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Abstract

The SARS-CoV-2 pandemic has entered an uncertain race between the emergence of variants that are more transmissible and vaccine roll-out. Here, we developed a mathematical model to evaluate how the interplay of variants, vaccines and non-pharmaceutical interventions might shape the pandemic dynamics, using the rise of the B.1.1.7 variant in metropolitan France as a case study. Our analysis highlights the challenges ahead for the management of the SARS-CoV-2 pandemic and shows how the quick roll-out of vaccines to at-risk individuals and non-pharmaceutical interventions are needed to mitigate the impact of the emerging variants.

Introduction

While the SARS-CoV-2 pandemic has been raging for more than a year, recent changes in the characteristics of SARS-CoV-2 variants and in the pharmaceutical tools available to fight the pandemic yield conflicting perspectives about its course for the coming months. On the one hand, the vaccination of at-risk individuals with vaccines that are safe and effective against the currently dominant variants is expected to reduce the stress on the healthcare system. On the other hand, the emergence of new variants is a cause for concern. For example, the B.1.1.7 variant that emerged in the UK in the fall 2020 was found to be 40-80% more transmissible than historical viruses [1,2]. Because of this competitive advantage, the variant became dominant in the UK in a couple of months, causing an important surge in COVID-19 cases, hospital admissions and deaths and eventually the implementation of a strict lockdown [3].

Countries where B.1.1.7 is not dominant yet are rightly concerned. This is the case for France. Although hospitalizations in France currently exhibit a slow decline following the implementation of a nationwide 6pm-to-6am curfew on January 16th, additional control measures (closure of large shopping centers, expansion of teleworks) on February 1st and regionalized school holidays (February 6th-March 8th), the rise in the B.1.1.7 prevalence from 3% on January 7th 2020 to 12-14% on January 27th 2020 [4,5] hints towards a worsening of the epidemiological situation in the future. This situation raises a number of questions. Will the current measures be sufficient to maintain the epidemic under control once B.1.1.7 becomes dominant? If not, when should a rise in hospitalisations be expected? Could the roll-out of vaccines targeting at-risk individuals balance the expected rise in hospitalisations? Would additional control measures be required to avoid a renewed pandemic wave? And if so, with what intensity? These questions resonate in many countries that are in a similar situation as France.

The outcome of such a race between variants and vaccines depends on a number of factors including the increased transmissibility associated with B.1.1.7, the characteristics of the vaccine roll-out as well as the intensity (including population compliance) and duration of control measures. Here, considering France as a case study, we develop mathematical models and explore scenarios that help understand how the interplay of the key drivers of the pandemic (the variants, the vaccines and the control measures) will shape its dynamics for the coming months. It highlights the challenges ahead for the management of the SARS-CoV-2 pandemic and shows how the quick roll-out of vaccines to at-risk individuals and non-pharmaceutical interventions are needed to mitigate the impact of those emerging variants. This understanding

is important to support timely decision making for the management of the pandemic in a context of high uncertainty.

Results

Dynamics of the B.1.1.7 variant and of the historical virus

Figures 1A and 1B show the calibration of our model to nationwide trends in the prevalence of the B.1.1.7 variant and in hospital admissions. While the prevalence of B.1.1.7 was 3.3% on January 8th [5], it increased to 12-14% on January 27th 2021 [4]. This increasing trend is well captured by our model that expects a prevalence of B.1.1.7 of 13% [11%, 16%] on January 27th, 2021 for an increased transmissibility of B.1.1.7 relative to the historical virus of 60% [50%, 70%] (Figure 1A). The slow decrease in hospital admissions (Figure 1B) that is concomitant with the rise in B.1.1.7 (Figure 1A) suggests that the number of infections due to the historical virus is declining (Figure 1C) with an effective reproduction number that dropped below 1 with the curfew ($R_{eff\text{-}non\text{-}B1.1.7}$=0.92) and decreased further in February ($R_{eff\text{-}non\text{-}B1.1.7}$=0.78) (see Methods). At the same time, the number of infections due to the B.1.1.7 variant is increasing (Figure 1C). The slow decrease is expected to end when the reductions in infections by the historical virus are insufficient to balance the increase in B.1.1.7 infections (Figure 1C).

We expect that the prevalence of B.1.1.7 will progressively increase to reach 56% [44%, 68%] at the national level on March 1st and 91% [82%, 96%] on April 1st, 2021 (Figure 1A), for an increase in transmission due to B.1.1.7 of 60% [50%, 70%]. Since the variant is more transmissible than the historical virus, the replacement is associated with an increase in the transmission rate of SARS-CoV-2, which is projected to be 34% [22%, 47%] and 55% [41%, 67%] higher on March 1st and April 1st than it would have been in the absence of B.1.1.7 (Figure 1D).

A race between the B.1.1.7 variant and vaccination

Figure 2 compares the epidemic trajectories with and without vaccination in our baseline scenario where, at the end of holidays (March 8th, 2021), the transmission rate of the historical

virus increases to the levels observed during the first two weeks of the curfew and remains constant until June 30th, 2021 (see Methods). On March 15th, 2021, only 10% of the French population is expected to have been vaccinated against SARS-CoV-2 (Figure 2A), with little impact on the dynamics of infection (Figure 2B). However, as vaccination is prioritized in favor of individuals the most likely to be hospitalized, we already expect a 19% reduction of hospitalisations due to vaccination at that date (Figure 2C). Seventy percent of those aged ≥75 y.o. are expected to have received a first vaccine dose on April 1st, 2021 (Table S1), leading to further reductions in hospitalizations. We expect that daily hospitalisations will be 28% and 46% lower on April 1st and May 1st, 2021, than what would be expected in a scenario with no vaccination.

We expect that the vaccination may help delay the rise in hospital admissions by about two weeks. However, its impact may not be sufficient to balance the effect of the increased transmissibility of B.1.1.7. Indeed, the number of hospital admissions might reach in the second half of April 2021 levels observed at the peak of the French second wave and more than 4,500 daily hospital admissions at the peak (Table S2) which would likely overwhelm the healthcare system.

