Evaluating the Roadmap out of Lockdown: modelling step 4 of the roadmap in the context of B.1.617.2

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1. Summary

In this report, we summarise the findings of our evaluation of the easing of non-pharmaceutical interventions (NPIs) as set out in the UK Government's Roadmap out of Lockdown focusing on the potential impact of B.1.617.2. Full methods, data used, and parameter values assumed for forward projections are given in the technical appendix. Key parameters relevant to interpretation of findings are provided in the text. Results and assumptions refer to England unless otherwise specified.

1. We estimate the current level of transmission, R_{eff}, is approximately 0.8 for B.1.1.7 and 1.5 for B.1.617.2 in England, with an overall R_{eff} of ~1.4 across both variants. This may not capture all changes in transmissibility since the 17 May reopening as R is a lagging indicator by 3 weeks.
2. Based on Public Health England (PHE) data available to 1 June 2021, 74% of the adult population in England have received at least one vaccine dose and 50% have received two doses.
3. Across all transmissibility and immune escape scenarios explored, we estimate that B.1.617.2 could lead to a significant third wave of hospitalisations and deaths similar to or larger than the winter wave.
4. Cases, hospitalisations, and deaths in the next month could grow rapidly. Large uncertainty remains regarding the scale of the future epidemic and resulting additional burden.
5. Delaying step 4 releases beyond 21 June should delay the projected third wave and reduce the estimated number of hospitalisation and deaths. This will also allow more time for alternative control strategies such as boosters doses and vaccination of <18 years to be considered and implemented.
6. *In the range of parameters we examined, immune escape properties of B.1.617.2 affected the magnitude of the third wave more than assumptions about transmissibility. However, there is considerable uncertainty regarding the levels of transmissibility and immune escape of B.1.617.2 which translate into large uncertainty on the possible future epidemic trajectory.*
7. Global collaborative efforts to control transmission abroad will be vital in preventing further emergence and importation of new VOCs which may trigger another wave and necessitate further reconsideration or reversal of the current roadmap. VOC importations over time should also be monitored carefully. Careful testing and quarantine measures will be critical as international travel restrictions are lifted.
8. Given the many uncertainties involved in making these projections and in light of the increasing B.1.617.2 cases in England, more time may be needed to fully assess the impact of Step 3 and better characterise the transmissibility, severity, and immune escape properties of B.1.617.2 before committing to Step 4 which will pose the greatest risk to increased transmission.

2. Introduction

The UK government has set out a roadmap for coming out of lockdown, with several defined stages for relaxing interventions that have been in place to control the spread of SARS-CoV-2. In this report

we focus on the potential impact of VOCs such as B.1.617.2 on “Step 4” of the roadmap occurring not before 21 June 2021.

Several key sources of data (as of 4 June 2021) feed into this analysis:

1. The degree of past infection over the course of the UK epidemic from January 2020. This determines the proportion of people who will have natural immunity due to prior infection and is estimated by fitting our transmission model [1] to data on infection prevalence surveys, serology, reported cases via Pillar 1 and Pillar 2, reported hospitalisations and deaths within 28 days of a positive test.
2. The proportion of S-gene positive cases on 21 May by NHS region which informed our assumptions about the proportion of B.1.617.2 cases at the start of the simulation on 4 June 2021 (see Methods and Supplementary Table 2).
3. The daily incidence of recent S-gene positive and negative cases used to infer the effective reproduction number for B.1.1.7 and B.1.617.2.
4. PHE data on vaccination coverage over time by age (Figure 1) and region, including the proportions receiving their first dose and second doses and the specific vaccine given to each age-group.
5. The effectiveness of vaccination against the circulating B.1.1.7 and B.1.617.2 variants in the UK. This is obtained from a review of clinical trial efficacy data and from UK and international studies on their real-world effectiveness (Table 1).

Forward projections also require assumptions to be made about three key determinants of the course of the epidemic:

1. The transmissibility of the circulating virus currently and as interventions are further relaxed at Step 4. We formulate this in terms of the reproduction number for B.1.1.7, R, that would occur in the absence of natural- and vaccine-induced immunity ($R_{excl\_immunity}$) (Table 4 and Supplementary Table 1). The range of $R_{excl\_immunity}$ for B.1.617.2 explored then depends on the immune escape and transmissibility advantage assumed (as illustrated in Figure 2)
2. Future vaccination programme progress - including the vaccine supply, speed of roll-out, product mix and uptake in younger age-groups (Table 2 and Table 3).
3. The proportion of current cases that are due to VOCs and their transmissibility and degree of immune escape of B.1.617.2 compared with the B.1.1.7 lineage (Table 1 and Supplementary Table 2).

2.1 Variants of Concern

The potential impact on the roadmap of the emergence and spread of VOCs, particularly B.1.617.2 which is now the dominant variant, is uncertain. We explored the impact of a range of different levels of immune escape and transmissibility properties for B.1.617.2, in line with the limited current available scientific evidence.

Key factors considered include:

- Current levels of B.1.617.2 in the community. We assumed that all S-gene positive pillar 2 cases are due to this variant (see Supplementary Table 2).
- Transmissibility of B.1.617.2 compared to the current circulating variant (B.1.1.7).
- Cross-protection from prior infection with wild-type or B.1.1.7 variants.
- Vaccine efficacy against B.1.617.2.

We consider three scenarios with respect to the level of immune escape of B.1.617.2 (Table 1). Our assumptions about vaccine efficacy against B.1.617.2 are principally based on a review of the

(limited) data from vaccine efficacy and effectiveness studies for other VOCs including the B.1.351 variant, as well as the latest PHE effectiveness study on B.1.617.2 [2]. We assumed that B.1.617.2 had lower immune escape properties compared to B.1.351 [3].

We considered different levels of increased transmissibility for B.1.617.2, from 100% (no increase) to 300% (threefold increase) relative to B.1.1.7. We define the *effective transmissibility advantage* as the advantage conferred by a mix of increased transmissibility and the degree of immune escape, measured as the ratio of the effective reproduction numbers between the two variants. We only report results for scenarios where this would result in an approximately 1.5 to 2-fold effective reproduction number multiplicative advantage (R_{eff}), consistent with the current growth rates for B.1.1.7 and B.1.617.2 (see section 2.5, as well as independent analysis of variant-specific time series data using EpiEstim (not shown here), and the latest PHE analysis). Namely for the central immune escape scenarios, we considered transmission advantages of 150% (where B.1.617.2 is assumed 50% more infectious than B.1.1.7), 165% and 180%, for the high immune escape scenario, we considered transmission advantages of 140%, 155% and 170% and for the low immune escape scenario we considered transmission advantages of 150%, 170% and 190%.

2.2 Vaccine Effectiveness

Our assumptions regarding the mode of action and effectiveness for each vaccine reflect the most recent evidence. Table 1 summarises these for the Pfizer, AstraZeneca and Moderna vaccines for B.1.1.7 and VOCs/B.1.617.2. We assume that vaccine protection against symptomatic disease as determined from the original trials and real-world data also provides a similar level of protection against asymptomatic infection. We further assume that, in those vaccinated individuals who do become infected, onward transmission is also reduced.

Table 1: Cross-immunity and vaccine efficacy assumptions for AstraZeneca (AZ), Pfizer (PF), and Moderna (Mod). "Central", "High", and "Low" immune escape refers to the degree to which B.1.617.2 can escape vaccine induced immunity or immunity due to prior infection with B.1.1.7 or prior variants. We assume individuals ≥50 years will receive the mix of vaccines observed thus far; 40-49 years will receive 60% AZ and 40% PF or Moderna; and individuals under 40 years will receive PF or Moderna only. *100% protection = complete cross-protection, 0% = no cross-protection

			"Central" immune escape	**"High" immune escape"**	**"Low" immune escape**	
Infection with VOC resulting in protection* vs B.1.1.7			100%	100%	100%	
Infection with B.1.1.7 or earlier variants resulting in protection* vs B.1.617.2	Infection/mild disease		85%	75%	100%	
	Hospitalisation		95% (as PF 2 doses)	90% (as PF 2 doses)	100%	
Vaccine Efficacy (VE)	**Vaccine**	**VE efficacy vs B.1.1.7**	**Central VE vs B.1.617.2**	**Pessimistic VE vs B.1.617.2**	**Optimistic VE vs B.1.617.2**	**Informed by (B.1.1.7/B.1.617.2)**
Vs severe disease	AZ (1)	80%	73%	68%	78%	Vasileiou 2021 [4], PHE [5], Hyams 2021 [6]/ Assumed higher than against mild disease, similarly to B.1.1.7
	AZ (2)	89%	85%	77%	87%	
	PF (1)	80%	73%	68%	76%	Hyams 2021 [6] Hall 2021 [7]
	PF (2)	95%	89%	84%	90%	PHE [8]/assumed higher than against mild disease, similarly to B.1.1.7
	Moderna	Assume same as PF for 1 and 2 doses				
Vs mild disease	AZ (1)	50%	33%	20%	45%	Voysey 2020 [9]
	AZ (2)	66%	55%	30%	60%	Voysey 2021 [10]/ PHE [2][9,10]
	PF (1)	50%	33%	20%	40%	PHE [11] Hall 2021 [7] / PHE [2]
	PF (2)	93%	85%	78%	86%	Hall 2021 [7]/ PHE [2]
	Moderna	Assume same as PF for 1 and 2 doses				
Vs infection	AZ (1)	50%	33%	20%	45%	Assumed same as disease
	AZ (2)	66%	55%	30%	60%	
	PF (1)	50%	33%	20%	40%	
	PF (2)	93%	85%	78%	86%	
	Moderna	Assume same as PF for 1 and 2 doses				
Vs infectiousness if infected	AZ/PF/Mod (1)	45%	33%	20%	45%	[12]/Assumed
	AZ/PF/Mod (2)	45%	33%	20%	45%	[12]/Assumed

2.3 Vaccination Coverage

Data on vaccine uptake by age and product were provided by PHE. These data are summarised in Figure 1. Note that these data are the same as reported on the COVID-19 dashboard [13].

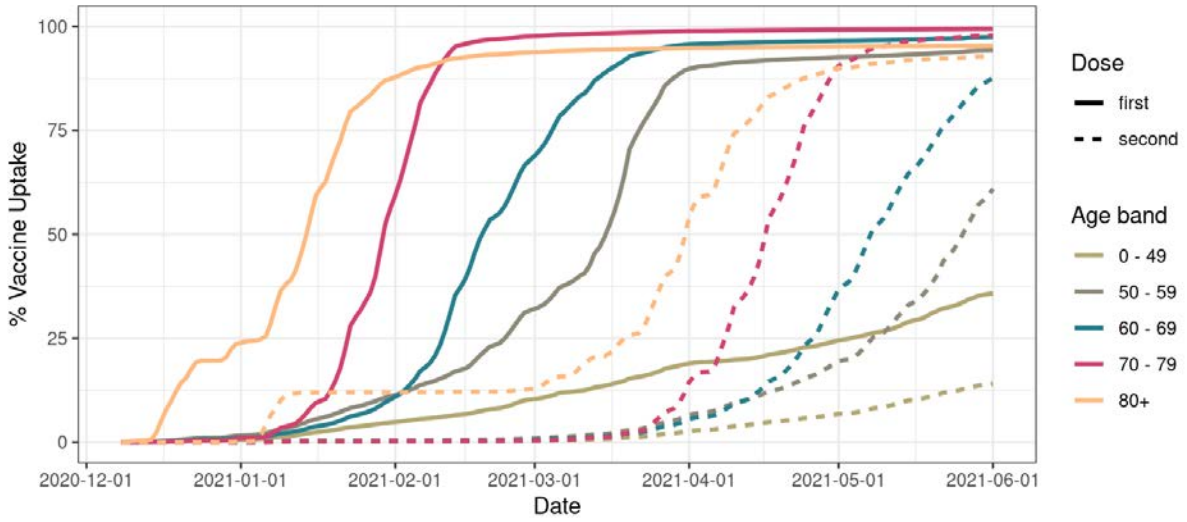

Figure 1: Cumulative vaccine uptake by 1 June 2021 by age for England shown for first (solid lines) and second (dashed lines) doses. Shown as the proportion of the population age group of England (ONS).

Projections of vaccine roll-out provided by DHSC for this exercise are summarised in Table 2.

Table 2: Pre-specified vaccination schedule (million doses per week)

	Weeks commencing	Average doses per week
England	31 May 2021	2.15M
	26 July 2021 onwards	2.0M

For the forward projections, the modelled uptake is summarised in Table 3. For the older age-groups, we use the vaccine coverage that has been obtained for dose 1 if this is higher than the assumed uptake and we assumed the same uptake will be achieved for dose 2. For the younger age-groups where uptake remains below our assumed levels, we use these values for both dose 1 and dose 2. [1]

[1] Paragraph and Table 3 added for clarity for release. Originally stated "For the forward projections, we model continued roll-out to all age-groups and assume an 80% uptake in the 18-39 year olds."

Table 3: Latest vaccine uptake reported by the NHS and our assumptions by group or age for England.

Group	Reported NHS first dose uptake data up to 30 May^	Modelled uptake at start of simulation (4 June)	Maximum uptake in the simulation
Care home residents (CHR)	-	92%	95%
Care home workers (CHW)	-	86%	86%
80+ years*	94.6%	94%	95%
75-79 years*	100%[+]	99%	99%
70-74 years*	97.5%	99%	99%
65-69 years*	95.0%%	97%	97%
60-64 years*	99.3%	99%	99%
55-59 years*	96.9	98%	98%
50-54 years*	91.2%	93%	95%
45-49 years*	83.8%	86%	90%
40-44 years*	84.9%	88%	90%
35-39 years*	68.3%	73%	80%
30-34 years*	47.4%	58%	80%
25-29 years*	Not reported	31%	80%
20-24 years*	Not reported	25%	80%
18-19 years*	Not reported	11%	80%

* Not working or residing in a care home. ^ COVID-19 weekly announced vaccinations 03 June 2021 (data up to 30th May). [+]Signifies the number who have received their first dose exceeds the latest official estimate of the population from the ONS for this group.

2.4 Estimating contact rates following step 3

We used data on S-gene positivity among cases reported in England between 1 April and 21 May, 2021 (discarding the last two weeks of available data) to estimate the current growth rates and corresponding effective reproduction numbers (R_{eff}) separately for B.1.1.7 and B.1.617.2. We used the resulting estimated R_{eff} for B.1.1.7 to determine the reproduction number excluding immunity ($R_{excl\_immunity}$) for B.1.1.7 reflecting the level of mixing after step 3 (see appendix "Transmissibility associated with re-opening steps" and Supplementary Table 1). Note that this will not fully capture changes in transmissibility due to Step 3 on 17 May due to lags in the data and the last date of data used for the estimation being 21 May. $R_{excl\_immunity}$ for B.1.1.7 was assumed to be 0.3 lower during the school holidays, due to lower contact rates between children. We assumed an average school holiday pattern across England until summer 2022. We assumed that B.1.617.2 had a constant multiplicative transmission advantage between 140% and 190% over B.1.1.7 which corresponds to between a 1.5-fold and 2-fold increase in the current effective reproduction number for B.1.617.2 depending on the scenario explored.

2.5 Projected increases in population contact rates resulting from roadmap step 4

Table 4 summarises our assumptions for Step 4 for England. To capture the easing of restrictions at Steps 4 in England, we do not model specific or detailed policy changes due to the uncertainty around their impact. Instead, we sample from a range of values for R in the absence of natural and vaccine-induced immunity (specified as a probability distribution, see Supplementary Figure 2) that could occur at that stage.

We examine two scenarios for the impact of step 4 – an increase of $R_{excl\_immunity}$ for B.1.1.7 to either 3.0 (which assumes ongoing control measures such as symptomatic case isolation and test-and-trace will reduce transmission by approximately 1/3 from an R_0 of 5 for B.1.1.7 [14]) or 4.5 (which assumes ongoing control measures will reduce transmission by approximately 10%). We made the same assumption that B.1.617.2 had a constant multiplicative transmission advantage between 140% and 190% over B.1.1.7, leading to $R_{excl\_immunity}$ for B.1.617.2 between 3.3 and 10.0 during step 4 (Figure 2).

We also explored four scenarios for the timing of Step 4 occurring on 21 June or delayed until: i) 5 July; ii) 26 July; or iii) until all adults have had both vaccine doses (estimated to occur in mid-December 2021). We further assumed a slight seasonal trend in SARS-CoV-2 transmissibility throughout the year (see appendix 3).

Table 4: Summary of NPI easing scenarios for England where restrictions are eased on specific dates resulting in an increase in transmissibility. The average R in the absence of immunity ($R_{excl\_immunity}$) and 95% quantiles of at each stage are shown. Further details are given in Supplementary Table 1.

<table>
<tr><th>Step 4</th><th></th><th>Date of lifting</th></tr>
<tr><th>B.1.1.7 $R_{excl\_immunity}$</th><th>B.1.617.2 $R_{excl\_immunity}$</th><th></th></tr>
<tr><td rowspan="4"><u>Central Scenario</u>

School holidays:
2.70 (2.04 – 3.51)
School terms:
3.00 (2.33 – 3.80)

<u>Higher R following full NPI lifting</u>

School holidays:
4.20 (3.51– 4.98)
School terms:
4.50 (3.81 – 5.28)</td><td rowspan="4">Relative transmission advantage of B.1.617.2 vs B.1.1.7 of between 140% and 190%

This corresponds to between a 1.5-fold and 2-fold increase in the effective reproduction number due to the fitness advantage which is a product of immune escape (natural and lower vaccine efficacy) and increased transmissibility (see also Figure 2).</td><td>21 June</td></tr>
<tr><td>Delay two weeks: 5 July</td></tr>
<tr><td>Delay five weeks: 26 July</td></tr>
<tr><td>Delay until all adults have received both vaccine doses: estimated mid-December 2021**</td></tr>
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**Threshold corresponds to date when vaccine doses distributed reaches <1000 per day nationally.

