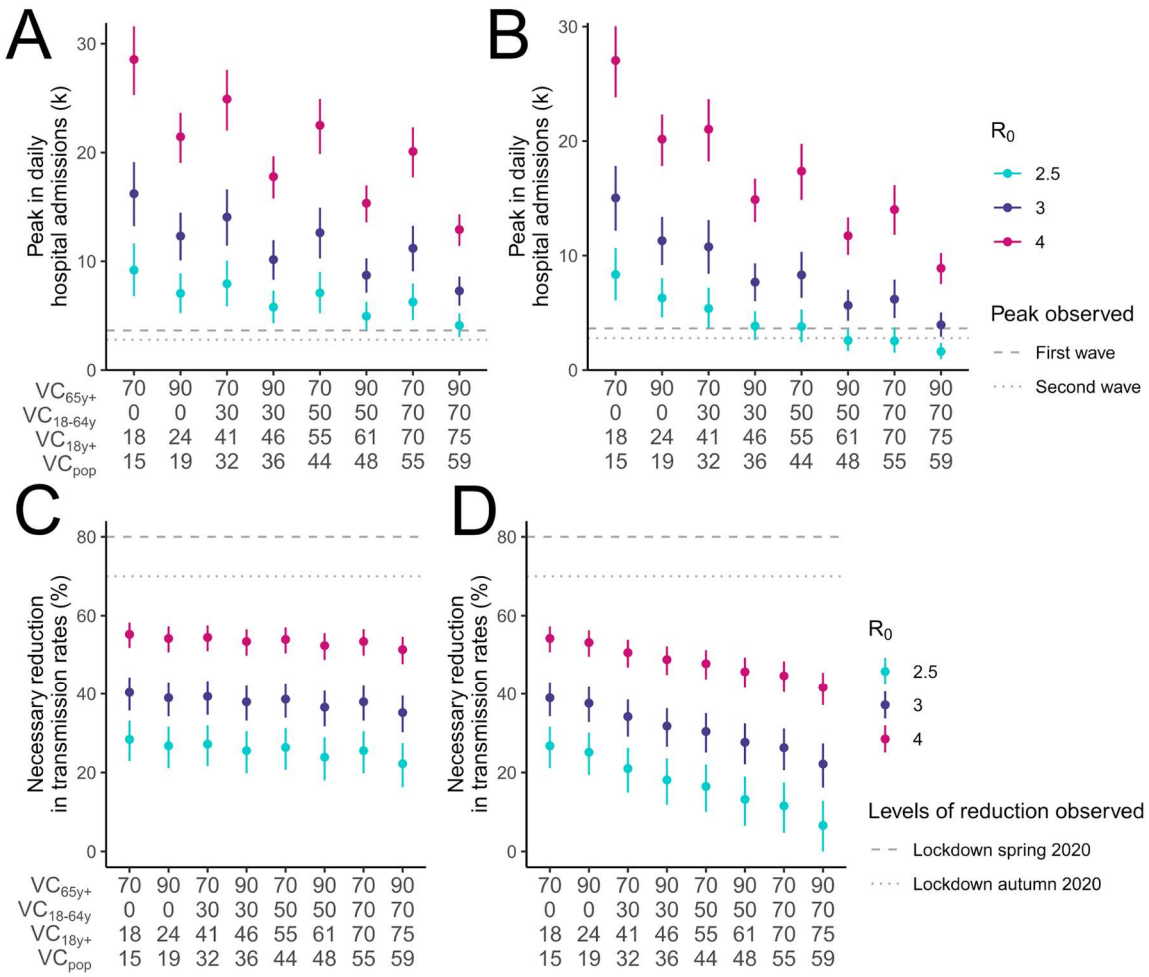

Figure S9: Sensitivity analysis for different vaccine characteristics - Manageable relaxation of measures by levels of vaccine coverage. Peak in daily hospital admissions for different combinations of vaccine coverages in 18-64 y.o. ($VC_{18\text{-}64y}$) and ≥65 y.o. (VC_{65y+}). **(A)** for the vaccine *Severity* and **(B)** for the vaccine *Transmission*. Reduction in transmission rates that remain necessary to avoid reaching 1,000 daily hospital admissions **(C)** for the vaccine *Severity* and **(D)** for the vaccine *Transmission*. For each combination of vaccine coverage in 18-64 y.o. and ≥65 y.o., we report the corresponding vaccine coverage in those older than 18 y.o. (VC_{18y+}) and in the general population (VC_{pop}).

