Road Map Scenarios and Sensitivity: Step 4

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Here we consider the likely epidemiological impacts of Step 4 of the relaxation roadmap and throughout model the spread of the B.1.617.2 variant. We use an age-structured model that captures the dynamics within the seven NHS regions of England. The model is matched to data from 4th June 2021 and projections reflect the underlying uncertainty in parameters.

Public Health Conclusions

1. There remains considerable uncertainty in the scale and timing of the projected third wave, principally due to: the unknown (and unknowable) behaviour after Step 4; the uncertainty in the scale of transmission advantage of the B.1.617.2 variant; and uncertainty in vaccine protection and uptake.
2. There are a range of plausible scenarios in which the mean projected number of hospital admissions in the third wave exceeds the peak and size of the first or second waves.
3. Promoting high vaccine uptake (especially amongst the vulnerable Phase 1) is critical to suppress the worst effects of the third wave.
4. We expect to observe considerable heterogeneity between regions and local areas in the scale of the third wave, reflecting past exposure, vaccine uptake and inferred parameters.
5. A delay to the relaxation roadmap would have three main epidemiological advantages:
   (a) delay and reduce the epidemic peak providing more time for additional vaccination and protection.
   (b) provide additional time to understand the degree to which the vaccine protects against B.1.617.2.
   (c) allow more confidence to separate the impacts of B.1.617.2 from changes due to Step 3.
6. We have assumed the same case hospitalisation rate and case fatality rate for both B.1.1.7 and B.1.617.2; there is some evidence that B.1.617.2 may have a slightly elevated case hospitalisation rate which would increase our projections by a multiplicative scaling.
7. Although the majority of this analysis reflects the greater transmission advantage of the B.1.617.2 variant, other novel variants may pose an even greater risk to the relaxation roadmap. In particular, variants of concern with high levels of vaccine escape or where past infection does not confer cross immunity could generate additional waves of infection on top of any predicted here.

Executive Summary

1. We consider the likely epidemiological impacts of Steps 4 of the relaxation roadmap. This is modelled for the seven NHS regions of England and then the data are combined, although regional heterogeneities are also considered.

2. Four major changes have been made to the model structure since the previous assessment of the roadmap:

   (a) the B.1.617.2 variant is now explicitly modelled with its transmission advantage inferred and its initial seeding matched to S-gene data.

   (b) parameters for Step 2 are now fully informed by the most recent data; unfortunately Step 3 parameters are confounded with estimation of the B.1.617.2 variant.

   (c) vaccine efficacy parameters have been re-assessed in light of recent data from PHE; three sets of efficacy assumptions are compared throughout the document.

   (d) the delay between first and second doses for the over 50s has been shortened to eight weeks, while those under 40 only receive the Pfizer or Moderna vaccines, in line with JCVI advice.

   The inclusion of the new variant leads to a far larger third wave than previously predicted; although for B.1.1.7 the action of the new vaccine efficacy parameters alone would reduce the scale of the third wave compared to previous roadmap documents.

3. We estimate that the B.1.617.2 variant has a 56% (CI 34-81%) transmission advantage over the B.1.1.7 variant. In keeping with the latest analysis we assume that one dose of vaccine offers lower protection against B.1.617.2 compared to B.1.1.7 although two doses of vaccine offer more similar levels of protection; we also assume complete cross immunity.

4. Under our default parameters, we predict a large third wave of *infections* exceeding those in the second wave - although, due to the action of vaccination, the number of hospital admissions is expected to be slightly lower, while deaths are further reduced.

5. We consider three different sets of vaccine efficacy values (default, optimistic and cautious) which correspond to the central, upper and lower ranges generated by PHE. All vaccine efficacy assumptions are projected to generate large peaks of hospital admissions in July, August and September 2021, reaching 2850 (PI 1530-4800) hospital admissions per day for the default efficacy assumptions, and 1760 (PI 918-3020) and 5990 (PI 3810-8910) for the optimistic and cautious assumptions respectively.

6. The size of the third wave (in terms of hospital admissions) is most sensitive to the transmission advantage of B.1.617.2, the estimated strength of vaccine efficacy and the estimated vaccine uptake in the older and more vulnerable populations.

7. Delays to the start of Step 4, greater restrictions (or greater caution in the general population) after Step 4, or a two-step process to complete relaxation all reduce the scale of the third wave by allowing more vaccinations to occur and hence greater population level immunity to develop.

8. The model does not account for multiple factors which could impact the projections:

   (a) waning immunity after infection or vaccination is ignored, which affects our ability to make longer-term predictions;

   (b) vulnerable risk groups are not explicitly included, all risks are an average for the 5-year age-groups that are modelled;

(c) although we recognise that there is likely to be spatial heterogeneity at relatively small scales during the third wave, the model operates and is parameterised with information from the 7 NHS regions;

(d) our methodology is formulated around deterministic differential equations which work well for large populations and significant levels of infection, but a stochastic approach may be needed if we approach exceedingly low levels of infection;

(e) finally, the model is unable to address either changing patterns in individual behaviour with changes in perceived risk or the finer nuances of control measures, as both of these are translated into a single parameter that captures the impact of NPIs at the population scale.

Methodology and Key Uncertainties

This work uses the model that has been developed in Warwick over the past year [1, 2] and matched to a variety of epidemiological data [3]. The model operates and is fitted to data from the seven NHS regions in England and the three devolved nations, although here we only present results for England (aggregating output from the seven NHS regions). The results of this model have been presented to SPI-M and SAGE on a number of occasions, and the model has been used to examine short-term and medium-term projections as well as reasonable worst-case scenarios. The model has previously been extended to include vaccination, initially to investigate priority ordering and has subsequently increased in complexity to include two-dose schedules and multiple actions of vaccine protection [2]. It also used the ratio of S-gene positive to S-gene negative PCR results to infer the spread of the B.1.1.7 variant (which is S-gene negative on TaqPath system) at the end of 2020. This approach has since been expanded to assess the spread of B.1.617.2 (which is S-gene positive).

Vaccine uptake within the model to date mirrors the recorded data in terms of dose and age of those vaccinated. Projecting forwards, we follow the strict JCVI priority ordering for both Phase 1 and Phase 2. The uptake of vaccines so far has been far higher than initially anticipated, exceeding 95% in many areas and age-groups. Here we assume that uptake in those 40 and over is determined by historical uptake, while for those 18-39 the uptake level is set at 80%. Although the number of vaccines delivered is well recorded, there is some uncertainty in the population size denominator – we therefore consider the implications if the uptake of vaccine is lower than reported.

We model the return of pupils to school from 8th March (as part of Step 1) and consider the impact of the remaining relaxation steps occurring at their earliest dates. School holidays modelled by changing the mixing patterns for school-aged children, and we include all school holidays over the simulation period. We have accounted for the changes in each step by modelling a reduction in the level of NPIs acting on the population, gradually bringing the population mixing back close to pre-COVID levels. We measure the degree of relaxation as both a change in the relative level of NPI controls, and by computing the reproduction number excluding immunity (R_{ei}), which can be conceptualised as the theoretical reproduction number at the start of the epidemic if such controls were in place (with separate estimates generated assuming either the B.1.1.7 variant or the B.1.617.2 variant was dominant). We assume that any changes in transmission that occurred following Step 1b on the 29th March 2021 (which is largely concerned with outdoor mixing) or following Step 2 on 12th April 2021 are already captured in parameter estimates. It has been impossible to rigorously estimate the changes in mixing patterns from Step 3; normally this is achievable with three weeks of data, but the inference is made more complex by the need to estimate additional parameters for the B.1.617.2 variant; we therefore use the methodology from previous roadmap documents and set a level of NPI control in Step 3 that is a proportional reduction to those already observed.

We now focus on three elements of the model to describe in some detail:

1) The B.1.617.2 variant. Previous assessments of the roadmap considered invasion of Variants of Concern (VoC) as an additional sensitivity analysis, looking at variants that are either more transmissible or can (partially) escape vaccine immunity. In the initial sensitivity analysis, we had limited data on existing variants so considered a range of parameters and assumed that any VoC had been growing in all regions of England from early March at very low levels. In this document, it is a priority to explicitly model the growth of B.1.617.2 and its regional spread. Parameter estimates for this new VoC are inferred together with all the other epidemiological variables, and we estimate the transmission advantage of B.1.617.2 and B.1.1.7 over the original wildtype variant in each region (Fig. 1 top); we also provide estimates of the competitive advantage of B.1.617.2 over B.1.1.7 (Fig. 1 middle). This inference is based on total number of cases, hospital admissions and deaths (for either variant) and the ratio of S-gene positive and S-gene negative samples (where available) as a rapid proxy for the

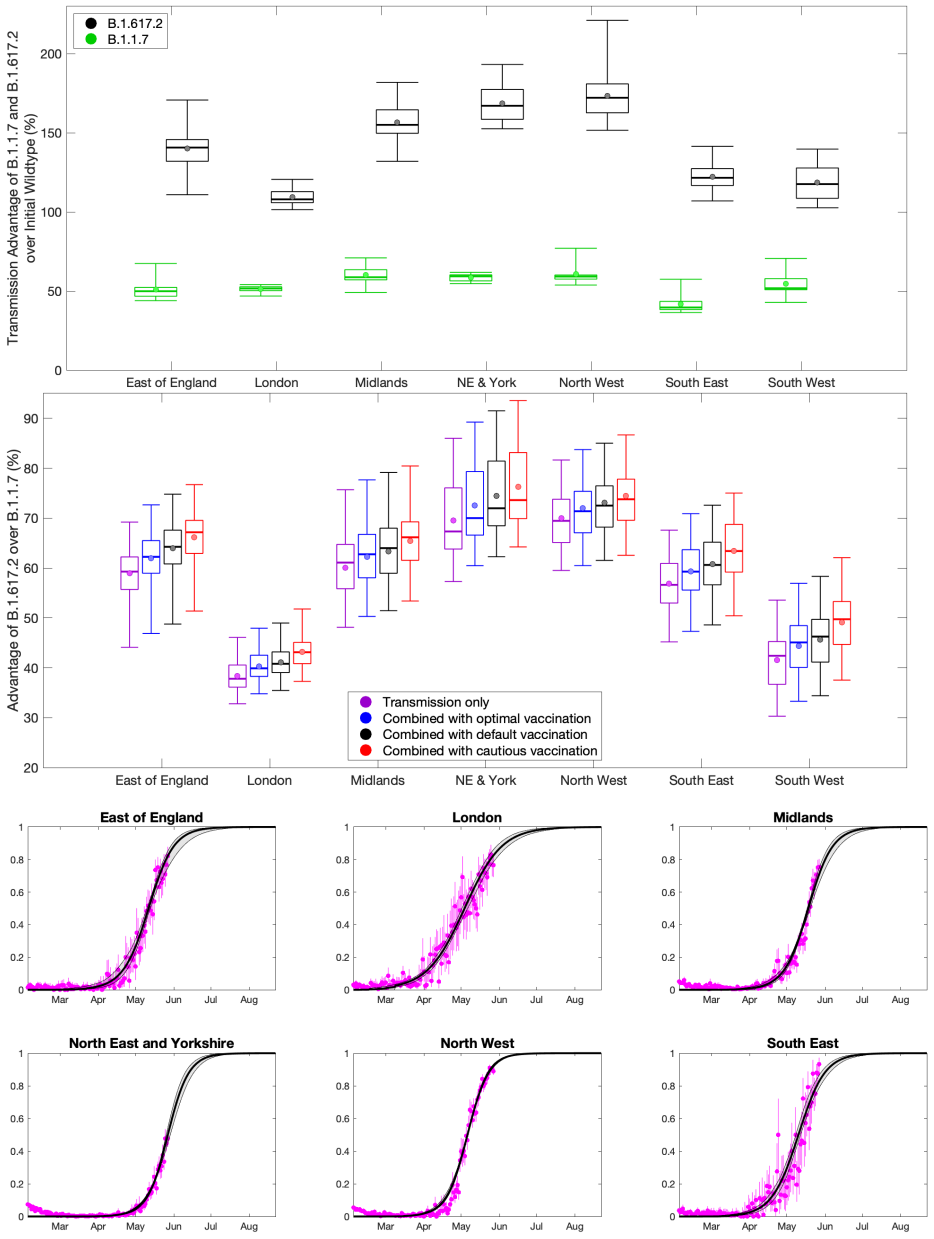

Fig. 1: Top: Estimated transmission advantage of B.1.1.7 (green) and B.1.617.2 (black) over the wildtype, as inferred from the Warwick MCMC model, which fits to the number of symptomatic Pillar 2 cases, hospital admissions and deaths, in addition to the proportion of symptomatic Pillar 2 cases that are S-gene positive. Middle: Estimated competitive advantage of B.1.617.2 over B.1.1.7: assuming all advantage comes from increased transmission (purple); assuming advantage comes from a combination of increased transmission and partial vaccine escape (optimistic efficacy assumptions in blue; default efficacy assumptions in black; and cautious efficacy assumptions in red - see below for description of these efficacies). Lower panels: the predicted proportion of infections that are attributable to B.1.617.2 (black line together with 95% prediction intervals) together with data on the proportion of S-gene positive samples with CT values below 30 (pink, and associated confidence intervals based on the number of samples.). Data and plots from the South West are excluded due to sparsity of samples.

proportion of cases that are B.1.617.2 as opposed to B.1.1.7. Fortuitously, B.1.1.7 is negative for the S-gene on TaqPath PCR, which provided a rapid assessment of its growth in late 2020 and its more

recent decline as it is replaced by B.1.617.2. Unfortunately, not all NHS regions use the TaqPath system – the South West region being the most notable exception – so there is considerable uncertainty in the ratio of B.1.617.2 to B.1.1.7 in some regions. We note that vaccine efficacy has been measured as lower against B.1.617.2 compared to B.1.1.7 (see below), and this is incorporated into the parameter inference framework. This lower vaccine efficacy will also contribute to the B.1.617.2 variant's more rapid growth (Fig. 1 lower panels). In the absence of other data, we optimistically assume that infection with B.1.1.7 or other variants provides complete cross immunity against B.1.617.2.