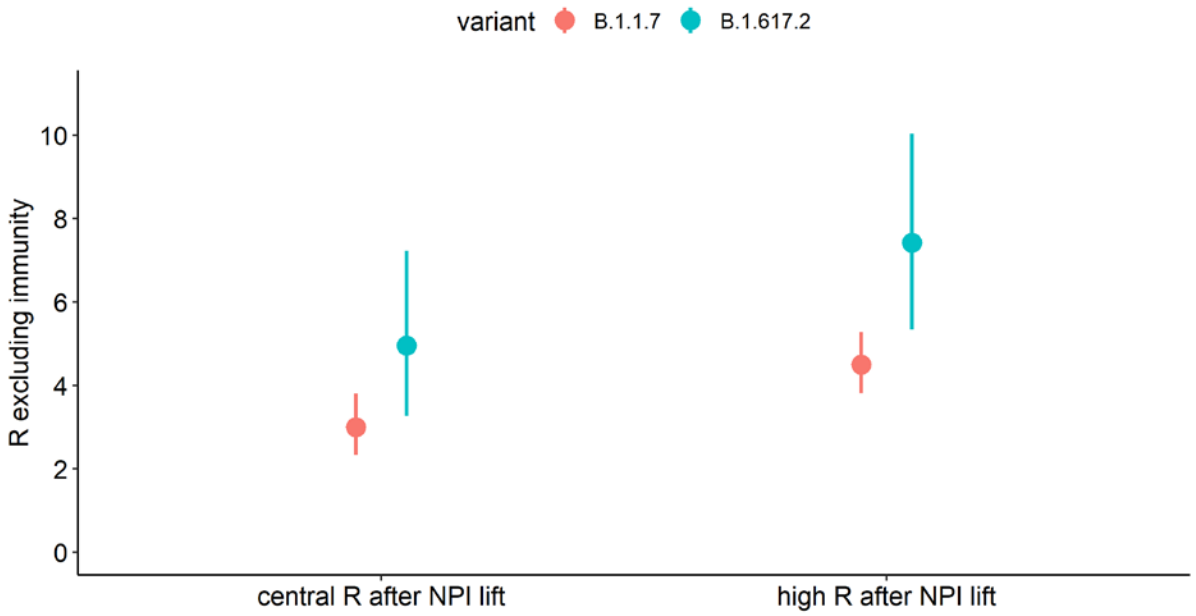


Figure 2: The range of $R_{excl\_immunity}$ values explored after NPIs are fully lifted after step 4 (shown here for when schools are open) for B.1.1.7 (pink) and B.1.617.2 (blue). Values are shown for central and higher R following NPI lifting.

3. Results

With an effective fitness advantage of B.1.617.2 over B.1.1.7 of between 1.5 to 2-fold, all scenarios modelled result in a third wave of infection, hospitalisations, and deaths after step 4 of the roadmap. The magnitude of this wave is highly uncertain, depending on the assumed transmissibility and immune escape level of B.1.617.2, the timing of step 4, and the level of mixing after that step.

If all but baseline NPIs are released on 21 June 2021 (Table 4), and assuming central immune escape and 165% increased transmissibility for B.1.617.2 (and central R after NPI lifting), our results suggest a third wave with an additional 59,180 (95% CrI: 33,140, 101,218) deaths could occur by 1 June 2022 (Table 5), with a peak in hospital bed occupancy about twice as high as that from early 2021 (Figure 7). Results are very sensitive to the assumed levels of transmissibility and immune escape for B.1.617.2. In the most optimistic scenario considered (low immune escape and 150% increased transmissibility, and central R after NPI lifting), an additional 26,854 (95% CrI: 11,639, 54,990) deaths could occur by 1 June 2022, with a wave of hospitalisations similar in magnitude to the last wave. In the most pessimistic scenario considered (high immune escape and 170% increased transmissibility), additional deaths could reach 136,377 (95% CrI: 94,307, 189,456). Should transmissibility after Step 4 be higher, there could be up to 203,824 (95% CrI: 179,600, 241,116) additional deaths by 1 June 2022.

For all levels of immune escape and increased transmissibility we considered, delaying step 4 until 5 July or 26 July is predicted to delay and substantially reduce the magnitude of the third wave. Delaying step 4 until all adults have received two vaccine doses is projected to delay the third wave. In some of our modelled scenarios, this long delay paradoxically leads to more total deaths since the third wave would be pushed into the winter, when transmission may be higher because of seasonality and increased indoors interactions, and when an increased proportion of individuals may have lost protection from prior infection. However, delaying step 4 also affords the opportunity to further increase population-level vaccine protection - for example through booster doses or

vaccinating children under 18 years. We did not model either of these scenarios, but their impact will depend on the speed of delivery, and this will be critical in terms of preventing a winter third wave.

4. Conclusions

Our results highlight that the uncertainties regarding the levels of transmissibility and immune escape of B.1.617.2 translate into large uncertainty on the possible future epidemic trajectory. If step 4 of the roadmap happens on 21st June 2021, a third wave of hospitalisations and deaths is predicted to happen, very likely as big as the second wave but potentially orders of magnitude larger. Delaying step 4 by a few weeks would reduce the size of the third wave, while simultaneously buying time to more accurately estimate the characteristics of B.1.617.2 and consider other control strategies (e.g. vaccination of <18 years old and distribution of booster doses) which could further help to mitigate a significant third wave.

Preventing the further importation and spread of variants of concerns (VOC) with moderate to high immune escape properties will be critical as these could lead to future waves orders of magnitude larger than the ones experienced so far. Whilst the impact of Test Trace Isolate (TTI), mask wearing, hand hygiene, and COVID security on R is difficult to quantify, it will be vital to emphasise the importance of normalising and ensuring adherence to all measures even after "full lifting" is achieved.

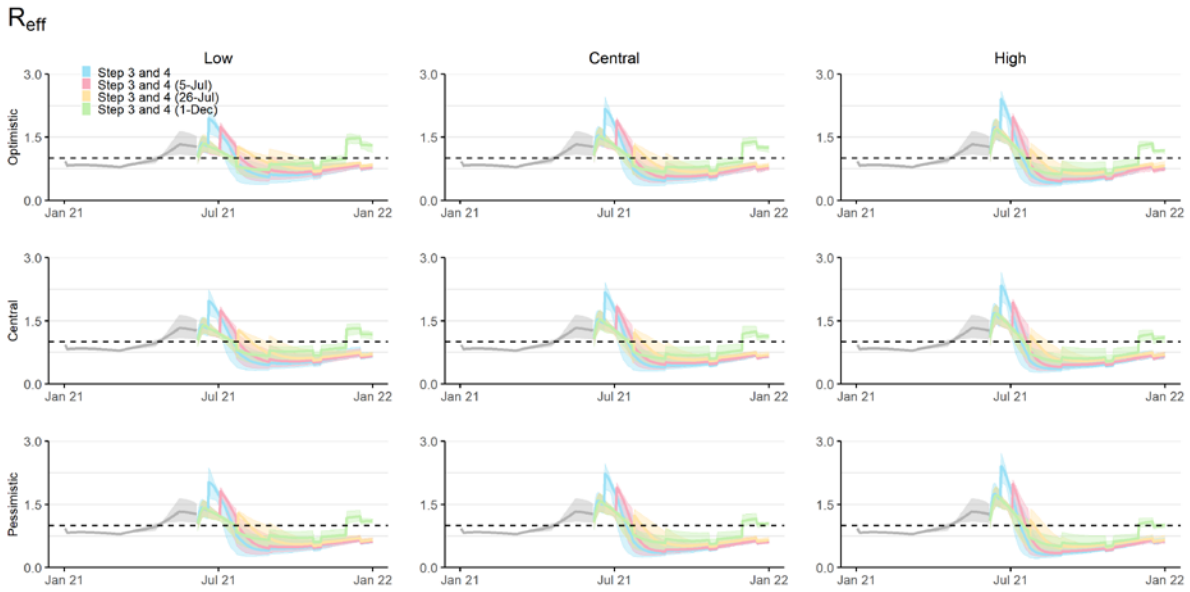


Figure 3: Effective reproduction number R accounting for natural- or vaccine-induced immunity (overall for both B.1.1.7 and B.1.617.2) in England assuming Step 4 occurring on 21 June (blue), 5 July (pink), 26 July (yellow), and early-December when all eligible adults have receive two vaccine doses (green) with central R after full NPI lifting (see Table 4), projecting forwards to 1 January 2022. We consider a variant of concern, B.1.617.2, with: (Left column) low transmissibility; (middle column) central transmissibility; and (right columns) high transmissibility relative to B.1.1.7 and with (top row) low; (middle row) central; and (bottom row) high immune escape properties. Namely for the for the central immune escape scenarios, we considered transmission advantages of 150% (where B.1.617.2 is assumed 50% more infectious than B.1.1.7), 165% and 180%, for the high immune escape scenario, we considered transmission advantages of 140%, 155% and 170% and for the low immune escape scenario we considered transmission advantages of 150%, 170% and 190%.

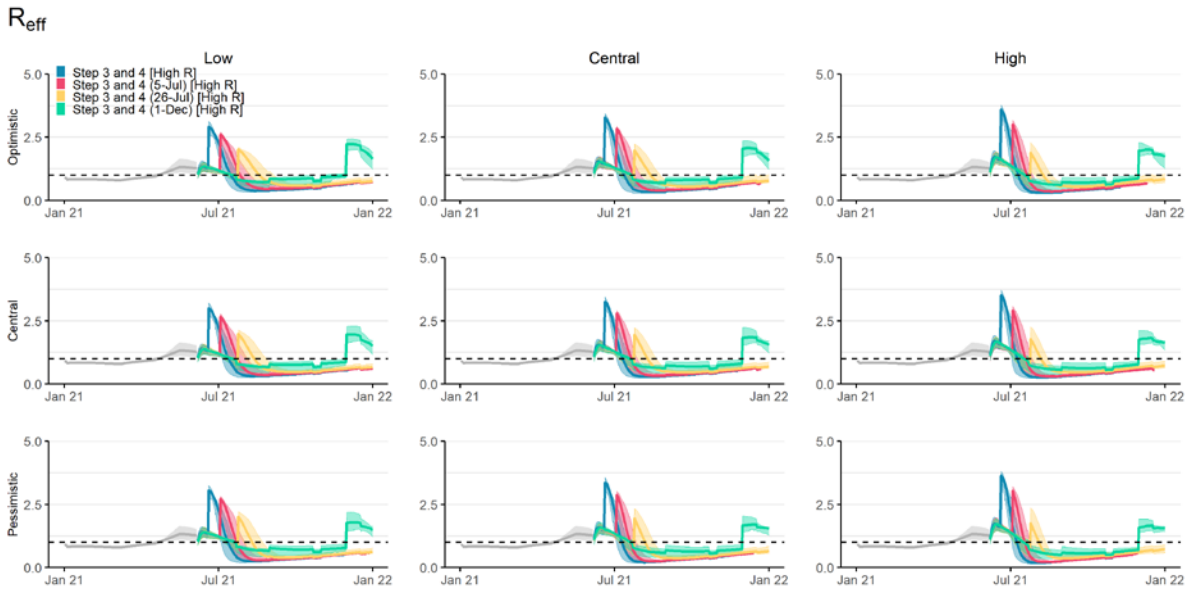


Figure 4: As Figure 3 but showing higher R after NPI lifting.

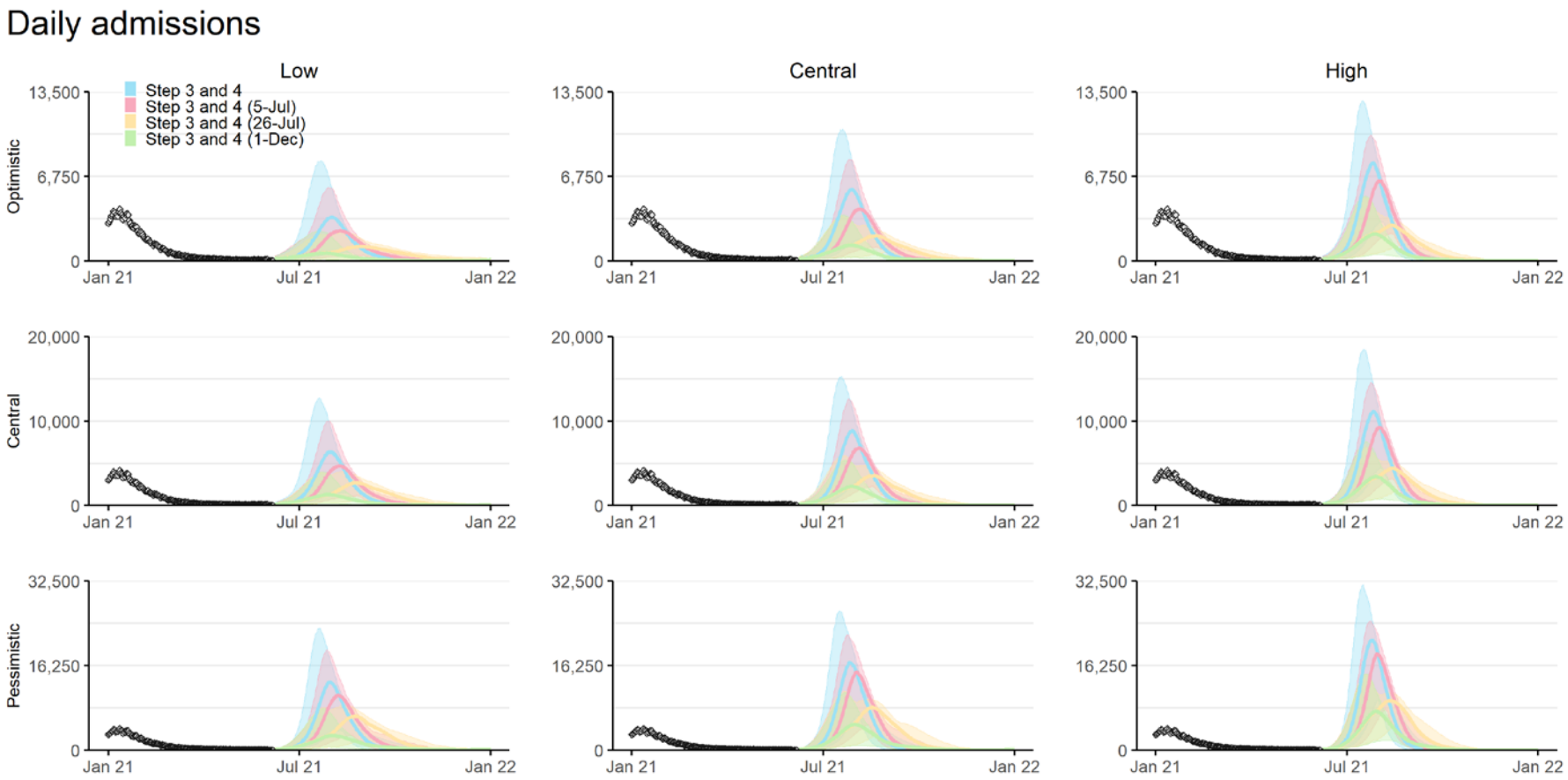


Figure 5: COVID-19 daily hospital admissions in England for Step 4 occurring on 21 June (blue), 5 July (pink), 26 July (yellow), and early-December when all eligible adults have receive two vaccine doses (green) with central R after full NPI lifting (see Table 4), projecting forwards to 1 January 2022. We consider a variant of concern, B.1.617.2, with: (Left column) low transmissibility; (middle column) central transmissibility; and (right columns) high transmissibility relative to B.1.1.7 and with (top row) low; (middle row) central; and (bottom row) high immune escape properties. Namely for the central immune escape scenarios, we considered transmission advantages of 150% (where B.1.617.2 is assumed 50% more infectious than B.1.1.7), 165% and 180%, for the high immune escape scenario, we considered transmission advantages of 140%, 155% and 170% and for the low immune escape scenario we considered transmission advantages of 150%, 170% and 190%. See Table 1 for VOC properties. The coloured lines show the mean and the shaded areas show 95% credible intervals. Note the y-axis scale is different in each row.

