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 occurring on 19th July 2021 and throughout model the transmission of the Delta variant. We use an age-structured model that captures the dynamics within the seven NHS regions of England. The model is matched to data up to 2nd July 2021 and projections reflect the underlying uncertainty in parameters.

Public Health Conclusions

1. In this document we acknowledge the unquantifiable nature of behaviour in Step 4, and explore a wide range of temporal profiles for the relaxation to pre-pandemic behaviours. We pick seven exemplar patterns of precautionary behaviour after 19th July 2021 that are used to underpin projections and sensitivity analysis.
2. All seven exemplar scenarios generate a third wave in the summer of 2021. Scenarios with the slowest decline in precautionary behaviour generate the smallest wave with a projected peak in daily hospital admissions of 668 (PI 530-951), while scenarios in which Step 4 leads to a relatively abrupt change in behaviour lead to the largest third waves with a peak of 2490 (PI 1270-4760) daily hospital admissions. These are lower than the third wave peaks estimated as part of the previous roadmap from 9th June 2021 (which peaked at 2850 (PI 1530-4800)), due to both the delay in relaxation and the increased vaccine efficacy estimates, but could still place a heavy burden on healthcare services. More cautious assumptions about the efficacy of the vaccines coupled with an abrupt change in behaviour could generate a large third wave with daily hospital admissions peaking at 6970 (PI 3660-12,600).
3. The interaction between seasonality and the slow decline in precautionary behaviour under some scenarios is projected to lead to a fourth wave in the winter of 2021 or early spring of 2022; for some scenarios this winter peak can be larger than the projected peak of the third wave. Predictions of a fourth wave are highly uncertain due to the impact of waning immunity, the uncertainty in the precise level of seasonality and the action of any booster vaccination programmes.
4. Many of the scenarios investigated lead to very large numbers of infected individuals, often in the younger age groups, which may have implications for how the third wave is managed. In particular, this large number of infections will: increase the risk associated with the emergence of vaccine escape mutants; place extra pressure on Test, Trace and Isolate and genomic sequencing making new variants more difficult to detect and control; increase the number of individuals suffering from long-COVID and other sequelae; and lead to significantly increased absenteeism from workplaces and schools.

Executive Summary

1. We consider the likely epidemiological impacts of Step 4 of the relaxation roadmap on 19th July 2021. 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 (9th June 2021):

   (a) seasonality and the estimated level of social mixing are now decoupled, providing a better assessment of seasonal effects on longer-term predictions.

   (b) parameters associated with Step 3 are inferred rather than being imposed on the dynamics.

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

   (d) we explicitly acknowledge the unquantifiable nature of behaviour in Step 4, and explore a wide range of temporal profiles.

   The uncertainty in human behaviour during Step 4, means that we cannot give a single estimate for the projected dynamics; instead we show the envelope of possible behaviours and focus on seven exemplar scenarios.

3. We estimate that the Delta variant has a 61% (CI 38-86%) transmission advantage over the Alpha variant. In keeping with the latest analysis we assume that one dose of vaccine offers lower protection against infection for Delta compared to Alpha although two doses of vaccine offer more comparable levels of protection; we also assume complete cross immunity.

4. We consider three different sets of vaccine efficacy values against the Delta variant (default, optimistic and cautious) which correspond to the central, upper and lower ranges generated by PHE.

5. The seven exemplar scenarios give third wave peaks in daily hospital admissions between 668 (PI 530-951) and 2490 (PI 1270-4760), with many scenarios giving a fourth wave in the winter due to increasing relaxation and seasonality.

6. There are multiple uncertainties that impact the projected dynamics.

   (a) Behaviour of the population in Step 4 has a substantial impact on the scale of future waves, with a sudden increase in mixing leading to the largest and earliest third waves. The peak heights and timing are also strongly influenced by the behaviour of the population from now until 19th July.

   (b) Although we have an excellent record of the number of doses administered, the underlying population estimates are less certain. Under-estimating regional population numbers by 5% or 10%, leads to a reciprocal reduction in estimated vaccine uptake which profoundly impacts the scale of the projected third wave.

   (c) Despite intensive work by PHE, there is still considerable uncertainty around vaccine efficacy; lower values of vaccine efficacy against infection raise the overall scale of the projected third wave, while lower efficacy against hospital admissions or deaths affect those particular components.

   (d) The precise size of any future peak is contingent on the proportion of the population that are susceptible, which in turn depends on an accurate assessment of the numbers infected in previous waves and whether vaccine uptake is correlated with the risks of prior infection.

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

   (a) waning immunity after infection or vaccination is not included, 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 seven 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 and precautionary behaviour 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). A comparison between model projections and data is shown in Appendix 1. 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 Alpha (B.1.1.7) variant (which is S-gene negative on TaqPath system) at the end of 2020, and the more recent spread of the Delta (B.1.617.2) variant (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 (2 and 3) occurring at their associated dates; Step 4 is modelled as occurring on 19th July 2021. School holidays are modelled by changing the mixing patterns for school-aged children, and we include all school holidays (half terms, Christmas, Easter and Summer holidays) over the simulation period.

We have accounted for the changes in behaviour, seasonality and restrictions over time, by inferring the effective level of 'social distancing' acting on the population (and hence capture changes to population-level mixing). However, as exemplified by gradual change during Step 3, we do not expect an abrupt return of population mixing back close to pre-COVID levels after Step 4, instead we explore a range of behaviours from an immediate change to a protracted relaxation over many months. To improve the estimation process (and better account for the projected impact of seasonality) we now decouple the inferred reduction of population mixing (which throughout we term the level of precautionary behaviour, PB) from the seasonal trends that are represented as a sine wave with a peak in mid-February and a trough in mid-August. We stress that what we term the level of precautionary behaviour is actually a combination of restrictions, recommendations and behavioural changes that combine to reduce the amount of population mixing that is relevant for transmission; this is scaled such that PB=1 corresponds to highly restrictive lock-down controls and PB=0 corresponds to a return to pre-pandemic behaviour.

We measure the degree of behavioural relaxation within the population as both a change in the relative level of precautionary behaviour, and by computing the instantaneous growth rate (r) and 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. We assume that any changes in transmission that occurred following Step 1b (on the 29th March 2021), Step 2 (on 12th April 2021) and Step 3 (on 17th May 2021) are already captured in parameter estimates.

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

1) The Delta variant. In keeping with the previous roadmap document, we have explicitly mod-