Figure S10

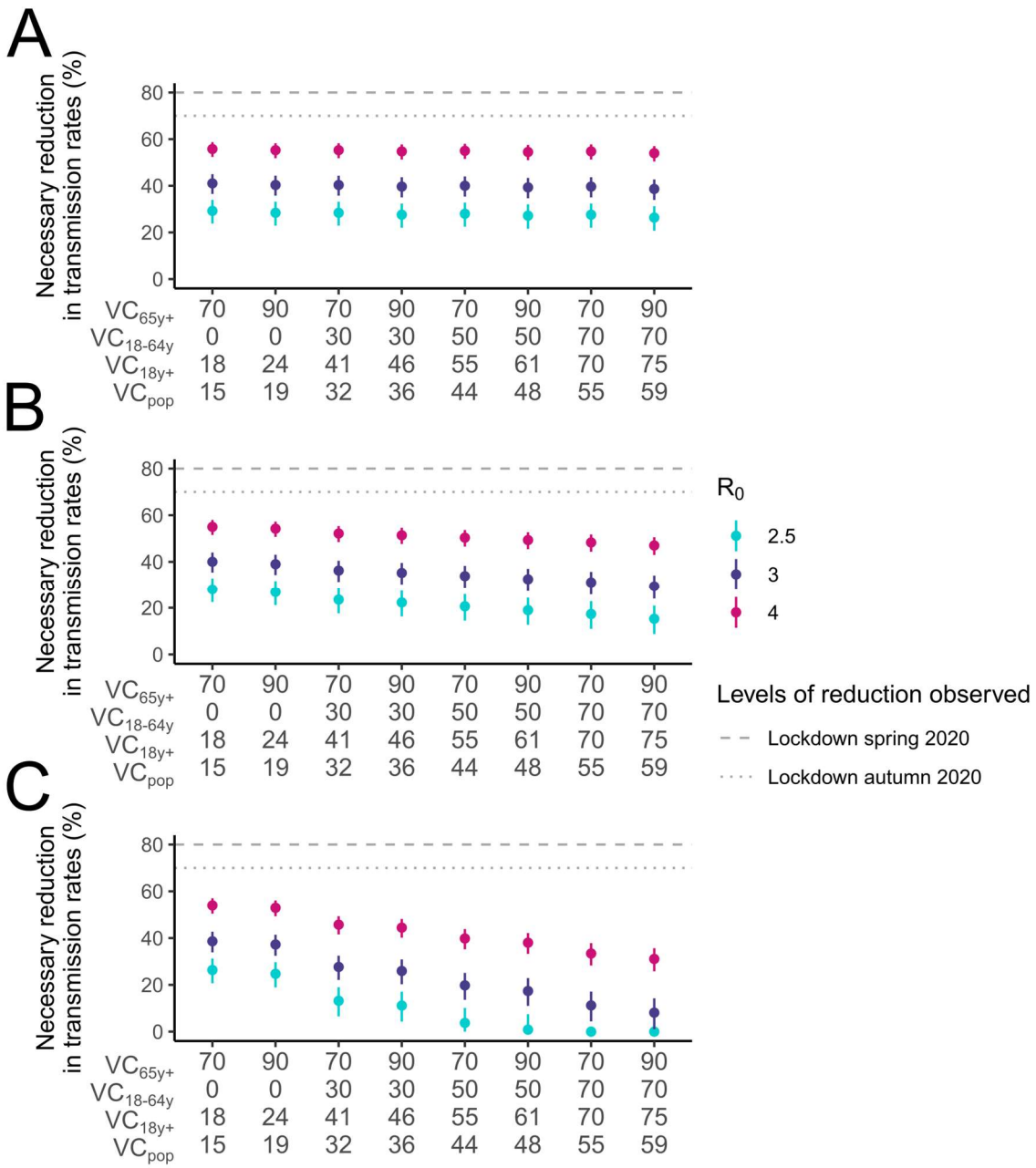

Figure S10: Sensitivity analysis with less efficient vaccines - Manageable relaxation of measures by levels of vaccine coverage ensuring the peak in daily hospital admissions remains below 1,000. Reductions in transmission that remain necessary in September **(A)** for a vaccine reducing the severity of the infection by 70%, (**B)** for a vaccine reducing the severity to the infection by 70% with a moderate impact on transmission (23%), **(C)** for a vaccine reducing the susceptibility (40%) to SARS-CoV-2 infection and the severity of the infection (70%). Different levels of vaccine coverage in 18-64 y.o. ($VC_{18\text{-}64y}$) and in ≥65 y.o. (VC_{65y+}) (in %) and values of the basic reproduction number R_0 assuming complete relaxation are explored. The reductions are computed assuming a proportion infected upon relaxation of 30% (range 25%-35%). For each combination of vaccine coverage in 18-64 y.o. and ≥65 y.o., we report the corresponding vaccine coverage in those older than 18 y.o. (VC_{18y+}) and in the general population (VC_{pop}).