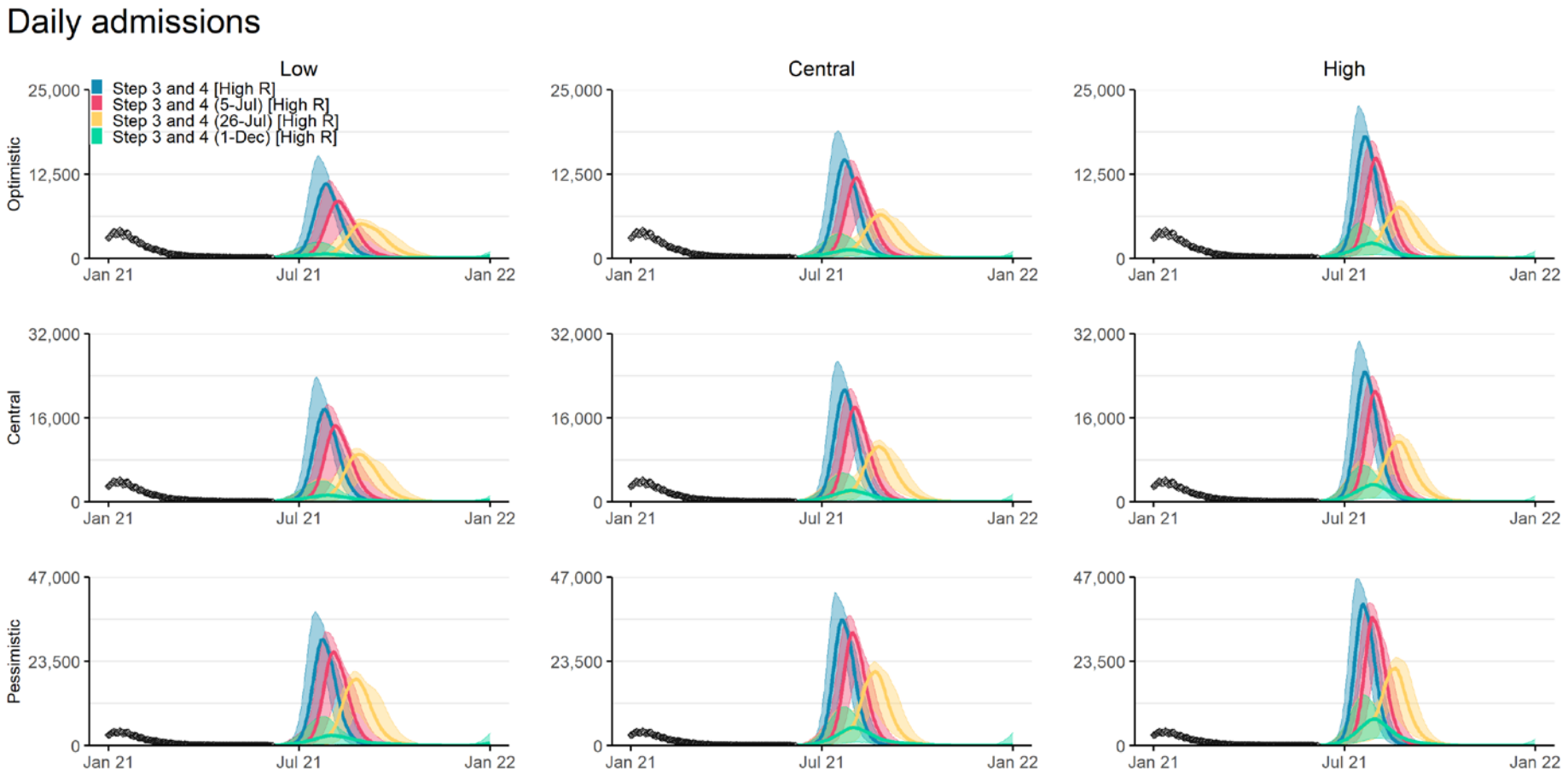


Figure 6: As Figure 5 but showing higher R after NPI lifting

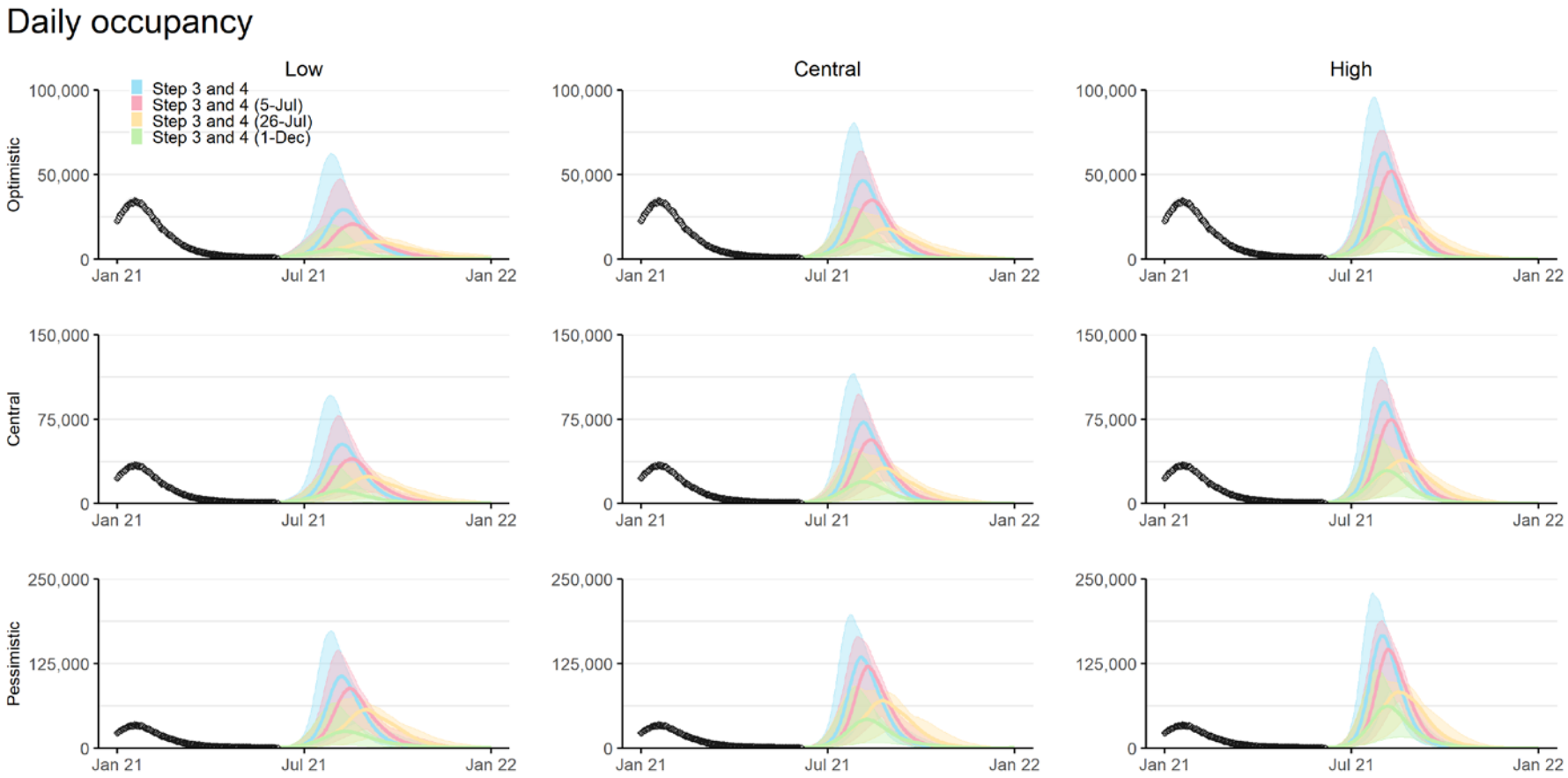


Figure 7: COVID-19 daily hospital occupancy in England for Step 4 occurring on 21 June (blue), 5 July (pink), 26 July (yellow), and early-December when all eligible adults have receive two vaccine doses (green) with central R after full NPI lifting (see Table 4), projecting forwards to 1 January 2022. We consider a variant of concern, B.1.617.2, with: (Left column) low transmissibility; (middle column) central transmissibility; and (right columns) high transmissibility relative to B.1.1.7 and with (top row) low; (middle row) central; and (bottom row) high immune escape properties. Namely for the central immune escape scenarios, we considered transmission advantages of 150% (where B.1.617.2 is assumed 50% more infectious than B.1.1.7), 165% and 180%, for the high immune escape scenario, we considered transmission advantages of 140%, 155% and 170% and for the low immune escape scenario we considered transmission advantages of 150%, 170% and 190%. See Table 1 for VOC properties. The coloured lines show the mean and the shaded areas show 95% credible intervals. Note the y-axis scale is different in each row.

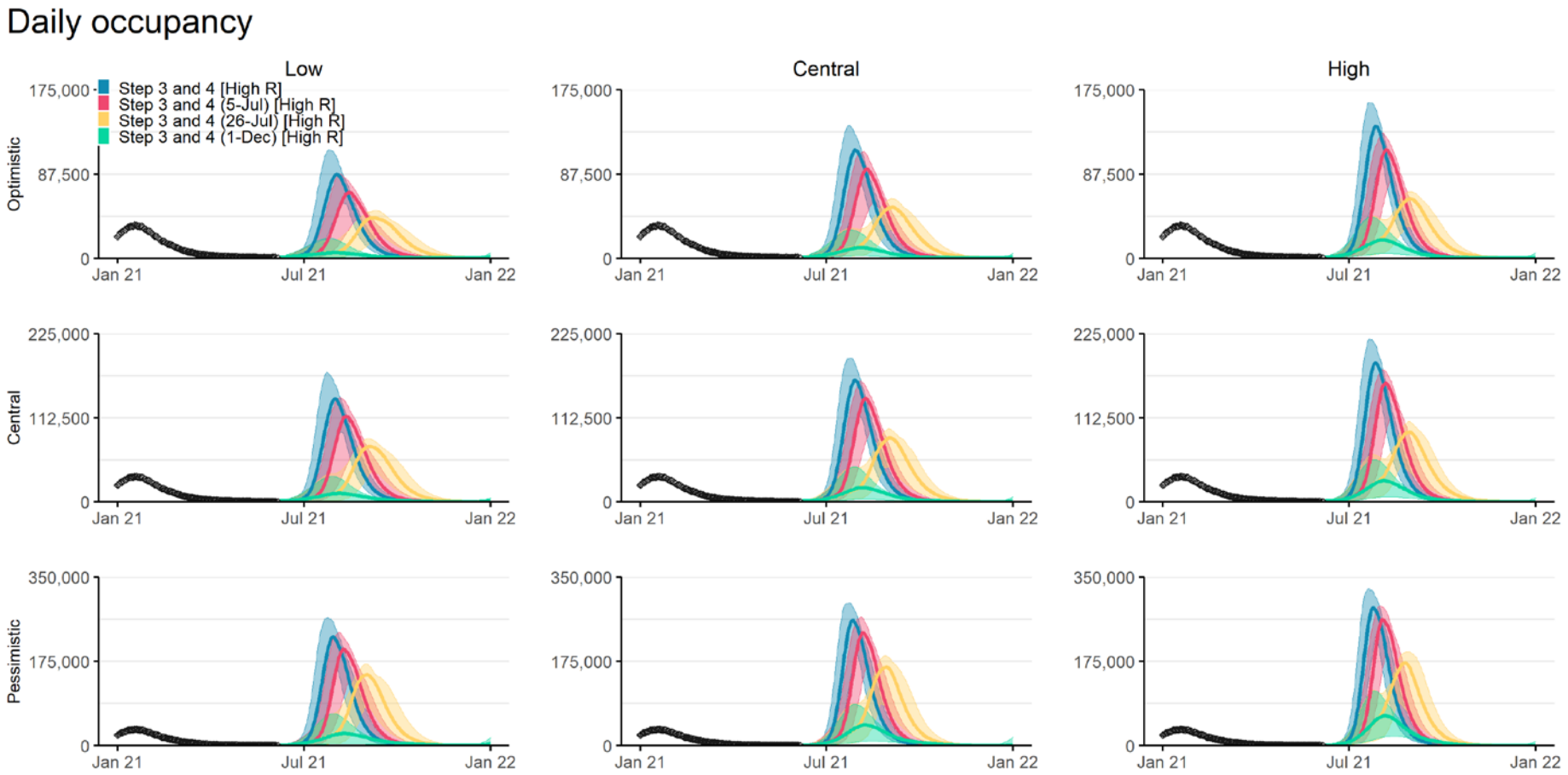


Figure 8: As Figure 7 but showing higher R after NPI lifting

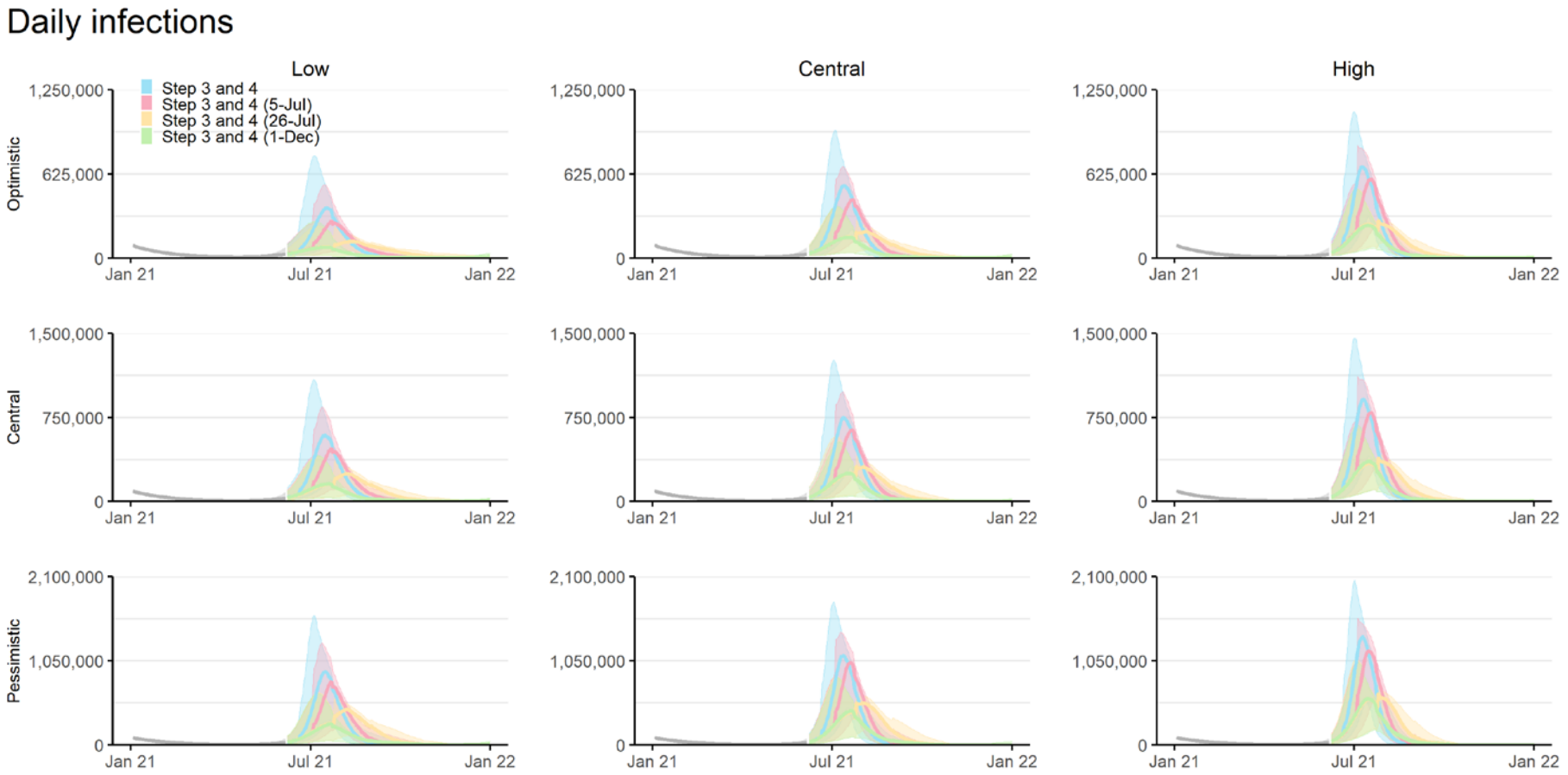


Figure 9: SARS-CoV-2 daily infections in England for Step 4 occurring on 21 June (blue), 5 July (pink), 26 July (yellow), and early-December when all eligible adults have receive two vaccine doses (green) with central R after full NPI lifting (see Table 4), projecting forwards to 1 January 2022. We consider a variant of concern, B.1.617.2, with: (Left column) low transmissibility; (middle column) central transmissibility; and (right columns) high transmissibility relative to B.1.1.7 and with (top row) low; (middle row) central; and (bottom row) high immune escape properties. Namely for the central immune escape scenarios, we considered transmission advantages of 150% (where B.1.617.2 is assumed 50% more infectious than B.1.1.7), 165% and 180%, for the high immune escape scenario, we considered transmission advantages of 140%, 155% and 170% and for the low immune escape scenario we considered transmission advantages of 150%, 170% and 190%. See Table 1 for VOC properties. The coloured lines show the mean and the shaded areas show 95% credible intervals. Note the y-axis scale is different in each row.