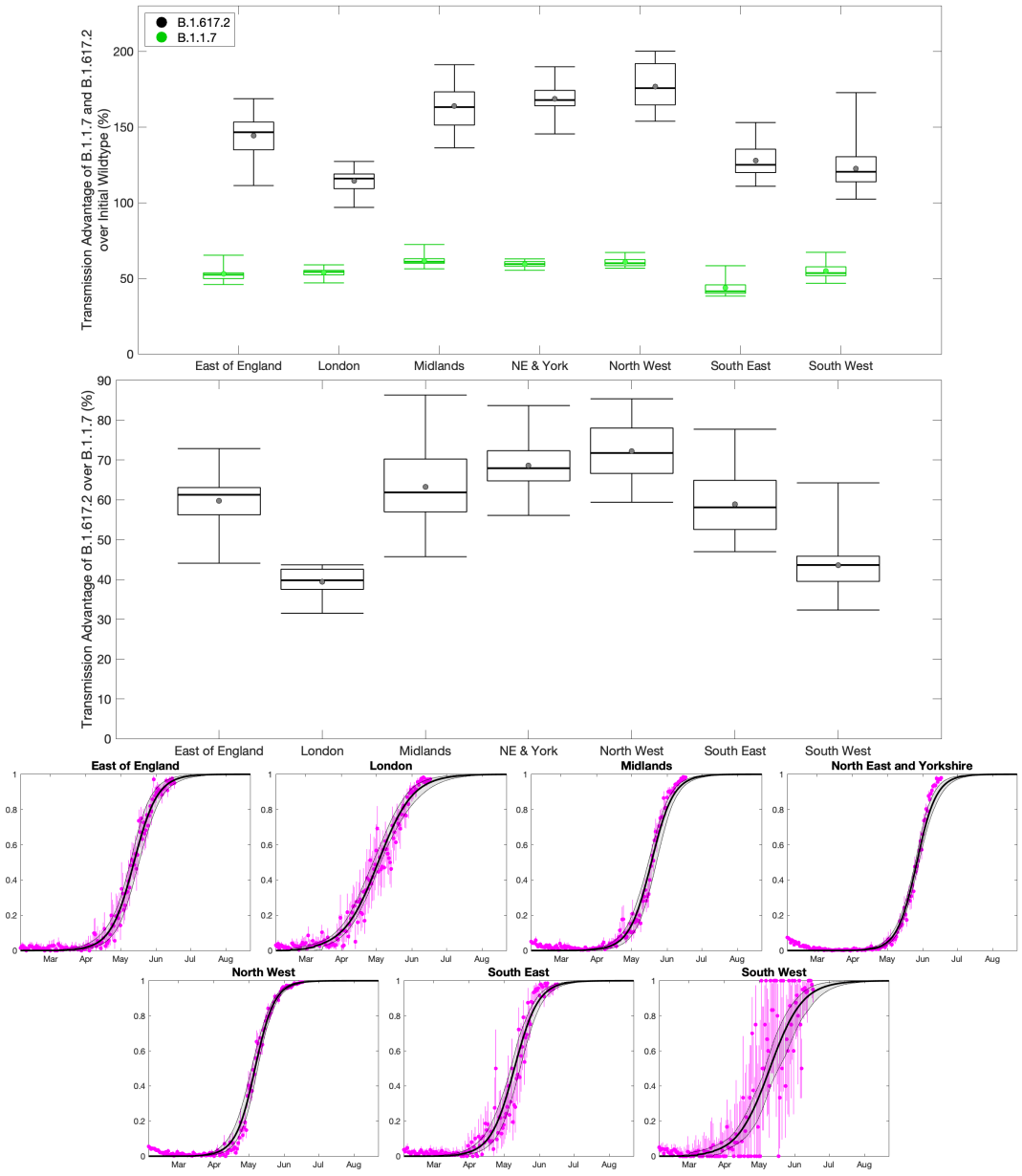

Fig. 1: Top: Estimated transmission advantage of Alpha (B.1.1.7, green) and Delta (B.1.617.2, black) over the wildtype, as inferred from the Warwick MCMC model, which fits to the number of symptomatic Pillar 2 cases, hospital admissions and deaths, in addition to the proportion of symptomatic Pillar 2 cases that are S-gene positive. Middle: Estimated transmission advantage of Delta over Alpha. Lower panels: the predicted proportion of infections that are attributable to Delta (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).

elled the spread of the Delta variant, using the ratio of S-gene positive and S-gene negative samples. Parameter estimates for the Delta variant are inferred together with all the other epidemiological variables; we estimate the transmission advantage of Delta and Alpha over the original wildtype variant in each region (Fig. 1 top); we also provide estimates of the competitive advantage of Delta over Alpha (Fig. 1 middle). This inference is based on proportion of Pillar 2 positive 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 proportion of cases that are Delta as opposed to Alpha. Fortu-

itously, Alpha 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 has been replaced by Delta. 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 Delta to Alpha in some regions. We note that vaccine efficacy against symptomatic infection has been measured as generally lower against Delta compared to Alpha (see below), and this is incorporated into the parameter inference framework. This lower vaccine efficacy will also contribute to the Delta variant's greater competitive advantage, allowing it to out compete in all regions (Fig. 1 lower panels). In the absence of other data, we optimistically assume that infection with Alpha or other variants provides complete cross immunity against Delta.

We estimate that Delta has a 61% (CI 38-86%) transmission advantage over Alpha, 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 can consider how these advantages (together with any vaccine escape) translate into the proportion of Delta 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 death. We can also allow different parameters for Pfizer and AstraZeneca vaccines, although the differences are generally small for protection against Alpha. 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.

Throughout we assume a fixed matrix of vaccine efficacy values against Alpha (Table 1), but explore a range of efficacy values against Delta (Table 2-Table 4) – reflecting the fact that vaccine efficacy against Alpha is an integral part of the inference process.

Table 1: Vaccine efficacy assumptions against Alpha variant. (∗=no data available from PHE)

	Pfizer/Moderna		**AstraZeneca**	
Efficacy	**1st Dose**	**2nd Dose**	**1st Dose**	**2nd Dose**
Symptoms	63%	88%	63%	80%
Hosp Adm	80%	93%	80%	90%
Mortality	80%	97%	80%	95%
Infection	63%	80%	63%	78%*
Transmission	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 both the Alpha and Delta variant there is currently a lack of data, in which case we have extrapolated from the protection offered by Pfizer or from the information available on Alpha. The default set of vaccine efficacy assumptions against Delta are based on recent data from PHE and is in broad agreement with the latest estimates (Table 2, [4]).

Table 2: Vaccine efficacy against Delta variant, default assumptions. (∗=no data available from PHE)

	Pfizer/Moderna		AstraZeneca	
Efficacy	**1st Dose**	**2nd Dose**	**1st Dose**	**2nd Dose**
Symptoms	56%	88%	34%	70%
Hosp Adm	90%	98%	81%	94%
Mortality	90%*	98%*	81%*	95%*
Infection	56%*	80%*	34%*	64%*
Transmission	45%*	45%*	45%*	45%*

We complement the default central set of vaccine efficacy assumptions with two others: an optimistic set of assumptions (Table 3); and a more cautious set of assumptions (Table 4). The optimistic set of assumptions are based upon the upper value of the range estimated by PHE against Delta; extrapolating to missing data where appropriate. The cautious set of efficacy assumptions are based on the lower bound of the range estimated by PHE. These alternative efficacy assumptions are meant to be indicative of potential dynamics if the default parameter are incorrect, rather than provide strict upper and lower bounds to the scale of the dynamics.

Table 3: Vaccine efficacy against Delta variant, optimistic assumptions. (∗=no data available from PHE)

	Pfizer/Moderna		AstraZeneca	
Efficacy	**1st Dose**	**2nd Dose**	**1st Dose**	**2nd Dose**
Symptoms	59%	89%	37%	77%
Hosp Adm	96%	99%	85%	97%
Mortality	96%*	99%*	85%*	97%*
Infection	59%*	80%*	37%*	65%*
Transmission	45%*	45%*	45%*	45%*

Table 4: Vaccine efficacy against Delta variant, cautious assumptions. (∗=no data available from PHE)

	Pfizer/Moderna		AstraZeneca	
Efficacy	**1st Dose**	**2nd Dose**	**1st Dose**	**2nd Dose**
Symptoms	53%	84%	31%	68%
Hosp Adm	75%	90%	70%	90%
Mortality	80%*	95%*	75%*	92%*
Infection	53%*	80%*	31%*	61%*
Transmission	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 April 2021 when cases of the Delta variant began to rise. However, given that simulations with different vaccine efficacies still produce a reasonable match to the available data, we expect the impact of other assumptions to be marginal on the inferred parameters. 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 1.9 million doses per week until 12th July and then 2.0 million 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 30th July 2021 and second doses will be completed by 24th 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. Uncertainty to the roll-out speed is also examined. In this analysis we do not model the vaccination of children (12-17 years old) nor the impact of an autumn booster programme.

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 19th July 2021. On-going inference, as part of the regular weekly estimate of the R number, has shown that there has been relatively little change in the inferred level of precautionary behaviour (and hence population mixing) due to Step 3. However, this may be in part due to seasonal changes (see Seasonality below) such that the lower levels of transmission during the summer are being captured by a higher level of precautionary behaviour. We therefore now separate the impact of precautionary behaviour from the underlying seasonality, which improves our forward projections with different levels of seasonality.

In the previous roadmap, we set a level of precautionary behaviour during Step 3 that was around 50% in the absence of available data. We now infer that the true value is closer to 75%, although this includes the reduction in transmission due to seasonality. In this document we now use the inferred value of precautionary behaviour in Step 3, leading to a slower growth of cases during the Step 3 period.

Considerable uncertainty remains about population behaviour in Step 4. Even if all controls are lifted on 19th July 2021, it is unlikely that the entire population will return to pre-COVID mixing patterns; many individuals are likely to still avoid crowds and limit their risky behaviours. We therefore focus on a range of possible behaviours in Step 4, characterised by (i) the instantaneous drop in the precautionary behaviour level (ie an increase in mixing) on 19th July and (ii) the time taken for the entire population to return to pre-COVID mixing patterns.

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 (and level of population mixing) if all individuals were susceptible to the virus. Throughout we report values of R excluding immunity for the Delta variant only.

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. 9. 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, but also consider 20% and 40%.

1 Comparison to previous roadmap

Here we consider the dynamics examined in this roadmap with the projections from the previous roadmap document, focussing on hospital admissions (Fig. 2). The red dashed line gives the results from the previous roadmap document, using the previously estimated parameters (including vaccine efficacy) assuming the precautionary behaviour level in Step 3 would drop to around 50% (dashed line on Fig. 2 right hand plot), and with Step 4 dropping to 13% starting on 19th July. This previous projection peaked at 1450 (PI 764 - 2640) daily hospital admissions on 24th July (PI 10th July - 8th August). This should be compared to the black dashed line, which has the same assumptions about Step 3 and 4, but uses the latest set of parameters; this peaks at 1420 (PI 749 - 2650) daily hospital admissions on 20th July (PI 12th July - 11th August). The slight differences compared to the previous roadmap are largely attributable to the higher levels of vaccine efficacy against hospitalisations estimated by PHE and more data on changes in precautionary behaviour.

We are now in a position where we can infer the level of interactions in Step 3, this was not possible in the last roadmap due to the confounding impact of the Delta variant. The solid black line shows the projected hospital admissions with the latest parameter values, and using the inferred level of interactions in Step 3 (corresponding to the solid black line on Fig. 2 right hand plot) although the precautionary behaviour in Step 4 remains at 13%. Unsurprisingly, this lower level of mixing between 17th May and 19th July pushes the epidemic peak later to 27th August (PI 25th August - 30th August), although the peak number of daily hospital admissions is projected to be comparable: 2540 (1290 - 4950). This latest projection (solid black) has increased significantly over the past two weeks (compare projections in different shades of dotted purple lines) as our estimate of precautionary behaviour in Step 3 has decreased. The model projections are clearly sensitive to the population behaviour until 19th July.