Strengthening of control measures

In this context we assess how a strengthening of control measures may be necessary to reduce healthcare burden, considering scenarios where such strengthening is of strong or intermediate intensity (i.e. leading to transmission rates similar to those measured during the French first and second lockdowns in March-May and November 2020, respectively; see Methods), for a duration of 4 or 6 weeks, starting on March 22nd, 2021 (Figure 3).

At this stage of the pandemic when the B.1.1.7 has become dominant, measures of intermediate intensity might only lead to a plateau (Figure 3) so that important hospitalisation levels might quickly be reached upon partial relaxation. In contrast, measures of strong intensity are still expected to generate important declines in infections, leaving more time to absorb an epidemic rebound following partial relaxation.

A strengthening with control measures of strong intensity for 6 weeks may shift the epidemic rebound at a time when a larger proportion of the population would already be vaccinated, reducing the growth in hospital admissions further than in other scenarios.

Impact of a more ambitious vaccination strategy

In our baseline scenario, we assume that 70% of all age groups will accept to get vaccinated and that from April 1st, 2021, 200,000 doses of mRNA vaccines and 100,000 doses of AstraZeneca vaccines will be distributed per day. We also investigate how the hospitalisation burden may be impacted by a more ambitious vaccination strategy characterized by a faster distribution of doses (More Optimistic MO roll-out: 400,000 doses of mRNA vaccines and 125,000 doses of AstraZeneca vaccines per day from April 1st, 2021) and/or a better vaccine coverage (90%) in those aged ≥75 y.o. We find that both improvements would contribute to reducing the hospitalisation burden with the largest reductions obtained when both are combined (Figure 4). In this latter situation, the number of hospitalisations at the peak could be reduced by 9-33% depending on the scenario for control measures (Figure 4). Also increasing the vaccine coverage to 90% in those aged 65-75 y.o. would only marginally improve impact at this stage of the epidemic (Figure 4). A Less Optimistic vaccine roll-out with no increase in the daily number of doses distributed in April would lead to larger numbers of hospitalisations (Figure 4).

Sensitivity analyses

In general, results are sensitive to assumptions about transmission rates in the different periods and about the increased transmissibility associated with B.1.1.7. A slight increase in the transmission rate of the historical virus (Figure 5A,B) or in the effect of B.1.1.7 on transmission (Figure 5C,D) would substantially degrade projections. These parameters also affect the duration of the plateau and the size of the epidemic peak. Besides, if the transmission rate starts increasing again before the end of holidays, the rebound in hospitalisations might occur earlier, highlighting the difficulty to precisely anticipate when the surge in hospitalisation is expected (Figure 5E,F). These results highlight that uncertainties remain very important. Of all the scenarios we considered, the only one where curfew conditions were sufficient to avoid a third large wave was when the transmission rate remained at the value measured in the first half of February for prolonged time periods, leading to transmission rates that would remain close to those we considered for measures of intermediate intensity (Figure 5A,B).

At this stage of the vaccination program, the impact of the vaccine on the circulation of the virus in the population is expected to remain limited. As a consequence, the impact of vaccination is relatively similar whether the vaccine has a small impact on transmission or not (Figures 5H-I).

Discussion

In this paper, we used a mathematical model to understand how the emergence of more transmissible SARS-CoV-2 variants, the roll-out of vaccines, and the implementation of non-pharmaceutical interventions might interplay and drive the course of the pandemic in the coming months. This was illustrated considering the situation of Metropolitan France.

In France, the epidemic dynamics has been characterized by both an important rise in the prevalence of B.1.1.7 and a slow decline in hospital admissions, which has puzzled observers. Our model provides a simple mechanistic explanation for the situation. The current curfew and conditions appear sufficient to control the spread of the historical virus but not that of B.1.1.7. As a result, the number of infections by the historical virus are going down while those due to B.1.1.7 are increasing. So far, the two trends have almost cancelled each other out, leading to the slow decline we are currently observing. However, as B.1.1.7 progressively becomes the driving force of the epidemic, hospital admissions may eventually start to rise again. We modeled the epidemic for Metropolitan France as a whole. However, spatial disparities exist with regions such as Ile-de-France (Paris' region) reporting larger prevalence of B.1.1.7 [5]. We expect that regions with larger prevalence of B.1.1.7 may see a rise in hospitalisations first [6], even though other factors may also influence local epidemic dynamics. This could lead to a situation where incidence is stable at the national level but is quickly increasing in some regions, potentially justifying a strengthening of control measures at the regional level.

We estimate that the transmission rate of the historical virus was low in February, with values close to those measured during the second French lockdown ($R_{0\text{-non-B1.1.7}}$=0.94 compared to 0.8-0.9 during the second French lockdown; see Methods). This might be explained by a combination of factors including the 6pm-to-6am curfew, additional measures implemented at the end of January, the holidays, weather conditions and potentially good adherence of the population to control measures at a time when there were intense discussions about the possibility of a new lockdown. If such low transmission rates were to be maintained for

prolonged time periods, our model anticipates that this might be sufficient to avoid a large third pandemic wave. In practice, however, this might be difficult to achieve without additional measures once we factor in the end of the holidays and a potential weariness of the population about the curfew. In our baseline scenarios where we assume a slight increase of transmission at the end of holidays, we observed an important rise in hospital admissions that would likely require a strengthening of control measures. We found that the dynamics were very sensitive to assumptions about transmission rates during the different time periods and the increased transmissibility due to B.1.1.7. Overall, the path to avoid strengthening control measures appears limited, even if it cannot be ruled out. In case of an epidemic rebound, measures of intermediate or strong intensity could substantially reduce the hospitalisation burden and delay the epidemic rebound to a time when more people are vaccinated. These scenarios were defined considering transmission rates estimated during the first and second French lockdown. We did not ascertain here which set of interventions would be required to reach such reductions in transmission; they could include further restrictions and/or a more effective way to Trace-Test-Isolate. Our sensitivity analyses indicate that the epidemiological situation could get substantially worse if control measures were relaxed too much during the spring. In practice, all our scenarios implicitly included some form of partial relaxation of control measures that would balance the effect of warmer temperatures on transmission (see Methods).

