Road Map Scenarios & Sensitivity

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University of Warwick, 29 March 2021

Executive Summary

1) We consider the likely epidemiological impacts 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) There is considerable uncertainty about the level of control in each of the relaxation steps, and hence the resultant growth rate; none of the steps are directly comparable to previous controls, and there may be additional confounding behaviour as controls are relaxed.

3) All simulations and sensitivity analysis predict a distinct third wave of infection, with hospital admissions peaking between late-July and mid-August, and deaths peaking approximately two weeks later. There is considerable uncertainty in the height of the epidemic peak, reflecting general uncertainty in the population-level immunity due to infection.

4) A reduced model, where we only considered Steps 1 and 2 of the relaxation process, generated a relatively small associated wave of infection that was rapidly damped by increasing vaccine-derived immunity. Including Steps 3 and 4 generates a far larger wave.

5) Multiple key uncertainties were investigated, including: transmission levels within Steps 2, 3 and 4; seasonality; vaccine roll-out speed; vaccine efficacy and vaccine uptake. Of these lower than expected vaccine efficacy or higher transmission after Step 4 lead to significantly larger epidemics; while seasonality acts to suppress the summer wave.

6) The recent data on the efficacy of vaccination against infection, symptoms, severe disease and death means that we are much more optimistic about the level of population immunity than in previous studies. We are also more optimistic about the uptake of vaccines with levels above 95% assumed for those above 50 years old.

7) In this work we are not accounting for waning immunity either due to natural infection or vaccination, which will begin to play a significant role over longer time scales, and may be important by the Autumn.

8) The level of suppression offered by population-level immunity (both infection-derived and through vaccination) could easily be overcome by vaccine escape variants. Preventing or containing the imports of B.1.351 or similar variants is therefore central to the relaxation plan.

1

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 7 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. More recently, the model has been extended to include vaccination, initially to investigate priority ordering but increasing in complexity to include two-dose schedules and multiple actions of vaccine protection[2].

Vaccine uptake within the model mirrors the recorded data in terms of dose and age of those vaccinated so far. Projecting forwards, we follow the strict JCVI priority ordering for both Phase 1 and Phase 2. The uptake of vaccine has been far higher than anticipated; the brief was to assume that 95% of those in Phase 1 will accept the vaccine and 90% of those in Phase 2 - and that uptake of the second dose will be the same as the first. We have slightly deviated from this format, by stipulating that no additional people over 70 are likely to now come forward for first doses. In many regions the number of over 70s already vaccinated reaches or exceeds the number of individuals from ONS population estimates; but in London the uptake has been lower and may fall below the 95% ideal, currently only vaccinating 91% of the population over 70.

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. 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, as well as computing the reproductive number excluding immunity (R_{ei}), which can be conceptualised as the theoretical reproductive number at the start of the epidemic if such controls were in place (and the B1.1.7 variant was the dominant form). We assume that any change on the 29th March (which is largely concerned with outdoor mixing) is unlikely to have a significant impact on the reproductive number.

In generating these predictions, we have not accounted for any possible variants that may evade the vaccine protection provided by the presently available vaccines. These could either arise through natural mutation from currently circulating variants within the UK or could be imported into the UK. The presence of such 'escape mutants' has the potential to undermine the huge gains that have been achieved by the vaccination programme to date.

[1] Keeling, M. J., Hill, E., Gorsich, E., Penman, B., Guyver-Fletcher, G., Holmes, A., McKimm, H., Tamborrino, M, Dyson, L., and Tildesley, M. (2020). Predictions of COVID-19 dynamics in the UK: short-term forecasting and analysis of potential exit strategies *PLoS Comput Biol 17(1):* e1008619. https://doi.org/10.1371/journal.pcbi.1008619

[2] Moore, S., Hill, E.M., Tildesley, M., Dyson, L., Keeling, M.J. (2021) Vaccination and non-pharmaceutical interventions for COVID-19: a mathematical modelling study. *Lancet Infectious Diseases* https://doi.org/10.1016/S1473-3099(21)00143-2

[3] Keeling, M.J., Dyson, L., Guyver-Fletcher, G., Holmes, A., Semple, M.G., ISASIC4C Investigators, Tildesley, M.J. & Hill, E. (2020) Fitting to the UK COVID-19 outbreak, short-term forecasts and estimating the reproductive number medRxiv https://doi.org/10.1101/2020.08.04.20163782

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

1) *Vaccine action*. Having been vaccinated, the protection generated can affect multiple components of the infection, illness and transmission process. This has been updated from the original calculations and now considers four elements separately: efficacy against infection; efficacy against disease (which also affects transmission, as our default assumption is that asymptomatic infections transmit less than symptomatic ones); efficacy against hospital admission and efficacy against ICU and death. We are also basing our central estimates of vaccine efficacy on the data that are slowly being generated on protection observed in the UK population and elsewhere.