Figure S11

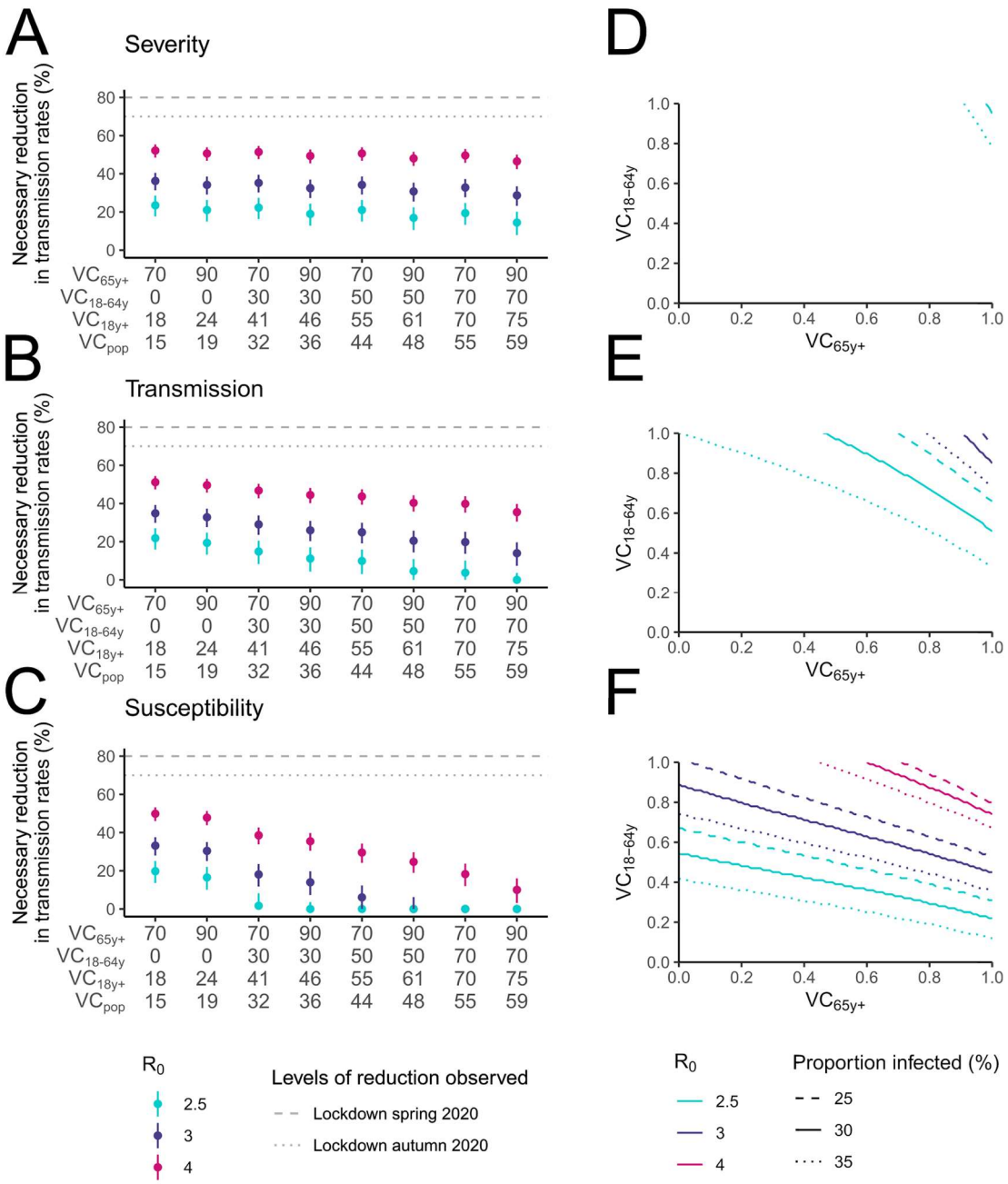

Figure S11: Sensitivity analysis - Manageable relaxation of measures by levels of vaccine coverage ensuring the peak in daily hospital admissions remains below 2,000. Reductions in transmission that remain necessary in September **(A)** for the vaccine *Severity*, **(B)** for the vaccine *Transmission*, **(C)** for the vaccine *Susceptibility*. Different levels of vaccine coverage in 18-64 y.o. ($VC_{18\text{-}64y}$) and in ≥65 y.o. (VC_{65y+}) (in %) and values of the basic reproduction number R_0 assuming complete relaxation are explored. The reductions are computed assuming a proportion infected upon relaxation of 30% (range 25%-35%). Combinations of vaccine coverages in 18-64 y.o. and ≥65 y.o. that are necessary to avoid reaching 2,000 daily hospital admissions **(D)** for the vaccine *Severity*, **(E)** for the vaccine *Transmission*, **(F)** for the vaccine *Susceptibility*. For each combination of vaccine coverage in 18-64 y.o. and ≥65 y.o., we report the corresponding vaccine coverage in those older than 18 y.o. (VC_{18y+}) and in the general population (VC_{pop}).