With vaccination targeting those at higher risk of hospitalisation, the burden on hospitals could quickly be alleviated. However, our assessment suggests that this effect may not be sufficient to compensate for the increased transmissibility of B.1.1.7. In a context where those aged ≥75 y.o. represent a large proportion of hospitalisations, we found that the hospitalisation burden could be substantially reduced if more vaccines could be quickly delivered to cover 90% of this age group. This result indicates that it is important to push for a very ambitious vaccination strategy towards this age group and other at-risk individuals, subject to the availability of a sufficient number of doses. A number of uncertainties remain regarding the COVID-19 vaccination campaign. We considered vaccination strategies based solely on age and did not account for the vaccination of younger at-risk groups (in the general population or among healthcare workers) during the first months of the campaign. The impact of the current vaccination campaign might be smaller if the actual vaccination pace of high risk groups is slower than the one we anticipate, for example if individuals with lower risks are vaccinated early on. We considered that 70% of all age groups being considered here would accept getting vaccinated. This currently seems optimistic for France [7,8], although a vaccine uptake of around 75% has

been reported in French elderly homes [9]. In our analyses, we assumed that all vaccines would be 90% effective against severe disease outcome and reduce transmission by 30%. Higher or lower values, as well as the spread of new variants for which vaccines might have a lower effectiveness are susceptible to modify the extent of hospitalizations averted through the vaccination campaign.

We only considered the British variant B.1.1.7 that has been associated with increased transmissibility and a fast rise of prevalence across many countries, even though other variants are also a cause for concern. We assumed that the variant B.1.1.7 did not increase the severity of infection even though there are conflicting reports about such possibility [2,10]. Our projections for hospital admissions in the coming months would be further degraded if B.1.1.7 increased the severity of infection. While vaccines are expected to be as effective against B.1.1.7 as they are against the historical virus, other variants, such as the South African B.1.351 and the Brazilian P.1, appear to partly escape the effect of the vaccines [11]. It will be important in subsequent analyses to determine how such variants may affect the management of the pandemic in the coming months or years.

The pandemic has often put mathematical models at the forefront of discussions about control strategies, sometimes with a degree of confusion about how modelling results should be interpreted and used. The current situation remains of great uncertainty. This is well reflected in the many different epidemic dynamics that appear possible according to our sensitivity analyses (Figure 5). This underlines once more that a single forecast for the coming months is not possible. Yet, we propose that modelling future trajectories based on a set of well defined assumptions becomes all the more necessary as more interventions become effectively available to change the drivers of the epidemic and especially their interplay to shape its future course.

This study highlights the challenges ahead for the management of the SARS-CoV-2 pandemic and shows how the quick roll-out of vaccines to at-risk individuals and non-pharmaceutical interventions are needed to mitigate the impact of emerging variants that are substantially more transmissible than the historical virus.

Methods

We use a mathematical model developed to describe transmission dynamics of SARS-CoV-2 in the different age groups of the Metropolitan French population as well as its impact on the healthcare system. More details about the model are available in [12,13]. The model has been extended to describe the impact of the roll-out of vaccines and the emergence of the variant B.1.1.7 on transmission dynamics and the health care system in Metropolitan France, as detailed below.

Characteristics of the vaccination campaign

Vaccination strategies

We assume that the vaccination campaign is prioritized towards older age groups. We account for the constraints imposed by the delay between the doses, the vaccination roll-out pace and the doses delivery calendar. We only consider SARS-CoV-2 vaccines which have been authorized by the European Medicines Agency by the end of January 2021 (Pfizer/BioNTech, Moderna and AstraZeneca). In line with the recommendations by the Haute Autorité de Santé (French National Authority for Health), AstraZeneca doses are distributed preferentially to individuals younger than 65 years-old (y.o.) [14]. More specifically, vaccination with mRNA vaccines begins among those older than 75 y.o.. Once the target vaccination coverage is reached within this group, doses start to be distributed among individuals aged 65-74 y.o.. Once the target vaccine coverage is reached among 65-74 y.o., doses are distributed towards 50-64 y.o. followed by 18-49 y.o.. AstraZeneca doses are distributed following the same scheme, starting from those aged 50-64 y.o.. We assume a loss rate of 5% compared to the vaccine delivery schedule (Table S3). We fix the vaccine coverage to 70% in every age group. As a sensitivity analysis, we explore a scenario with a higher vaccine coverage of 90% in individuals older than 75 y.o. or older than 65 y.o.. We fix the delay between the doses to 21 days for mRNA vaccines and 42 days for AstraZeneca vaccines.

Vaccine efficacy

In our baseline scenario, we consider that all vaccines are characterized by an efficacy of 90% on the risk of developing a severe form of COVID-19 and of 30% on transmission. We also explore a scenario in which vaccines do not have an effect on transmission but reduce by 90% the risk of developing a severe form of COVID-19 among vaccinated individuals. In all our scenarios, vaccine efficacy is reached 15 days after the distribution of the first dose. We assume that the vaccine efficacy is the same against the historical virus and the B.1.1.7 variant.

Vaccination roll-out pace

We explore several scenarios regarding the vaccination roll-out pace. Scenarios account for an increase in the vaccination roll-out of mRNA vaccine from April 1st as more doses are scheduled for delivery. In our baseline scenario, we assume that the vaccination roll-out pace of mRNA vaccines increases from 100,000 doses per day (in line with current roll-out in France) starting on January 24th to 200,000 doses per day in April. The AstraZeneca vaccines are distributed at a pace of 100,000 doses per day starting on February 1st. As a sensitivity analysis, we explore a more optimistic scenario (MO) regarding the roll-out, with 125,000 AstraZeneca doses per day and an increase to 400,000 mRNA doses per day from April 1st, 2021 ; and a less optimistic scenario (LO) with no increase in mRNA vaccines roll-out (Table S4). We save 1.6 million doses of mRNA doses for the healthcare workers.