We estimate that B.1.617.2 has a 56% (CI 34-81%) transmission advantage over B.1.1.7, which itself had a transmission advantage over the original wildtype (Fig. 1 top panels). This advantage is inferred at a regional scale, although there are hyperpriors that constrain the advantages to be similar. We observe that B.1.617.2 has a consistent advantage over B.1.1.7 and hence a much larger advantage over the wildtype. We can consider how these advantages (together with any vaccine escape) translate into the proportion of B.1.617.2 in comparison to total infections within the model (Fig. 1 lower panels), which takes a sigmoidal form. Here the model projections are shown in black (together with the associated 95% prediction intervals); the pink dots are the proportion of S-gene positive samples relative to the total number of COVID positive samples (with CT value < 30), which is a reasonable approximation to the required quantity.

2) Vaccine action. Having been vaccinated, the protection generated can affect multiple components of the infection, disease and the onward transmission process. This has been updated from the initial calculations and now considers five elements separately: efficacy against infection; efficacy against disease (which also affects transmission, as our default assumption is that asymptomatic infections transmit less than symptomatic infections); efficacy against onward transmission; efficacy against hospital admission and efficacy against admission to ICU and death. We can also allow different parameters for Pfizer and AstraZeneca vaccines, although the differences are generally small for protection against B.1.1.7. Three vaccines are now in use in the UK (Pfizer, AstraZeneca and Moderna). The efficacy for Moderna is not currently well defined and we therefore make the assumption that Moderna and Pfizer are equivalent given their similar mode of action. We base our central (default) estimates of vaccine efficacy on the data generated recently by PHE; taking the mid-point in the estimated range of vaccine efficacy against B.1.1.7. This includes the reduction in onward transmission from those who are vaccinated but who do still become infected [4]. We note that for many measures of vaccine efficacy real world data is not yet available for the second dose of AstraZeneca, in which case we have extrapolated from the protection offered by Pfizer given the similarity for the first dose.

Table 1: Central vaccine efficacy assumptions

	Pfizer/Moderna				**AstraZeneca**			
Efficacy	**1st Dose**		**2nd Dose**		**1st Dose**		**2nd Dose**	
against	B.1.1.7	B.1.617.2	B.1.1.7	B.1.617.2	B.1.1.7	B.1.617.2	B.1.1.7	B.1.617.2
Infection	63%	34%	80%	73%	63%	34%	78%	71%
Symptoms	63%	34%	88%	83%	63%	34%	86%	82%
Hosp Adm	80%	64%	93%	91%	80%	64%	93%	90%
Mortality	78%	60%	97%	96%	78%	60%	97%	96%
Transmission	45%	45%	45%	45%	45%	45%	45%	45%

As shown in Table 1, to fully describe the complexities of vaccine efficacy requires a large number of parameters to be estimated, and for the B.1.617.2 variant there is currently a lack of data. To simplify the calculation and minimise the number of parameters needed, we assume in the default model a fixed reduction in efficacy against infection (here taken as a 47% reduction after dose 1 and 9% reduction after dose 2) but the level of protection conditional on infection remains unaffected. As such B.1.617.2

has a significant level of vaccine escape for those that have only received one dose, but the level of protection for those having two doses is close to that for B.1.1.7. As an example, after 1 dose of either vaccine the efficacy against B.1.1.7 infection is 63%, such that 37% remain susceptible, this is increased by 47% for the B.1.617.2 variant leading to 66% (37%+ 63% × 47%) remaining susceptible or an efficacy against infection of 34%. For simplicity, and given the huge uncertainties in the data, we assume a single reduction in efficacy irrespective of vaccine type, such that, the efficacy against B1.617.2 remains very similar for the two vaccines.

Table 2: Optimistic vaccine efficacy assumptions

	Pfizer/Moderna				**AstraZeneca**			
Efficacy	**1st Dose**		**2nd Dose**		**1st Dose**		**2nd Dose**	
against	B.1.1.7	B.1.617.2	B.1.1.7	B.1.617.2	B.1.1.7	B.1.617.2	B.1.1.7	B.1.617.2
Infection	70%	45%	90%	84%	70%	45%	90%	84%
Symptoms	70%	45%	90%	84%	70%	45%	90%	84%
Hosp Adm	85%	85%	95%	95%	85%	85%	95%	95%
Mortality	80%	80%	99%	99%	80%	80%	99%	99%
Transmission	50%	50%	50%	50%	50%	50%	50%	50%

We complement the default central set of vaccine efficacy assumptions with two others: an optimistic set of assumptions (Table 2); and a more cautious set of assumptions (Table 3). The optimistic set of assumptions are based upon the upper value of the range estimated by PHE against B.1.1.7 and B.1.617.2; extrapolating to missing data where appropriate. However, unlike the default assumptions, we do not rescale protection against severe illness (leading to hospital admission or death), but assume that B.1.617.2 and B.1.1.7 have the same efficacy.

Finally, we consider a more cautious set of efficacy assumptions (Table 3), where the efficacy values are based on the lower bound of the range estimated by PHE in Report 22. In keeping with the default model, we again assume that the vaccine efficacy against severe disease is lower, and is calculated by assuming that protection conditional on infection remains unchanged between the two variants.

Table 3: Cautious vaccine efficacy assumptions

	Pfizer/Moderna				**AstraZeneca**			
Efficacy	**1st Dose**		**2nd Dose**		**1st Dose**		**2nd Dose**	
against	B.1.1.7	B.1.617.2	B.1.1.7	B.1.617.2	B.1.1.7	B.1.617.2	B.1.1.7	B.1.617.2
Infection	55%	30%	70%	58%	60%	33%	70%	58%
Symptoms	55%	24%	85%	64%	55%	27%	70%	64%
Hosp Adm	75%	58%	90%	86%	75%	60%	90%	86%
Mortality	75%	58%	95%	93%	75%	60%	95%	93%
Transmission	40%	40%	40%	40%	40%	40%	40%	40%

Ideally, all the model parameters should be inferred separately for each of these vaccine efficacy assumptions, as the assumptions will impact the projected epidemic trajectory since December 2020. However, given that the epidemic has been generally declining since January 2021, the precise efficacy levels do not have a major impact on parameter inference (although they do substantially impact future waves). We therefore use a model where the parameters are inferred for the default assumptions only.

The three vaccine efficacies (for Pfizer, AstraZeneca and Moderna) are combined by taking the time-varying age-related weighted average based on the amount of the three vaccines used to date in the

UK. Moving forward we assume that those over 40 receive vaccines in the ratio 60% AstraZeneca, 30% Pfizer, 10% Moderna, while those under 40 are exclusively given Pfizer and Moderna. No account is given for the single dose Johnson and Johnson vaccine that has just been approved. All protective effects are assumed to begin 14 days after each dose of vaccine, although there is some data to suggest that the delay may be slightly longer for AstraZeneca and in older individuals.

Future vaccine rollout follows a Cabinet Office agreed scenario with an average of 2.15 million doses per week in England until the 25th July 2021 and then 2 million doses per week thereafter. This rollout speed, coupled with our assumptions about vaccine uptake across age-groups, means that first doses to the adult population (over 18) will be completed by 03 August 2021 and second doses will be completed by 28 September 2021. However, it is likely to be a further 2-3 weeks before the protection offered by these vaccines is fully realised, pushing maximal protection into October, by which point we generally predict that the third wave of infection has declined to very low levels. Uncertainty to the roll-out speed is also examined.

3) Controls, timings and estimates of R (excluding immunity). Our default scenario is to follow the timing of the existing roadmap, with Step 4 occurring on 21st June 2021. It has been impossible from the currently available data to reliably infer the true impact of Step 3, due to the strong confounding effects of the B.1.617.2 variant. The level of control in Step 3 is therefore modelled as a fixed reduction of that observed so far in 2021. There obviously exists considerable uncertainty about the level of control and the degree of social mixing that will occur in the early stages of Step 4, and this is the subject of extensive sensitivity analysis. Our default assumption is that there remains some level of control or natural hesitancy within the population, such that after Step 4 interactions do not return to pre-COVID levels.

The most natural way to characterise the level of control at any point in time is by measuring R excluding immunity: the value the reproduction number would take with a given set of controls if all individuals were susceptible to the virus. This differs for the B.1.617.2 and B.1.1.7 variants due to inherent differences in transmission, and for different regions of the country due to sociodemographic factors; here we report a simple average across all seven NHS regions. For the default assumptions, R excluding immunity for B.1.1.7 increases from approximately 1.27 (CI 1.16-1.38) during the main January-February lockdown, to 1.72 (CI 1.49-1.91) in Step 1 due to school reopening, to 1.87 (CI 1.66-2.07) after Step 2, to 2.45 (CI 2.32-2.59) after Step 3, and finally 3.6 (CI 3.42-3.76) after Step 4. For the B.1.617.2 variant these values are higher at 3.85 (CI 3.63-4.1) after Step 3, and 5.66 (CI 5.4-5.95) after Step 4, highlighting the new variant's competitive advantage. In the extreme case where after Step 4 we return to pre-COVID behaviour then the R excluding immunity for B.1.617.2 rises further to 6.68 (CI 6.37-7.02).

4) Seasonality. Like many respiratory infections, we expect there to be a considerable degree of seasonality, both due to climatic factors (which affect the virus's ability to persist) but also in terms of behaviour (less indoor mixing and greater ventilation in the summer). There are limited data on this aspect of transmission [5], hence different levels of seasonality are examined in Fig. 17. One inherent difficulty with incorporating seasonal forcing into future predictions is the absence of seasonal forcing in our historic estimates – therefore the values of NPI control estimated over the summer of 2020 could have been inflated by the impact of seasonal forces. We model the action of seasonal forcing as a sine wave perturbation to the transmission rate with a peak in mid-February and a trough in mid-August - based on the peak and trough of specific humidity [5]. We report the level of seasonality (ϕ) as the drop in transmission over the summer relative to the peak in the winter months:

$$\beta(t) = \beta_0 \left[1 - \tfrac{1}{2}\phi - \tfrac{1}{2}\phi \sin(2\pi t + \omega)\right]$$

Based on available data [5], 10% seasonality would not be an unreasonable assumption, but the value

could be larger if good summer weather has a substantive impact on behaviour, reducing indoor mixing. Throughout this document, we have used 10% seasonality ($\phi = 0.1$) as our default assumption.

1 Default dynamics

We consider all four steps of the roadmap and analyse the impact of this relaxation upon infection (both symptomatic and asymptomatic), hospital admissions, hospital occupancy and daily deaths. The results are summarised in Fig. 2 - Fig. 5 below. It is worth noting that for all estimated quantities, such as R excluding immunity, we quote means and 95% credible intervals (CI) from the MCMC inference scheme; for quantities that are derived from the simulations, such as peak hospital admissions, we quote means and the associated 95% prediction intervals (PI) which capture the distribution of values that are generated by passing the parameter uncertainty through the epidemic simulation.

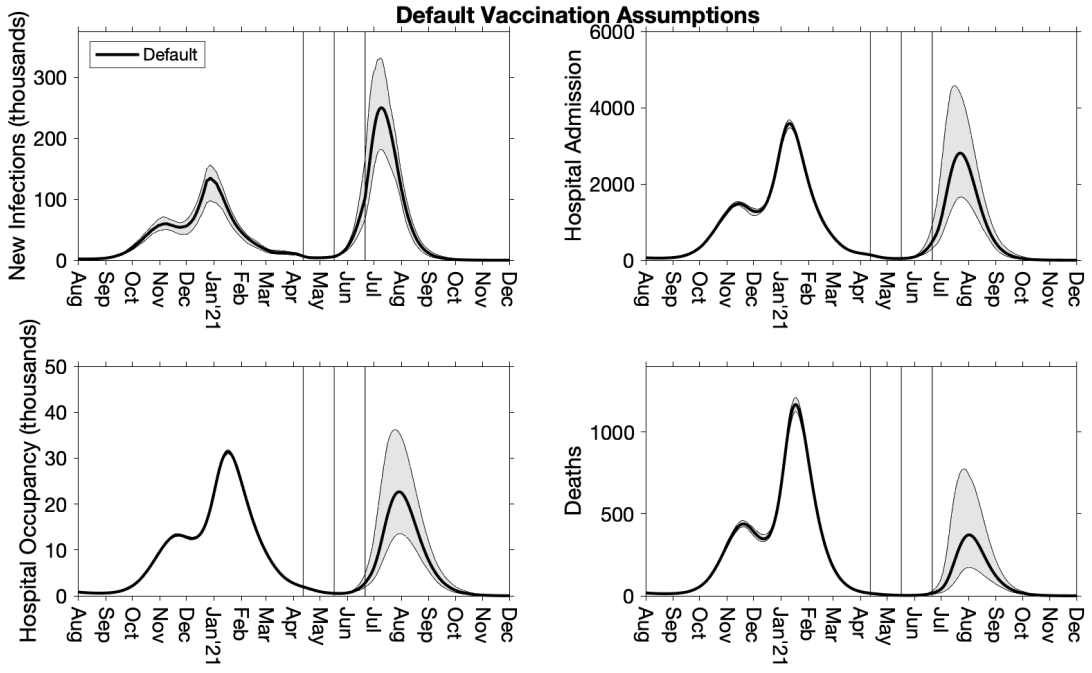

Fig. 2: New daily infections both symptomatic and asymptomatic (top left), daily hospital admissions (top right), hospital occupancy (bottom left) and daily deaths (bottom right) for England under the default assumptions for the relaxation roadmap, and using the *default* vaccine assumptions. Models using the default vaccine assumptions are generally shown in the top plot of all sensitivity analyses. Vertical lines denote the timing of Steps 2, 3 and 4 of the roadmap; shaded regions show the 95% prediction intervals (containing 95% of all simulations) while the black lines show the means.