Figure S12

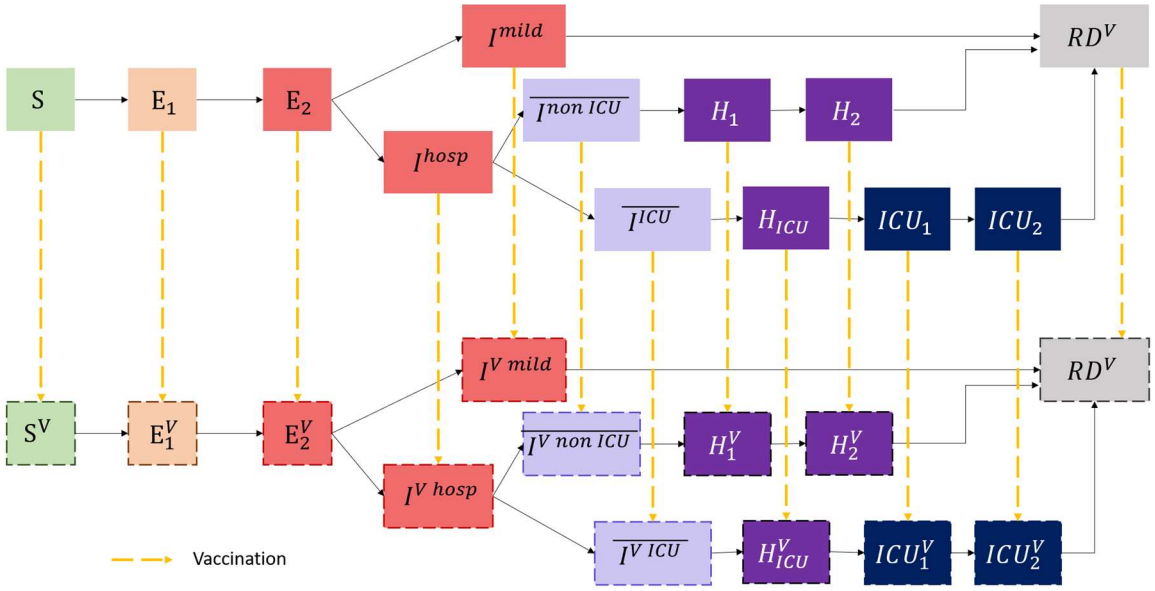

Figure S12: Model diagram

Figure S13

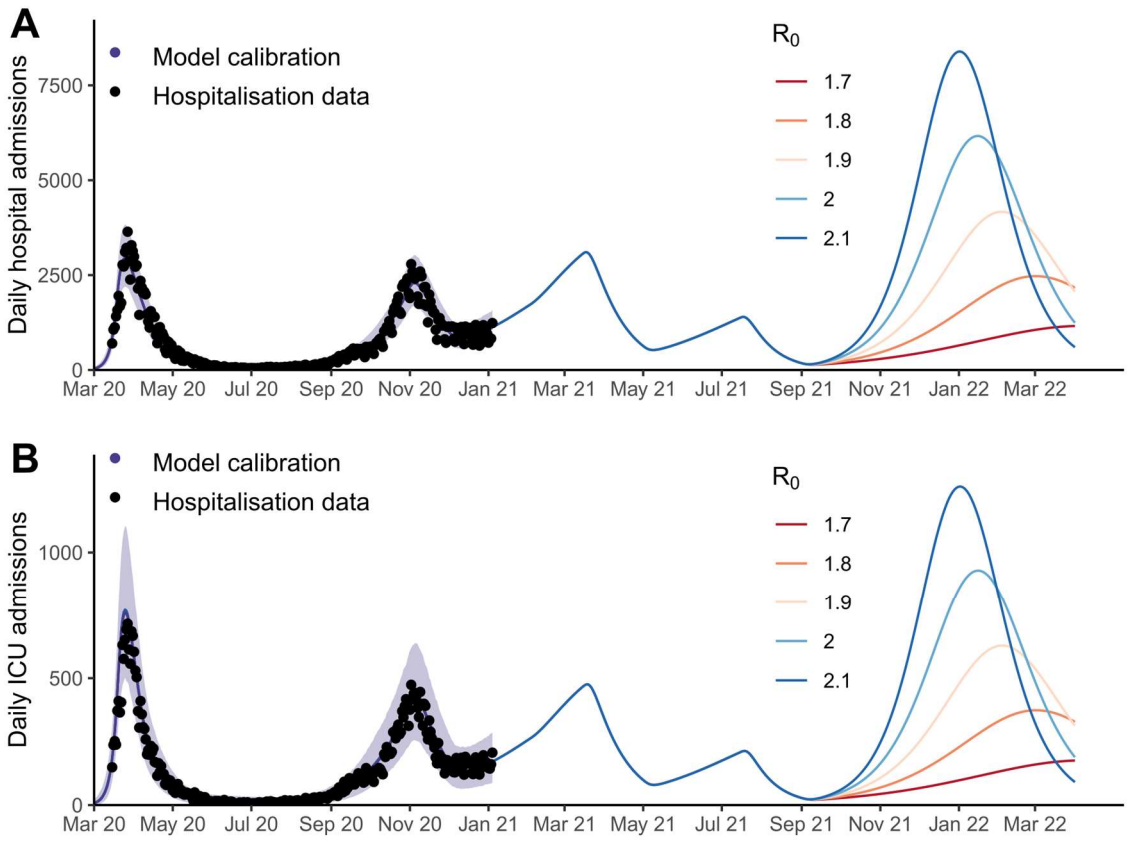

Figure S13: Examples of rebound scenarios used to study the relaxation of control measures. (A) Daily hospital admissions and **(B)** daily ICU admissions through time. The results are presented for different values of the basic reproduction number R_0 upon measures relaxation on September 1st, 2021 and in the absence of vaccination. In the plotted scenario, 28% of the population has been infected by SARS-CoV-2 on September 1st, 2021.

Table S1: Delivery calendar used for doses allocation (million doses). As monthly information was not available for the second semester of 2021, we assume that doses will be delivered homogeneously throughout this period (one sixth every month of the doses of the second semester).

Date	Doses (million)
February 2021	5.23
March 2021	7.79
April 2021	17.77
May 2021	20.62
June 2021	20.43
July-December 2021	163.21