Scenarios for epidemic dynamics and control measures

The effect of control measures on transmission is parametrized with the basic reproduction number R_0 (i.e. the average number of infections caused by a case under the control measures if the population was completely susceptible). We also report the effective reproduction number R_{eff} (i.e. the average number of infections caused by a case) at a given time, that accounts for the impact of both control measures and immunity on transmission rates.

Dynamics of the B.1.1.7 *variant and transmission of the historical virus (non-*B.1.1.7*) during the ongoing curfew and holidays*

We assume that the prevalence of the B.1.1.7 variant among cases was equal to 3.3% on January 8th, 2021, as estimated in a nationwide survey [5]. We then calibrate the model so that it captures nationwide trends in the prevalence of the B.1.1.7 variant and in hospital admissions, in January and February 2021. As a result of this calibration, in our baseline scenario, i) the basic reproduction number of the historical virus is equal to $R_{0\text{-non-B1.1.7}}$= 1.11 (corresponding to $R_{\text{eff-non-B1.1.7}}$=0.92 on January 16th) from January 16th (the start of the curfew) to January 30th,

when it drops to $R_{0\text{-non-B1.1.7}}$= 0.94 (corresponding to $R_{\text{eff-non-B1.1.7}}$=0.78 on January 16th 2021) ; and ii) the transmissibility of B.1.1.7 increases by 60% compared to the historical virus, in line with estimates from England [1,2].

In our baseline scenario, we assume that, at the end of holidays (March 8th, 2021), the transmission rate of the historical virus increases to the levels observed during the first two weeks of the curfew ($R_{0\text{-non-B1.1.7}}$= 1.11) and remains constant until June 30th, 2021. We also consider i) a more optimistic scenario where it remains equal to the value measured in February ($R_{0\text{-non-B1.1.7}}$= 0.94) and ii) less optimistic scenarios where there is a further increase in transmission (+8%, $R_{0\text{-non-B1.1.7}}$= 1.19 or +16% $R_{0\text{-non-B1.1.7}}$= 1.28) compared to our baseline scenario, for example due to reduced compliance of the population to control measures. We also consider a scenario where the change in transmission occurs before the end of holidays (February 22nd).

We also explore scenarios where the transmission rate of the B.1.1.7 variant is 50% and 70% higher than the historical virus.

Strengthening of control measures

If the curfew is insufficient to avoid an important epidemic rebound, policy makers may decide to strengthen control measures. We consider two scenarios: i) strong strengthening of control measures leading to transmission rates similar to those measured during the first nationwide lockdown in March-May 2020 ($R_{0\text{-non-B1.1.7}}$=0.6-0.7) [12]; ii) intermediate strengthening of control measures leading to transmission rates similar to those measured during the second lockdown in November 2020 ($R_{0\text{-non-B1.1.7}}$=0.8-0.9), when more people could go to work and schools remained open [15]. Once we account for the larger proportion of infected individuals compared to the period when these measures were implemented, these estimates translate into an effective reproduction number on January 16th 2021 equal to $R_{\text{eff-non-B1.1.7}}$=0.50-0.58 for strong strengthening and $R_{\text{eff-non-B1.1.7}}$=0.64-0.72 for intermediate strengthening.

For each scenario, we explore two values of the transmission rate and present in the figures the average trajectory. We do not ascertain here which set of interventions would be required to reach such reductions in transmission. We assume strengthening of control measures starts on March 22nd for a duration of 4 or 6 weeks. After that, control measures are partially relaxed.

Partial relaxation of control measures and impact of warmer temperatures on transmission

After a time period when control measures have been strengthened, we assume in our baseline scenario that the transmission rate goes back to the value estimated at the beginning of the curfew ($R_{0\text{-non-B1.1.7}}$= 1.11) until June 30th, 2021. We also consider scenarios where a more important relaxation of control measures leads to larger transmission rates: +8% increase ($R_{0\text{-non-B1.1.7}}$= 1.19) and +16% increase ($R_{0\text{-non-B1.1.7}}$= 1.28).

Warmer temperatures are expected to reduce transmission rates. The scenario where the transmission rate remains constant until the summer can therefore be seen as a scenario where control measures are partially relaxed as temperatures get warmer so that the effects of warmer temperatures and the relaxation of control measures balance each other. As a reminder, the effective reproduction number of the historical virus was 1.2 in August 2020 at the national level [16].

Assumptions in the baseline scenario are listed in Supplementary Table S5.