Fig. 2 shows the projected dynamics for both the second and third wave for default assumptions about vaccine efficacy (Table 1); results for the optimistic and cautious vaccine efficacy assumptions are shown in Fig. 4 and Fig. 5. Here we see that the third wave is projected to be slightly greater in height than the second wave peak (in late December 2020) in terms of new infections. The overwhelming majority of these infections are due to the B.1.617.2 variant, which we expect to dominate. Many of these are in younger individuals (who will not be fully protected by the vaccine, but have a lower risk of severe sequelae) or in older individuals (who are protected against more severe outcomes by vaccine efficacy against hospital admission or mortality). Consequently, the levels of hospital admissions, hospital occupancy and deaths are projected to be lower than observed in the second wave, although there are wide confidence intervals.

For this default set of parameters and default assumptions about the vaccine, the projected peak number of hospital admissions is 2850 (PI 1530-4800), which occurs on 22 July (PI 16 July-28 July), and in total we expect 131,000 (PI 78,300-221,000) admissions from June 2021 until the end of the

simulations in June 2022. Deaths are relatively lower due to the protection offered by the vaccine, but we still project 17,100 (PI 8490-36,800) over the third wave (June 2021 - June 2022).

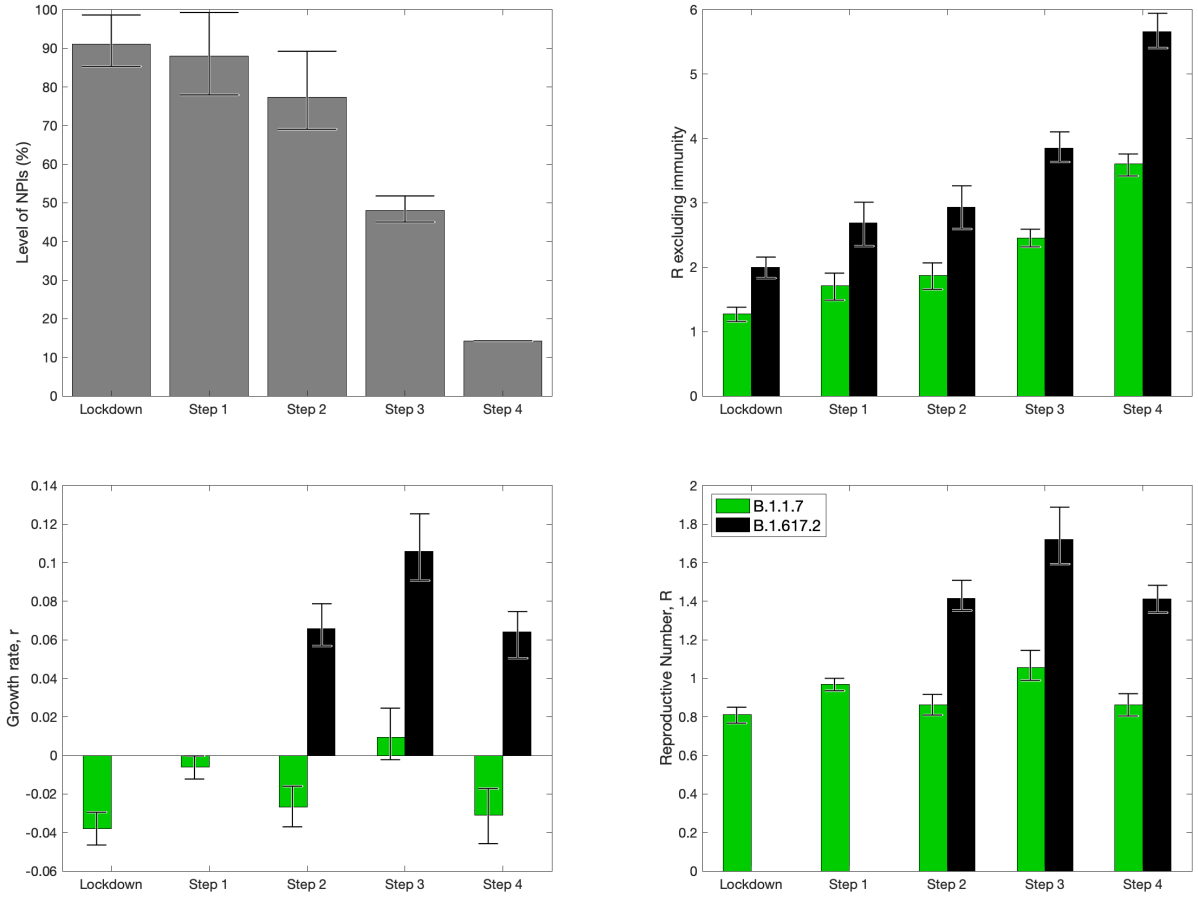

Fig. 3: Change in the estimated NPI restrictions (top left) and hence the change in the value of R excluding immunity (top right) through different step phases of the default model. This highlights the non-linear dependence of R excluding immunity on the level of NPI restrictions and how population-level immunity is key in translating this to an instantaneous growth rate (bottom left) and reproduction number, R (bottom right).

The level of restrictions in lockdown (measured as an average during January and February 2021) and Steps 1 and 2 are now estimated from the current data, by fitting the model to the evolving epidemic. Step 2 is now firmly based on the latest data and has a growth rate that is negative for B.1.1.7 (shown in green in Fig. 3) but positive for B.1.617.2 (shown in black) . We assume that NPI restrictions decline further in Steps 3 and 4, which leads to an increase in the reproduction number excluding immunity, and an increase in the realised growth rate (r) although this is also influenced by the changing levels of population immunity. The level of NPIs in Step 3 is taken as a fraction of the values during the January lockdown, while the level in Step 4 is by default a constant value. It is clear that the B.1.617.2 variant (shown in black in Fig. 3) has a clear advantage over the B.1.1.7 variant (shown in green); in particular, R excluding immunity in Step 4 for B.1.617.2 is 5.66 (CI 5.4-5.95) whereas for B.1.1.7 it is only 3.6 (CI 3.42-3.76). In terms of the unfolding epidemic, both variants have their highest growth during Step 3 (as extra immunity is accrued by Step 4) leading to estimates of the reproduction number R (at the start of Step 3) of 1.06 (CI 0.99-1.15) and 1.72 (CI 1.59-1.89) for the B.1.1.7 and B.1.617.2 variants respectively. We note that the growth rate for B.1.1.7 in the early stages of Step 4 is negative ($R < 1$) which is attributable to the number of cases of B.1.617.2 in

Step 3 leading to substantial population immunity.

To contrast with the default vaccine efficacy parameters, we simulate the same dynamics assuming either more optimistic parameters (Fig. 4) or more cautious parameters (Fig. 5) for vaccine efficacy. We find that the optimistic efficacy parameters generate a smaller third wave compared to the default, although the total number of infections is still large. Most notably, the change in vaccine efficacy against death from a central estimate of 96% (two doses against B.1.617.2) to an optimistic estimate of 99%, would reduce deaths to a quarter even if the projected outbreaks were otherwise equal. To be more quantitative, while the default assumptions lead to 131,000 (PI 78,300-221,000) hospital admissions and 17,100 (PI 8490-36,800) deaths in the projected third wave (June 2021 - June 2022), the optimistic assumptions reduces this to 82,400 (PI 46,500-145,000) and 6320 (PI 3280-13,500) respectively.

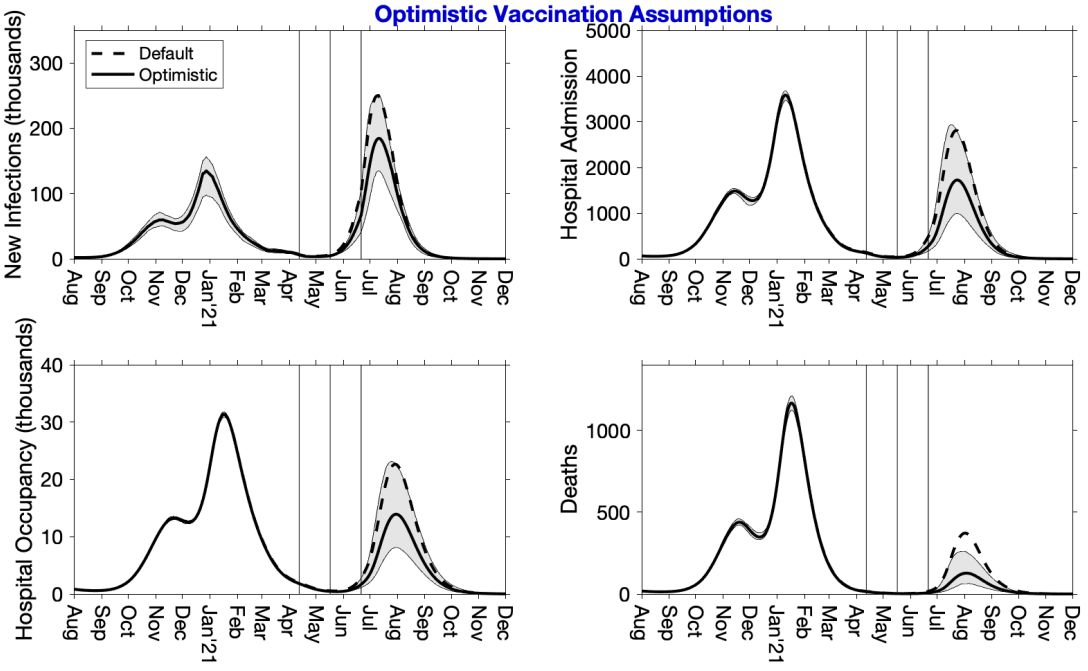

Fig. 4: New daily infections both symptomatic and asymptomatic (top left), daily hospital admissions (top right), hospital occupancy (bottom left) and daily deaths (bottom right) for England under the default assumptions for the relaxation roadmap, and using the *optimistic* vaccine assumptions (solid line) compared to the default efficacy assumptions (dashed line, often overlapping with the solid line). Vertical lines denote the timing of Steps 2, 3 and 4 of the roadmap; shaded regions show the 95% prediction intervals for the optimistic simulations (containing 95% of all simulations) while the black lines show the means. Models using the optimistic vaccine assumptions are generally shown to the lower left in all sensitivity analyses that follow.

The more cautious vaccine assumptions (given in Table 3 and shown in Fig. 5) have a far more substantive impact, firstly because all the vaccine efficacy values are lower and secondly because B.1.617.2 possesses a significant amount (17%) of vaccine escape against infection for two doses of the vaccine. In particular, peak hospital admissions are now raised to 5990 (PI 3810-8910) and we project 267,000 (PI 194,000-384,000) hospital admissions over the third wave. More striking is the impact on deaths, where the departure from the default assumption results is more extreme; under these assumptions we expect a peak daily deaths of 1780 (PI 932-3230) (compared to 379 (PI 166-812) for the default assumptions) and a total of 72,400 (PI 44,100-128,000) (compared to 17,100 (PI 8490-36,800)) deaths over the third wave (June 2021 - June 2022).

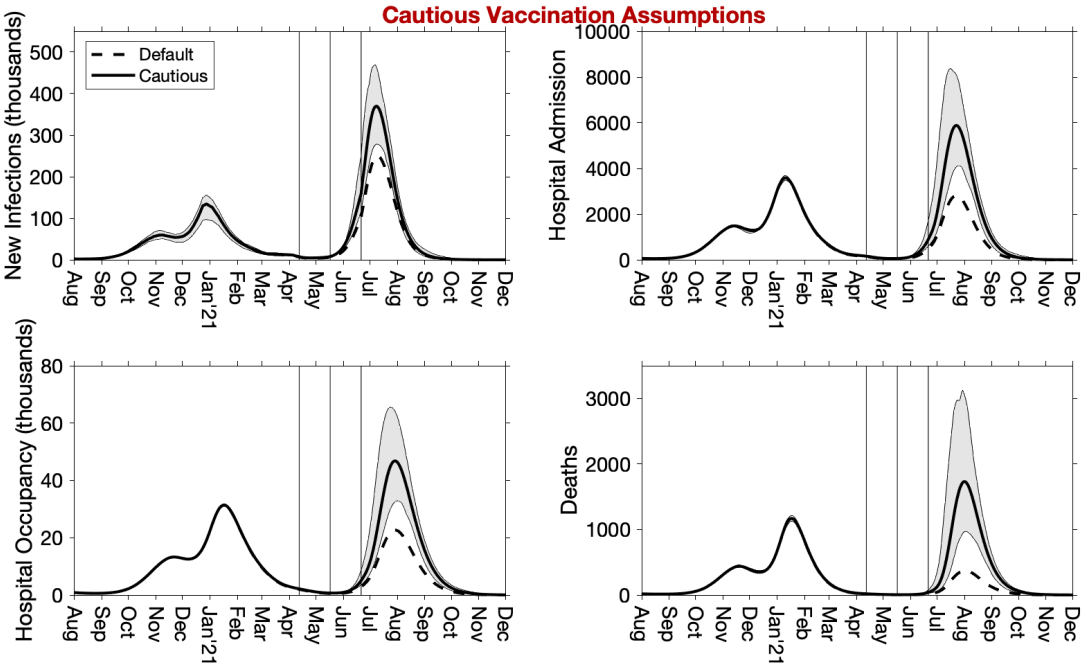

Fig. 5: New daily infections both symptomatic and asymptomatic (top left), daily hospital admissions (top right), hospital occupancy (bottom left) and daily deaths (bottom right) for England under the default assumptions for the relaxation roadmap, and using the *cautious* vaccine assumptions (solid line) compared to the default efficacy assumptions (dashed line). Vertical lines denote the timing of Steps 2, 3 and 4 of the roadmap; shaded regions show the 95% prediction intervals for the cautious simulations (containing 95% of all simulations) while the black lines show the means. Models using the cautious vaccine assumptions are generally shown to the lower right in all sensitivity analyses.

Compared to the default model, the greatest disparity and the greatest cause for concern comes from the cautious efficacy assumptions. In general, the prediction intervals for the optimistic assumptions overlap the mean for the default model while the same is not generally true for the more cautious assumptions. The extreme differences in the projected number of deaths is due to the considerable uncertainty in the estimates of vaccine efficacy. Throughout the sensitivity analysis that follows we concentrate on the default assumptions, only reporting values in the text from this model, however numerical values for the optimistic and cautious assumptions are given in Table 5 and Table 6 respectively which can be compared to the values in Table 4.