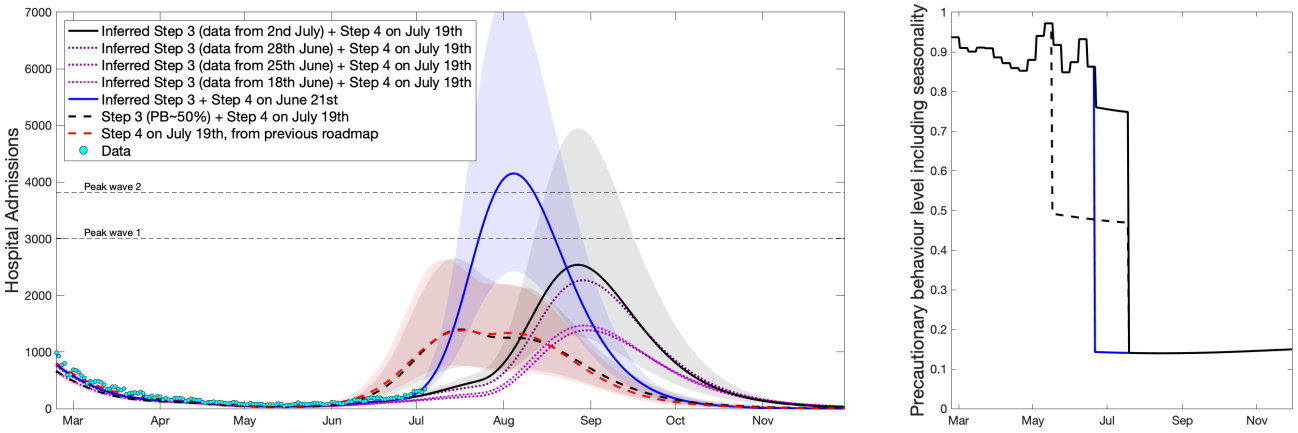

Fig. 2: Comparison of projected dynamics for the number of daily hospital admissions under different inferred parameters and different assumptions about mixing in Steps 3 and 4. Dashed lines refer to the assumption used in the previous road map that precautionary behaviour would drop to around 50% in Step 3 and would drop again to 13% in Step 4 on 19th July, with the red dashed line being the results from the previous road map and the black dashed line using the most recent parameter estimates. The solid lines use the inferred level of precautionary behaviour during Step 3 (precautionary behaviour of around 75-80%) dropping to 13% in Step 4 which is either on 19th July (solid black line and purple dotted) or the 21st June (blue line). Purple dotted lines are from historical estimates of recent population mixing over the past two weeks. The light blue dots are the most recent data. Shaded regions correspond to the 95% prediction intervals (which contain 95% of all projections for a given set of assumptions and reflect parameter uncertainty from the inference process). The right-hand figure shows the inferred level of precautionary behaviour (including the impacts of seasonality), the solid blue, black and dashed black lines correspond to different assumptions about Step 3 and 4 and correspond to similar lines on the left-hand figure.

Finally, we compare the inferred Step 3 with Step 4 on 19th July (black line) with the projections from inferred Step 3 but allowing Step 4 on 21st June (blue line). This early relaxation leads to a projected peak of 4170 (2430 - 7360) daily hospital admissions on 4th August (PI 2nd August - 10th August). Even though we have changed vaccine efficacy parameters and reassessed the mixing in Step 3, this comparison (of black and blue lines) demonstrates the considerable advantages that are likely to have been accrued by the four-week delay allowing more individuals to be vaccinated and providing a longer period of lower growth.

2 Exploration of Step 4 Dynamics

Projecting the epidemic is critically dependent on the behaviour of the population immediately following Step 4 and moving forward in time, as well as the proportion of the population that are susceptible to infection. We estimate that by 19th July there will have been 15.3 million (PI 13-17.5 million) total infections (including symptomatic and asymptomatic infections, and those that have escaped detection) this means that 27.4% (PI 23.3-31.3) of the English population will have been infected and therefore have natural immunity. When we couple this with the vaccine deployed so far, and expected to be deployed by 19th July, we estimate that 33% (PI 30.3-36.1) of the population remain susceptible

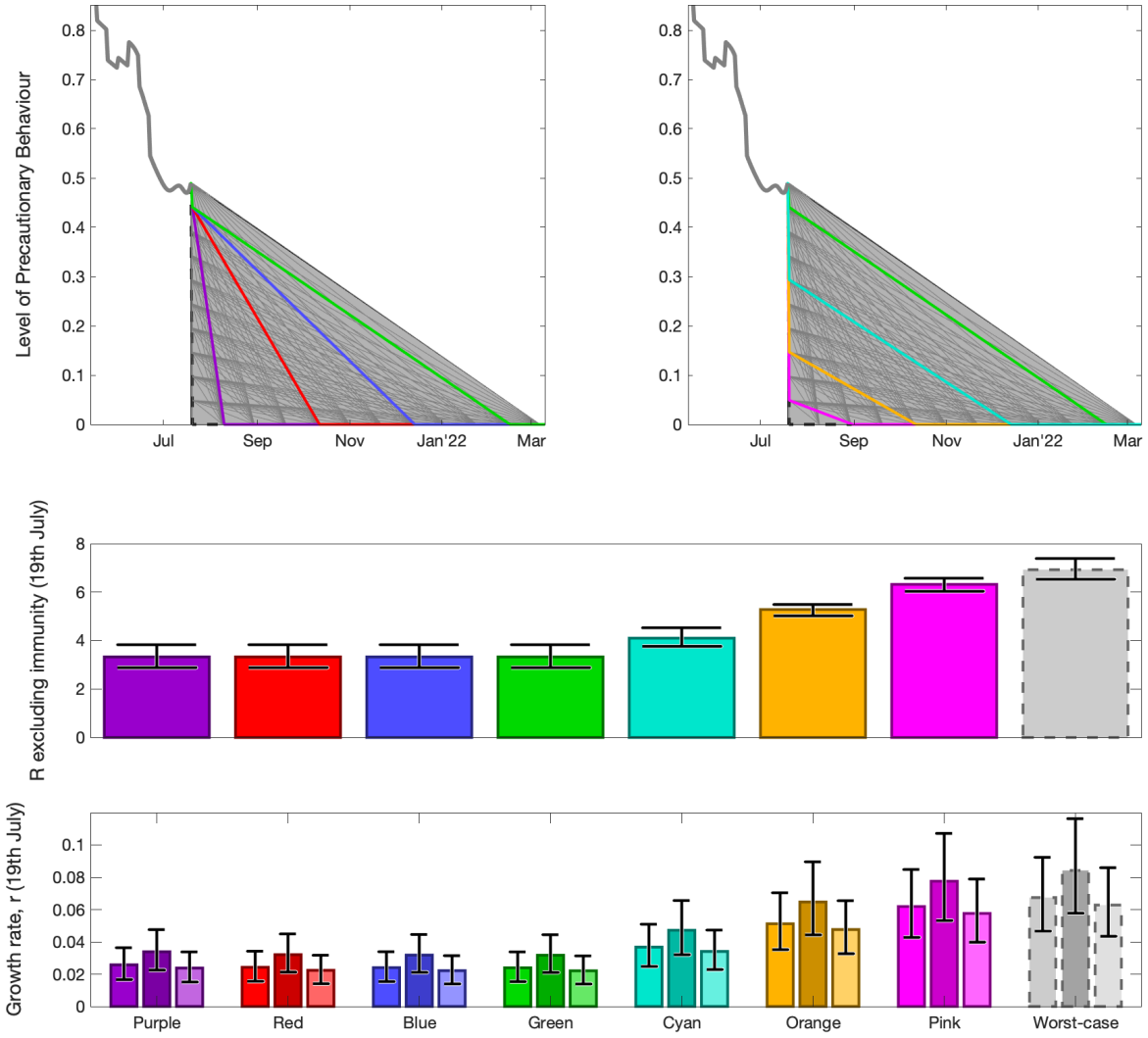

Fig. 3: Precautionary behaviour levels (excluding seasonal effects) for the envelope of parameters (grey shaded) and seven example behaviours that feature in subsequent plots. The left-hand plot shows 4 possible behaviours where there is only a small drop at Step 4 (on the 19th July) and relaxation to pre-COVID levels takes between 1 and 7 months; the right-hand plot considers combinations of different initial drops and times to complete relaxation. The green line is the same in the two plots, while the black dashed line is the worst-case scenario of an immediate return to pre-COVID mixing. The thin grey lines are all the two-parameter combinations that we have considered. The two lower plots show R excluding immunity and the instantaneous growth rate (r) for the seven example behaviours and the worse-case assumption; the growth rate is further subdivided into that calculated for the default vaccination assumptions (left), cautious assumptions (centre and darker colours) and optimistic assumptions (right and lighter colours).

to the Delta variant, accounting for the vaccine efficacy against infection.