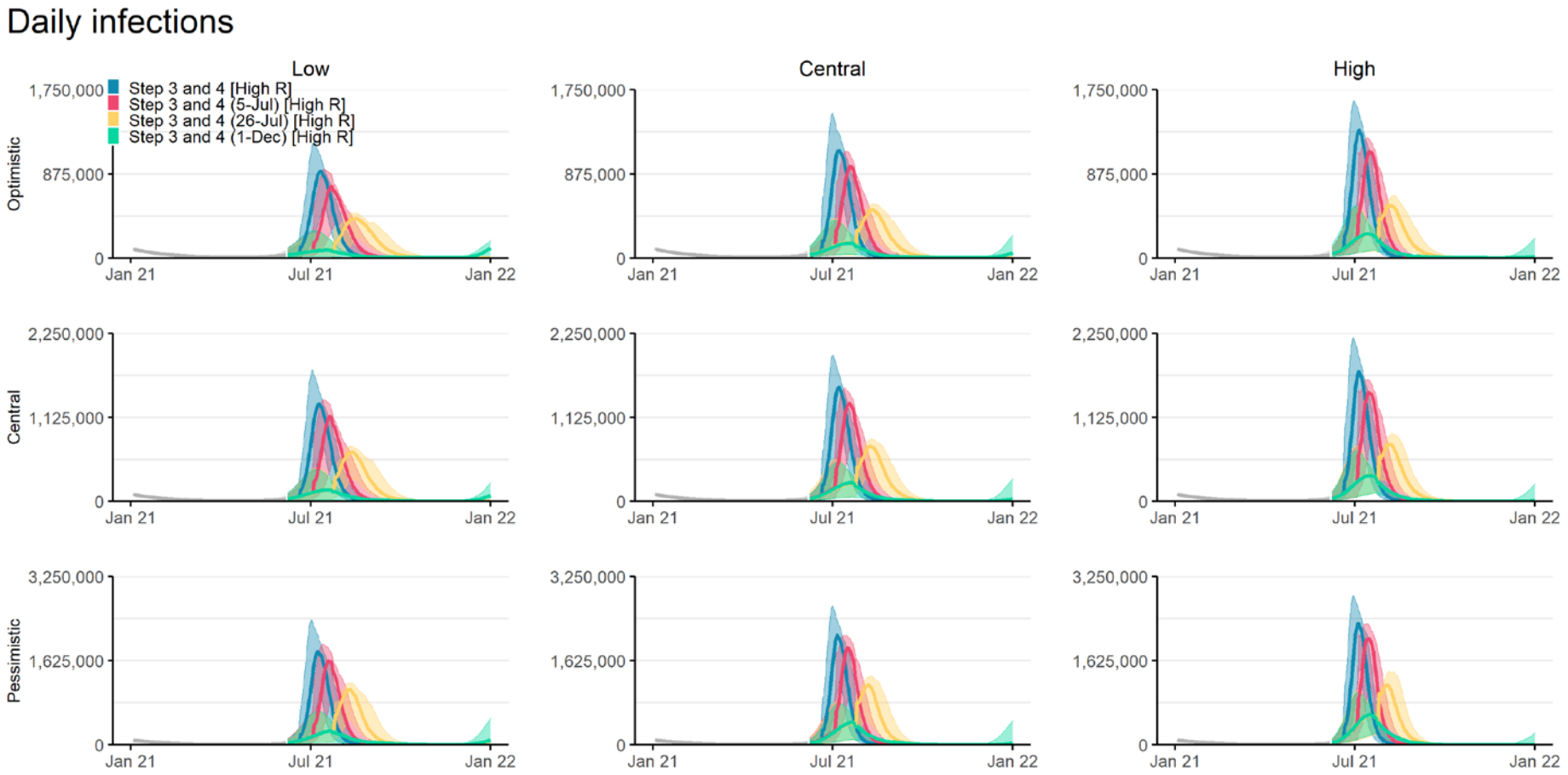


Figure 10: As Figure 9 but showing higher R after NPI lifting

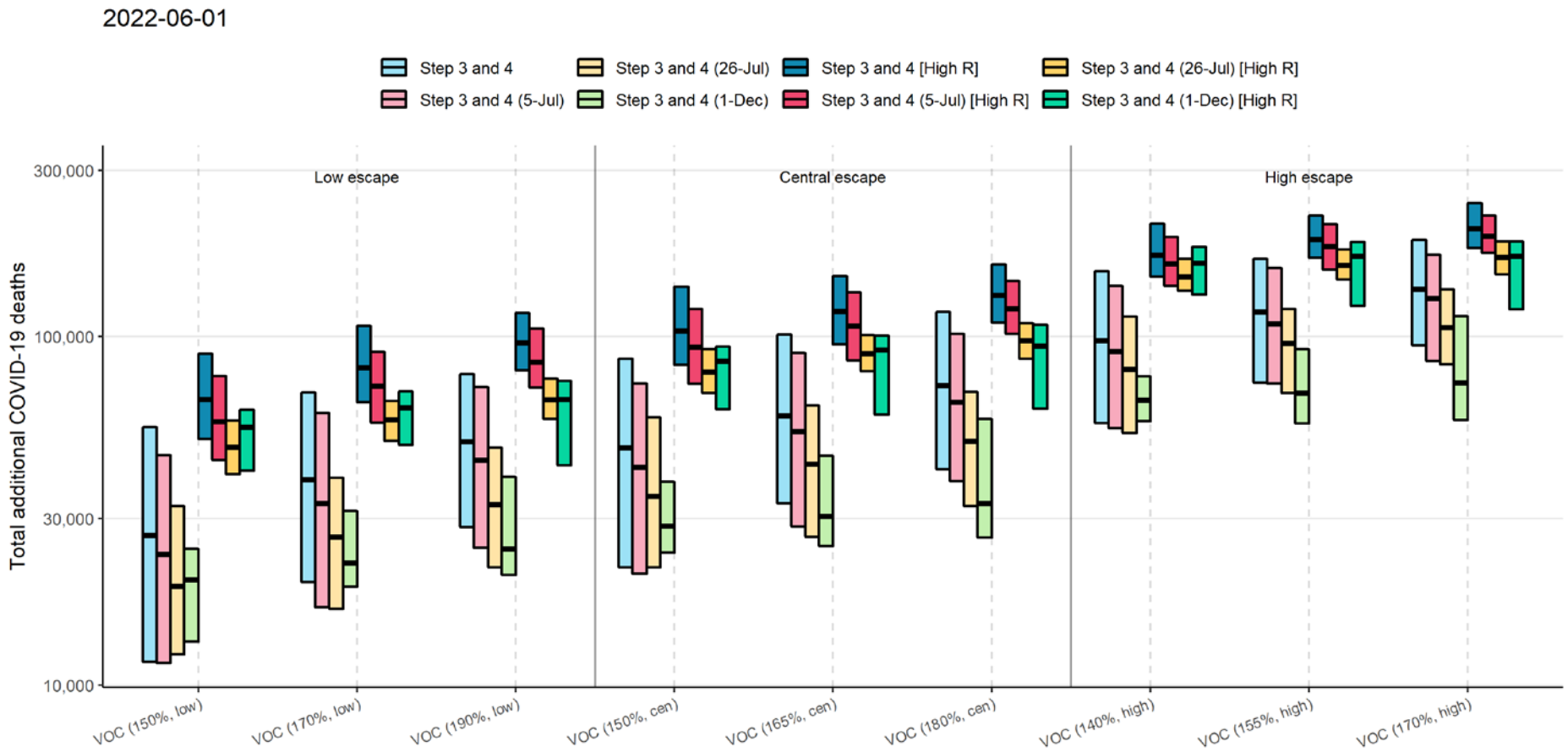


Figure 11: Sensitivity analysis showing cumulative COVID-19 deaths in England (counted from 4 June 2021 up to 1 Jun 2022) for Step 4 occurring on 21 June (blue), 5 July (pink), 26 July (yellow), and early-December when all eligible adults have receive two vaccine doses (green) for central (lighter colours) and higher (darker colours) R after full NPI lifting (see Table 4 and Supplementary Table 1). Results from left to right: (Low escape) assume B.1.617.2 has "low" immune escape and 150%, 170%, and 190% transmissibility relative to B.1.1.7 respectively; (Central escape) B.1.617.2 has central immune escape and 150%, 165%, and 180% transmissibility relative to B.1.1.7 respectively; (High escape) B.1.617.2 has high immune escape and 140%, 155%, and 170% transmissibility relative to B.1.1.7 respectively (see Table 1 for B.1.617.2 properties). Note that the y-axis is on a logarithmic scale.

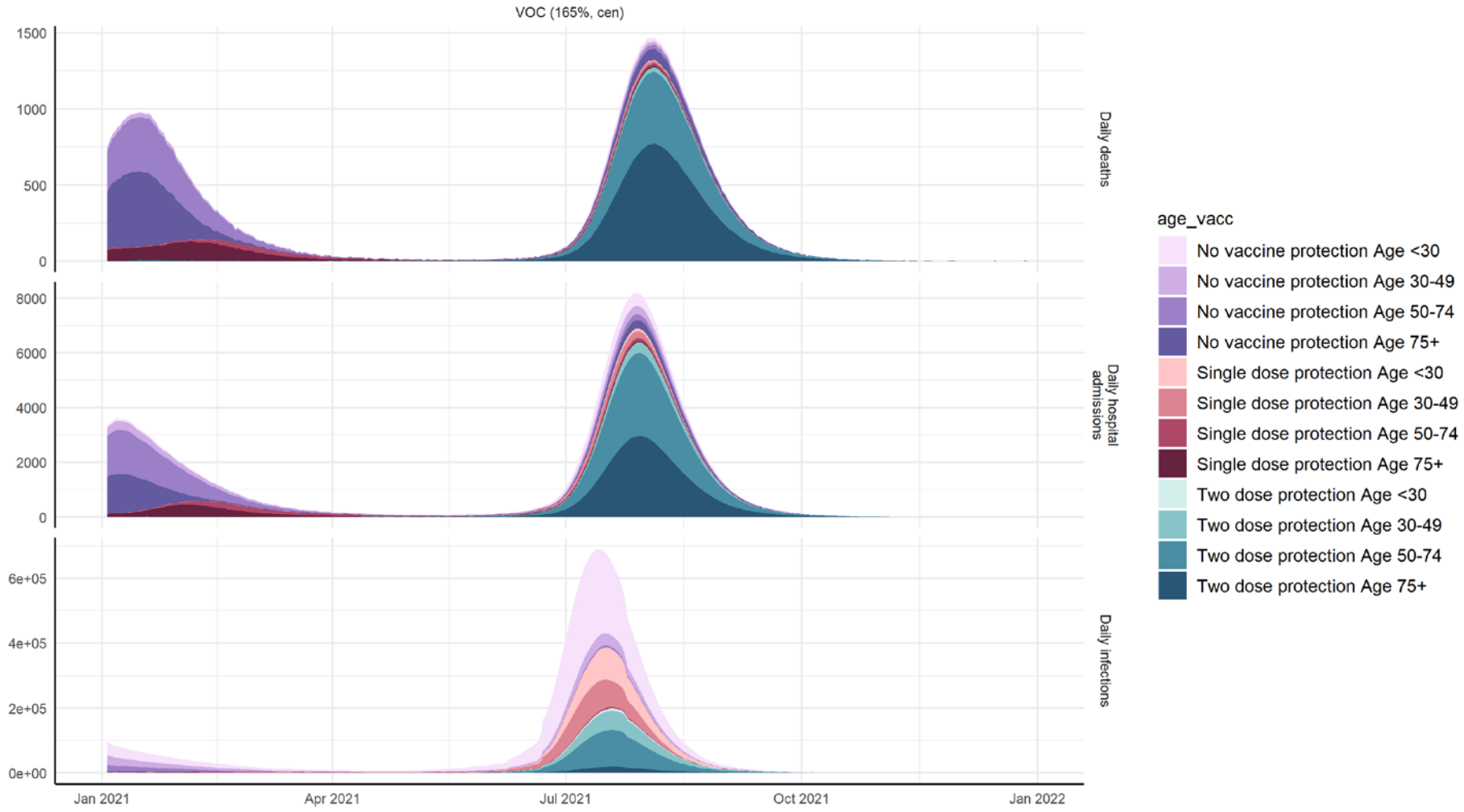


Figure 12: England COVID-19 daily (top) deaths, (middle) hospital admissions, (bottom) infections by age group and vaccination status assuming B.1.617.2 has central immune escape properties and a 165% relative transmissibility advantage compared to B.1.1.7 (Table 1 and Table 4)

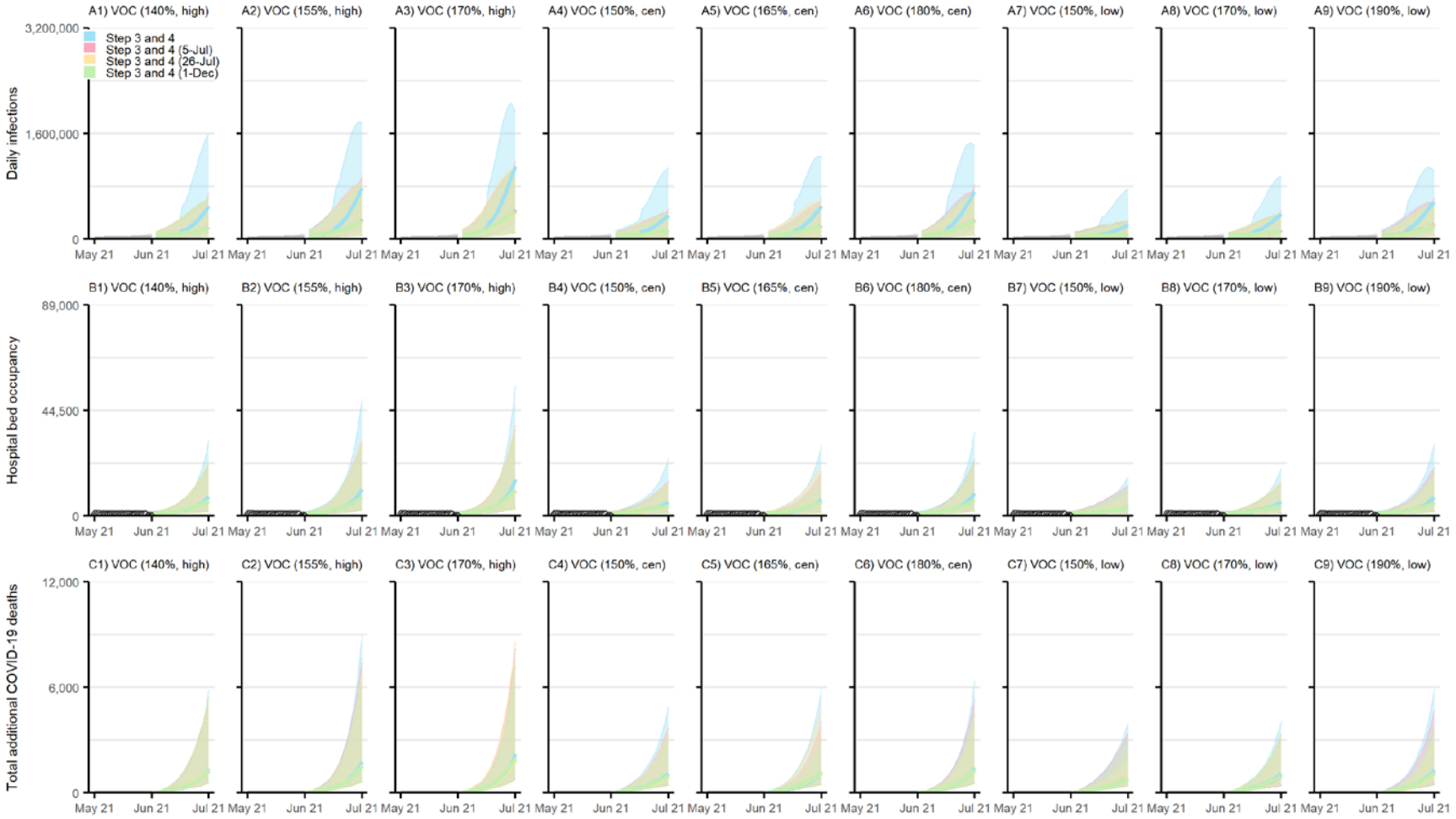


Figure 13: England COVID-19 daily (from top to bottom row) infections, hospital bed occupancy, and deaths up to 1 July 2021 for Step 4 occurring on 21 June (blue), 5 July (pink), 26 July (yellow), and early-December when all eligible adults have receive two vaccine doses (green) with higher R after full NPI lifting (see Table 4), projecting forwards to 1 July 2021. We consider a variant of concern, B.1.617.2, with: different levels of transmissibility relative to B.1.1.7 and with low, central (cen), and high immune escape properties. Namely for the central immune escape scenarios, we considered transmission advantages of 150% (where B.1.617.2 is assumed 50% more infectious than B.1.1.7), 165% and 180%, for the high immune escape scenario, we considered transmission advantages of 140%, 155% and 170% and for the low immune escape scenario we considered transmission advantages of 150%, 170% and 190%. See Table 1 for VOC properties. The coloured lines show the mean and the shaded areas show 95% credible intervals. Note the y-axis scale is different in each row.

Table 5: Cumulative deaths, hospital admissions, incidence, and peak hospital occupancy in England (median (95% CrI), nearest 100) between 4 June 2021 and 1 June 2022. Results assume return to different baseline NPIs of $R_{excl\_immunity}$ = 3.5 (when schools are open) depending on the scenario (see Table 4, Figure 2, Supplementary Table 1 and SI text for details).