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Figures

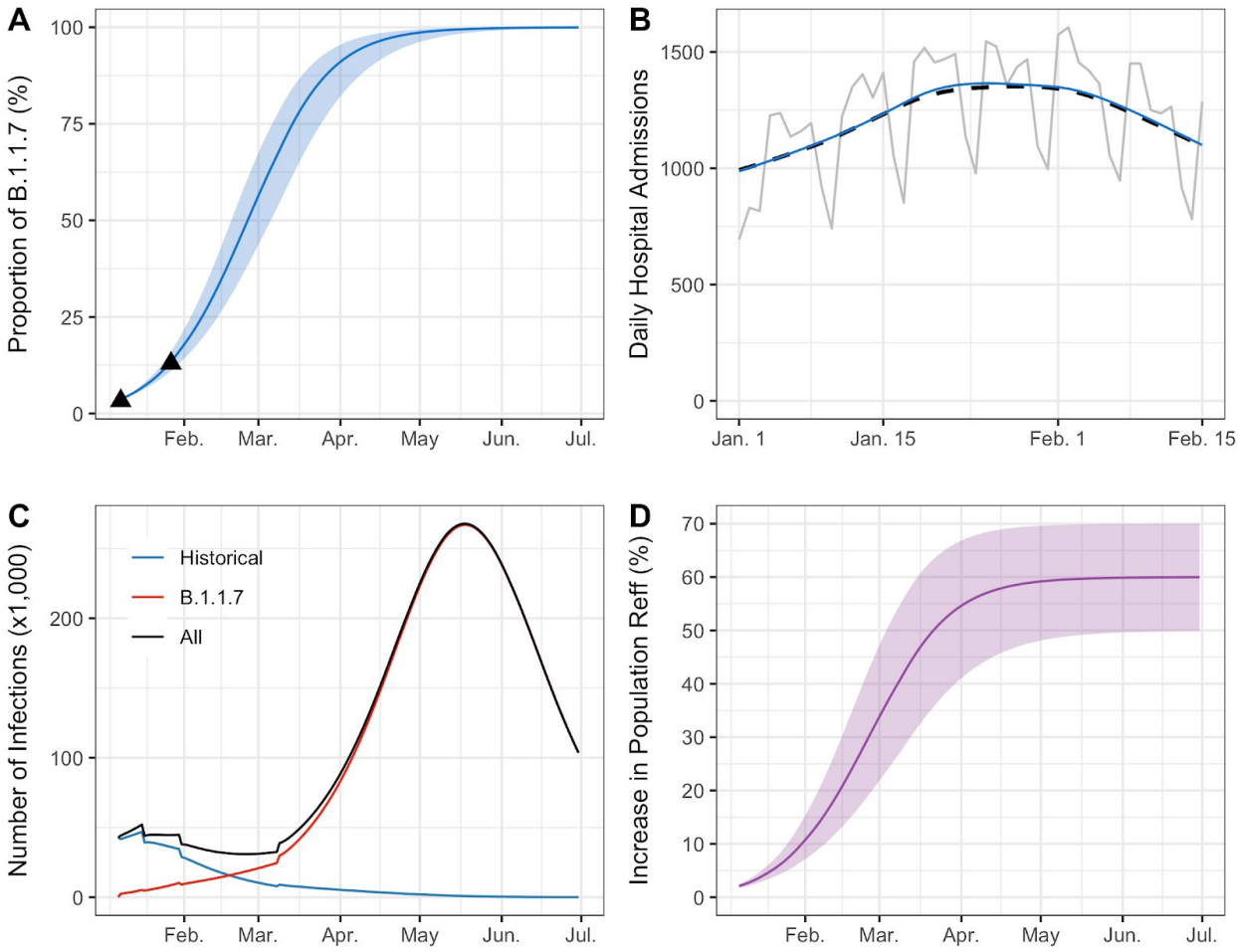

Figure 1. Epidemic dynamics of the historical virus and the B.1.1.7 variant. A. *Proportion of B.1.1.7 among cases. The black triangles correspond to the prevalence measured in France [4,5]. **B.** Model fit to the hospitalisation data: the blue line corresponds to model simulations, the grey line to raw data, and the dashed black line to smoothed data. **C.** Projected number of infections due to the historical virus and to the B.1.1.7 variant. We assume that, at the end of the holidays (March 8th, 2021), the transmission rate of the historical virus goes back to levels estimated during the two first weeks of the curfew and remains constant until June 30th, 2021. **D.** Increase in the overall transmission rate of SARS-CoV-2 due to B.1.1.7 prevalence compared to a scenario with no circulation of B.1.1.7. In panels A and D solid lines correspond to the hypothesis of a 60% increased transmissibility of B.1.1.7 with respect to the historical virus, while colored areas correspond to the lower (50%) and upper (70%) bounds of the transmissibility increase.*