The insights we have gained from Step 3 suggest there is unlikely to be a large sudden change in behaviour from the majority of the population, even if this is permitted by the relaxation of the rules. We therefore explore a range of possible behaviours in Step 4 ranging from an abrupt change in mixing back to pre-COVID levels to a slow relaxation over several months (shown as fine grey lines in Fig. 3); the precise pattern is determined by two parameters: the level of precautionary behaviour at the start of Step 4 relative to the end of Step 3; and the time taken for relaxation to pre-COVID levels (precautionary behaviour, PB=0). The envelope of this two-parameter family of behaviour is shown by the grey shaded area (Fig. 3), from which we highlight seven exemplar scenarios (coloured lines) corresponding to different initial drops at the start of Step 4 and different relaxation times. (Note that the green line is the same in the right and left hand panels of Fig. 3). We extrapolate this two-parameter family of different Step 4 behaviours through our modelling framework to derive the projected number of daily hospital admissions (Fig. 4). It should be stressed that the grey shaded region represents the envelope of values from across all Step 4 behaviours that have been considered; it is not a 95% interval (as it is not possible to attribute probabilities to each of the Step 4 behaviours), neither does it represent a single best or worst trajectory - rather it shows the maximum and minimum that could be expected at any point in the future.

Table 5: Peak number of daily hospital admissions (means and 95% prediction intervals) for the scenarios considered using default vaccine efficacy assumptions. Fourth wave heights and peak dates are considered until the end of simulations in June 2022.

Scenario	**Third wave height**	**Third wave peak**
Purple	1850 (PI 813-3850)	14th September '21 (PI 9th Sep-18th Sep)
Red	713 (PI 536-1280)	22nd August '21 (PI 9th Aug-2nd Nov)
Blue	672 (PI 532-960)	11th August '21 (PI 9th Aug-14th Aug)
Green	668 (PI 530-951)	11th August '21 (PI 9th Aug-13th Aug)
Pink	2490 (PI 1270-4760)	31st August '21 (PI 29th Aug-4th Sep)
Orange	1680 (PI 929-3180)	29th August '21 (PI 24th Aug-2nd Sep)
Cyan	948 (PI 650-1560)	20th August '21 (PI 16th Aug-26th Aug)
Worst case	2820 (PI 1430-5370)	30th August '21 (PI 29th Aug-3rd Sep)
Scenario	**Fourth wave height**	**Fourth wave peak**
Purple	no winter peak	no winter peak
Red	611 (CI 190-1600)	21st December '21 (PI 23rd Nov-17th Feb)
Blue	611 (CI 212-1520)	7th March '22 (PI 28th Jan-28th Apr)
Green	515 (CI 111-1400)	25th April '22 (PI 20th Mar-15th Jun)
Pink	no winter peak	no winter peak
Orange	no winter peak	no winter peak
Cyan	214 (CI 69-506)	5th March '22 (PI 19th Dec-22nd Apr)
Worst case	no winter peak	no winter peak

Of the seven exemplar scenarios, dark purple (starting at PB=59% and dropping to PB=0 by 9th August 2021) and pink (starting at PB=7% and dropping to PB=0 by 30th August 2021) trajectories, which most rapidly return to pre-COVID mixing lead to the largest projected epidemics. These are lower than the worst case where mixing immediately returns to pre-COVID levels on 19th July (Table 5). These purple and pink scenarios produce a single third wave that peaks in August/September 2021, but does not extend significantly into the winter of 2021/22. In contrast, scenarios in which the relaxation to pre-COVID mixing takes far longer (for example the red and blue scenarios which start at PB=59% and drop to PB=0 by 11th October 2021 and 13th December 2021 respectively)

show lower third waves over the summer of 2021, but lead to fourth waves over the winter of 2021/22. These later epidemic waves are driven purely by the interaction between increasing relaxation and seasonality.

We also compute the number of daily hospital admissions for the cautious (Fig. 4, centre column) and optimistic (Fig. 4, right column) vaccine efficacy assumptions. The more cautious assumptions are slightly less pessimistic and therefore generate smaller third waves than projected in the previous road map document. Fig. 5 shows results from the same projections (for the default vaccine efficacy assumptions) but focusing on infections (both symptomatic and asymptomatic), hospital occupancy and death. A systematic comparison of the key important quantities is shown in Appendix 3.

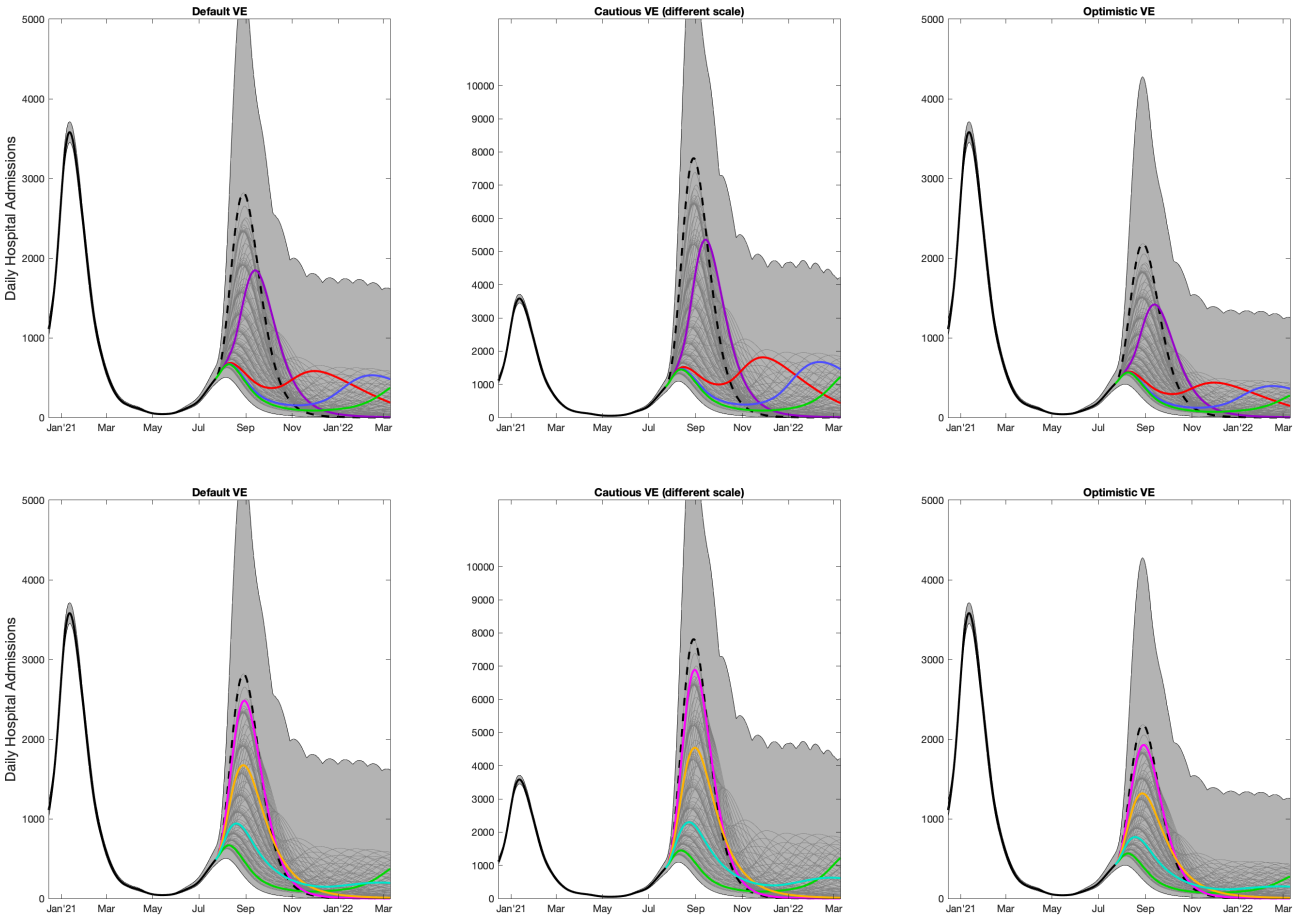

Fig. 4: Projected mean number of daily hospital admissions under a range of behavioural assumptions for Step 4 – as illustrated in Fig. 3. The grey regions represent the envelope of daily hospital admissions from across all Step 4 behaviours (such that the 95% prediction interval from all the two-parameter combinations of behaviour investigated are contained within the shaded region), while the coloured lines given the mean trajectories for the seven exemplar scenarios. The mean trajectory for the worst case assumption of immediate return to pre-COVID mixing on 19th July is shown with a dashed black line. The thin grey lines are the mean trajectories for all the two-parameter combinations of behaviour that have been considered. The left, centre and right columns are for the default, cautious and optimistic vaccine efficacy scenarios respectively. Note that the results for the cautious assumptions are on a different y-scale.