2 Sensitivity Analysis

We now conduct extensive sensitivity analysis, focusing on: the transmission advantage of the B.1.617.2 variant; the inherent uncertainties surrounding Step 4; the scale and speed of vaccine deployment and the magnitude of seasonal forcing. In each of the sensitivity analyses, we use all three sets of vaccine efficacy assumptions (default, optimal and cautious) and focus on the number of daily hospital admissions as a key quantity of epidemiological interest. We show the wave of hospital admissions in the third wave together with horizontal lines for the observed peaks of wave 1 and wave 2, to aid visual comparison.

2.1 Transmission advantage of B.1.617.2

Currently, the greatest unknown is the transmission advantage of B.1.617.2 compared to B.1.1.7. There has been considerable effort placed into quantifying this advantage, but there remains considerable uncertainty due to the spatially localised nature of B.1.617.2 focal hot-spots and the additional control measures that have been put in place in the worst affected regions. In the default model, we inferred the additional transmission advantage of B.1.617.2 over B.1.1.7 by factoring in the growth in the total number of cases (of all variants) and the ratio of S-gene target failures (a signature of B.1.1.7 infection) to S-gene positive (potentially indicating B.1.617.2) infections. This approach estimates a 56% (CI 34-81%) transmission advantage for B.1.612.7, with the wide uncertainty attributable to strong regional heterogeneity (Fig. 1); during Step 2, this advantage equates to an R number of 1.41 (CI 1.35-1.51) compared to an R number of 0.863 (CI 0.81-0.917) for B.1.1.7.

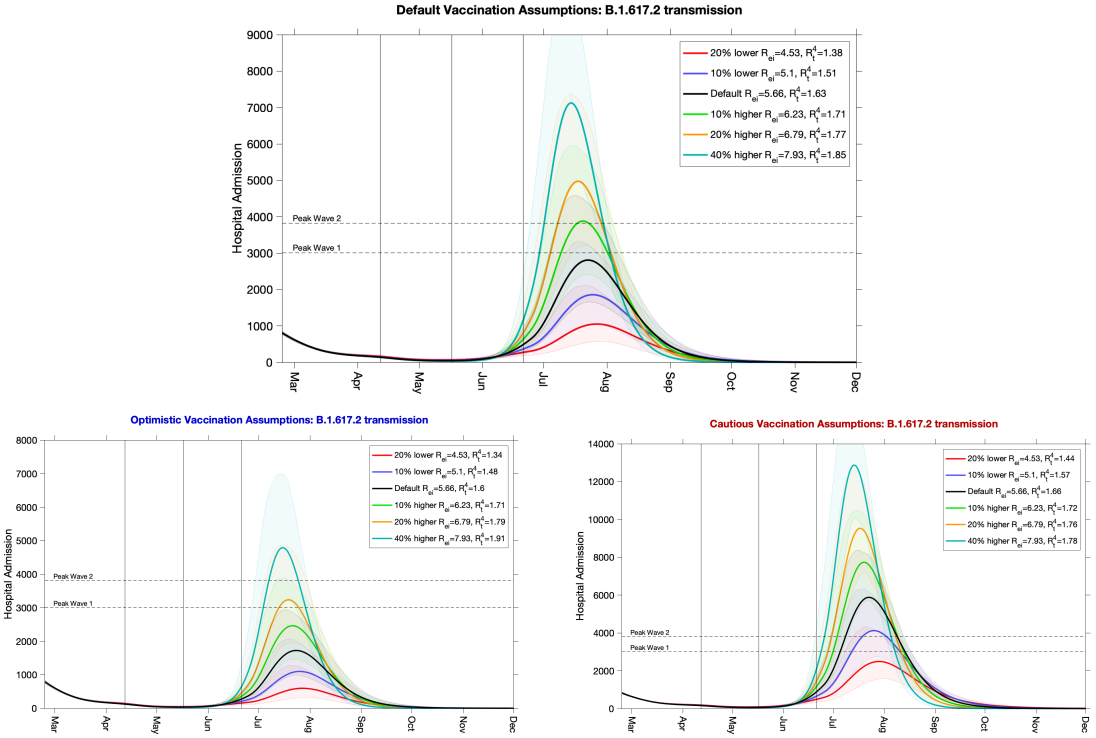

Fig. 6: Impact of assuming higher or lower transmission of B.1.617.2 on the number of daily hospital admissions in England. The panel on the top is for the default vaccine efficacy assumptions, the panel on the left is for the optimistic efficacy assumptions while the panel on the right is for the cautious efficacy assumptions. In the legend we give the value of R excluding immunity for B.1.617.2 and the reproduction number R_t at the start of Step 4 for the B.1.617.2 variant. Vertical lines are the dates of Steps 2, 3 and 4. We note that initial levels of B.1.617.2 have been rescaled for each transmission level to achieve a better level of fit to the case and hospital admission data.

There have been a wide range of estimates of the competitive advantage of B.1.617.2 – which incorporates both the inherent transmission advantage and any advantage gained by partial vaccine escape. Some of these predict a greater advantage than is inferred by our approach, hence we consider parameter sets where B.1.617.2 has an increased or decreased transmission rate (which in turn changes the relative transmission advantage). For these scenarios, a 10% increase in transmission speed roughly equates to a 0.5 increase in R excluding immunity. Hence for an additional 20% extra transmission (such that B.1.612.7 has a 88% (CI 61-117%) advantage over B.1.1.7), R excluding immunity increases from 5.66 (CI 5.4-5.95) to 6.79 (CI 6.42-7.09) (estimated for the 12% NPI controls in Step 4), whereas if we assume an additional 40% increase in transmission (such that B.1.612.7 has a 119% (CI 88-153%) advantage over B.1.1.7) then R excluding immunity jumps to 7.9 (CI 7.49-8.27). Fig. 6 shows the epidemic wave of hospital admissions when assuming greater or less transmission from B.1.617.2, a higher transmission advantage leads to an earlier and higher peak.

Fig. 7 shows the same data as Fig. 6 but focuses on more recent dynamics and shorter-term projections (June and July 2021). This zoomed in figure clearly highlights that there is expected to be minimal separation between the number of hospital admissions, with wide overlapping confidence intervals between all scenarios, until the end of June. The structure of this figure also provides an easy comparison to output from SPI-M's Medium-Term Projections - where different R numbers are assumed to hold after 21st June. (An alternative plot showing the dynamics of daily incidence over the same time scale is given in Appendix A, Fig. 21).

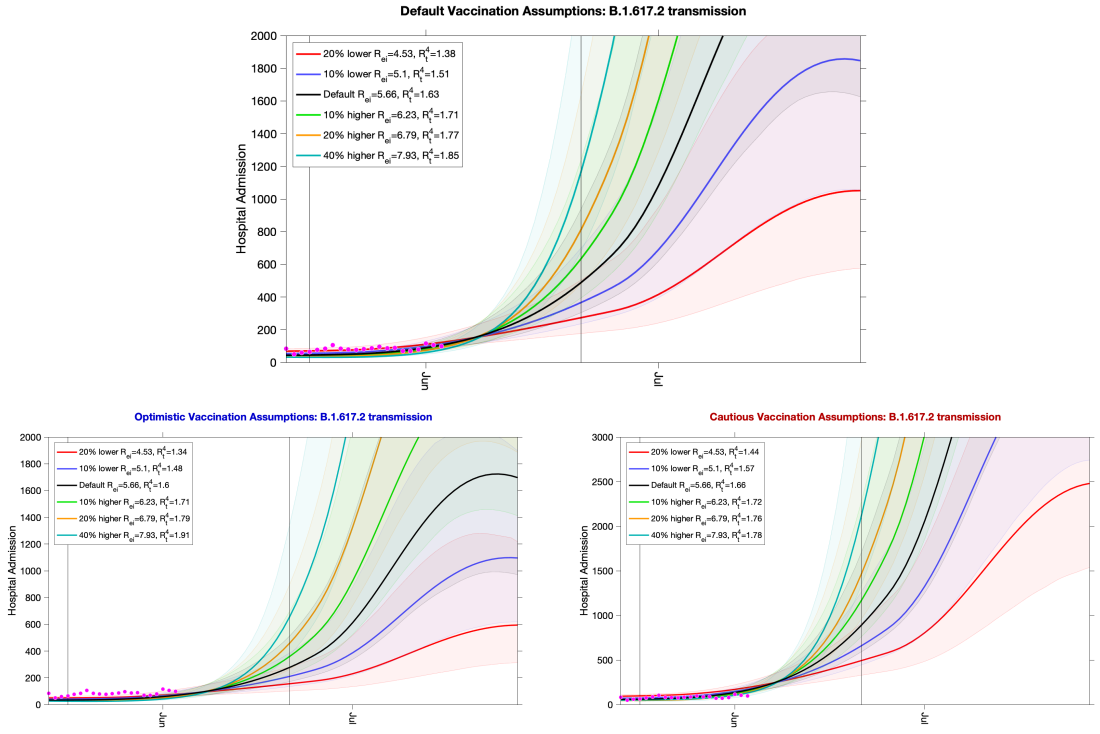

Fig. 7: Impact of assuming higher or lower transmission of B.1.617.2 on the number of daily hospital admissions in England. The panel on the top is for the default vaccine efficacy assumptions, the panel on the left is for the optimistic efficacy assumptions while the panel on the right is for the cautious efficacy assumptions. In the legend we give the value of R excluding immunity for B.1.617.2 and the reproduction number R_t at the start of Step 4 for the B.1.617.2 variant. Vertical lines are the dates of Steps 3 and 4, pink dots are hospital admission data for England. We note that initial levels of B.1.617.2 have been rescaled for each transmission level to achieve a better level of fit to the case and hospital admission data.

An alternative approach is to focus on the total hospital admissions during the third wave, June 2021

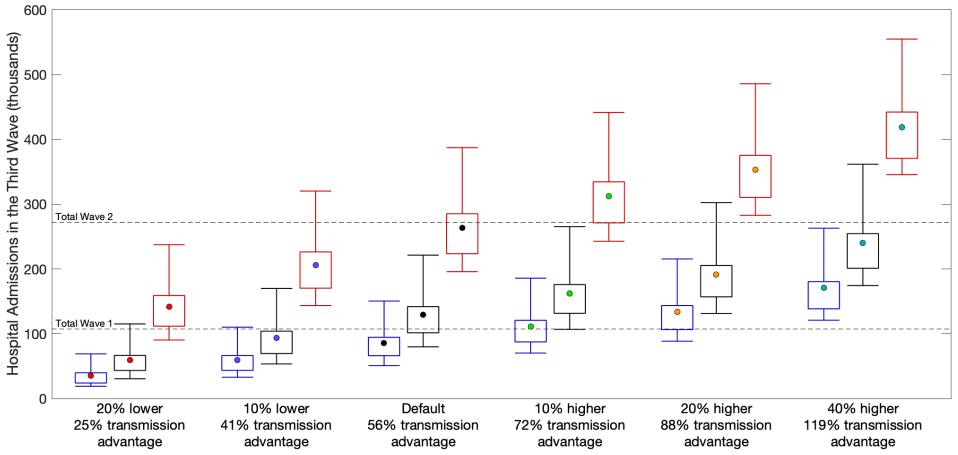

Fig. 8: Impact on the total number hospital admissions during the third wave (June 2021 - June 2022) of assuming higher or lower transmission of B.1.617.2. Blue, black and red bars and whiskers are for the optimistic, default and cautious vaccine efficacy assumptions, respectively. The total size of waves 1 and 2 is shown by the horizontal lines for comparison. For each value of higher or lower transmission, we also state the transmission advantage of B.1.617.2 over B.1.1.7 on the x-axis.

- June 2022 (Fig. 8).Even relatively small changes in the transmission advantage of B.1.617.2 translate into a considerable change in hospital admissions and deaths. If the transmission rate is 20% lower than we infer, we expect to experience 59,200 (PI 30,500-115,000) hospital admissions over the third wave and 5570 (PI 2490-13,000) deaths. However, when the growth rate is 20% higher we project higher total hospital admissions at 194,000 (PI 130,000-300,000) over the third wave and higher total deaths at 33,500 (PI 18,300-67,000).

Finally, if we consider the extreme but plausible assumption that the transmission of B.1.617.2 is increased by 40% from our inferred values, we project 243,000 (PI 173,000-358,000) total hospital admissions and 51,900 (PI 30,600-98,200) deaths over the entire third wave (June 2021 - June 2022). These high values are a considerable cause for concern.

2.2 Sensitivity to Assumptions about Step 4

Here we consider sensitivity to various measures associated with Step 4 of the relaxation roadmap. These are generally elements that are under human control and therefore reflect different decisions that can be made.

2.2.1 Sensitivity to NPIs and transmission in Step 4

A key unknown (and unknowable) quantity is the level of control and mixing after Step 4. In part this depends on the reaction of the general public and the level of precautions taken on average (whether a significant proportion of individuals still take precautionary actions and maintain social distancing). We capture this with a single NPI parameter which incorporates both legislative rules and human reaction. We therefore consider a wide spectrum of values for the level of NPIs during Step 4, from 0 (which equates to pre-COVID levels) through 13% (which is the default) and as high as 50%. As a comparison, Step 3 is estimated to be 48% (CI 45-51.8%).