Analysis type			NPI lifting date	Cumulative deaths (95%CrI)	Cumulative hospital admissions (95%CrI)	Cumulative incidence (95%CrI)	Peak hospital occupancy (95%CrI)
Immune escape of B.1.617.2*	Transmissibility of B.1.617.2 relative to B.1.1.7**	R after full lift***	Step 4	Up to 1 June 2022			
None	100%	Central	21 June	4190 (763, 13661)	26884 (4378, 78142)	3691374 (562023, 9359830)	2304 (828, 11951)
			5 July	4000 (530, 10708)	25381 (2875, 60128)	3466520 (328996, 7534366)	1568 (853, 6754)
			26 July	4233 (430, 8778)	26125 (2189, 51060)	3497278 (235612, 6311913)	1626 (826, 4953)
			mid-Dec****	1127 (388, 7844)	7767 (2135, 45142)	1001048 (175986, 5801006)	1506 (862, 4410)
Low	150%	Central	21 June	26854 (11639, 54990)	153600 (64014, 272990)	14734251 (7215980, 22089186)	29273 (6202, 62636)
			5 July	23646 (11583, 45738)	132173 (62033, 238764)	12827498 (6895615, 19705292)	20758 (4537, 47630)
			26 July	19187 (12238, 32568)	109048 (64446, 172652)	10816574 (6954410, 15746682)	10545 (4438, 20552)
			early-Dec****	20030 (13325, 24572)	114052 (68805, 132364)	11202660 (7272774, 13081503)	8021 (6322, 20480)
		High	21 June	66023 (50831, 89128)	348124 (259366, 430584)	25157679 (21109180, 28064210)	87989 (59492, 113368)
			5 July	57005 (44274, 77127)	303886 (221870, 374265)	22970407 (18658978, 26054706)	69350 (44212, 88477)
			26 July	48081 (40270, 57534)	256711 (204678, 285251)	19688180 (16473374, 21573080)	43550 (34272, 50022)
			early-Dec****	54895 (41220, 61580)	287281 (214582, 307908)	20019003 (17848076, 21427994)	35633 (17560, 43893)
	170%	Central	21 June	38762 (19747, 69217)	213311 (100332, 328400)	18637784 (10773122, 24799885)	46535 (15286, 80706)

			5 July	33163 (16672, 60409)	184541 (88557, 293135)	16651851 (9471054, 22381469)	34890 (10090, 64080)
			26 July	26579 (16538, 39358)	147253 (85553, 209600)	13782212 (8964054, 18143388)	18319 (8100, 30460)
			early-Dec****	22361 (19184, 31536)	125789 (102169, 164746)	12561600 (10027197, 15644318)	11153 (6608, 30950)
		High	21 June	81259 (64848, 107350)	421041 (318597, 497682)	27954740 (24332704, 30370396)	113437 (80006, 138117)
			5 July	72033 (56570, 90322)	376346 (281226, 441185)	26018122 (22110573, 28235058)	94118 (63473, 110922)
			26 July	57574 (50248, 65358)	300014 (258264, 325049)	22255493 (19528499, 24011498)	53789 (36985, 62068)
			early-Dec****	62448 (48896, 69490)	324726 (259086, 350082)	22119152 (19633268, 23564224)	35398 (20766, 49017)
	190%	Central	21 June	49965 (28392, 78066)	267229 (142300, 381970)	21620113 (14158400, 26573548)	63052 (26770, 96725)
			5 July	44126 (24718, 71583)	242085 (123370, 336786)	20044499 (12347504, 25143740)	52171 (18782, 76462)
			26 July	32903 (21763, 48094)	181901 (112104, 244263)	16329733 (11177498, 20381777)	25999 (11895, 41701)
			early-Dec****	24504 (20694, 39590)	137734 (120320, 204158)	13592561 (11802831, 18264547)	18373 (7836, 42836)
		High	21 June	95613 (80106, 117047)	487632 (391641, 567928)	29979816 (27263916, 31950400)	138166 (106475, 163067)
			5 July	84321 (71437, 105454)	434279 (348364, 497560)	28219058 (25330414, 30054038)	114404 (86969, 130878)
			26 July	65681 (57953, 75717)	341157 (296910, 367122)	24090626 (21871576, 26369522)	63039 (43724, 69504)
			early-Dec****	65916 (42658, 74670)	344409 (214736, 374254)	23258322 (18809892, 25042408)	34942 (21020, 52106)
Central	150%	Central	21 June	47941 (21723, 86506)	256644 (109778, 410876)	21739444 (11164284, 30071153)	52784 (13614, 96223)
			5 July	42060 (20854, 73366)	226392 (105833, 360150)	19574593 (10559484, 27499268)	40034 (10638, 78347)
			26 July	34743 (21767, 58718)	190230 (107621, 273496)	16705798 (10166041, 22662658)	24287 (9686, 36348)

			early-Dec****	28578 (23975, 38286)	155387 (118318, 191290)	14457336 (10765066, 17816926)	12020 (8321, 33906)
		High	21 June	103500 (83011, 139072)	521674 (401368, 629126)	33790624 (29317222, 37383322)	138815 (98012, 174824)
			5 July	93132 (73106, 119985)	475769 (356256, 555742)	31681580 (26354020, 34923195)	116792 (76756, 141184)
			26 July	79071 (68848, 91876)	403975 (333389, 443908)	27837749 (23817136, 29459878)	76300 (56471, 85126)
			early-Dec****	84974 (61805, 93522)	429842 (319268, 461675)	27269528 (23861095, 28847701)	48682 (26028, 67369)
	165%	Central	21 June	59180 (33140, 101218)	320797 (169155, 462044)	25177838 (15903083, 32301362)	72565 (28448, 115496)
			5 July	53380 (28514, 89680)	283800 (143250, 429330)	22979548 (13660030, 30159124)	56916 (20064, 97432)
			26 July	42939 (26628, 63506)	230735 (132830, 313116)	19446317 (12459675, 24787558)	32544 (14942, 49352)
			early-Dec****	30517 (25040, 45474)	165577 (144100, 233473)	15481303 (12899338, 20400687)	19621 (9236, 45323)
		High	21 June	117899 (94954, 149322)	590939 (464760, 683544)	36124088 (31687467, 39187874)	164432 (121068, 194104)
			5 July	107096 (85363, 133677)	543537 (432888, 623619)	34236414 (29804124, 36892560)	140530 (104142, 162186)
			26 July	89281 (79588, 101054)	447617 (398784, 478512)	29981549 (27112486, 31419614)	87170 (56755, 97776)
			early-Dec****	91334 (59615, 100732)	464547 (309037, 497842)	28818782 (24168730, 30530737)	47670 (27298, 69921)
	180%	Central	21 June	72160 (41567, 117584)	375682 (202984, 532375)	27942316 (18595005, 34579564)	90069 (38404, 139646)
			5 July	64741 (38404, 101833)	340697 (178145, 471025)	26088352 (16389496, 32473098)	74918 (28431, 110102)
			26 July	50062 (32566, 69346)	266825 (165130, 345444)	21679853 (14902952, 26399362)	40172 (19500, 57270)
			early-Dec****	33180 (26450, 57935)	179645 (152676, 289288)	16863303 (14232118, 23621264)	29296 (10048, 61822)
		High	21 June	131198 (109468, 160909)	653754 (531264, 749936)	38084493 (34146490, 40838086)	188359 (143424, 220298)

			5 July	119895 (101882, 144508)	601188 (490758, 666086)	36248664 (32373784, 38313332)	162040 (124438, 177350)
			26 July	97214 (86348, 109394)	486374 (444236, 520835)	31569370 (29410042, 34129120)	95724 (63786, 107944)
			early-Dec****	93787 (62066, 108066)	480683 (327632, 511446)	29913700 (25422956, 31689482)	45705 (30524, 71182)
High	140%	Central	21 June	97167 (56490, 153946)	491109 (272512, 684790)	31494444 (19844761, 39980271)	107219 (37870, 174018)
			5 July	90600 (54620, 139724)	456266 (255290, 630584)	29634899 (18427684, 37781759)	89754 (29774, 146239)
			26 July	80515 (52968, 114076)	408148 (247958, 507872)	26664698 (17263034, 32313126)	59323 (27622, 75734)
			early-Dec****	65498 (57062, 76849)	329470 (285402, 363676)	22695421 (18530484, 26102810)	25863 (18928, 67330)
		High	21 June	171344 (148834, 210871)	820384 (703440, 915828)	43213466 (39430175, 46180758)	231848 (185538, 269192)
			5 July	161236 (139710, 192950)	777080 (657735, 864793)	41753941 (37669558, 44292352)	206276 (161948, 237090)
			26 July	148413 (135553, 167420)	710918 (646126, 757964)	38890636 (35512714, 39748910)	151819 (111249, 170968)
			early-Dec****	162508 (131673, 180818)	776203 (627189, 809042)	39450202 (36477568, 41646304)	92326 (52594, 141997)
	155%	Central	21 June	117756 (73793, 167321)	577216 (355592, 744474)	35262304 (24868018, 41683268)	136261 (62238, 198336)
			5 July	108682 (73300, 157118)	546375 (326098, 691400)	33651262 (22923462, 40141509)	122521 (49040, 166044)
			26 July	95477 (68839, 120050)	470918 (324858, 563191)	29791686 (21783730, 34595608)	73945 (41672, 92364)
			early-Dec****	68729 (56305, 91994)	344719 (305706, 434698)	23805664 (21613133, 29663578)	42732 (19463, 92490)
		High	21 June	189985 (168330, 222173)	903974 (775662, 984894)	45310212 (41989537, 47697074)	265766 (220300, 300209)
			5 July	181163 (155352, 210173)	855392 (737323, 943422)	44002411 (40455537, 45865763)	240362 (195419, 268704)
			26 July	159823 (145519, 177730)	760753 (709246, 808254)	40817823 (38528582, 41568330)	168567 (102868, 188207)

			early-Dec****	169578 (122352, 186918)	812508 (629710, 851262)	41457417 (37493601, 43110065)	81238 (56023, 133382)
	170%	Central	21 June	136377 (94307, 189456)	662581 (437327, 832108)	38196480 (29140981, 43838602)	168664 (89878, 231318)
			5 July	128265 (85260, 171606)	624443 (402292, 755236)	36639622 (27023756, 41868670)	149309 (72796, 190114)
			26 July	106169 (83230, 136658)	522755 (390990, 612339)	32302949 (25396951, 36578738)	88354 (58491, 115620)
			early-Dec****	73451 (57634, 114590)	361168 (310458, 518951)	25590610 (22401614, 32982673)	62506 (19289, 116744)
		High	21 June	203824 (179600, 241116)	959015 (858064, 1039374)	46826239 (44266094, 48736814)	292665 (255135, 330458)
			5 July	193488 (173644, 222618)	916780 (810398, 994060)	45769670 (42608242, 47396306)	267315 (226828, 292118)
			26 July	168855 (150973, 187560)	797457 (755100, 840722)	41947858 (40421530, 44341301)	177742 (116330, 197639)
			early-Dec****	169550 (119694, 187765)	824754 (585122, 876423)	42414882 (35848488, 44258280)	81918 (61590, 122774)

* See Table 1 for B.1.617.2 vaccine efficacy/immune escape details. ** Transmissibility is relative to B.1.1.7 (see section 2.5). *** $R_{excl\_immunity}$ used after NPI relaxation (see Table 4, Figure 2, Supplementary Table 1 and SI text for details). ****Estimated date by which all eligible adults would have received two vaccine doses.

5. Appendix 1: Caveats and key assumptions

1. The gradual lifting of NPIs has been modelled as a step-wise increase in R. We do not model any specific policy change, rather an assumed change in the corresponding level of transmission. Note that there is **considerable uncertainty around these assumptions**.
2. We assume that some level of transmission control remains even after "fully lifting" NPIs (Table 4 and Supplementary Table 1) through measures such as TTI and hand hygiene *(optimistic)*
3. Note that not all scenarios under "Step 4" have reached an equilibrium with respect to the number of additional deaths by 1 June 2022.
4. We do not model any "booster" vaccines designed to be efficacious against VOC or expansion of vaccine eligibility to <18 years (*pessimistic*).
5. We have not modelled different dosing schedules by age group.
6. We estimate the date at which all eligible adults have received both vaccine doses defined as when daily distributed doses reaches <1000 nationally (mid-December 2021), in the absence of VOCs. Depending on their characteristics, VOCs could delay this date as individuals who are symptomatic, recently tested positive, quarantining, or isolating will need to wait until they are eligible to receive the vaccination.
7. We model the potential impact of B.1.617.2, but we note that there is substantial uncertainty regarding its level of transmissibility and immune escape. In particular, there is considerable uncertainty regarding the efficacy of vaccines against B.1.617.2 infection, severe disease and onward transmission [2].
8. We assumed the same severity for B.1.617.2 and B.1.1.7. Recent evidence however suggests that the probability of hospitalisation with B.1.617.2 is ~2.5x higher than B.1.1.7 (*optimistic*).
9. Our current estimates of the duration of hospital stay range from 7.9 days (95% CrI: 6.4, 9.8) in North East and Yorkshire, to 12.7 days (95%CrI: 9.9, 16.7) in London.
10. We estimate R_{eff} and $R_{excl\_immunity}$ for B.1.1.7 and B.1.617.2 separately based on the growth rate of S-gene – and S-gene+ cases, in England between 1 April and 21 May 2020. We then use these estimates for our forward projections.
11. We assume **infection-induced immunity wanes exponentially over time**, with an average time to loss of protection of 3 years (*pessimistic)*.
12. Our central scenario **incorporates seasonality in transmission** with a +/-10% relative change in transmissibility throughout the year.
13. We assume that vaccine roll-out pace of 2.0M doses/week from 26 July 2021 onwards can be maintained (unclear).
14. We assume **high vaccine uptake for both doses** (*optimistic*) and further assume that uptake is homogeneous within and across regions.
15. We assume the vaccines provide protection against infection in addition to protection from severe disease and death *(optimistic)*.
16. We assume the vaccines prevent to a certain extent, an infected person who is vaccinated from transmitting the virus *(optimistic, assumed as part of "central" assumptions)*.
17. We model school holidays by assuming an average decrease in $R_{excl\_immunity}$ for B.1.1.7 of 0.3 whilst schools are closed.
18. We assume **no correlation between vaccine uptake and risk of severe infection**. If uptake were to be lower in groups at higher risk of severe disease (e.g. ethnic groups), our results would be too optimistic in terms of hospitalisations and deaths *(optimistic)*.
19. We do not model differential infectivity or susceptibility by age.
20. We assume no dynamic replenishment of the care-home population *(optimistic)*.
21. We fit our stochastic model to multiple data sources simultaneously. In our latest iteration, the model has captured hospitalisation trends well, but has slightly overestimated the recent number of daily deaths. Additional data regarding vaccine efficacy against severe disease caused by B.1.617.2 may help to capture these trends better.

22. We model Moderna vaccine distribution assuming it has the same efficacy as Pfizer (*unclear*).
23. We assume that all individuals under 40 years will now receive the Pfizer or Moderna vaccine, 40-49 year olds will receive 60% AZ and 40% Pfizer or Moderna, and 50+ will continue to receive the distribution of vaccines observed thus far.
24. We have not modelled a slower vaccine roll-out (*optimistic).*

6. *Appendix 3: Methods*

We used a stochastic compartmental model of SARS-CoV-2 transmission fitted to multiple data streams from each NHS region in England. The model is stratified into 17 five-year age groups (0-4, 5-9, …, 75-79, 80+), a group of care home residents (CHR) and a group of care home workers (CHW). The model has been described in detail elsewhere [1]. The model was extended to include vaccination where each compartment in the model is further stratified to account for vaccination status. We used parameter values calibrated to data from 4 June 2021. The model was fitted with vaccination (both first and second doses) as reported by DHSC to SPI-M (Figure 1).

Definitions of the reproduction number

Throughout, we consider two definitions of the reproduction number:

- **The reproduction number in the absence of immunity, $R_{excl\_immunity}$,** defined as the average number of secondary infections that an infected individual would generate in a large population with no immunity. $R_{excl\_immunity}$ depends on the virulence of the pathogen and the contact patterns in the population, but not the level of population immunity. We use different values of $R_{excl\_immunity}$ to reflect different levels of mixing associated with different levels of restrictions, irrespective of the level of immunity in the population (see next section). $R_{excl\_immunity}$ also captures the increase in transmissibility resulting from the emergence of the B.1.1.7 variant during the autumn.
- **The effective reproduction number, R_{eff},** defined as the average number of secondary infections that an infected individual will generate with current levels of population immunity. R_{eff} depends on the virulence of the pathogen, the contact patterns in the population and the level of immunity in the population. We use R_{eff} to characterise the extent to which the epidemic is under control, with $R_{eff} > 1$ in a growing epidemic and $R_{eff} < 1$ in a declining epidemic.

$R_{excl\_immunity}$ and R_{eff} are linked through the proportion of the population who is immune (because of infection- or vaccine-induced immunity) p_{immune}, with $R_{eff} = R_{excl\_immunity} * (1-p_{immune})$.