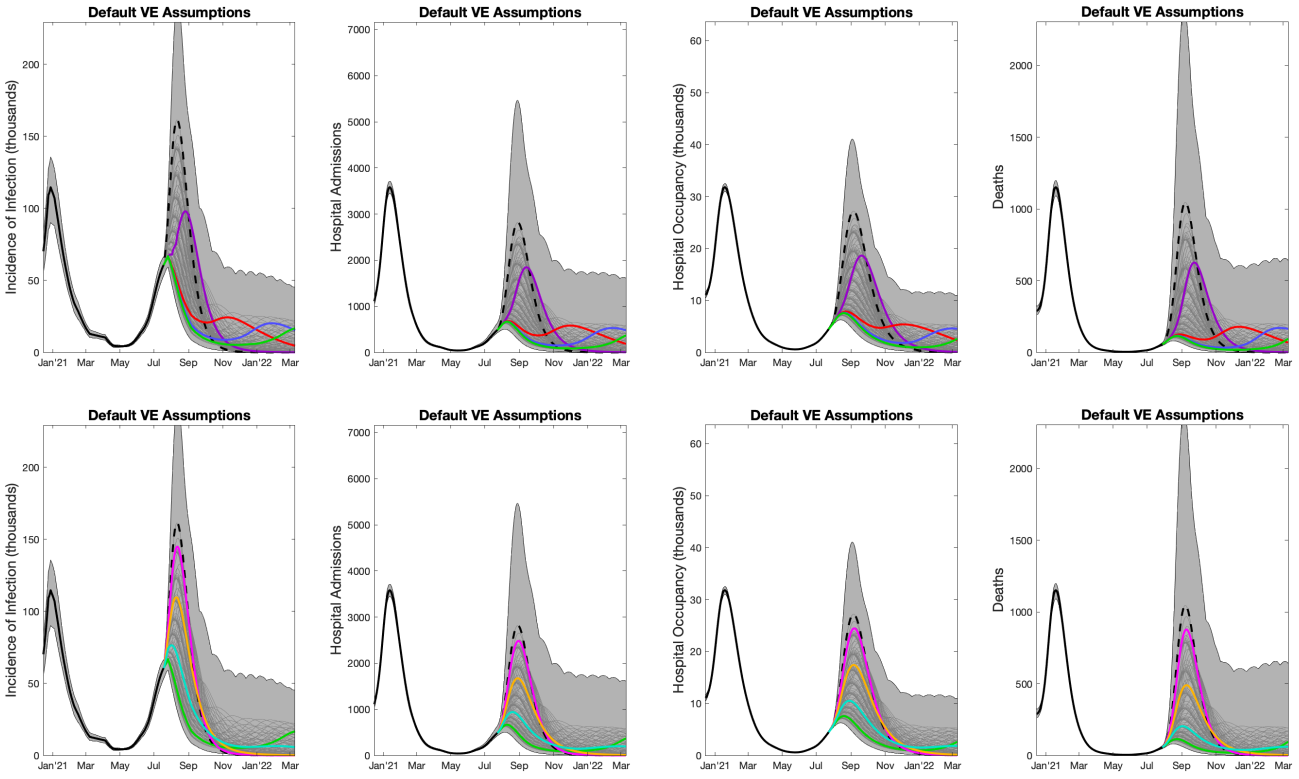

Fig. 5: Projected means for (i) daily incidence of infection (both symptomatic and asymptomatic), noting that this is not reported cases which depends on test seeking behaviour (ii) daily hospital admissions (iii) hospital occupancy (iv) deaths, under a range of behavioural assumptions for Step 4 – as illustrated in Fig. 3. All results are for the default vaccination assumptions. Results for the cautious and optimistic assumptions are shown in Appendix 2.

3 Sensitivity Analysis

3.1 Vaccination Speed

Here we consider 25% faster and slower deployment of vaccines in the future; there is unsurprisingly an interaction between vaccine deployment speed and the rate at which relaxation takes place. For scenarios that decline the most rapidly (dark purple: starting at precautionary behaviour PB=59% and dropping to PB=0 by 9th August 2021; pink: starting at PB=7% and dropping to PB=0 by 30th August 2021 and orange: starting at PB=20% and dropping to PB=0 by 11th October 2021) the speed of vaccination over the next few months plays a significant role in the size of the outbreak. In particular, for the pink scenario a 25% slower deployment of vaccine can increase the peak number of hospital admissions by 16% (15 - 20), compared to the default.

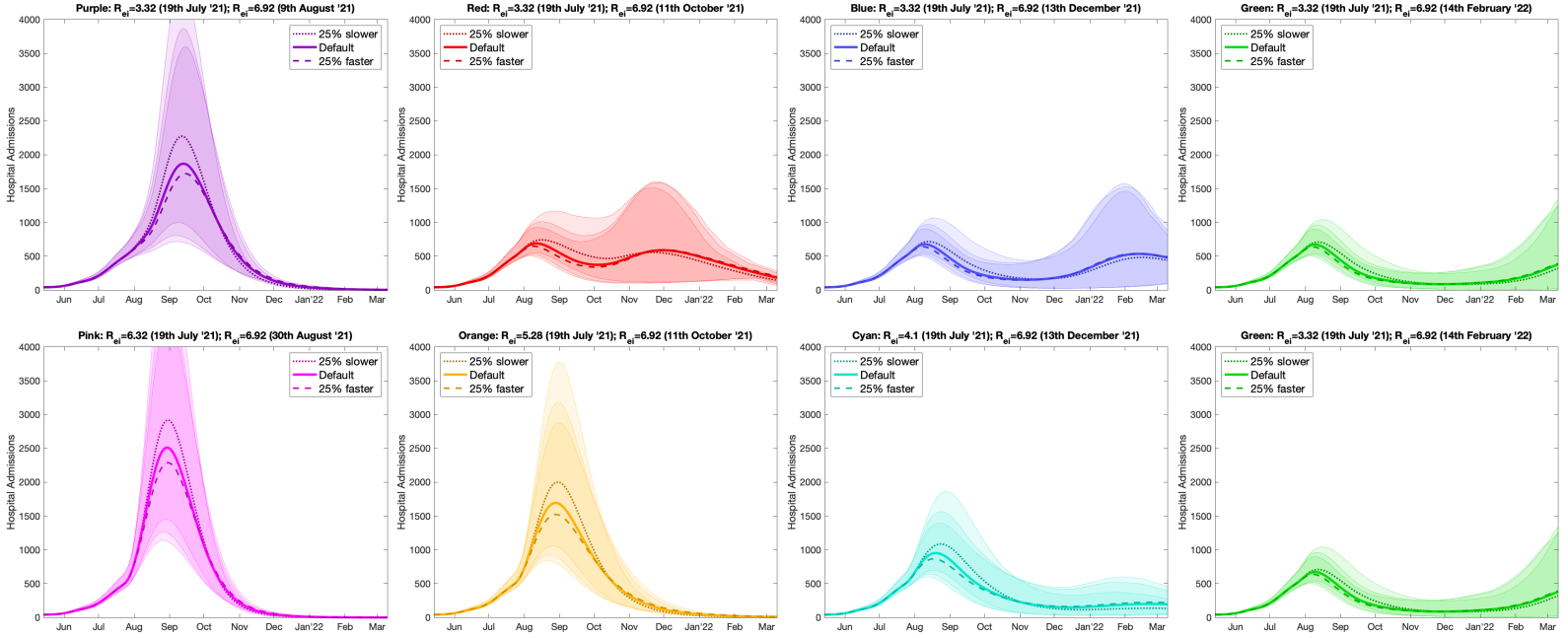

Fig. 6: Under different assumptions for the future deployment speed of vaccine doses, the projected mean number of daily hospital admissions (together with 95% prediction interval shown as the shaded interval) for seven exemplars of behavioural assumptions for Step 4 – as illustrated in Fig. 3. Different colours represent different assumptions about the behaviour in Step 4, while the 3 line-types refer to different vaccination speeds.

3.2 Historic Uptake

The level of historic vaccine uptake, reflecting uncertainty in the underlying population estimates for each region, has a pronounced and consistent impact on the projected dynamics raising the height of the third wave as well as any subsequent waves. We note that a 10% reduction in vaccination (generated by a 10% under-estimate of local population size) leads to an increase in the peak number of hospital admissions by 271% (194 - 400).