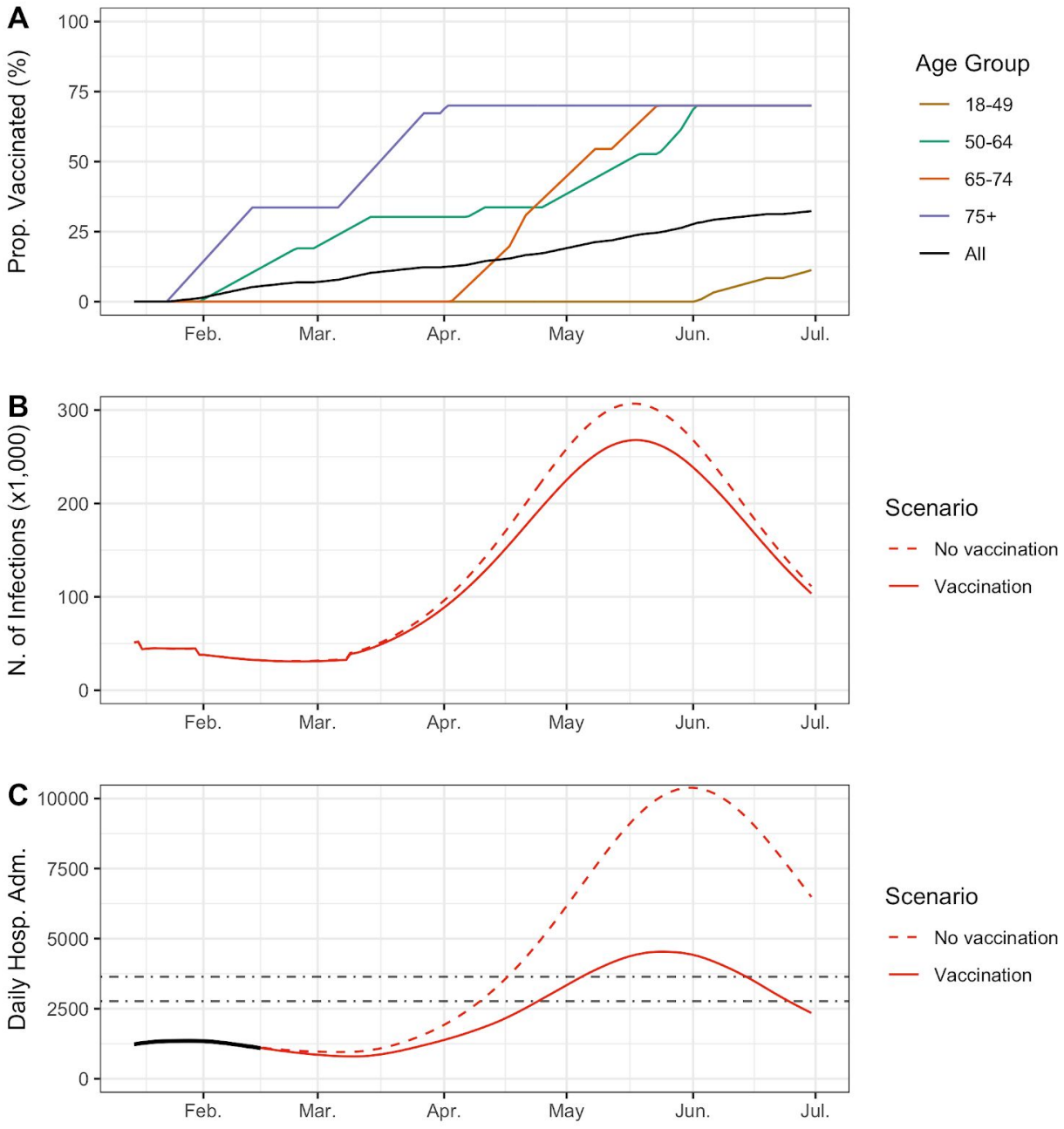

Figure 2. Comparison of epidemic trajectories with and without vaccination. ***A.*** *Proportion of individuals having received the first vaccine dose through time and for different age groups.* ***B.*** *Daily number of infections in thousands.* ***C.*** *Daily hospital admissions. We assume that, at the end of the holidays (March 8th, 2021), the transmission rate of the historical virus goes back to levels estimated during the first two weeks of the curfew and remains constant until June 30th, 2021. The horizontal dashed lines in panel C represent the hospital admissions peaks observed during the first (highest) and second (lowest) epidemic waves. The black line in panel C represents smoothed data.*

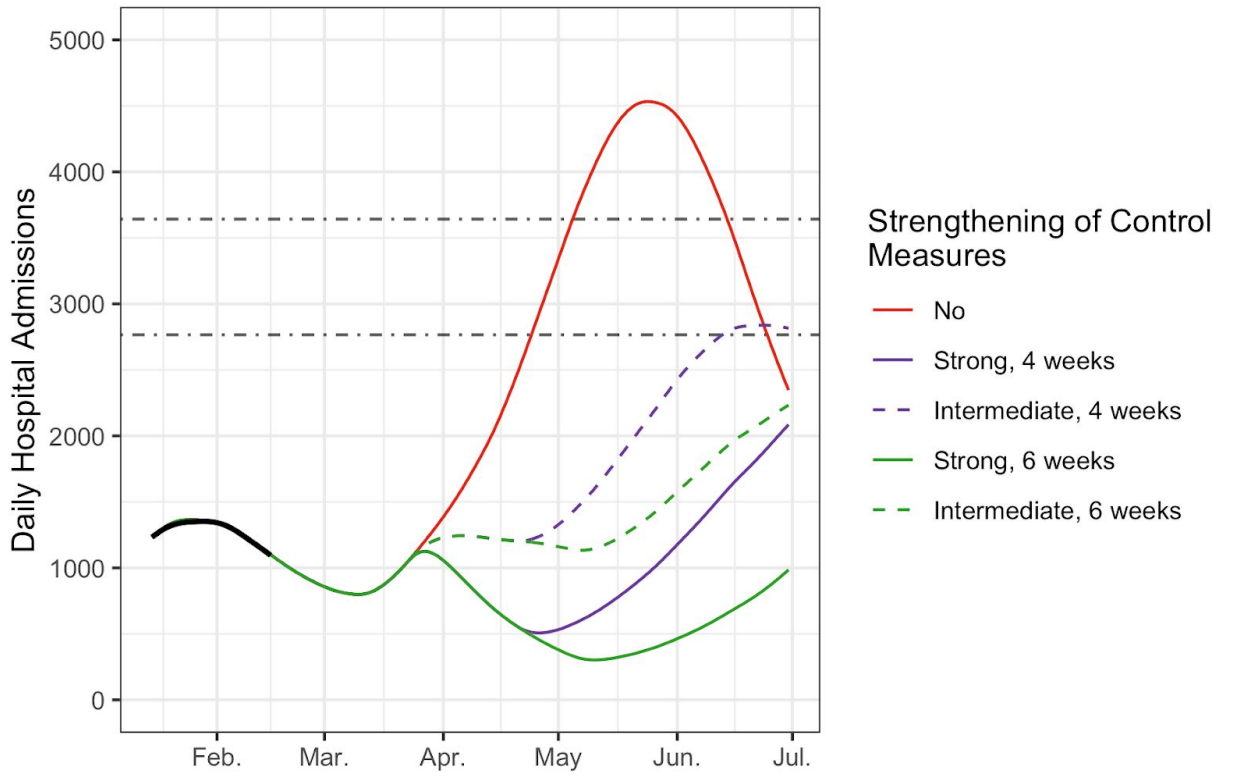

Figure 3. Scenarios where control measures are strengthened for a duration of 4 or 6 weeks with measures of intermediate or strong intensity, starting on March 22nd, with vaccination. *Strengthening of strong and intermediate intensity lead to transmission rates equal to those measured during the French lockdown of March-May 2020 and November 2020, respectively (see Methods). The horizontal dashed lines represent the hospital admissions peaks observed during the first (highest) and second (lowest) epidemic waves. The black line represents smoothed data. In all scenarios, we assume that at the end of holidays (March 8th, 2021), the transmission rate of the historical virus goes back to levels observed during the first two weeks of the curfew.*