For each level of NPI we show in the figure legend the R excluding immunity for the B.1.617.2 variant and the projected reproduction number R_t at the start of Step 4. The values of R excluding immunity for B.1.617.2 range from 6.68 (CI 6.37-7.02) in the absence of controls to 3.51 (CI 3.2-3.75) when the

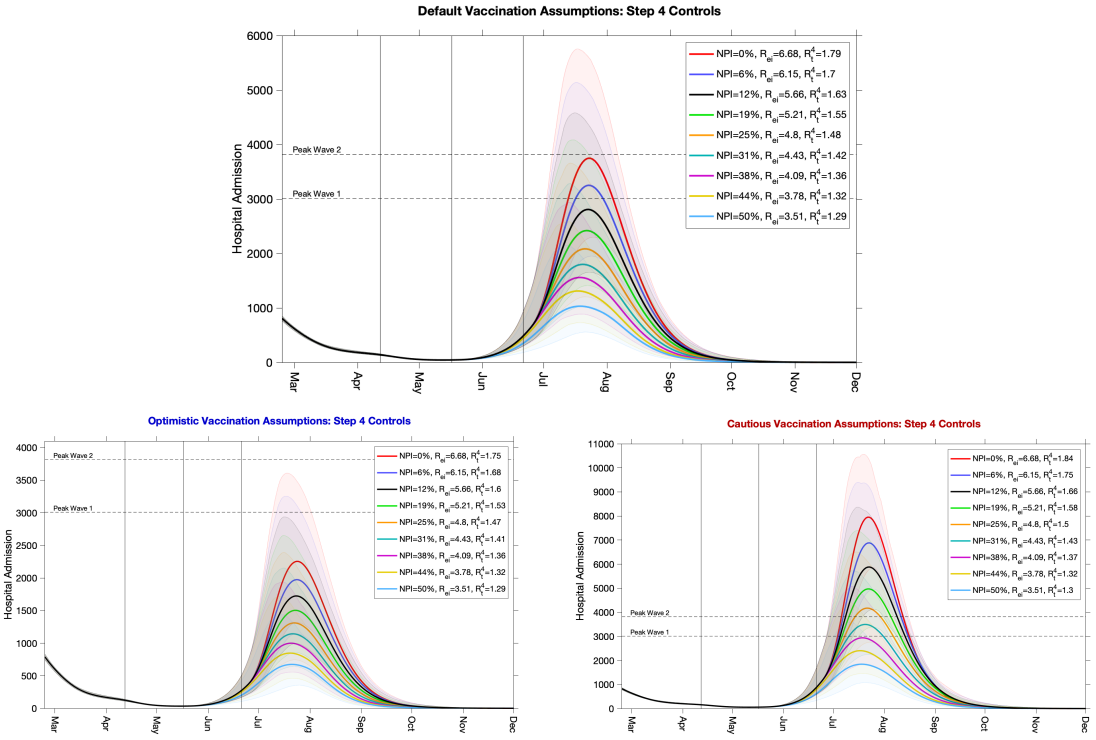

Fig. 9: Impact of different levels of NPI control in Step 4 (NPI=12% is the default) on the number of daily hospital admissions in England. The panel on the top is for the default vaccine efficacy assumptions, the panel on the left is for the optimistic efficacy assumptions while the panel on the right is for the cautious efficacy assumptions. In the legend we give the value of R excluding immunity and the reproduction number R_t for the B.1.617.2 variant associated with that level of NPIs. Vertical lines are the dates of Steps 2, 3 and 4.

NPIs are at 50%. Given that vaccination does not impact R excluding immunity, the values for the three vaccine efficacy assumptions generate identical values, although R_t at the start of Step 4 is larger for the more cautious vaccine efficacy assumptions.

A summary of values is given in Table 4, Table 5 and Table 6, but for the default vaccine efficacy assumptions the peak hospital admissions range from 3800 (PI 2110-6140) for 0% NPIs to 1070 (PI 536-2210) for 50% NPIs. This peak of hospitalisations for the zero control and cautious vaccine efficacy assumptions is expected to exceed the peak height of the second wave, while the 95% prediction intervals (which captures the variability of the simulations) extend far higher.

2.2.2 Timing of Step 4

One potential mechanism for mitigating the worst impacts of the new variant (B.1.617.2) is to delay Step 4, keeping the control levels as set by Step 3 for longer. This has the advantage that it leads to a more gradual increase in cases and does not realise the lowest levels of control until greater population level immunity has developed. Here we assume that during Step 3 R excluding immunity is approximately 3.85 (CI 3.63-4.1), this increases to 5.66 (CI 5.4-5.95) after Step 4, which corresponds to 12% NPIs still being in place.

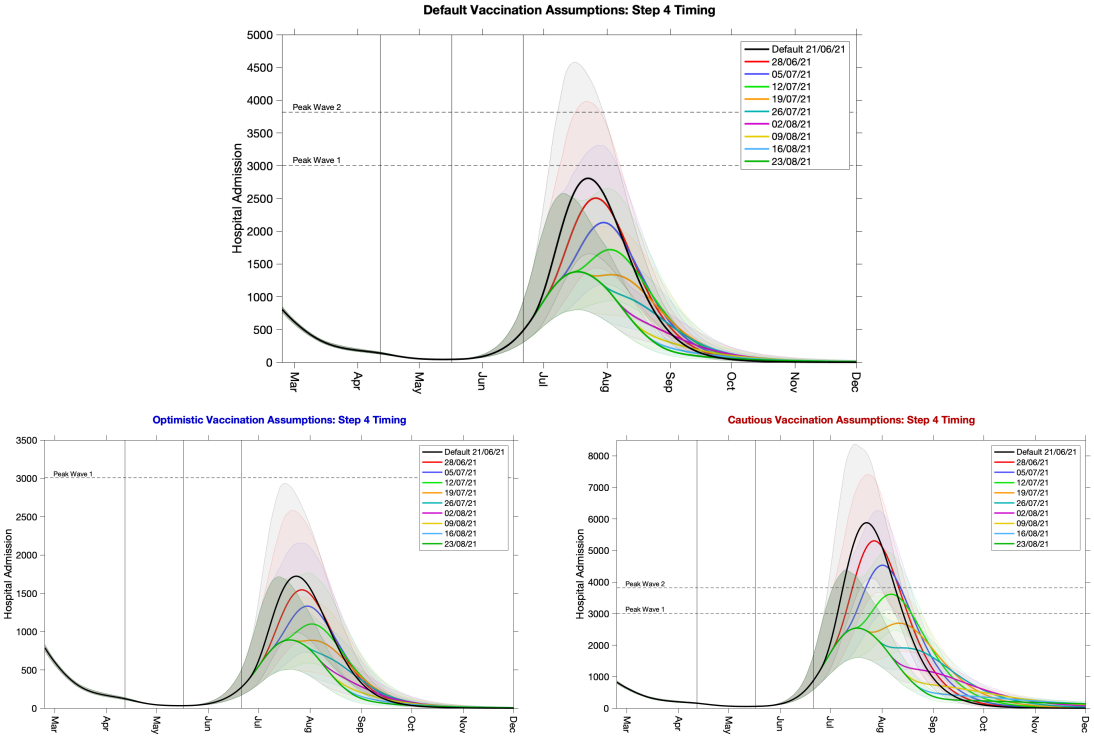

Fig. 10: Impact of different delays to the start of Step 4 on the number of daily hospital admissions in England. The panel on the top is for the default vaccine efficacy assumptions, the panel on the left is for the optimistic efficacy assumptions while the panel on the right is for the cautious efficacy assumptions. Vertical lines are the dates of Steps 2, 3 and 4.

Delaying Step 4 has a dramatic impact on the projected epidemic (Fig. 10); all curves follow the same basic trajectory until Step 4 occurs so we see sequential departures from the underlying 'Step 3 only' epidemic. Delaying Step 4 into August or beyond minimises the peak number of hospital admissions to 1420 (PI 764-2640), although even longer delays lead to the lowest number of hospital admissions and deaths. The impact of the delay on the total number of hospital admissions over the entire third wave (June 2021 - June 2022) is depicted in Fig. 13.

2.2.3 Two steps to complete lifting of restrictions

It is clear that eventually there must be a cessation to control measures. In the default setting we assume some level of control after Step 4 (NPI=12%) leading to R excluding immunity of 5.66 (CI 5.4-5.95) for B.1.617.2. Here we consider a scenario in which *all* controls are removed on 21st June 2021 (NPI=0%, R excluding immunity is 6.68 (CI 6.37-7.02)- as shown in Fig. 9, red curve), and compare this with a two step process consisting of Steps 4a and 4b (Fig. 11). Step 4a is half way between Step 3 and no control (such that the level of NPI is 24% (CI 22.5-25.9%) and R excluding immunity is 5.05 (CI 4.83-5.31)) and Step 4b, which occurs 5 weeks after Step 4a, is the complete lifting of controls

(NPI=0%). We consider three timings of the two-step model, with Step 4a commencing on 21st June (blue line), 26th July (green line) or 30th August (orange line).

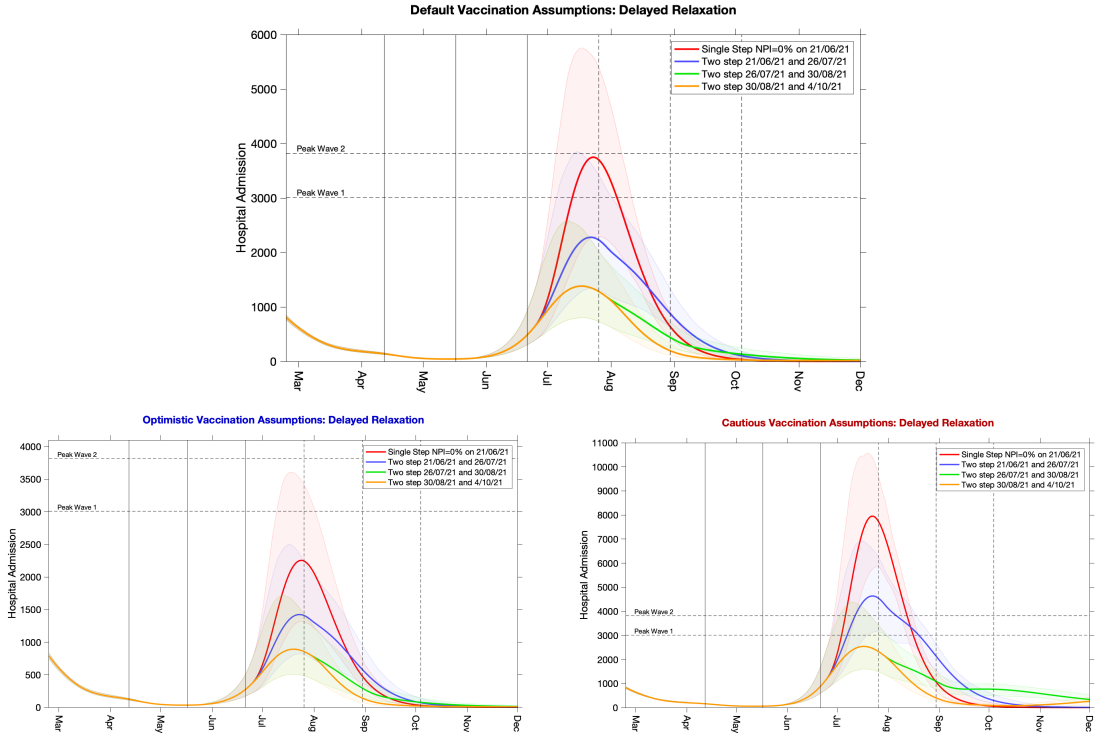

Fig. 11: Impact of different patterns to Step 4 relaxation on the number of daily hospital admissions in England. Four scenarios are examined: Single step, NPI=0% on 21st June (red); Two steps, NPI=24% on 21st June, NPI=0% on 26th July (blue); Two steps, NPI=24% on 26th July, NPI=0% on 30th August (green); and Two steps, NPI=24% on 30th August, NPI=0% on 4th October (orange). The panel on the top is for the default vaccine efficacy assumptions, the panel on the left is for the optimistic efficacy assumptions while the panel on the right is for the cautious efficacy assumptions. Solid vertical lines are the dates of Steps 2, 3 and 4, dashed vertical lines are the other dates of simulated Step 4a and Step 4b.

The first Step 4 only scenario leads to peak hospital admissions of 3800 (PI 2110-6140) per day and a total of 165,000 (PI 106,000-263,000) hospital admissions between June 2021 and June 2022, while the two-model approach (with Step 4a on 21st June) generates a peak of 2320 (PI 1230-3920) per day and a total of 130,000 (PI 79,400-216,000) hospital admissions. When delaying the start of Step 4a by either five or ten weeks, this further reduces the total number of hospital admissions in the third wave to 86,300 (PI 49,300-153,000) or 73,700 (PI 41,000-134,000). Under the more cautious vaccination assumptions, we observed that the most delayed two-step relaxation assumptions (orange line) can give rise to two smaller waves of hospital admissions, one in the summer followed by a later wave in the winter driven by seasonal effects.

We can extend this analysis to consider a range of NPI control levels during Step 4a (starting on 21st June 2021) and a range of starting dates for Step 4b (Fig. 12). Here we show the peak daily admissions (top left), the peak hospital occupancy (top right) and total hospital admission (bottom) over the third wave (from June 2021 to June 2022). All three of these measures show very similar patterns as the level and timing of controls varies. As expected, longer delays to Step 4b and greater control in Step 4a lead to the lowest peaks and total number of hospital admissions; however, the advantage of delaying Step 4b beyond the middle of September 2021 is marginal (as by this point we estimate that the vast majority of the adult population who wish to be vaccinated will have received their second dose).