	Pfizer		AZ	
	1st Dose	**2nd Dose**	**1st Dose**	**2nd Dose**
Efficacy against infection	72% (63-78%)[A] 46% (40-51%)[B] **60%**	85% (73-92%)[A] 92% (88-95%)[B] **85%**	64% (46-77%)[C] **60%**	60% (36-75%)[C] **65%**
Efficacy against symptoms	91% (74-97%)[D] 58% (49-65%)[E] 57% (50-63%)[B] **60%**	95% (90-98%)[F] 85-90%[E] 94% (87-98%)[B] **90%**	76% (59-86%)[C] 58% (38-72%)[E] **60%**	81% (60-91%)[C] ~60%[E] **70%**
Efficacy against hospital admission	75% (47-95%)[E] 74% (46-86%)[B] 85% (76-91%)[F] 79% (47-92%)[G] **80%**	87% (55-100%)[B] **90%**	72%[E] 94% (73-99%)[F] 80% (36-94%)[G] **80%**	**90%**
Efficacy against death	80% (50-99%)[E] 72% (19-100%)[B] **80%**	**90%**	**80%**	**90%**

A. Latest SIREN study data. B. Data from Israel NEJM[4]. C. Phase 3 Trial[5]. D. PHE analysis of trial data. E. PHE analysis of Pillar 2 data. F. PHS analysis[6]. G. Bristol Hospital analysis[7].

[4] Dagan *et al* (2021) BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N.E.J.M.* 10.1056/NEJMoa2101765

[5] Voysey *et al* (2021) Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet* **397** 881-891 https://doi.org/10.1016/S0140-6736(21)00432-3

[6] Vasileiou *et al.* (2021) Effectiveness of first dose of covid-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people. www.ed.ac.uk/files/atoms/files/scotland_firstvaccinedata_preprint.pdf.

[7] Hyams *et al* (2021) Assessing the Effectiveness of BNT162b2 and ChAdOx1nCoV-19 COVID-19 Vaccination in Prevention of Hospitalisations in Elderly and Frail Adults: A Single Centre Test Negative Case-Control Study. *Lancet PrePrint.* https://dx.doi.org/10.2139/ssrn.3796835

The two vaccine efficacies are combined by taking the weighted average based on the amount of the two vaccines used in the UK; since 1st February approximately 30% of vaccinations have been Pfizer with the remainder AstraZeneca, and we assume this ratio going forwards. This leads to a combined efficacy against infection of 60% and 71% after first and second doses; an efficacy against symptoms of 60% and 76% after first and second doses; an efficacy against severe illness and hospitalisation of 80% and 90% after first and second doses; and an efficacy against death of 80% and 90% after first and second doses. We assume that there is a 2-week delay between vaccination and protection for both the first and second doses.

2) *Controls, timings and estimates of R (excluding immunity)*. Two sets of predictive scenarios are considered: in the first (Part 1) relaxation is stopped after Step 2, allowing us to examine the likely sensitivity to variations in predicted growth rate at the start of this period; in the second (Part 2) all relaxation steps are performed at their earliest date (Step 2 on 12th April, Step 3 on 17th May and Step 4 on 21st June). Each of the steps is envisaged as a proportionate reduction in the level of NPIs control, relative to levels estimated for early March (~75% for step 2, ~35% for step 3 and 15% for step 4). For our default assumptions, R excluding immunity (which captures the impact of controls) increased from approximately 1.24 (CI 1.08-1.48) during the main January-February lockdown, to 1.49 (CI 1.27-1.65) in Step 1 due to school reopening, to 1.76 (CI 1.59-1.90) after Step 2, to 2.53 (CI 2.40-2.69) after Step3, and finally 2.97 (2.79-3.14) after Step 4. Sensitivity to these assumptions is investigated within the document.

3) *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 is limited data on this aspect of transmission[8], which has therefore not been incorporated in the main simulation, but seasonality is examined in Figure 2.8. 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[8]. We report the level of seasonality (ϕ) as the drop in transmission over the summer relative to the peak in the winter months:

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

Based on available data[8], 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.