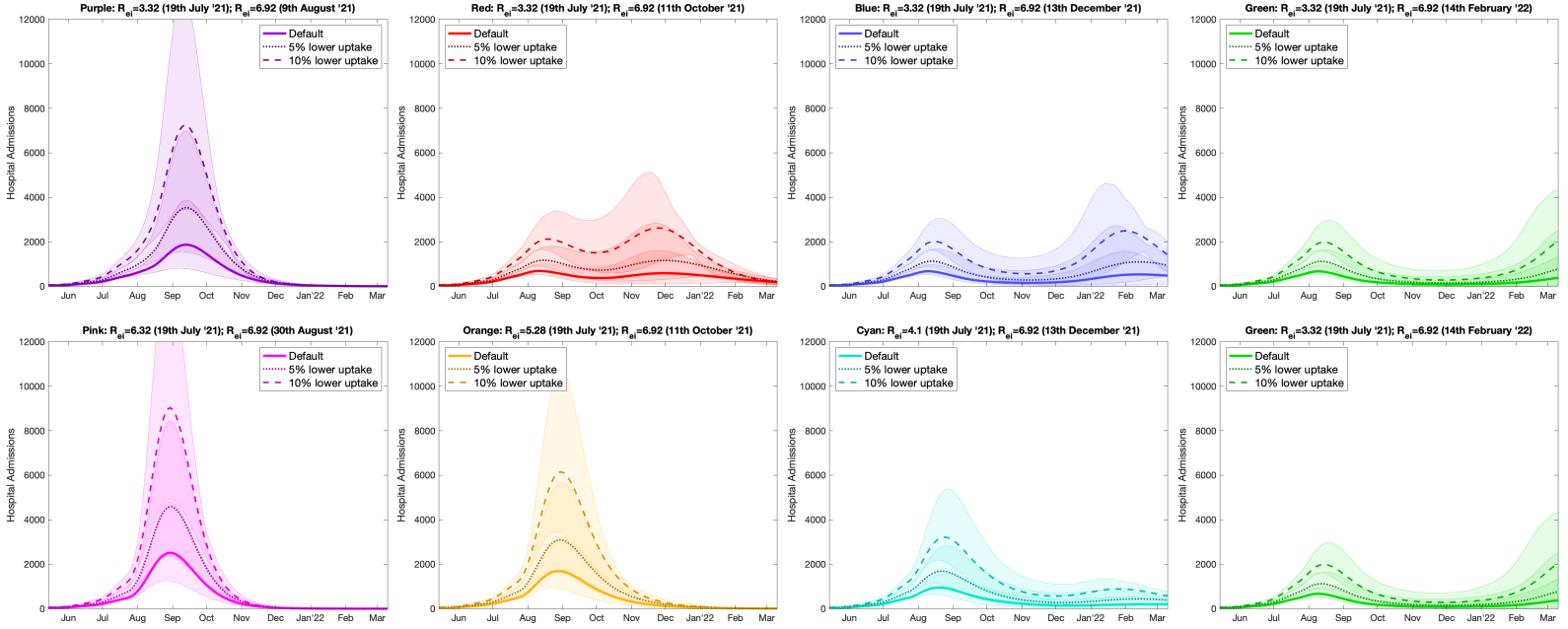

Fig. 7: Under different assumptions for the historic uptake of vaccine, the projected mean number of daily hospital admissions (together with 95% prediction interval shown as the shaded interval) for seven exemplars of behavioural assumptions for Step 4 – as illustrated in Fig. 3. Different colours represent different assumptions about the behaviour in Step 4, while the 3 line-types refer to different levels of vaccination to date.

3.3 Future Uptake

An additional uncertainty in the level of vaccine uptake in the younger age-groups. First doses in the over 50s are approaching a plateau, whereas doses in those 18-40 continues to rise and the eventual level remains uncertain. Our default assumption is that uptake will reach 80%, but here we compare that to 60% and 90%.

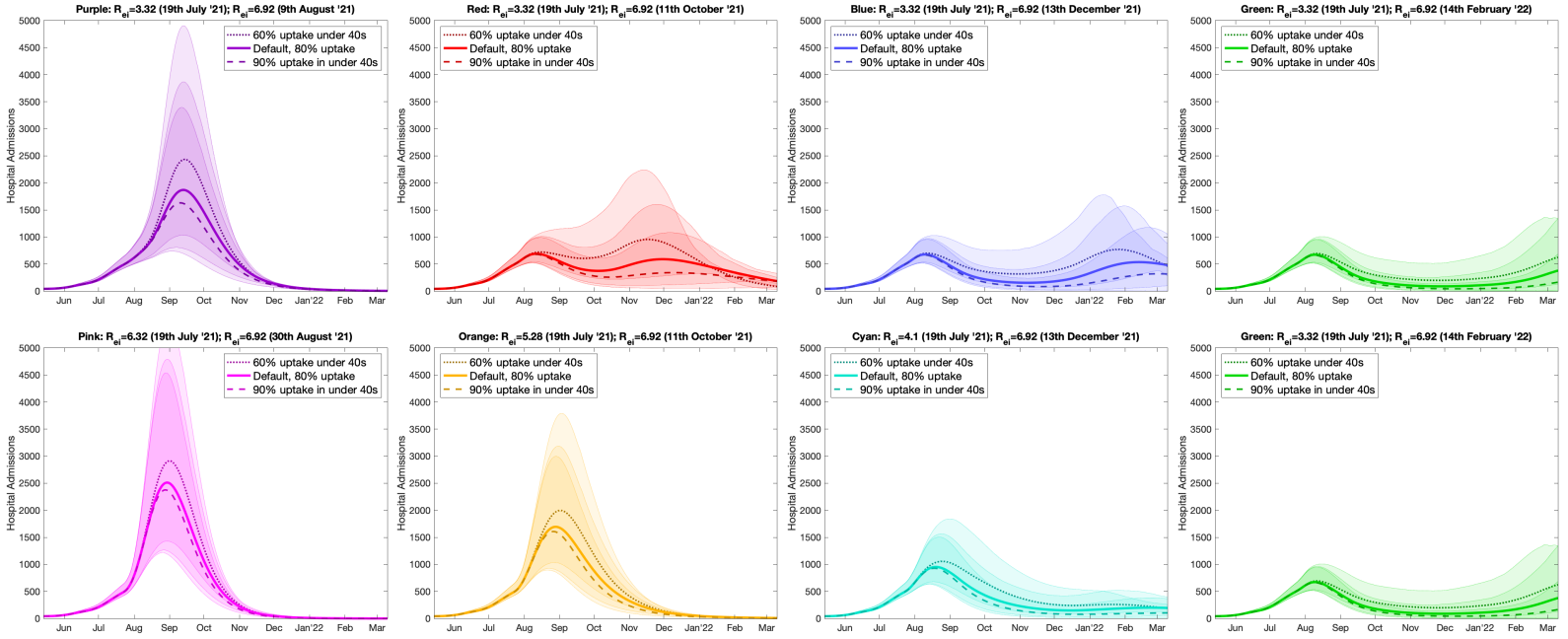

Fig. 8: Under different assumptions for the uptake of vaccine in the under 40s, the projected mean number of daily hospital admissions (together with 95% prediction interval shown as the shaded interval) for seven exemplars of behavioural assumptions for Step 4 – as illustrated in Fig. 3. Different colours represent different assumptions about the behaviour in Step 4, while the 3 line-types refer to different levels of vaccination in the under 40s: 60%, 80% (the default) or 90% (more comparable to older age-groups).

3.4 Seasonality

There is a very strong and non-linear interaction between declining levels of precautionary behaviour (increasing relaxation) and seasonality. Here we compare the default level of seasonality at 10% (such that transmission in the summer trough is 90% of the transmission in the winter), with 20% and 40% seasonality. The inference process is performed in the absence of seasonality, with the inferred temporal changes capturing both behavioural changes and variation due to climate and weather. When projecting the future trajectory of the epidemic we need to account for the fact that we are currently in a seasonal trough, which changes our estimate of mixing patterns. Higher levels of seasonality require greater mixing at the current time to achieve the same instantaneous growth rates. As such, the model with 40% seasonality and hence a very low summer trough requires the population to be mixing at close to pre-COVID levels (precautionary behaviour at 10-15%), this means that there is limited impact of future relaxations such that the seven scenarios (different colours) all generate similar projections at 40% seasonality. At these higher levels of seasonality, the third wave is generally suppressed while there is always a winter wave of infection.

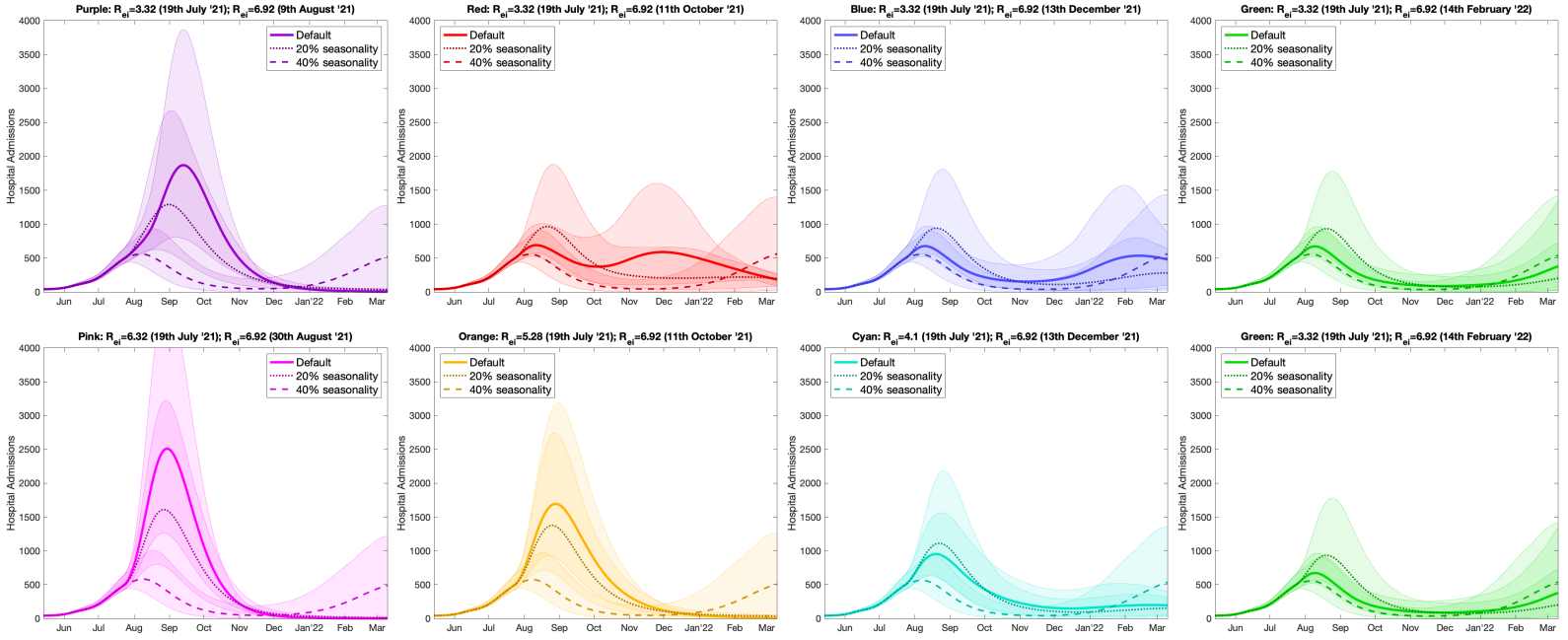

Fig. 9: Under different assumptions for the level of seasonality experienced, the projected mean number of daily hospital admissions (together with 95% prediction interval shown as the shaded interval) for seven exemplars of behavioural assumptions for Step 4 – as illustrated in Fig. 3. Different colours represent different assumptions about the behaviour in Step 4, while the 3 line-types refer to different levels of seasonality.