Transmissibility associated with re-opening steps

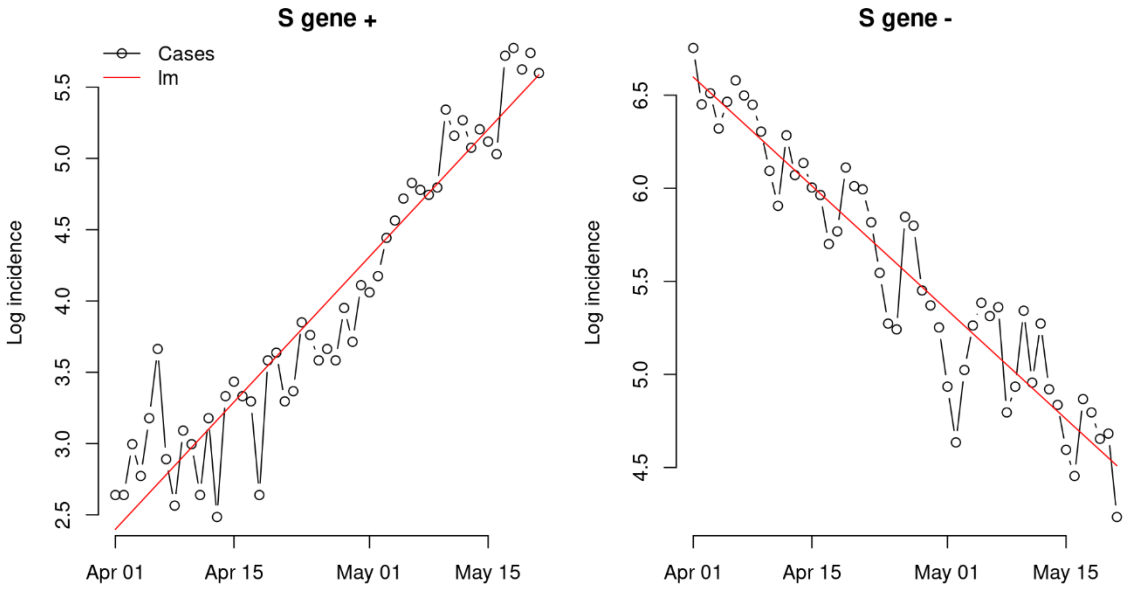
We modelled levels of restrictions in line with the reopening steps set out in the roadmap [15]. For step 4, this includes baseline NPIs with TTI, hand washing & masks and some Covid-secure measures in places such as public transport and crowded indoor spaces.

Our model is fitted without B.1.617.2 (which is only explicitly represented in the forward simulations), so the most recent estimates of the reproduction number from the fitted model reflect transmissibility of both B.1.1.7 and B.1.617.2. We therefore used a complementary approach to estimate the most recent estimate of the reproduction number for B.1.1.7. We fitted a linear regression model to the log incidence of S-gene positive and negative cases in pillar 2 data in England between 1 April and 21 May (discarding the last 2 weeks of data). We assumed all S-gene positive cases were due to B.1.617.2 and all S-gene negative to be due to B.1.1.7, as informed by data from the same period on the frequency of these two strains amongst cases with genomic sequence in England (not shown here). Cases with missing S-gene information were allocated proportionally to be S-gene positive and S-gene negative each day, thereby assuming equal probability of missing data for S-gene positives and S-gene negatives. We thereby obtained estimates of the recent growth rates (Supplementary Figure 1) separately for B.1.1.7 and B.1.617.2.

These growth rates were converted into effective reproduction number estimates (R_{eff}) for each of B.1.1.7 and B.1.617.2 using the relationship described in Wallinga and Lipsitch [16], and assuming a generation time with mean 6.7 days and standard deviation 3.5 days, compatible with our dynamic transmission model structure and parameterisation [1]. The estimated R_{eff} was 0.75 (95%CI 0.73-0.77) for B.1.1.7 and 1.50 (95%CI 1.44-1.55) for B.1.617.2. We note that these are in line with the most recent overall estimate of R_{eff} (across the two variants) from our dynamic transmission model, at 1.20 (95%CI 1.01-1.41).

We used the resulting estimated R_{eff} for B.1.1.7, and the proportion of the population protected against B.1.1.7 as estimated from our dynamic transmission model, to determine the reproduction number excluding immunity ($R_{excl\_immunity}$) for B.1.1.7, reflecting the current level of mixing after step 3 (Supplementary Table 1). This corresponded to a reproduction number excluding immunity ($R_{excl\_immunity}$) for B.1.1.7 of 1.7 with schools closed and 2.0 for schools opened during step 3. This reproduction number was then used for the whole period until step 4 for B.1.1.7. The reproduction number for B.1.617.2 was assumed to be a constant multiplier times that of B.1.1.7.

We define the effective transmission advantage as the advantage conferred by a mixture of increased transmissibility and the degree of immune escape by B.1.617.2. Our log-linear analysis as well as other (unpublished) studies have found similar values of the effective transmission advantage in a range from 1.5 to 2. We therefore selected the combinations of immune escape levels and transmissibility advantages for B.1.617.2 which yielded effective transmission advantages between 1.5 and 2.



Supplementary Figure 1: Daily incidence (on a log scale) of S-gene positive (left) and S-gene negative (right) cases between 1 April and 21 May 2021 (discarding the last two weeks of data). The points show the data and the red line the log-linear regression.

The final baseline transmissibility for B.1.1.7 once all NPIs are lifted is assumed to be on average $R_{excl\_immunity}$ = 3.0 with wide uncertainty, consistent with an increase in transmissibility due to B.1.1.7 (wild type R0 ~2.8 to 3.0, relative increase in B.1.1.7 transmissibility ~75% [14]) but with a ~30% reduction due to residual measures such as hand hygiene and TTI. To capture the considerable uncertainty in predicting the behaviour of individuals after lifting most restrictions, we also consider a baseline $R_{excl\_immunity}$ of 4.5 (~10% marginal effect of remaining measures) as a sensitivity analysis.

There is substantial uncertainty around the level of transmissibility associated with specific policy changes. To capture this uncertainty, we assumed $R_{excl\_immunity}$ under each level of restrictions was distributed around the mean values described above, using lognormal distributions with parameters shown in Supplementary Table 1 and Supplementary Figure 2.

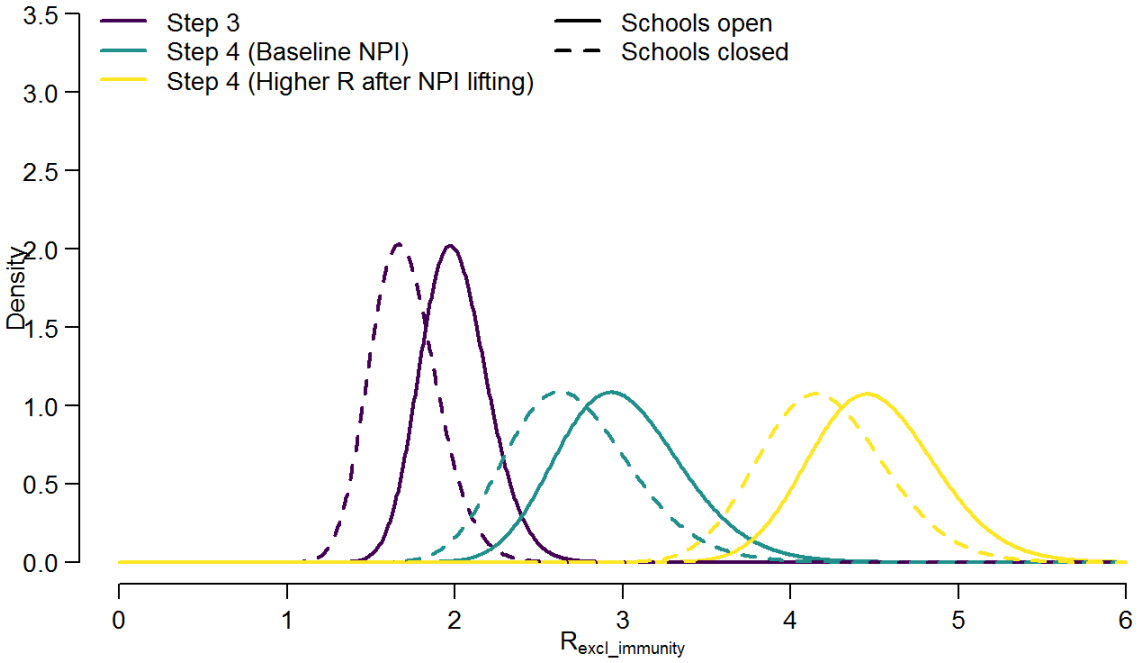
The reproduction numbers assumed in the steps above are assuming schools are opened. In addition, we assumed that closing schools, e.g. during school holidays, will decrease $R_{excl\_immunity}$ for B.1.1.7 by an average -0.3. This is based on the consensus value from SPI-M accounting for the increase in transmission due to the B.1.1.7 variant. This is consistent with the impact seen during Step 2. As some of the “not before” dates for the next step of NPI release overlap with school holidays, we adjusted the assumed transmissibility during this time accordingly with an average -0.3 in $R_{excl\_immunity}$ when schools are closed.

For each NPI lifting scenario, we sampled from the relevant distributions of $R_{excl\_immunity}$ at each step of lifting (including school holidays) and generated sampled trajectories of $R_{excl\_immunity}$ over time by matching the ranked values obtained for each step. This constraint was added to ensure that $R_{excl\_immunity}$ could only increase over time except for the time period when schools were closed. The resulting distributions of R over time (shown in Figure 3 and Figure 4) may therefore differ slightly from those shown in Supplementary Table 1 and Supplementary Figure 2 because of this additional constraint.

Supplementary Table 1: Overview of transmissibility and uncertainty associated with each release step in England, excluding immunity ($R_{excl\_immunity}$) for B.1.1.7 (see Methods "Definitions of the reproduction number"). Note that the $R_{excl\_immunity}$ for B.1.617.2 will be higher (see Figure 2 for example).

	$R_{excl\_immunity}$: mean (95% CI)	sd	meanlog	sdlog
Step 3	1.70 (1.34-2.12)	0.2	0.52	0.12
Schools closed				
Schools open	2.00 (1.64-2.42)	0.2	0.69	0.10
Step 4 (full lift)^	2.70 (2.04-3.51)	0.375	0.98	0.14
Schools closed	(moderate baseline NPIs retained)			
	4.20 (3.51-4.98)	0.375	1.43	0.09
	(higher R after full NPI lifting**)			
Schools open	3.00 (2.33-3.80)	0.375	1.09	0.125
	(moderate baseline NPIs retained)			
	4.50 (3.81-5.28)	0.375	1.5	0.08
	(higher R after full NPI lifting**)			

**Higher R after full NPI lifting or "Lower adherence to baseline NPIs" values were used for sensitivity analyses only. ^Assumes some control such as TTI and hand hygiene continue.



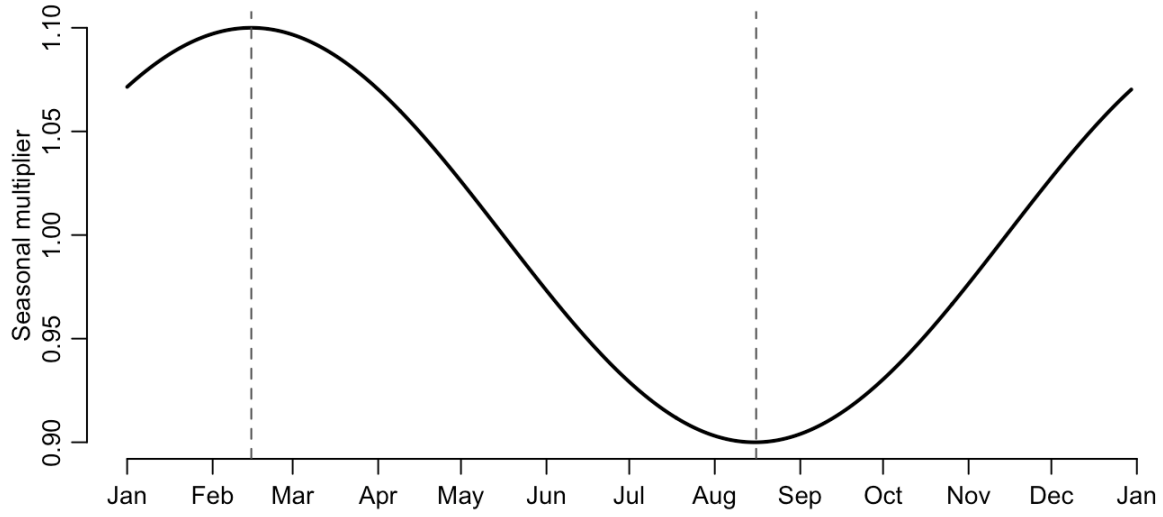
Supplementary Figure 2: Distributions of transmissibility ($R_{excl\_immunity}$) for B.1.1.7 associated with each step of NPI lifting in England. Values of $R_{excl\_immunity}$ were constrained so they could only increase over time except during school holidays when $R_{excl\_immunity}$ was decreased on average by -0.3. (For full details see Supplementary Table 1).

Seasonality in transmissibility

In our main analyses we assumed a slight seasonal trend in SARS-CoV-2 transmissibility throughout the year in England with 20% relative peak to trough variation. We computed a daily multiplier for transmissibility which was:

- Maximal at 1.1 in mid-February of each year (10% relative increase compared to the mean transmissibility)
- Minimal at 0.9 on in mid-August (day 228) of each year (10% relative decrease compared to the mean transmissibility)

We then applied this daily seasonal multiplier (Supplementary Figure 3) to $R_{excl\_immunity}$ in each phase (see Table 4 and Supplementary Table 1).



Supplementary Figure 3: Seasonal daily multiplier for transmissibility ($R_{excl\_immunity}$) applied to each phase (Supplementary Table 1).

First dose vaccine roll-out

We assume first doses were delivered in England between 8 December 2020 and 4 June 2021 as reported in data received from PHE and DHSC via SPI-M. We then assume a vaccine dose roll-out as in Table 2. To account for second doses, we assumed that the number of available first doses on a given day is given by the total available doses on that day and subtract the number of first doses administered 77 days (11 weeks) prior. If the resulting value was negative, this was set to 0. From 4 June onwards, we assumed first doses are split between NHS regions in proportion of their population size. We assumed that a mixture of Pfizer and AstraZeneca vaccines as observed thus far in each age group continue to be distributed to individuals 50+ years. For 40-49 year olds we assumed a 60% AZ and 40% PF or Moderna mix, and <40 years will receive PF or Moderna only.

We assume doses are distributed following the JCVI priority list i.e. to:

1. Care home workers and residents
2. Individuals 50 or over by decreasing 5-year age band priority as well as health care workers (we assume a fraction of the working age population to be within this group) and vulnerable individuals (also modelled as a fraction of the population)
3. Individuals under 50

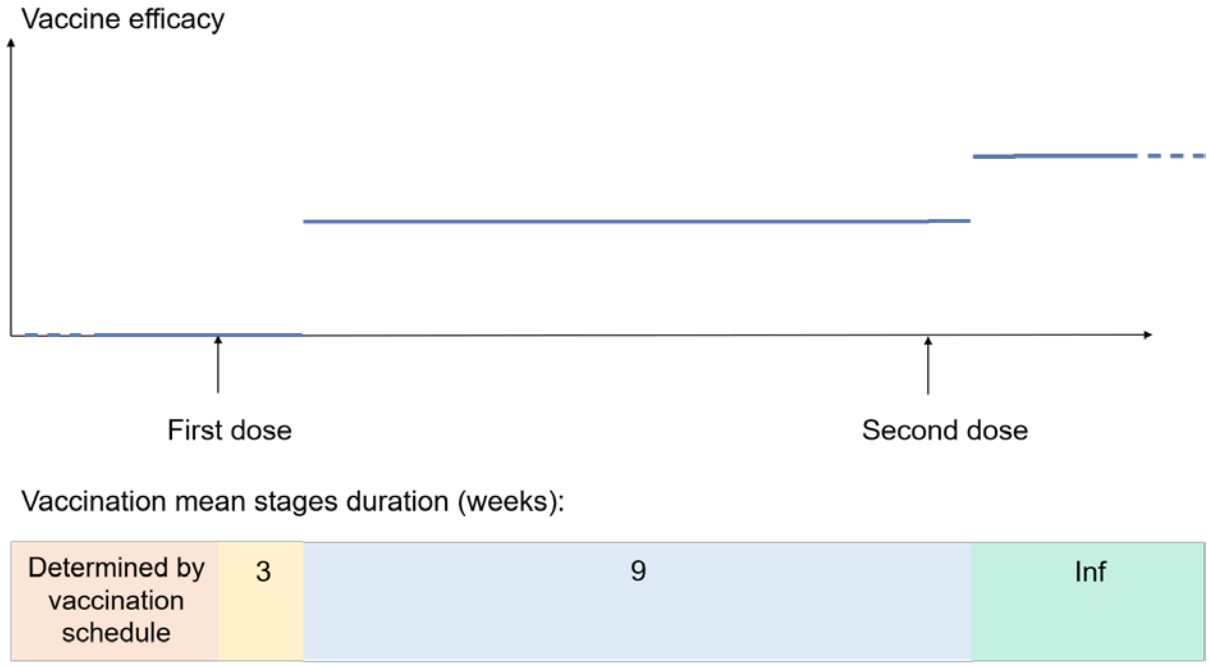
Children under 18 years are not vaccinated. As our model is stratified using 5-year age classes, we model the vaccination of individuals aged 18-19 by assuming the uptake in the 15-19 age group is 2/5 of the uptake in the 20-24 year olds.

2nd dose vaccine roll-out and vaccine efficacy after each dose

We assume degree-type protection from vaccination: all vaccinees have their likelihood of acquiring infection reduced by a factor of (*1 – vaccine efficacy*), see section on vaccine efficacy below for more detail.

For each compartment in the model, 4 successive vaccination stages (duration of each stage and efficacy of vaccine in each stage are shown on Supplementary Figure 4):

- Unvaccinated
- Vaccinated with 1st dose before onset of vaccine efficacy
- Vaccinated with 1st dose with full efficacy from 1st dose – this includes individuals having received the second dose before the onset of efficacy of the second dose
- Vaccinated with 2nd dose with full efficacy from 2nd dose



Supplementary Figure 4: Vaccination stage duration and associated vaccine efficacy. The lower panel depicts mean duration of vaccination stages in weeks (numbers denote number of weeks in each stage). The top panel shows the associated vaccine efficacy and delays to protection over time.