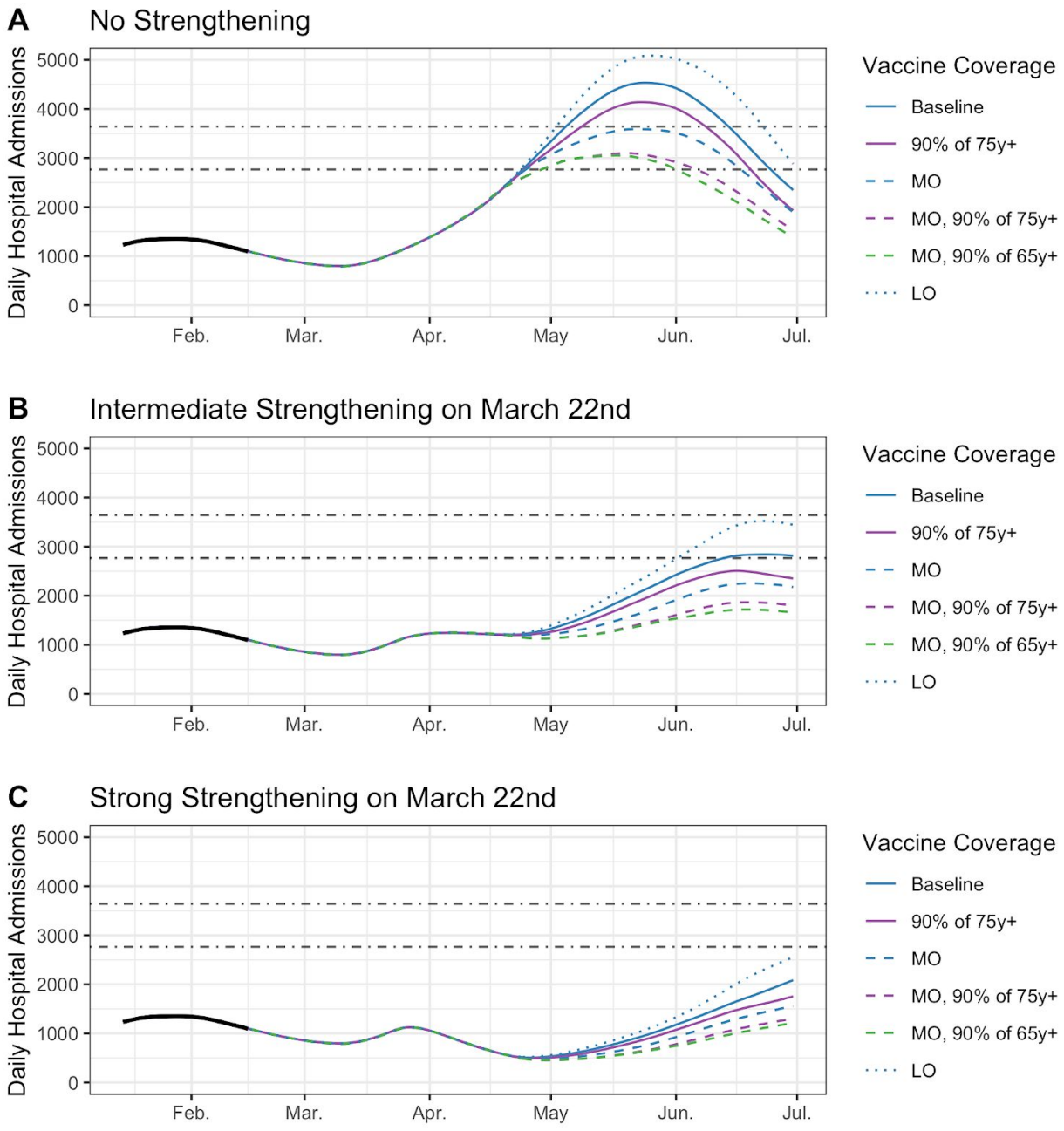

Figure 4. Impact of the characteristics of the vaccination campaign on hospital admissions. *Number of daily hospital admissions with no strengthening of control measures (**A**), with a strengthening of intermediate **(B)** or strong **(C)** intensity for 4 weeks starting on March 22nd, 2021. Different colors indicate different vaccine coverages: blue (baseline, i.e. 70% in every age group), purple (90% coverage of 75y+), green (90% coverage of 65y+). Solid lines indicate the baseline roll-out (from April 1st, 2021, 200,000 doses of mRNA vaccines and 100,000 doses of AstraZeneca vaccines per day) scenario, dashed lines indicate the More Optimistic (MO) roll-out (from April 1st, 2021, 400,000 doses of mRNA vaccines and 125,000 doses of AstraZeneca vaccines per day), while dotted lines indicate the Less Optimistic (LO)*

roll-out (100,000 doses per day for all vaccines with no increase from April 2021). The horizontal dashed lines represent the hospital admissions peaks observed during the first (highest) and second (lowest) epidemic waves.