4 Structure within the epidemics

Here we consider the composition within the projected third and fourth wave epidemics in terms of age-structure and vaccine status (Fig. 10). For simplicity we focus on just two of the seven exemplar scenarios: red, which starts at a relatively high level of precautionary behaviour, leading to R_{ei} =3.32 (PI 2.88-3.83), and drops to pre-COVID mixing by 11th October 2021 (Fig. 10, top panels); and pink, which starts at a low level of precautionary behaviour, leading to R_{ei} =6.32 (PI 6.03-6.57), and drops to pre-COVID mixing by 30th August 2021 (Fig. 10, lower panels). It is clear that while infections (right-hand column) are dominated by younger age-groups, hospital admissions (second column) are dominated by older age groups.

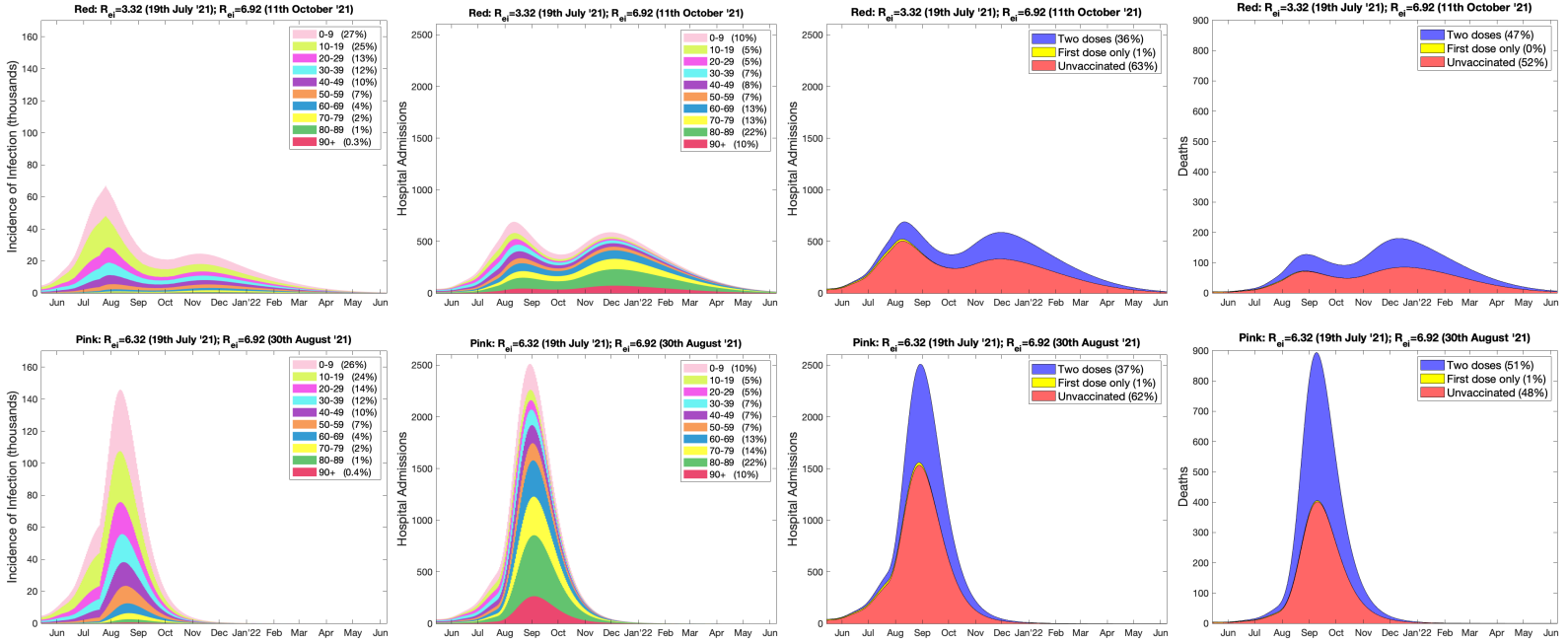

Fig. 10: For the red (top panels) and pink (lower panels) behaviour scenarios, as defined within Fig. 3. Here we show the mean age-structured breakdown of infections (left-hand column, noting that this is not reported cases which depends on a number of behavioural factors) and hospital admissions (second column), and the breakdown of hospital admissions (third column) and deaths (right-hand column) by vaccination status. In the legend of each figure we show the proportion of each plotted quantity (from 19th July 2021 to 31st June 2022) in each age or vaccine group.

Appendix 1: Comparison on model results and data.

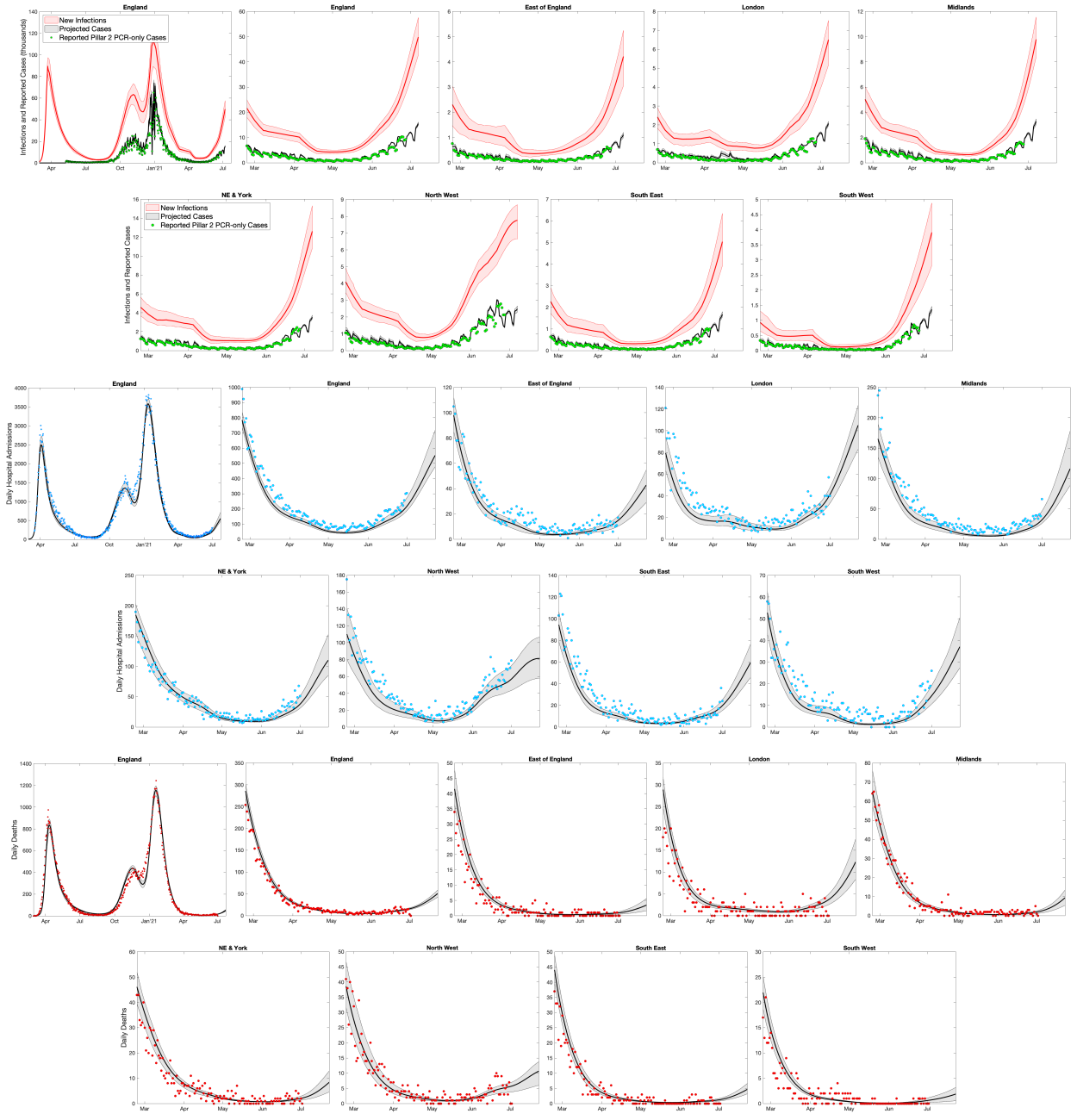

Fig. 11: Agreement between the model (line) and data (dots) for reported Pillar 2 PCR-only cases (top two rows, green dots), hospital admissions (middle two rows, blue dots) and deaths within 28 days of a positive test (bottom rows, red dots). These plots show the entire epidemic summing the regions to give a total for England (top left for each set), and for the most recent four months the values in England and the seven NHS regions. The figures showing reported cases also show infections (in red) for comparison. The model results are from the medium term projections, where there is no change in behaviour associated with Step 4.