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[8] Baker et al (2020) Susceptible supply limits the role of climate in the early SARS-CoV-2 pandemic. *Science* **369** 315-319 10.1126/science.abc2535

PART 1. Only Step 2 occurs.

We initially assume that only Step 2 of the road map takes place and analyse the impact of this relaxation upon hospital admissions, hospital occupancy and daily deaths. The results are summarised in Figures 1.1-1.4.
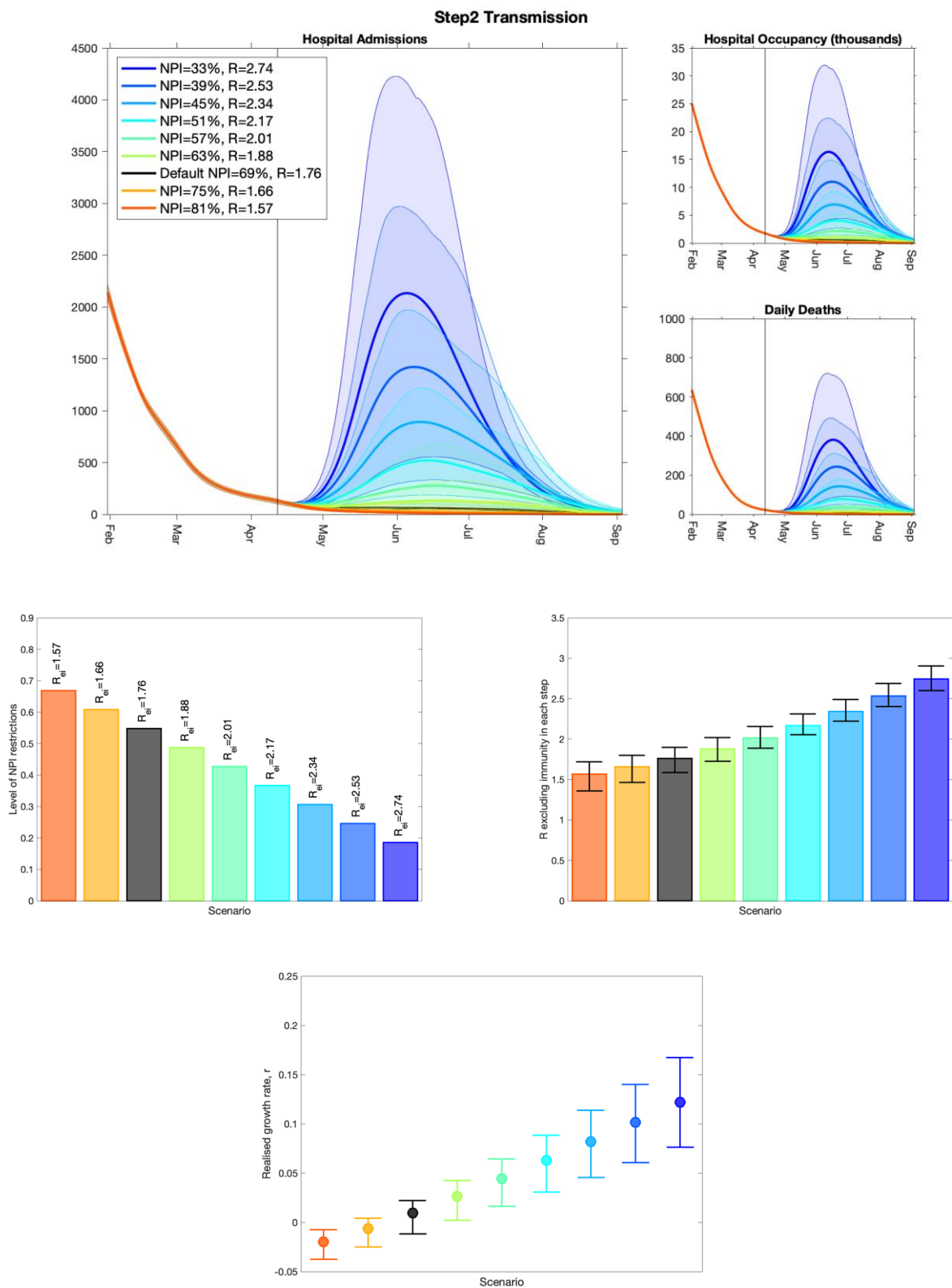
Predictions for Hospital Admissions, Hospital Occupancy & Deaths: Step 2 only.
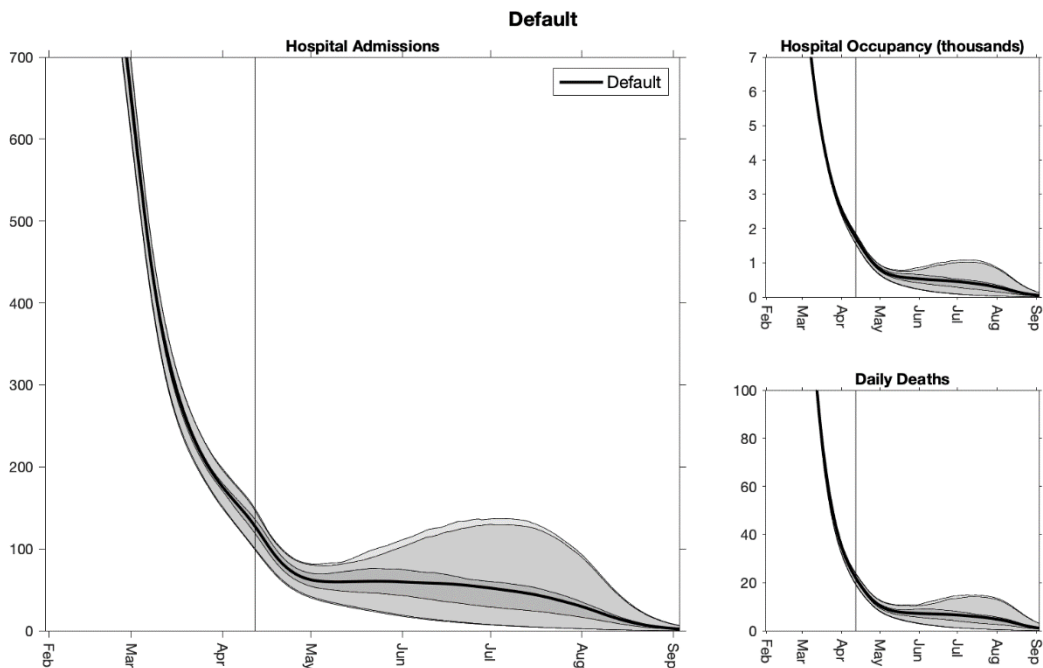
Figure 1.1 Daily Hospital Admissions (left), Hospital Occupancy (top right) and Daily Deaths (bottom right) for England under the default assumptions for the relaxation roadmap. Shaded regions show the 95%, 90% and 50% prediction intervals, while the solid line shows the mean.