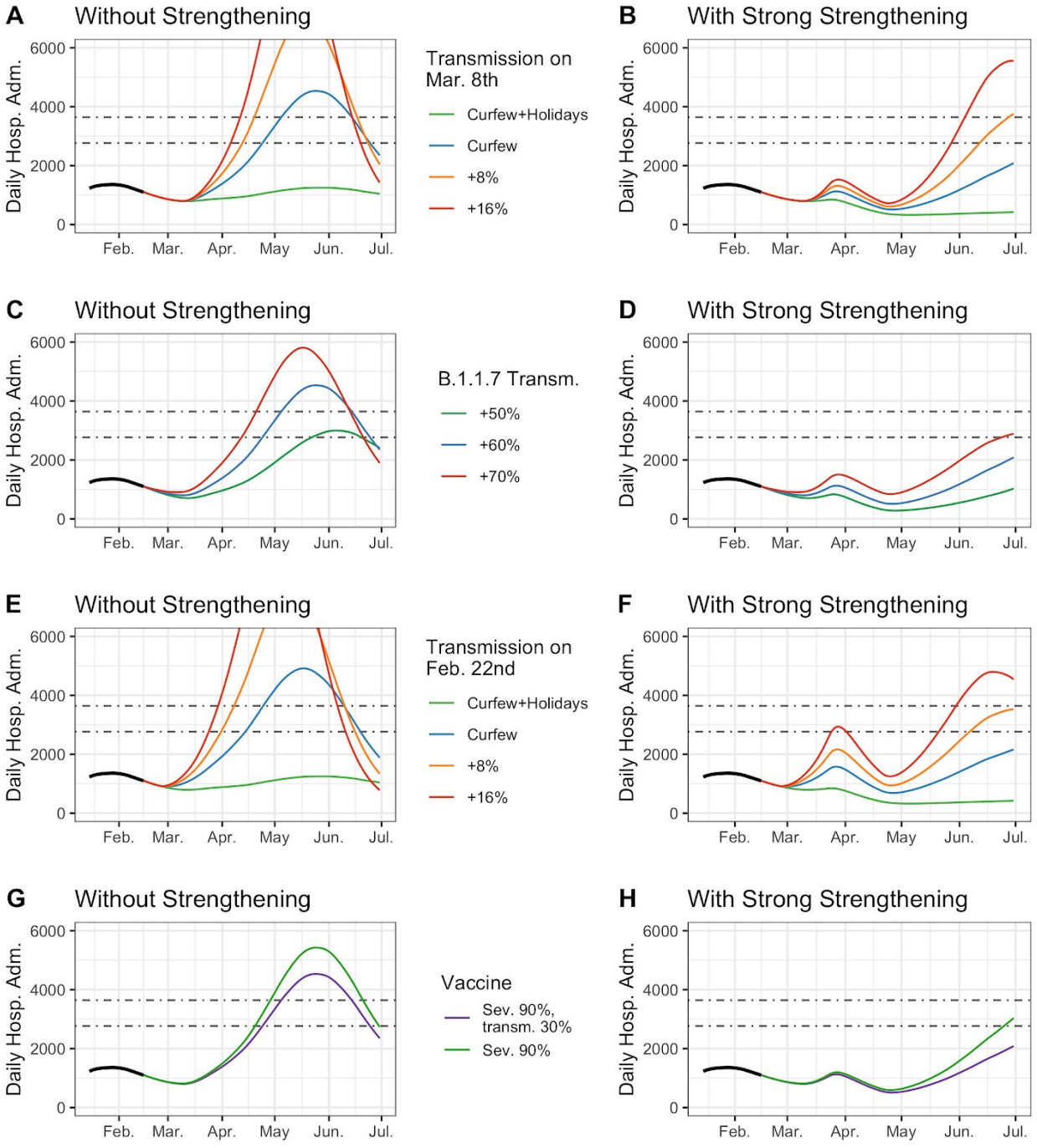

Figure 5. Sensitivity analyses. *Daily number of hospital admissions as a function of* ***A and B.*** *the transmission rate of the historical virus after the end of holidays on March 8th assuming it remains similar to the value estimated in February (green), it goes back to the value during the first two weeks of the curfew (blue; baseline), there is a further increase of +8% (orange) or +16% (red) compared to the baseline scenario.* ***C and D.*** *Effect of the increase in the*

transmissibility of B.1.1.7 with respect to the historical virus. ***E and F.*** *Like A and B but assuming the change occurs on February 22nd, 2021.* ***G and H.*** *Effect of vaccine characteristics. Scenarios with and without strengthening of control measures are on the left hand side and the right hand side, respectively. Strengthening of control measures is enforced on March 22nd for 4 weeks. The horizontal dashed lines in all panels represent the hospital admissions peaks observed during the first (highest) and second (lowest) epidemic waves. The black line in all panels represents smoothed data.*

Table S1: Time required to reach different levels of vaccine coverage in the different vaccination roll-out scenarios.

	Date by which 60% of individuals over 75 y.o. received a first dose	Date by which 70% of individuals over 75 y.o. received a first dose
Baseline scenario	March 23rd, 2021	April 2nd, 2021
Scenario with more optimistic assumptions regarding the roll-out (MO)	March 23rd, 2021	April 1st, 2021
Scenario with much less optimistic assumptions regarding the roll-out (LO)	March 23rd, 2021	April 19th, 2021

Table S2: Cumulative number of hospitalisations between March 8th and June 30th depending on control measures. Strengthening of strong and intermediate intensity lead to transmission rates equal to those measured during the French lockdown of March-May 2020 and November 2020 (see Methods).

		Cumulative number of hospitalisations between March 8th and June 30th (in thousands)	
	Duration	Strong intensity	Intermediate intensity
Strengthening of the control measures starting on March 22nd, 2021	4 weeks	118	199
	6 weeks	75	157
No strengthening of the control measures	Maintained until June 30th	324	

Table S3: Delivery schedule by vaccine type and month used to inform the model (in million doses).

Month	February	March	April	May	June
Pfizer/BioNTech	2.5	4	10.3	10.2	10.3
Moderna	0.5	0.9	1.5	2	1.7
AstraZeneca	2.5	3.3	4.2	4.2	4.2

Table S4: Hypotheses made in the different vaccination roll-out scenarios

	mRNA vaccines		AstraZeneca vaccines
	Before April 1st	After April 1st	
Baseline scenario	100,000 doses / day	200,000 doses / day	100,000 doses / day
Scenario with more optimistic assumptions regarding the roll-out (MO)	100,000 doses / day	400,000 doses / day	125,000 doses / day
Scenario with less optimistic assumptions regarding the roll-out (LO)	100,000 doses / day	100,000 doses / day	100,000 doses / day

Table S5: Summary of assumptions in the baseline scenario and parameters explored in sensitivity analyses

Parameters		Baseline scenario	Sensitivity analyses
Increased transmissibility of the B.1.1.7 compared to the historical virus		60%	50% - 70%
Basic reproduction number of the historical virus at the end of the holidays (March 8th)		1.11 (As estimated during the first two weeks of the curfew)	0.94 (As estimated in February) 1.19 (Increase of 8%) 1.28 (Increase of 16%)
Strengthening of the current interventions	Date of strengthening	March 22nd, 2021	
	Length of strengthening	4 weeks	6 weeks
	Strength of interventions implemented	No strengthening	Intermediate or strong strengthening (see Methods)
Vaccination roll-out pace (doses per day)	mRNA vaccines	100,000 until April 1st 200,000 from April 1st	M0: 400,000 from April 1st LO: 100,000 from April 1st
	AstraZeneca vaccines	100,000	MO: 125,000 LO: 100,000
Vaccine efficacy		90% on severity an 30% on transmission	90% on severity and 0% on transmission
Vaccine coverage		70% in every age group	90% for those older than 75 y.o. - 90% for those older than 65 y.o.