Table S2: Size of age and comorbidity groups considered in the different vaccination strategies (in millions)

Number of conditions	0	1	At least 2	Total
Age group				
18-49 y.o.	21.22	3.58	0.38	25.18
50-64 y.o.	8.65	2.39	1.43	12.47
65-74 y.o.	4.2	1.46	1.55	7.21
Over 75 y.o.	-			6.25

Table S3: Severity parameters stratified by age and number of conditions used in the simulations for the year 2021.

Age group	Number of conditions	Probability of hospitalisation given infection	Probability of ICU admission given hospitalisation	Probability of death given hospitalisation
0-9 y.o.	0	0.002	0.176	0.001
	1	0.005	0.176	0.001
	2	0.011	0.176	0.001
	≥ 3	0.011	0.229	0.002
10-17 y.o.	0	0.001	0.176	0.001
	1	0.002	0.176	0.001
	2	0.004	0.176	0.001
	≥ 3	0.005	0.229	0.002
18-29 y.o.	0	0.003	0.101	0.006
	1	0.008	0.101	0.006
	2	0.018	0.101	0.006
	≥ 3	0.019	0.132	0.011
30-39 y.o.	0	0.004	0.129	0.012
	1	0.012	0.129	0.012
	2	0.026	0.129	0.012
	≥ 3	0.028	0.167	0.021
40-44	0	0.006	0.169	0.03