Vaccine efficacy after first and second dose was varied across scenarios (see Table 1), but we assume:

- No efficacy in the 21 days following the first dose
- No efficacy of the second dose for the 7 days following dose 2

Phase 2 PF and AZ vaccine trial results indicated substantial increase in immunogenicity only after 2 to 3 weeks post-dose 1, and one-week post-dose 2 [17,18]. We therefore assumed a 21-day (respectively 7-day) delay between receiving the first (respectively second) dose and the onset of dose-specific efficacy.

Vaccine effectiveness

We assumed that the vaccine has four effects (Table 1):

1. Efficacy *against infection,* e_{inf}: Reducing the risk of infection in vaccinated individuals, compared to those not vaccinated.
2. Efficacy *against symptoms conditional on infection,* $e_{sympt\,|\,inf}$: Reducing the risk of symptoms in vaccinated individual who become infected, compared to those non vaccinated who become infected.
3. Efficacy *against severe symptoms requiring hospitalisation, conditional on symptomatic infection,* $e_{hosp\,|\,sympt}$: Reducing the risk of severe symptoms requiring hospitalisation in a vaccinated individual who becomes infected and symptomatic, compared to those non vaccinated who become infected and symptomatic.
4. Efficacy against *onward transmission conditional on infection* $e_{transmit\,|\,inf}$: Reducing the risk of onward transmission from a vaccinated individual who became infected, compared to those non vaccinated who became infected (used in sensitivity analysis only)

The first two effects combined reduce the risk of symptomatic infection ("Efficacy *against symptomatic infection,* e_{sympt}", non-conditional on infection) in vaccinated individuals, compared to those not vaccinated. The first three effects combined reduce the risk of severe infection ("Efficacy *against severe infection,* e_{hosp}", non-conditional on symptomatic infection) in vaccinated individuals, compared to those not vaccinated.

Assumed values of effectiveness for e_{inf} , and e_{sympt} and e_{hosp} are shown in Table 1.

The reduction in the risk of being symptomatically infected (e_{sympt}), as reported in clinical trials, is determined by both the reduction in the risk of being infected (e_{inf}) and the reduction in the risk of becoming symptomatic if infected ($e_{sympt\,|\,inf}$) as follows:

$$e_{sympt} = e_{inf} + (1 - e_{inf}) * e_{sympt\,|\,inf}$$

Similarly, the reduction in the risk of being severely infected (e_{hosp}), as reported in some clinical trials, is determined by the reduction in the risk of being infected (e_{inf}), the reduction in the risk of becoming symptomatic if infected ($e_{sympt\,|\,inf}$), and the reduction in the risk of developing severe symptoms if infected and symptomatic ($e_{hosp\,|\,sympt}$) as follows:

$$e_{hosp} = e_{inf} + (1 - e_{inf}) * e_{sympt\,|\,inf} + (1 - e_{inf}) * (1 - e_{sympt\,|\,inf}) * e_{hosp\,|\,sympt}$$

Vaccine uptake

We assume vaccine uptake was age dependant with 80% uptake in those aged 18-39 years. We assumed every individual having received their first dose would go on to also receive a second dose.

Modelling the introduction and spread of the variant of concern (VOC) B.1.617.2

Overview

We model the potential introduction and spread of a hypothetical variant of concern (VOC) in England by extending our model to a two-variant model. Variant 1 represents the dominant variant in circulation, i.e. B.1.1.7 in the UK; variant 2 represents a hypothetical VOC, here B.1.617.2. Transmissibility, efficacy of vaccines and natural immunity differ between the two variants. We assumed a proportion of cases at the start of the simulation on 4 June 2021 were due to a VOC. This was estimated by NHS region assuming that all reported S-gene positive pillar 2 cases were due to B.1.617.2 (Supplementary Table 2). For each region, a 7-day rolling average was calculated

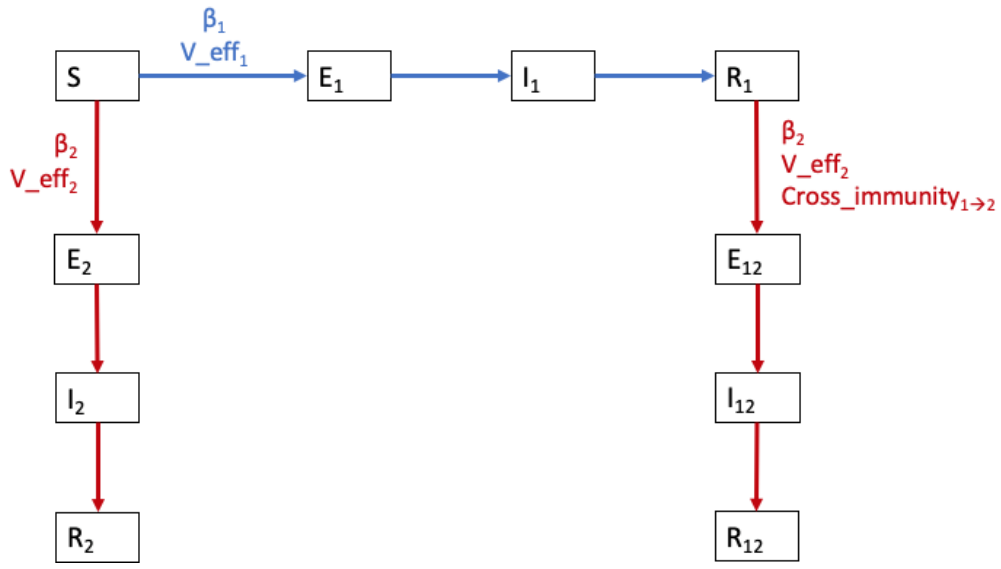
to estimate the proportion of S-gene positive pillar 2 data as of 21 May 2021, with the last 14 days of data discarded due to backfill. From 21 May 2021, we applied a factor, *f,* informed by a logit model fitted to the logistic growth rate of B.1.617.2 (i.e. as a proportion of all sequenced cases at a national level). We thus explicitly accounted for regions being at different points of the logistic growth curve (not shown here).

Supplementary Table 2: Reported and assumed proportions of S-gene positive pillar 2 cases

NHS Region	Reported % as of 21 May	Assumed % at start of simulation*
East of England	74%	94%
London	72%	93%
Midlands	63%	90%
NE and Yorkshire	35%	69%
North West	87%	97%
South East	74%	93%
South West	54%	85%

*Given logistic growth factor *f* from logit model fitted to B.1.617.2 prevalence amongst all cases with genomic sequence data in England.

A simplified flowchart for our two-variant model is shown in Supplementary Figure 5. The age/care home structure and vaccine class structure for the second variant is equivalent to that for the first.



Supplementary Figure 5: Flowchart summarising the two-variant structure of the model. S denotes susceptibles, E exposed (infected not infectious), I infectious and R recovered. Indexes denote infection with variant 1 (e.g. E1), variant 2 (e.g. E2) or variant 1 and 2 in turn (e.g. E12). In the model, each compartment is further split by age/care home resident/care home worker class (as described in [1]**), and by vaccination class, not shown in this figure. The I compartment is also further split to distinguish between symptomatic and asymptomatic cases, and to describe in detail the hospital pathways of severely affected cases** [1]**. Deaths are not pictured on this figure but are also modelled as described in** [1]**. Blue and red arrows denote infection and clinical progression for the first and second variant respectively. Parameters next to an arrow denote parameters which influence the risk of infection for that arrow and include β_i, the transmission rate for variant i, $cross\_immunity_{j->i}$, the cross protection against variant i provided by prior infection with the other variant (j), and V_eff_i, the vaccine efficacy against variant i. Note that vaccine efficacy will also alter the probability of symptomatic and severe infection.**

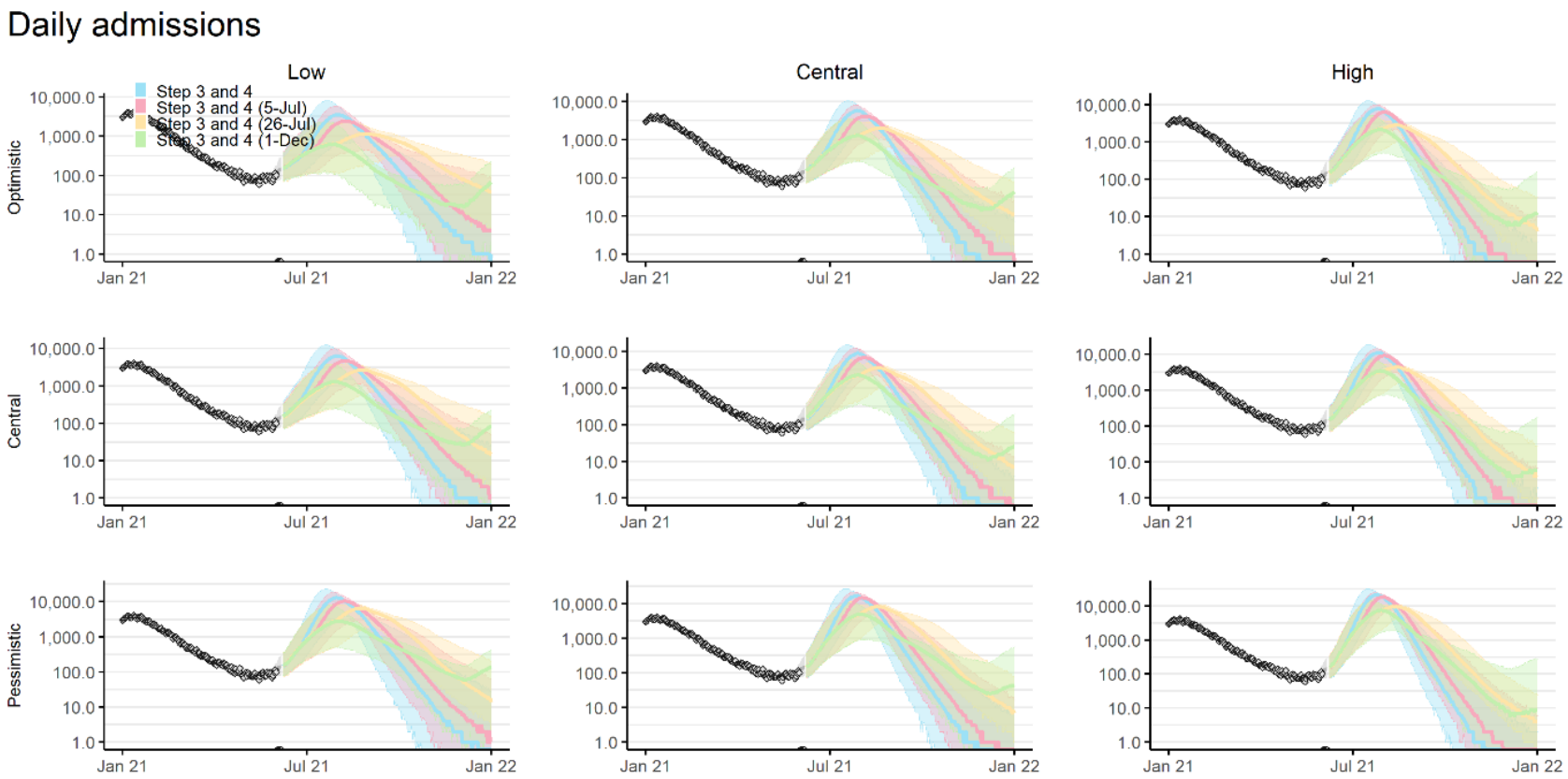
Transmissibility of B.1.617.2

Transmissibility for the second variant is modelled as proportional to that for the first variant, with a constant multiplier through time (see section Projected increases in population contact rates resulting from roadmap step 4). Therefore, increases in the reproduction number for the first variant automatically triggers corresponding increases in the reproduction number for the second variant. Unless otherwise specified, values of the reproduction numbers (both excluding immunity and effective) described in the text and in Figures and Tables all correspond to B.1.1.7. Unless otherwise specified, numbers of infections, hospitalisations, bed occupancy and deaths are shown for both variants together.

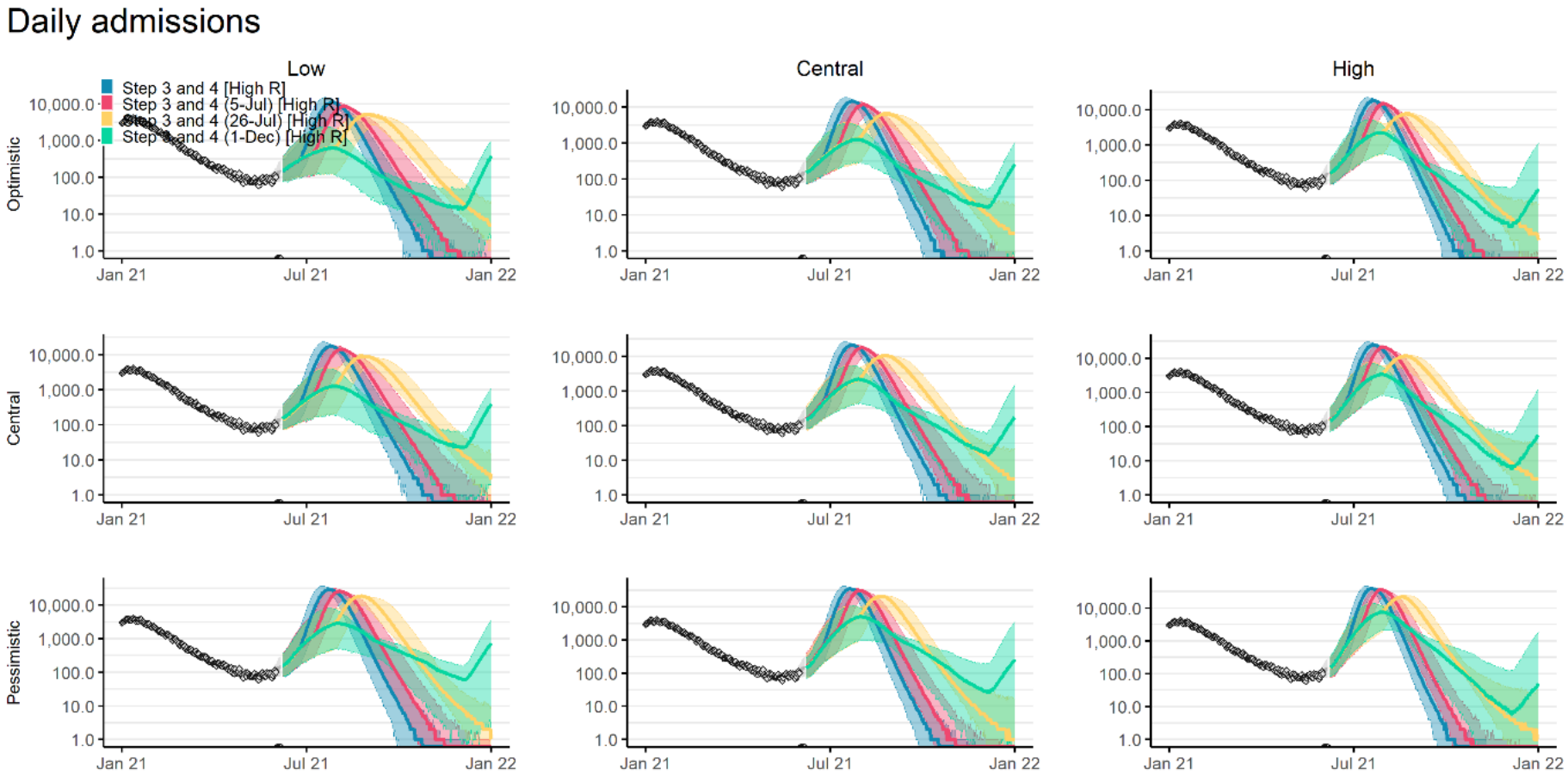
Immune escape properties of the VOC

We assume that vaccines may be less efficacious against B.1.617.2 (Table 1). We also model a non-symmetrical cross immunity between the two variants; we assume that infection with variant 2 (the VOC) confers perfect immunity to variant 1, but infection with variant 1 is only partially protective against infection with variant 2 (Table 1). In addition, for individuals infected by each variant in turn, we assume that if the second infection is symptomatic, the probability of hospitalisation is reduced compared to individuals with no prior infection history (Table 1).