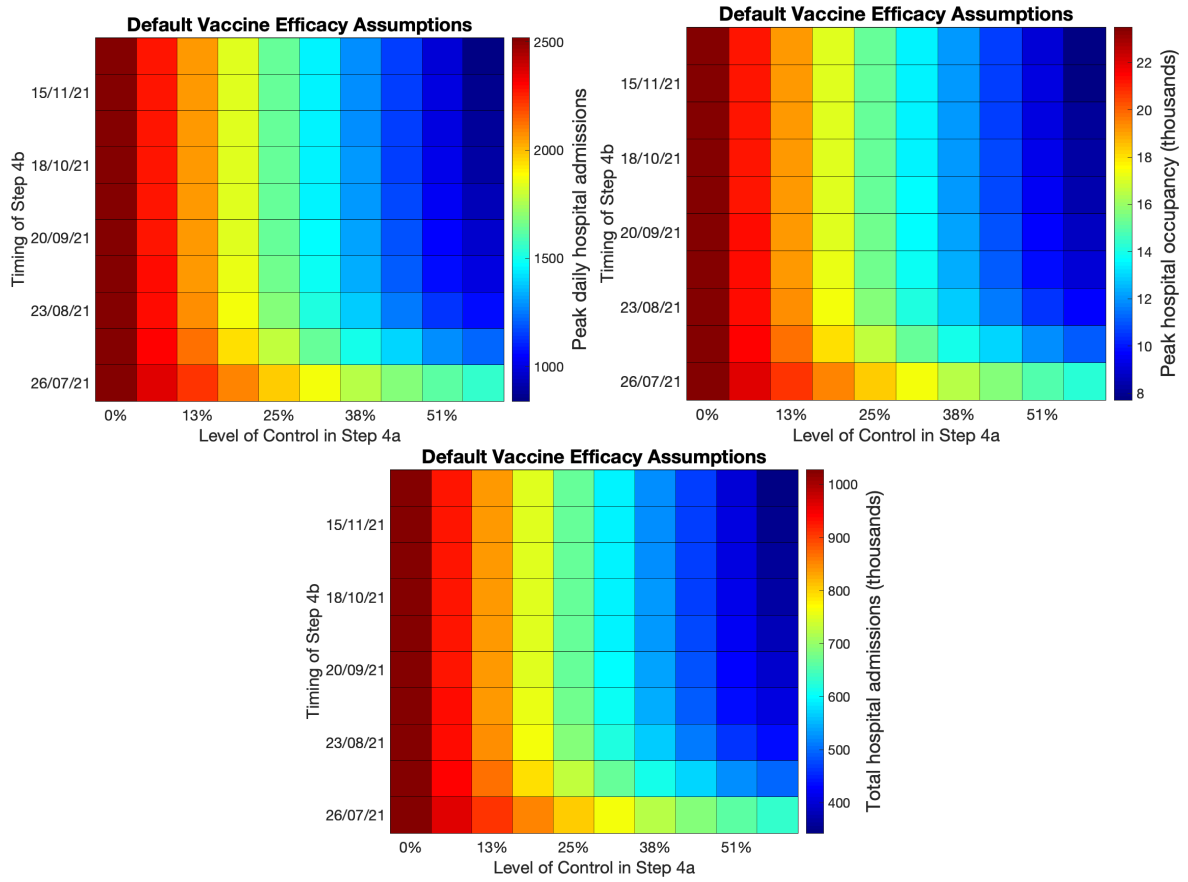

Fig. 12: Impact of changes to Step 4 on peak daily hospital admissions (top left), peak hospital occupancy (top right) and total hospital admissions over the third wave (bottom) for the default vaccine efficacy assumptions. The x-axis shows the level of control after Step 4a on 21st June 2021, for comparison the level of NPI control in Step 3 is 48% (CI 45-51.8%); the y-axis is the date at which Step 4b occurs when all controls are lifted (NPI=0%).

2.2.4 Comparison of all measures associated with Step 4

Considering the full range of sensitivities associated with Step 4 that we have simulated so far, we plot the total number of hospital admissions projected for the third wave (June 2021 - June 2022) showing the means (coloured marker, with the colour matching that used in the figures above) together with the interquartile and 95th percentiles (Fig. 13). Results for the default assumptions about vaccine efficacy are shown with black bar and whisker plots, results for the optimistic and cautious assumptions are in dark blue and red respectively. Given the behaviour after Step 4 is (partially) controllable, it is important to gauge the different restrictions against each other. While maintaining high NPIs leads to the lowest total levels of hospital admission, it is obviously not a long-term solution. Of those strategies that achieve complete relaxation of controls (NPI=0%, shown with a square in Fig. 13) adopting a delayed two-step process leads to the fewest hospitalised cases.

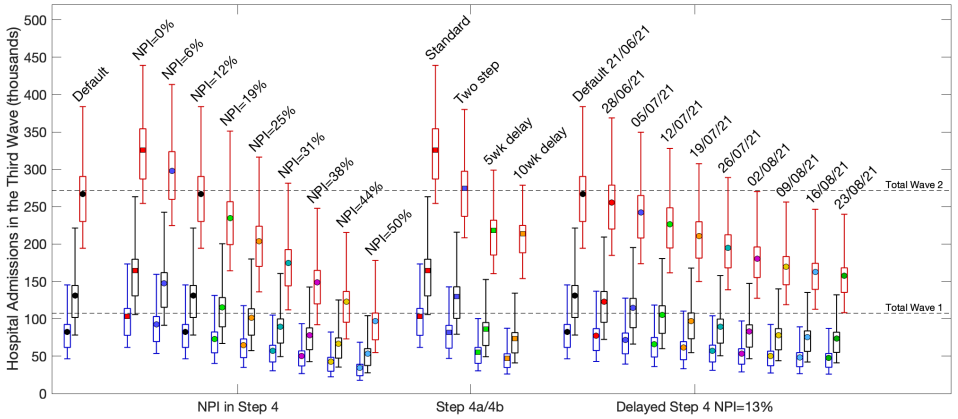

Fig. 13: Projected total number of hospital admissions from 1st June 2021 to 30th June 2022, corresponding to the profiles shown in Fig. 9 - Fig. 11. Blue, black and red bars and whiskers are for the optimistic, default and cautious vaccine efficacy assumptions, respectively. The coloured marker indicates the mean, and is a square if the controls modelled reach the pre-COVID state of NPI=0% or a circle otherwise.

2.3 Sensitivity to Assumptions about Vaccination

Although we consider sensitivity to vaccine efficacy throughout this work (contrasting the default, cautious and optimistic assumptions), there are two other elements where there is also considerable uncertainty: the future speed of vaccine deployment and the historic level of vaccine uptake.

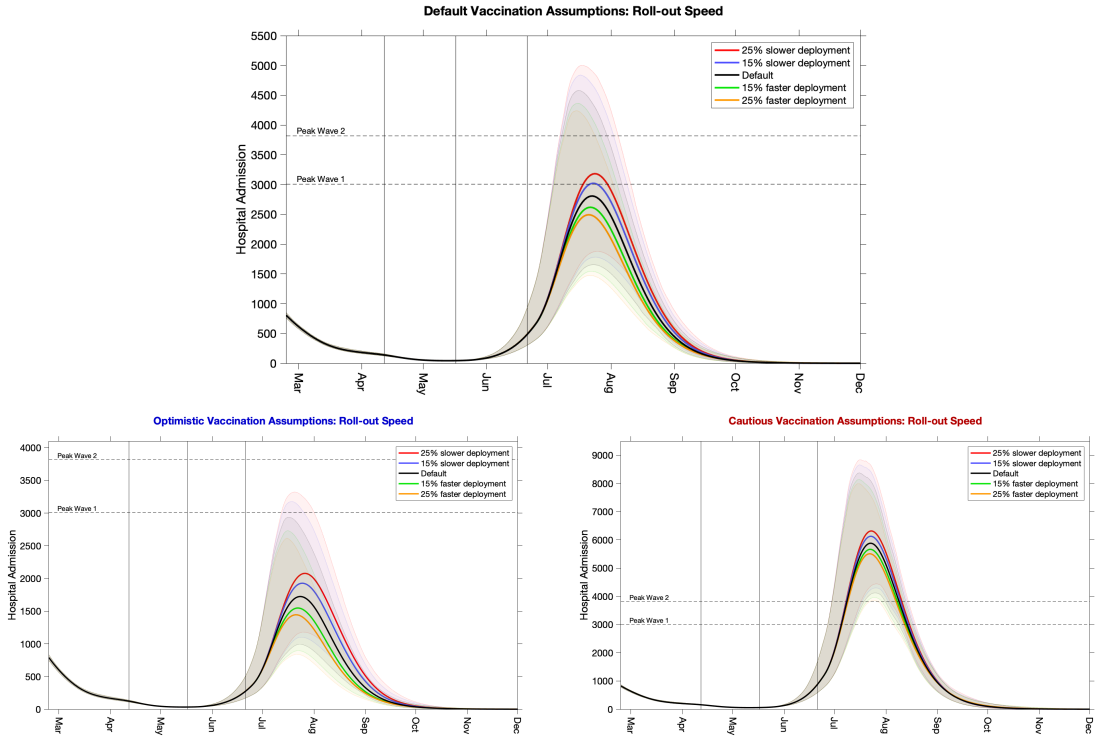

Fig. 14: Impact of the speed of future vaccine deployment on the number of daily hospital admissions in England. The panel on the top is for the default vaccine efficacy assumptions, the panel on the left is for the optimistic efficacy assumptions while the panel on the right is for the cautious efficacy assumptions. Vertical lines are the dates of Steps 2, 3 and 4.

2.3.1 Vaccine Rollout Speed

The speed of vaccine deployment has varied dramatically over the course of the vaccine programme, reaching over 760,000 individuals vaccinated in one day on 20th March 2021 but averaging around 400,000 per day over the last three months. While the default vaccine deployment schedule of approximately 2.15 million doses per week (310,000 per day) until 25th July and then 2 million per week (290,000 per day) thereafter is the most plausible rollout over the coming months, it is important to consider variations to this pattern.

Rapid deployment of vaccine, while still of considerable benefit, does not have the same magnitude of impact that it did in previous assessments of the roadmap. This is attributable to the large proportion of the population that have already been vaccinated, such that different roll-out speeds do not greatly affect the number of more vulnerable individuals that will have received their second dose of vaccine before the third wave. A 25% faster deployment reduces the peak of the third wave to 2530 (PI 1370-4380) hospital admissions per day, whereas a 25% slower deployment increases the peak to 3230 (PI 1720-5330) hospital admissions per day.

2.3.2 Vaccine Uptake in Older Age-groups

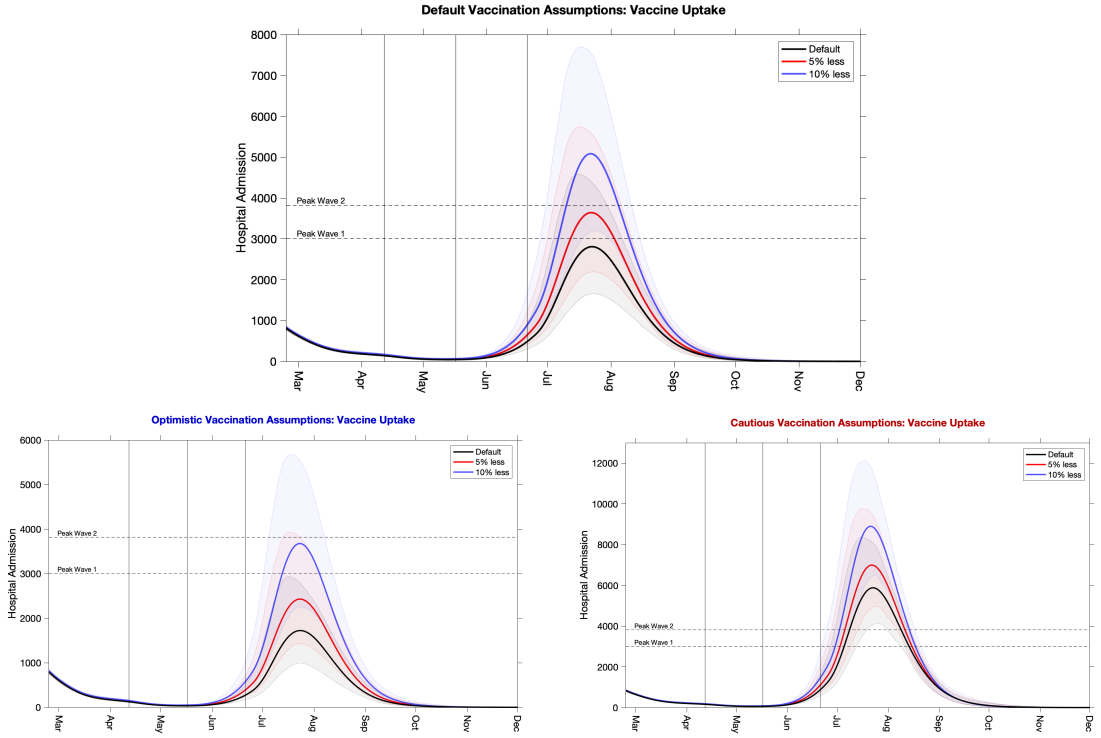

Fig. 15: Impact of different historic estimates for the proportion of the population already vaccinated on the number of daily hospital admissions in England. The panel on the top is for the default vaccine efficacy assumptions, the panel on the left is for the optimistic efficacy assumptions while the panel on the right is for the cautious efficacy assumptions. Vertical lines are the dates of Steps 2, 3 and 4.

One potential source of uncertainty is the uptake of vaccine in the older age-groups. While the number of vaccines delivered is recorded precisely, there is some uncertainty in the underlying population size, leading to uncertainty in the associated vaccine uptake. Here we examine the sensitivity in the model to a generally lower level of vaccine uptake in relation to the population size (which also translates to a slower deployment relative to the population size). The Warwick model uses ONS population estimates to determine both the population sizes within the model and to calculate the level of vaccine

uptake. This generates a relatively high uptake compared to using other data sources, therefore we consider the implications of vaccine uptake being 5% or 10% less than in the default model.

At 10% lower uptake (equating to a 10% error in the underlying population sizes), daily hospital admissions peak at 5150 (PI 2970-8250) compared to 2850 (PI 1530-4800) for the default assumptions, and the total number of hospital admissions over the third wave is 231,000 (PI 153,000-359,000) compared to 131,000 (PI 78,300-221,000) for the default. The uncertainty in this measure of vaccine uptake has a considerable impact on the scale of third wave as it determines the proportion of the vulnerable population that will have received two doses of vaccine before the bulk of the third wave.