y.o.	1	0.016	0.169	0.03
	2	0.035	0.169	0.03
	≥ 3	0.037	0.219	0.053
45-49 y.o.	0	0.012	0.183	0.03
	1	0.012	0.183	0.03
	2	0.034	0.183	0.03
	≥ 3	0.063	0.238	0.054
50-54 y.o.	0	0.021	0.202	0.041
	1	0.021	0.202	0.041
	2	0.06	0.202	0.041
	≥ 3	0.112	0.263	0.073
55-59 y.o.	0	0.029	0.208	0.058
	1	0.029	0.208	0.058
	2	0.084	0.208	0.058
	≥ 3	0.157	0.27	0.106
60-64 y.o.	0	0.04	0.221	0.101
	1	0.04	0.221	0.101
	2	0.116	0.221	0.101
	≥ 3	0.216	0.288	0.183
65-69	0	0.052	0.226	0.126

y.o.	1	0.052	0.226	0.126
	2	0.052	0.226	0.126
	≥ 3	0.2	0.294	0.228
70-74 y.o.	0	0.096	0.204	0.163
	1	0.096	0.204	0.163
	2	0.096	0.204	0.163
	≥ 3	0.37	0.266	0.294

Table S4: Prevalence of comorbidities estimated from the Esteban survey. Results are reported in %.

	Age-group				
Number of conditions	18-49 y.o.	50-64 y.o.	65-74 y.o.	≥ 75 y.o.	Total
0	84.2 (81.0-87.4)	69.4 (64.8-73.9)	58.3 (51.7-65.0)		75.6 (73.2-78.1)
1	14.2 (11.1-17.3)	19.2 (15.4-23.0)	20.2 (15.0-25.4)		16.7 (14.5-18.9)
2	1.3 (0.4-2.3)	6.2 (3.8-8.5)	13.2 (7.9-18.5)		4.6 (3.4-5.8)
At least 3	0.2 (0.0-0.5)	5.3 (3.0-7.7)	8.3 (4.5-12.1)		3.1 (2.1-4.0)

Table S5: Relative risk by comorbidity levels used to derive comorbidity specific probabilities of severe outcomes. * indicates when relative risks where considered significant.

	Source	Age	0	1	2	3 and more
Relative risk of hospitalisation given infection	[9]	< 45 y.o.	1.0 (Ref.)	2.6 (2.0-3.5) *	5.8 (4.0-8.3) *	6.2 (3.1-12.7) *
		45-64 y.o.	1.9 (1.4-2.6)	2.2 (1.4-3.6)	5.5 (3.5-8.7) *	10.3 (4.3-24.7) *
		≥ 65 y.o.	3.3 (2.3-4.6)	2.7 (2.0-3.6)	5.3 (2.1-12.9)	12.7 (4.4-37.1) *
Relative risk of ICU admission given hospitalisation	[37]	-	1.0 (Ref.)	0.95 (0.75-1.2)	1.1 (0.9-1.34)	1.30 (1.09-1.54) *
Relative risk of death given hospitalisation	[37]	-	1.0 (Ref.)	0.81 (0.56-1.18)	0.93 (0.67-1.28)	1.81 (1.44-2.28) *

Table S6: Parameter estimates with 95% credible interval

Parameter	Estimate [95% credible interval]
Reproduction number before 17 March 2020	3.36 [3.02 - 3.73]
Reproduction number 17 March 2020 - 11 May 2020	0.62 [0.61 - 0.63]
Reproduction number 11 May 2020 - 1 August 2020	1.02 [1.01 - 1.03]
Reproduction number 1 August 2020 - 30 October 2020	1.42 [1.41 - 1.43]
Reproduction number 30 October 2020 - 30 November 2020	0.82 [0.79 - 0.84]
Reproduction number after 30 November 2020	1.34 [1.29 - 1.38]
Parameter associated to the change in the probability of ICU admission between 30 March 2020 and 7 April 2020 α_1	0.59 [0.5 - 0.68]
Parameter associated to the change in the probability of ICU admission between 1 July 2020 and 1 October 2020 α_2	0.79 [0.71 - 0.9]
Parameter associated to the change in the probability of ICU admission between 1 October 2020 and 12 December 2020 α_3	0.57 [0.51 - 0.65]
Initial number of infected individuals	6.89 [1.68 - 27.82]
Overdispersion parameter δ	0.5 [0.47 - 0.52]

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