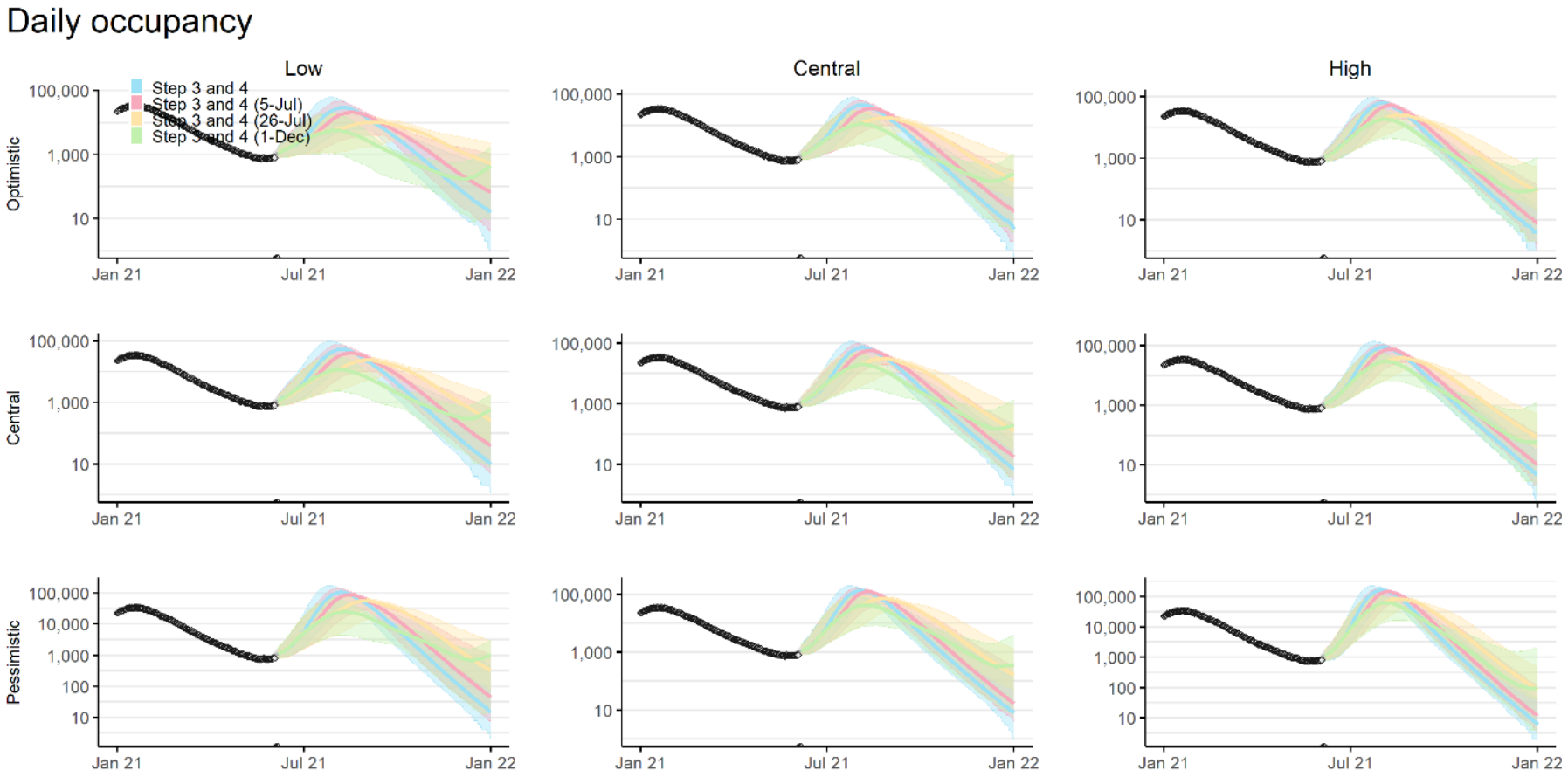
7. Supplementary Results



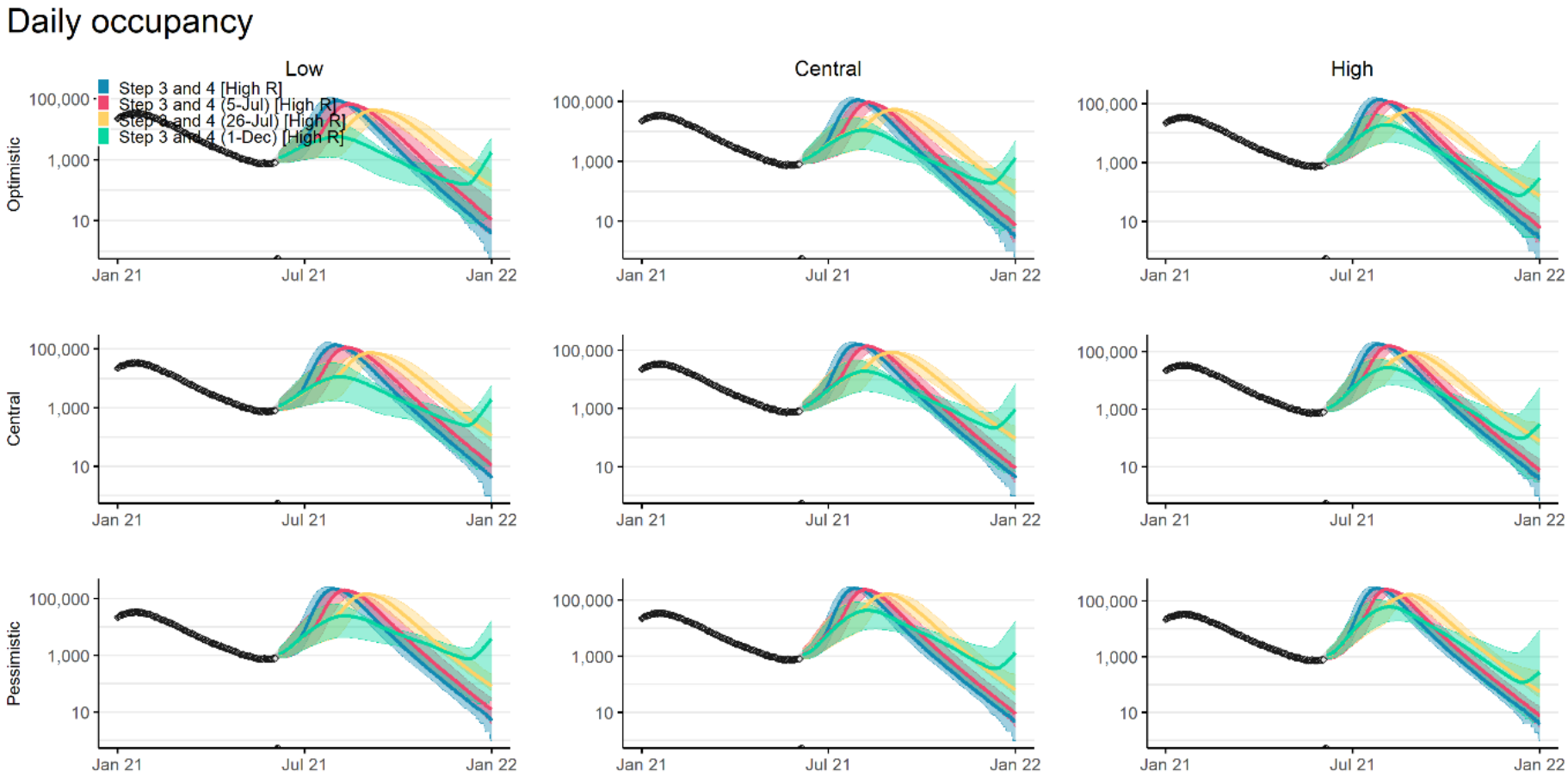
Supplementary Figure 6: COVID-19 daily hospital admissions in England shown on a log scale for Step 4 occurring on 21 June (blue), 5 July (pink), 26 July (yellow), and early-December when all eligible adults have receive two vaccine doses (green) with central R after full NPI lifting (see Table 4), projecting forwards to 1 January 2022. We consider a variant of concern, B.1.617.2, with: (Left column) low transmissibility; (middle column) central transmissibility; and (right columns) high transmissibility relative to B.1.1.7 and with (top row) low; (middle row) central; and (bottom row) high immune escape properties. Namely for the central immune escape scenarios, we considered transmission advantages of 150% (where B.1.617.2 is assumed 50% more infectious than B.1.1.7), 165% and 180%, for the high immune escape scenario, we considered transmission advantages of 140%, 155% and 170% and for the low immune escape scenario we considered transmission advantages of 150%, 170% and 190%. See Table 1 for VOC properties. The coloured lines show the mean and the shaded areas show 95% credible intervals. Note the y-axis scale is different in each row.



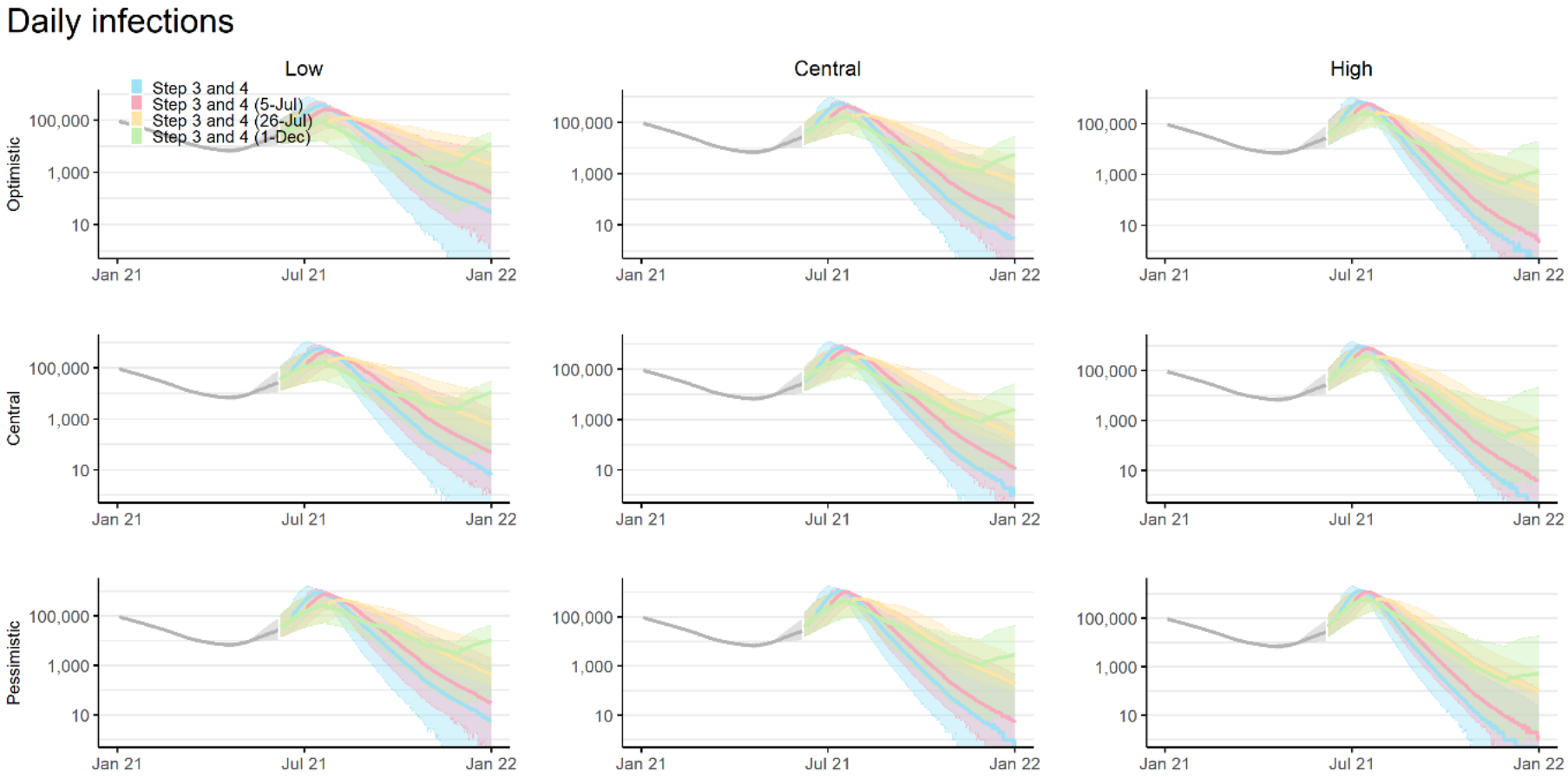
Supplementary Figure 7: As Supplementary Figure 6 but showing higher R after NPI lifting



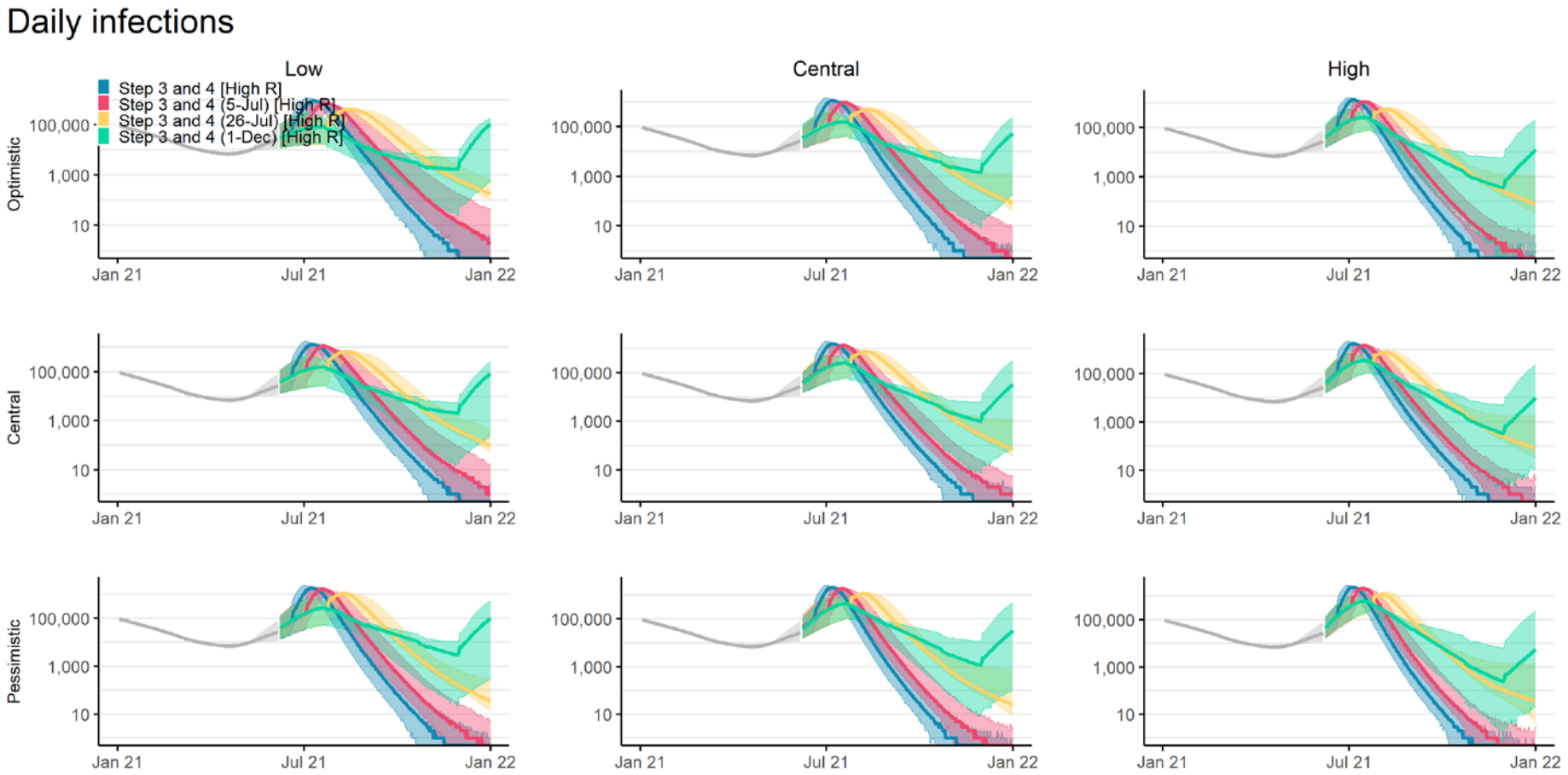
Supplementary Figure 8: COVID-19 daily hospital occupancy in England shown on a log scale for Step 4 occurring on 21 June (blue), 5 July (pink), 26 July (yellow), and early-December when all eligible adults have receive two vaccine doses (green) with central R after full NPI lifting (see Table 4), projecting forwards to 1 January 2022. We consider a variant of concern, B.1.617.2, with: (Left column) low transmissibility; (middle column) central transmissibility; and (right columns) high transmissibility relative to B.1.1.7 and with (top row) low; (middle row) central; and (bottom row) high immune escape properties. Namely for the central immune escape scenarios, we considered transmission advantages of 150% (where B.1.617.2 is assumed 50% more infectious than B.1.1.7), 165% and 180%, for the high immune escape scenario, we considered transmission advantages of 140%, 155% and 170% and for the low immune escape scenario we considered transmission advantages of 150%, 170% and 190%. See Table 1 for VOC properties. The coloured lines show the mean and the shaded areas show 95% credible intervals. Note the y-axis scale is different in each row.



Supplementary Figure 9: As Supplementary Figure 8 but showing higher R after NPI lifting



Supplementary Figure 10: SARS-CoV-2 daily infections in England shown on a log scale for Step 4 occurring on 21 June (blue), 5 July (pink), 26 July (yellow), and early-December when all eligible adults have receive two vaccine doses (green) with central R after full NPI lifting (see Table 4), projecting forwards to 1 January 2022. We consider a variant of concern, B.1.617.2, with: (Left column) low transmissibility; (middle column) central transmissibility; and (right columns) high transmissibility relative to B.1.1.7 and with (top row) low; (middle row) central; and (bottom row) high immune escape properties. Namely for the central immune escape scenarios, we considered transmission advantages of 150% (where B.1.617.2 is assumed 50% more infectious than B.1.1.7), 165% and 180%, for the high immune escape scenario, we considered transmission advantages of 140%, 155% and 170% and for the low immune escape scenario we considered transmission advantages of 150%, 170% and 190%. See Table 1 for VOC properties. The coloured lines show the mean and the shaded areas show 95% credible intervals. Note the y-axis scale is different in each row.



Supplementary Figure 11: As Supplementary Figure 10 but showing higher R after NPI lifting

8. References

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