2.3.3 Comparison of all measures associated with vaccination

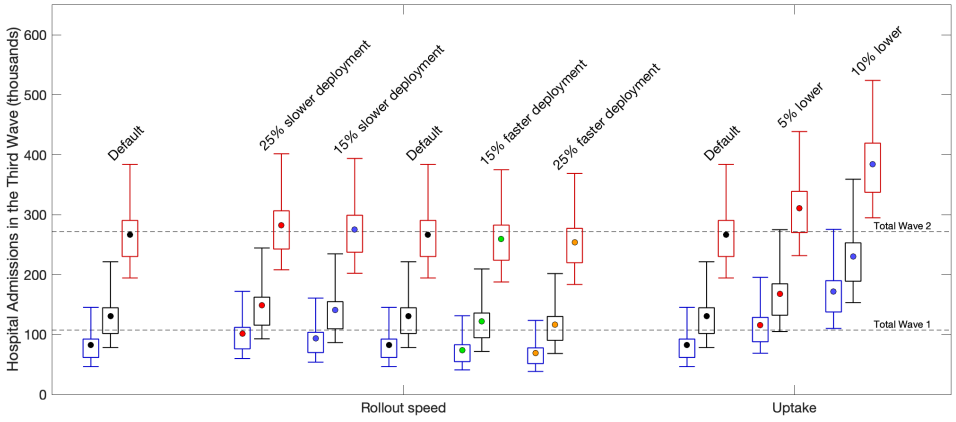

Fig. 16: Projected number of hospital admissions from 1st June 2021 to 30th June 2022, corresponding to the profiles shown in Fig. 14 - Fig. 15. Blue, black and red bars and whiskers are for the optimistic, default and cautious vaccine efficacy assumptions, respectively. The coloured marker indicates the mean, all models use the default Step 4 control of 13% NPIs.

Considering the full range of sensitivities associated with vaccination that we have simulated, we plot the total number of hospital admissions projected for the third wave (June 2021 - June 2022) showing the means (coloured marker, with the colour matching that used in the figures above) together with the interquartile and 95th percentiles (Fig. 16). Results for the default assumptions about vaccine efficacy are shown with black bar and whisker plots, while results for the optimistic and cautious assumptions are in blue and red respectively. The differences shown here, which can be quite substantial, correspond to uncertainties in our measurements of vaccine uptake so far and vaccine efficacy, and the projections of vaccine deployment over the next few months. Compared to the default scenario, which is projected to generate a third wave of 131,000 (PI 78,300-221,000) hospital admissions, the most optimistic scenario of 25% faster rollout with optimistic efficacy generates 68,700 (PI 38,400-124,000) hospital admissions while the most pessimistic scenario of lower efficacy and 10% lower uptake generates 384,000 (PI 295,000-524,000) hospital admissions.

2.4 Seasonality

Seasonality has a small but noticeable impact on the third wave. Estimates from Baker *et al.* [5] suggest that seasonality in the UK is between 6 and 14% based on the observed dynamics of coronavirus OC43, and coronavirus HKU1; although both higher and lower values are plausible depending on characteristics of SARS-CoV-2 and the weather during the 2021 summer. Throughout we take 10% as our baseline assumption, but note that higher levels of seasonality lead to suppressed summer waves, but do not noticeably affect the timing of the peak.

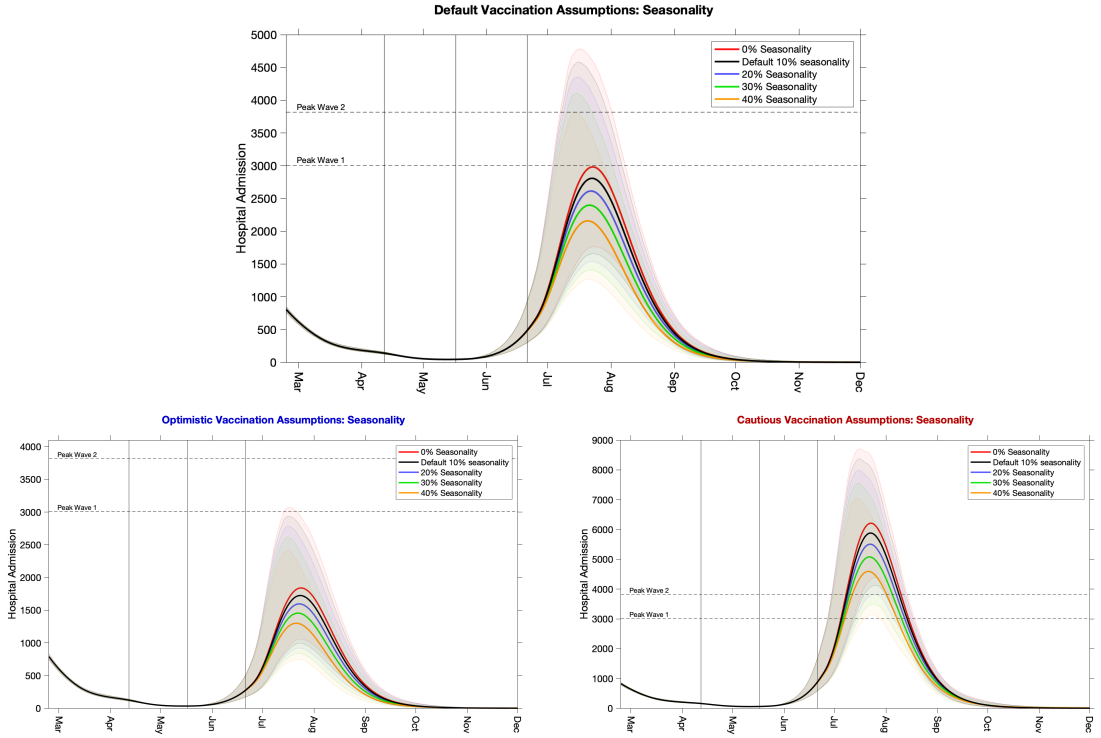

Fig. 17: Impact of different seasonality assumptions on the number of daily hospital admissions in England; where seasonality defines the relative scale of the drop in transmission from the winter peak to the summer low, influenced by both behaviour and climate. The panel on the top is for the default vaccine efficacy assumptions, the panel on the left is for the optimistic efficacy assumptions while the panel on the right is for the cautious efficacy assumptions. Vertical lines are the dates of Steps 2, 3 and 4.

3 Heterogeneties arising from the dynamics

3.1 Regional Heterogeneity

One important aspect of this pandemic has been the considerable heterogeneity at regional and finer spatial scales. In Fig. 18 we show the number of infections per 100 individuals, the number of hospital admissions per 100,000 individuals and the number of deaths per 100,000 individuals in each of the NHS regions for Wave 1 (up to 31st August 2020), Wave 2 (1st September 2020 - 31st May 2021) and Wave 3 (1st June 2021 until simulations end on 30th June 2022). The predicted scale of the third wave for all three measures is a function of historical cases, vaccine uptake, vaccine efficacy and the competitive advantage inferred for B.1.617.2 (Fig. 1). All regions except London are predicted to have large numbers of infections in the third wave (equivalent or more than in wave 2 for both the default and cautious efficacy assumptions, Fig. 18 top left), with the North East and Yorkshire suffering the highest burden. As expected we observe smaller levels of infection for the optimistic efficacy assumptions giving the smallest outbreak sizes while the cautious assumptions give the largest.

When considering deaths due to COVID-19 (top right), the protective effects of the vaccine are even more marked, with none of the regions expected to experience more deaths in the third wave compared to wave 2 for the optimistic and default efficacy assumptions, but many regions projected to experience a larger third wave (compared to the second) for the more cautious assumptions. This pattern is echoed in the total hospital admissions projections (lower graph), the mean number of hospital admissions in the third wave under the optimistic and default assumptions is consistently lower than during the second wave, but the cautious efficacy assumptions lead to a substantial increase for many regions. Again, the North East and Yorkshire suffers the highest projected burden of hospital admissions.

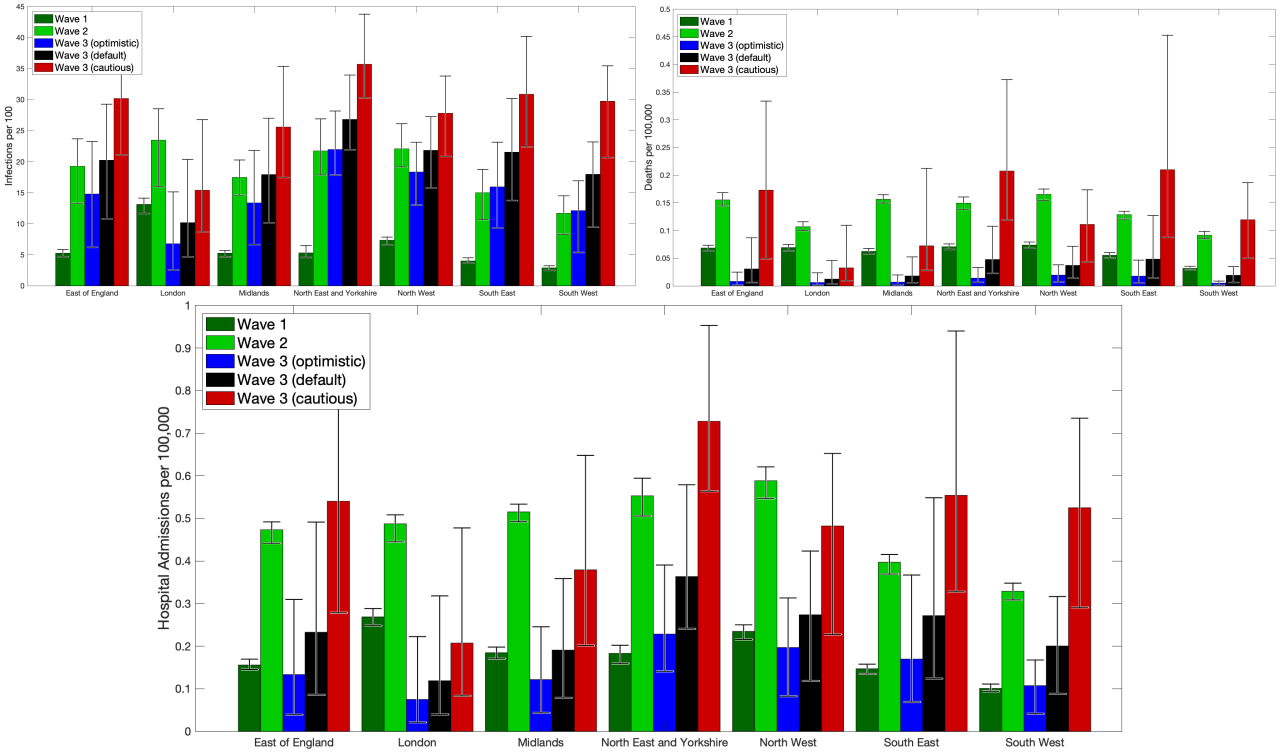

Fig. 18: Projected pattern of infections, hospital admissions and deaths in waves 1 (dark green), 2 (light green), 3 with optimistic efficacy assumptions (blue), 3 with default efficacy assumptions (black), 3 with cautious efficacy assumptions (red). This clearly shows that while infections are comparable between waves 2 and 3, the action of the vaccine reduces the number of hospital admissions and deaths.

3.2 Age-structure and Vaccine status of Hospital Admissions

Here we consider the vaccine status (red and diagonal hashing is unvaccinated; green solid colour is 1 dose of vaccine only; and blue with horizontal hashing is 2 doses of vaccine) and age (darker colours are younger age groups, with under 50s on top and over 80s at the bottom) of projected hospital admissions (Fig. 19). We show the entire epidemic projection and focus on both the number of hospital admissions (left) and the proportion of hospital admissions (right) – noting that vaccinated individuals are only present in the latter half of the pandemic. Using the default vaccine assumptions, we project that during the peak of the third wave 60-70% of hospital admissions will be in unvaccinated individuals (red) some of whom are too young to receive the vaccine.

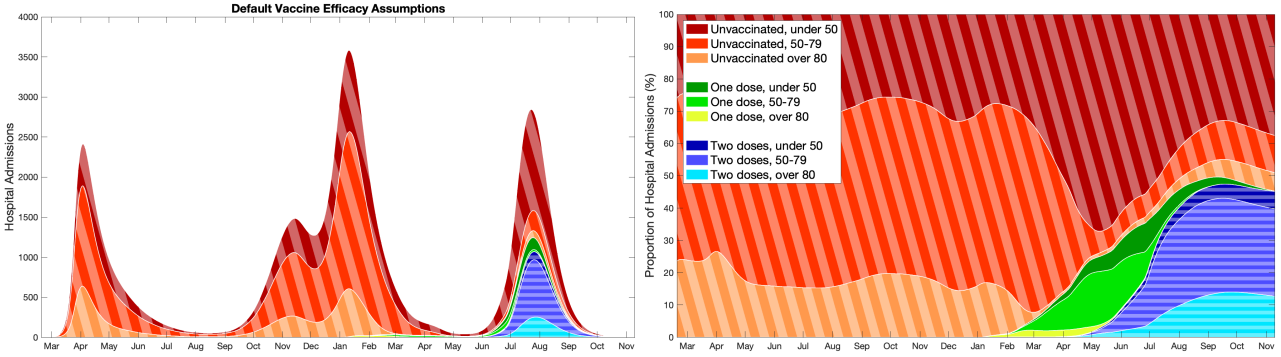

Fig. 19: Age and vaccine status of hospital admissions from the model using default vaccine efficacy assumptions. Unvaccinated individuals are in red (with diagonal hashing), those that have received one dose are in green (solid colour), and those with two doses are in blue (horizontal hashing). The left-hand graph shows the number of hospital admissions, while the right-hand graph shows the proportion of admissions in each group.

3.3 Age-structure and Vaccine status of Deaths

Deaths show a similar pattern with age and vaccination status; the age-pattern remains relatively constant until January 2021, following which there is initially an increase in the proportion of individuals who have received one dose (green), although the total number of deaths remain low. During the third wave, there is an increase in the proportion of deaths in those that have received two doses of vaccine, peaking at around 55%.