Appendix 2: Projected Dynamics for Cautious and Optimistic Vaccine Efficacy Assumptions

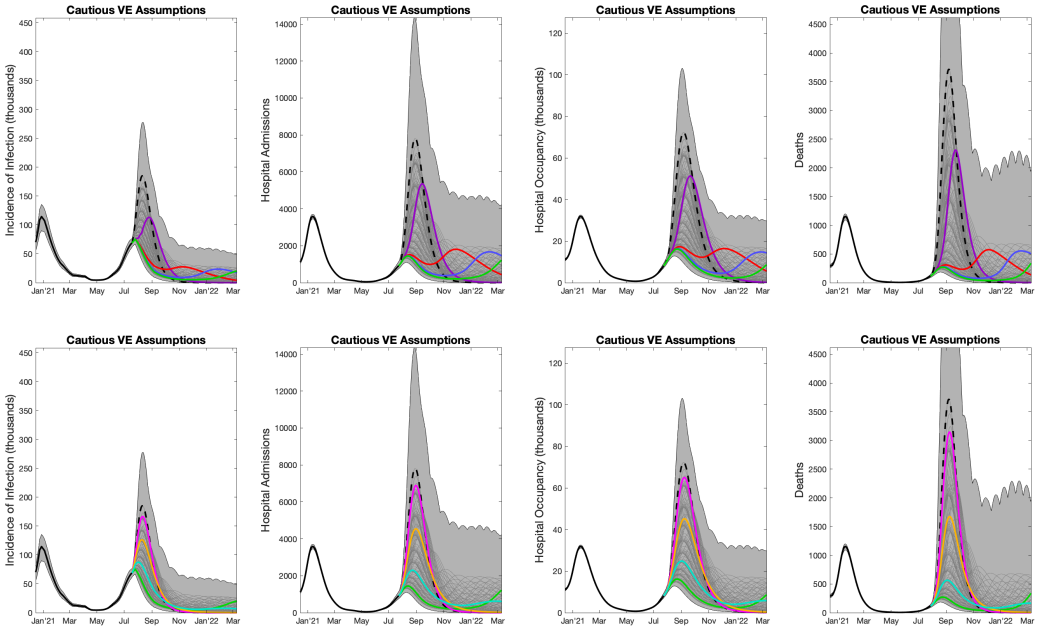

Fig. 12: Projected mean numbers of (i) daily incidence of infection (both symptomatic and asymptomatic), noting that this is not reported cases which depends on test seeking behaviour (ii) daily hospital admissions (iii) hospital occupancy (iv) deaths, under a range of behavioural assumptions for Step 4 – as illustrated in Fig. 3. All results are for the cautious vaccination assumptions.

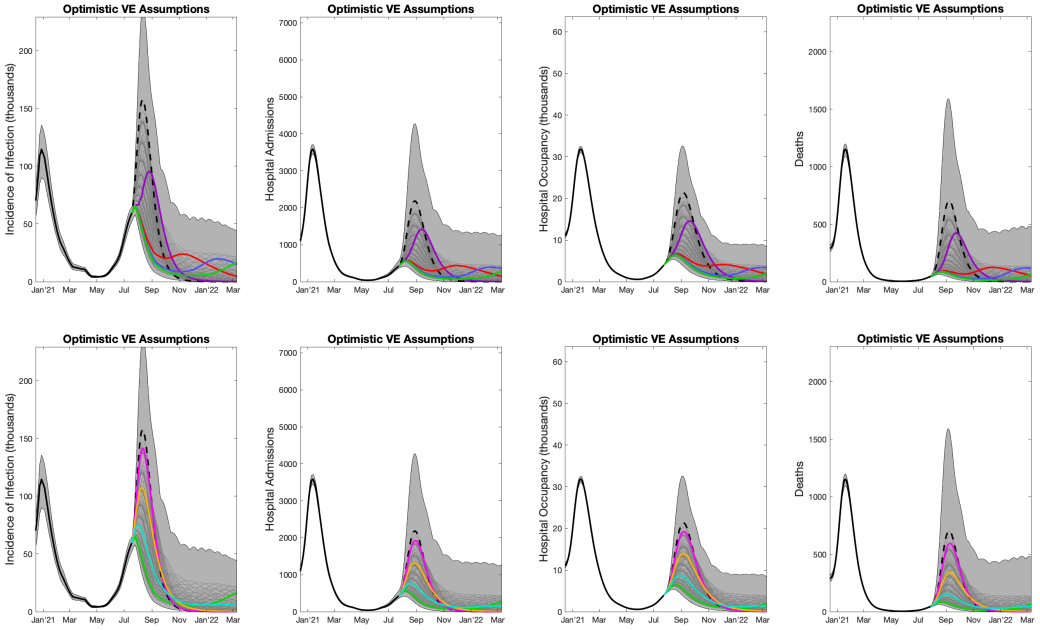

Fig. 13: Projected mean numbers of (i) daily incidence of infection (both symptomatic and asymptomatic), noting that this is not reported cases which depends on test seeking behaviour (ii) daily hospital admissions (iii) hospital occupancy (iv) deaths, under a range of behavioural assumptions for Step 4 – as illustrated in Fig. 3. All results are for the optimistic vaccination assumptions.

Appendix 3: Comparison of Key Quantities of Interest

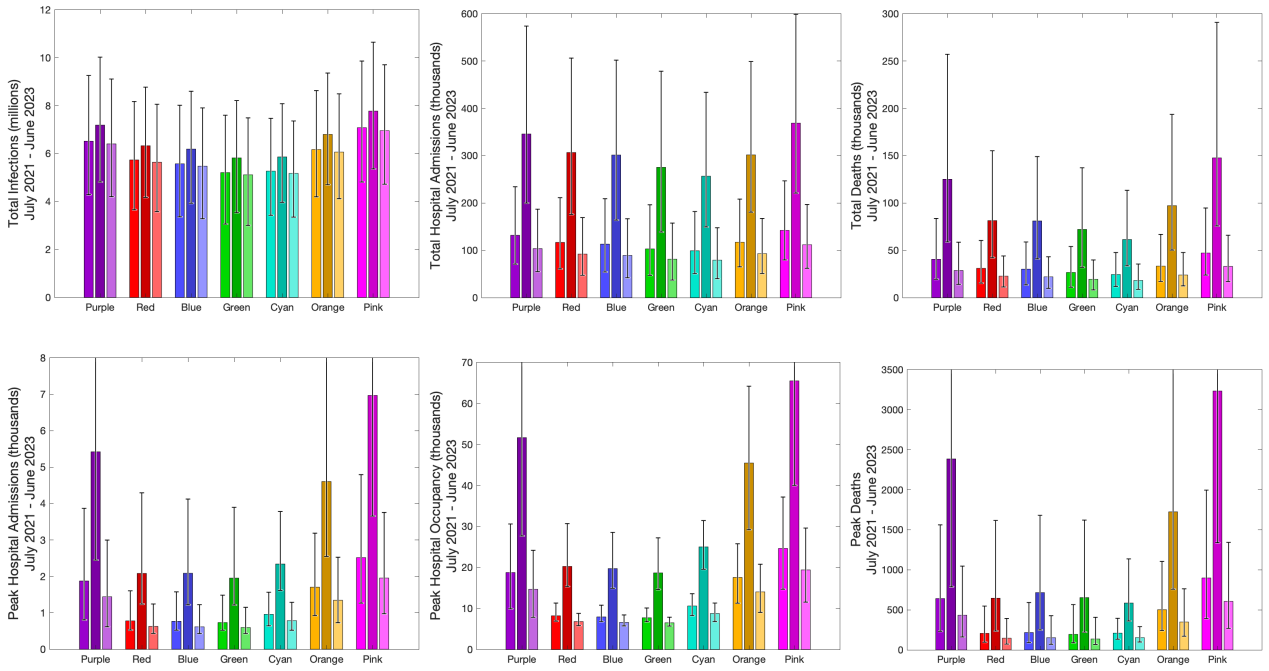

Fig. 14: Key quantities of interest (showing mean and 95% prediction intervals) calculated from 19th July 2021 to June 2023; for each scenario (colours) we present the results for the default (left bars), cautious (centre bars) and optimistic (right bars) vaccine efficacy assumptions. Top row show the total number of infections, hospital admissions and deaths. Bottom row shows the peak number of hospital admissions, the peak hospital occupancy and the peak number of deaths; for these peak values the y-scale has been truncated for greater clarity.

We observe two key findings from these results. Firstly, for our choice of vaccine efficacy parameters, the cautious assumption leads to a far more dramatic change in hospital admissions and deaths than infections. Secondly, while the pink and purple scenarios (which reach pre-COVID mixing earliest) are consistently associated with the largest future waves, the impact is far greater on the peaks than the total numbers; pink and purple scenarios lead to more peaky third waves whereas other behavioural scenarios spread the burden over a longer time scale. We stress again that 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 April 2021.

References

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