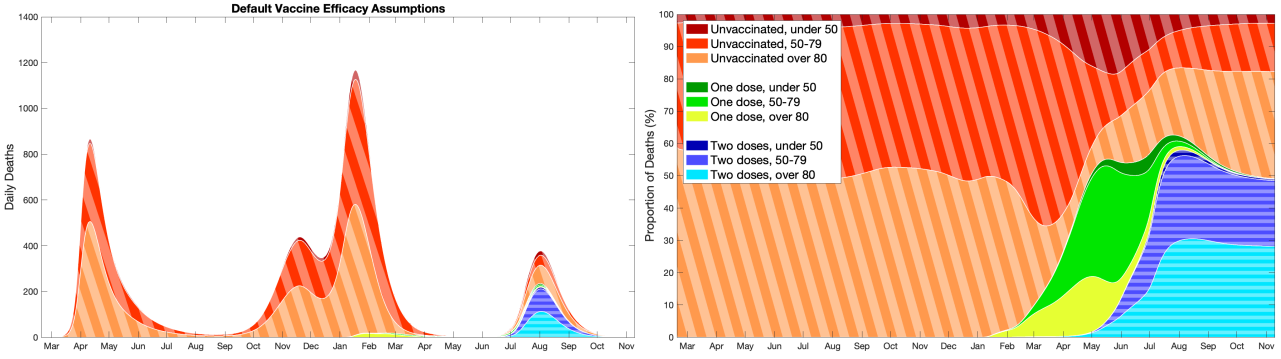

Fig. 20: Age and vaccine status of deaths from the model using default vaccine efficacy assumptions. Unvaccinated individuals are in red (with diagonal hashing), those that have received one dose are in green (solid colour), and those with two doses are in blue (horizontal hashing). Darker colours refer to younger age-groups. The left-hand graph shows the number of deaths, while the right-hand graph shows the proportion in each age and vaccine group.

3.4 Values of Key Quantities for a Selected Set of Sensitivity Analyses

Table 4: Values of key quantities over the third wave (June 2021 - June 2022) for a selected set of sensitivity analyses and using the default vaccine efficacy assumptions.

Scenario	Default Efficacy			
	R_{ei} Step 4	Peak Hosp Ad	Total Hosp Ad	Total Deaths
Default	5.66 (CI 5.4-5.95)	2850 (PI 1530-4800)	131,000 (PI 78,300-221,000)	17,100 (PI 8490-36,800)
Step 4 NPI=0%	6.68 (CI 6.37-7.02)	3800 (PI 2110-6140)	165,000 (PI 106,000-263,000)	26,200 (PI 14,000-53,400)
Step 4 NPI=25%	4.8 (CI 4.56-5.04)	2130 (PI 1120-3740)	102,000 (PI 57,400-180,000)	10,900 (PI 5180-24,200)
Step 4 26 July	5.66 (CI 5.4-5.95)	1420 (PI 764-2640)	89,600 (PI 50,500-158,000)	8500 (PI 4140-18,200)
Step 4 23 Aug	5.66 (CI 5.4-5.95)	1420 (PI 764-2640)	73,600 (PI 41,100-132,000)	6160 (PI 3090-13,600)
Two step 21June/26July	5.66/6.68	2320 (PI 1230-3920)	130,000 (PI 79,400-216,000)	16,300 (PI 8370-33,600)
Two step 26July/30Aug	5.66/6.68	1420 (PI 764-2640)	86,300 (PI 49,300-153,000)	7920 (PI 3970-17,000)
25% slower rollout	5.66 (CI 5.4-5.95)	3230 (PI 1720-5330)	149,000 (PI 92,900-244,000)	19,900 (PI 10,100-42,100)
25% faster rollout	5.66 (CI 5.4-5.95)	2530 (PI 1370-4380)	117,000 (PI 68,400-202,000)	15,000 (PI 7390-32,500)
10% lower uptake	5.66 (CI 5.4-5.95)	5150 (PI 2970-8250)	231,000 (PI 153,000-359,000)	65,400 (PI 35,900-130,000)
20% lower B.1.617.2 transmission	4.53 (CI 4.32-4.76)	1080 (PI 543-2180)	59,200 (PI 30,500-115,000)	5570 (PI 2490-13,000)
10% lower B.1.617.2 transmission	5.08 (CI 4.82-5.32)	1890 (PI 978-3390)	95,000 (PI 52,400-172,000)	10,600 (PI 4920-23,600)
10% faster B.1.617.2 transmission	6.21 (CI 5.89-6.5)	3930 (PI 2220-6340)	164,000 (PI 105,000-264,000)	24,900 (PI 13,100-51,500)
20% faster B.1.617.2 transmission	6.79 (CI 6.42-7.09)	5030 (PI 2970-7920)	194,000 (PI 130,000-300,000)	33,500 (PI 18,300-67,000)
40% faster B.1.617.2 transmission	7.9 (CI 7.49-8.27)	7200 (PI 4680-10,700)	243,000 (PI 173,000-358,000)	51,900 (PI 30,600-98,200)

Table 5: Values of key quantities over the third wave (June 2021 - June 2022) for a selected set of sensitivity analyses and using the optimistic vaccine efficacy assumptions.

Scenario	Optimisitic Efficacy			
	R_{ei} Step 4	Peak Hosp Ad	Total Hosp Ad	Total Deaths
Default	5.66 (CI 5.4-5.95)	1760 (PI 918-3020)	82,400 (PI 46,500-145,000)	6320 (PI 3280-13,500)
Step 4 NPI=0%	6.68 (CI 6.37-7.02)	2290 (PI 1210-3790)	103,000 (PI 61,800-173,000)	9390 (PI 5140-19,400)
Step 4 NPI=25%	4.8 (CI 4.56-5.04)	1340 (PI 694-2420)	64,500 (PI 35,000-118,000)	4210 (PI 2140-9200)
Step 4 26 July	5.66 (CI 5.4-5.95)	914 (PI 486-1760)	57,400 (PI 31,100-104,000)	3450 (PI 1760-7290)
Step 4 23 Aug	5.66 (CI 5.4-5.95)	914 (PI 486-1760)	47,500 (PI 26,000-87,200)	2600 (PI 1410-5470)
Two step 21June/26July	5.66/6.68	1450 (PI 761-2530)	82,000 (PI 47,000-143,000)	6170 (PI 3250-13,000)
Two step 26July/30Aug	5.66/6.68	914 (PI 486-1760)	55,100 (PI 30,400-100,000)	3230 (PI 1710-6820)
25% slower rollout	5.66 (CI 5.4-5.95)	2110 (PI 1080-3510)	102,000 (PI 60,000-172,000)	8010 (PI 4210-16,900)
25% faster rollout	5.66 (CI 5.4-5.95)	1470 (PI 785-2650)	68,700 (PI 38,400-124,000)	5160 (PI 2720-11,100)
10% lower uptake	5.66 (CI 5.4-5.95)	3720 (PI 2090-6010)	172,000 (PI 110,000-276,000)	38,600 (PI 21,200-76,400)
20% lower B.1.617.2 transmission	4.53 (CI 4.32-4.76)	611 (PI 304-1310)	33,500 (PI 17,100-66,900)	1910 (PI 944-4410)
10% lower B.1.617.2 transmission	5.08 (CI 4.82-5.32)	1130 (PI 578-2100)	57,000 (PI 30,000-107,000)	3750 (PI 1880-8330)
10% faster B.1.617.2 transmission	6.21 (CI 5.89-6.5)	2500 (PI 1330-4100)	107,000 (PI 64,900-179,000)	9520 (PI 5180-19,700)
20% faster B.1.617.2 transmission	6.79 (CI 6.42-7.09)	3270 (PI 1810-5210)	129,000 (PI 82,500-207,000)	13,100 (PI 7410-26,300)
40% faster B.1.617.2 transmission	7.9 (CI 7.49-8.27)	4840 (PI 2980-7430)	165,000 (PI 113,000-253,000)	20,900 (PI 12,500-40,500)

Table 6: Values of key quantities over the third wave (June 2021 - June 2022) for a selected set of sensitivity analyses and using the cautious vaccine efficacy assumptions.

Scenario	Cautious Efficacy			
	R_{ei} Step 4	Peak Hosp Ad	Total Hosp Ad	Total Deaths
Default	5.66 (CI 5.4-5.95)	5990 (PI 3810-8910)	267,000 (PI 194,000-384,000)	72,400 (PI 44,100-128,000)
Step4 NPI=0%	6.68 (CI 6.37-7.02)	8090 (PI 5420-11,300)	326,000 (PI 254,000-439,000)	106,000 (PI 70,700-166,000)
Step4 NPI=25%	4.8 (CI 4.56-5.04)	4250 (PI 2550-6800)	204,000 (PI 136,000-316,000)	44,300 (PI 24,300-86,600)
Step4 26 July	5.66 (CI 5.4-5.95)	2600 (PI 1520-4440)	195,000 (PI 139,000-289,000)	36,900 (PI 22,000-64,100)
Step4 23 Aug	5.66 (CI 5.4-5.95)	2590 (PI 1520-4440)	157,000 (PI 108,000-240,000)	25,200 (PI 15,100-46,400)
Two step 21June/26July	5.66/6.68	4710 (PI 2910-7190)	274,000 (PI 208,000-380,000)	70,000 (PI 44,700-115,000)
Two step 26July/30Aug	5.66/6.68	2590 (PI 1520-4440)	219,000 (PI 160,000-299,000)	40,700 (PI 26,100-63,900)
25% slower rollout	5.66 (CI 5.4-5.95)	6420 (PI 4100-9490)	282,000 (PI 208,000-402,000)	77,300 (PI 47,600-136,000)
25% faster rollout	5.66 (CI 5.4-5.95)	5610 (PI 3560-8450)	254,000 (PI 184,000-369,000)	68,300 (PI 41,300-122,000)
10% lower uptake	5.66 (CI 5.4-5.95)	9040 (PI 6090-13,000)	384,000 (PI 295,000-524,000)	170,000 (PI 111,000-270,000)
20% lower B.1.617.2 transmission	4.53 (CI 4.32-4.76)	2550 (PI 1480-4380)	144,000 (PI 89,500-239,000)	27,700 (PI 14,400-56,600)
10% lower B.1.617.2 transmission	5.08 (CI 4.82-5.32)	4210 (PI 2540-6630)	209,000 (PI 142,000-320,000)	48,400 (PI 27,300-91,500)
10% faster B.1.617.2 transmission	6.21 (CI 5.89-6.5)	7860 (PI 5280-11,300)	316,000 (PI 241,000-436,000)	97,500 (PI 63,200-161,000)
20% faster B.1.617.2 transmission	6.79 (CI 6.42-7.09)	9670 (PI 6670-13,600)	358,000 (PI 281,000-481,000)	122,000 (PI 82,500-190,000)
40% faster B.1.617.2 transmission	7.9 (CI 7.49-8.27)	13,000 (PI 9730-17,400)	423,000 (PI 339,000-548,000)	168,000 (PI 120,000-237,000)

Appendix A: Infections over time with sensitivity to B.1.617.2 transmission advantage

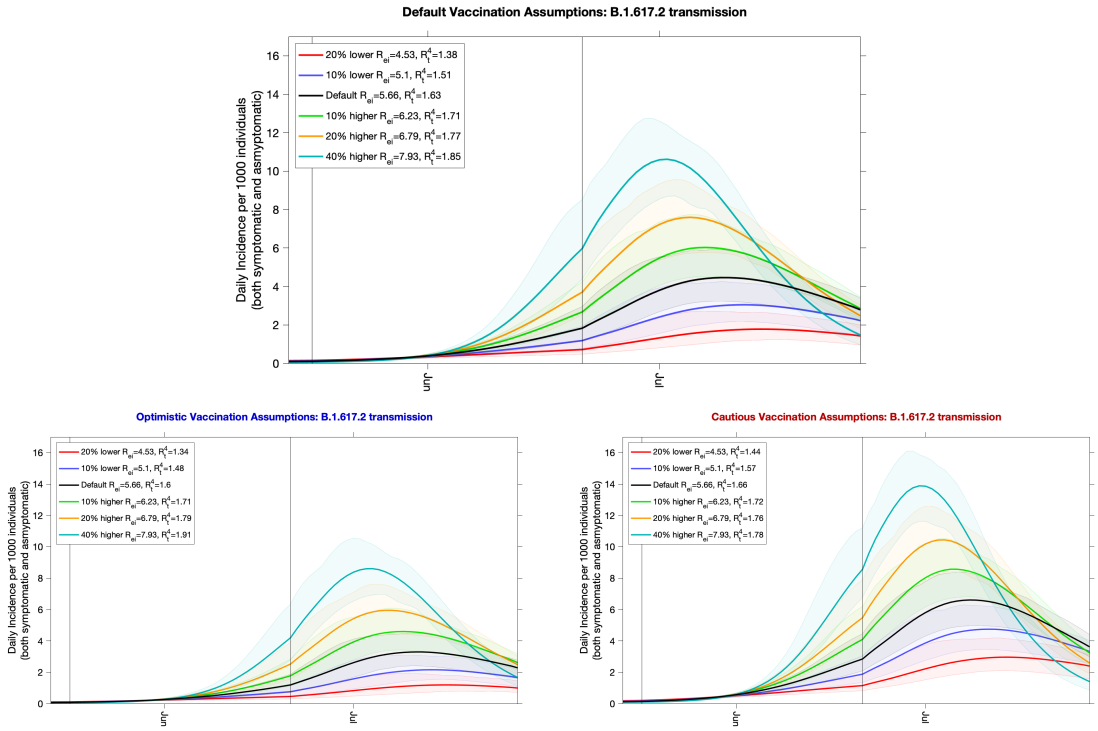

Fig. 21: Impact of assuming higher or lower transmission of B.1.617.2 on the daily incidence (per 1000 individuals) in England. The panel on the top is for the default vaccine efficacy assumptions, the panel on the left is for the optimistic efficacy assumptions while the panel on the right is for the cautious efficacy assumptions. In the legend we give the value of R excluding immunity for B.1.617.2 and the reproduction number R_t at the start of Step 4 for the B.1.617.2 variant. Vertical lines are the dates of Steps 3 and 4. We note that initial levels of B.1.617.2 have been rescaled for each transmission level to achieve a better level of fit to the case and hospital admission data. All graphs are plotted on the same y-axis scale to allow comparison.

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