Using our default parameters, the model predicts a very small resurgence across all metrics in late Spring and early Summer (Figure 1.1), due to the relatively small change in control measures occurring in step 2. In this model, R excluding immunity has increased from approximately 1.24 (CI 1.08-1.48) during the main January-February lockdown, to 1.49 (CI 1.27-1.65) due to school reopening, to approximately 1.76 (CI 1.59-1.90) after Step 2. (Note that values of R excluding immunity above 1.0 do not necessarily correspond to growth of infection due to the substantial impact of infection and vaccine derived immunity). Under these default assumptions, and ignoring relaxation Steps 3 and 4, we expect to observe 7000 hospital admissions (CI 2600-13,500) and 1050 deaths (CI 490-1760) from 12th April 2021 until June 2022.

However, there is considerable uncertainty concerning how restriction in Step 2 will translate into epidemic growth rates and how the population will respond to these changes. We therefore consider a range of realised control levels after Step 2 (Figure 1.2), which lead to mean values of R excluding immunity between 1.57 and 2.74, which translates to mean growth rates between -0.02 and 0.12 per day. Unsurprisingly, lower levels of control lead to higher growth rates and larger subsequent epidemic waves. As expected, peak hospital admissions occur earlier than peak hospital occupancy, with peak deaths occurring later.

Figure 1.2 Top Panels. Daily Hospital Admissions (left), Hospital Occupancy (top right) and Daily Deaths (bottom right) in England for Step 2 of the relaxation roadmap, and considering a range of different adherence levels to non-pharmaceutical interventions (from 0.19 to 0.67). Shaded regions show the interquartile prediction intervals, while the solid line shows the mean. The R values given in the legend represent reproductive numbers excluding immunity and range from 1.57 to 2.74.

Lower Panels. The level of NPI restrictions for each scenario, the theoretical R number excluding immunity for each NPI level and the realised growth rate, r during Step 2. The colour of each bar corresponds with the line colours in the Top Panels, with the default parameters in black.
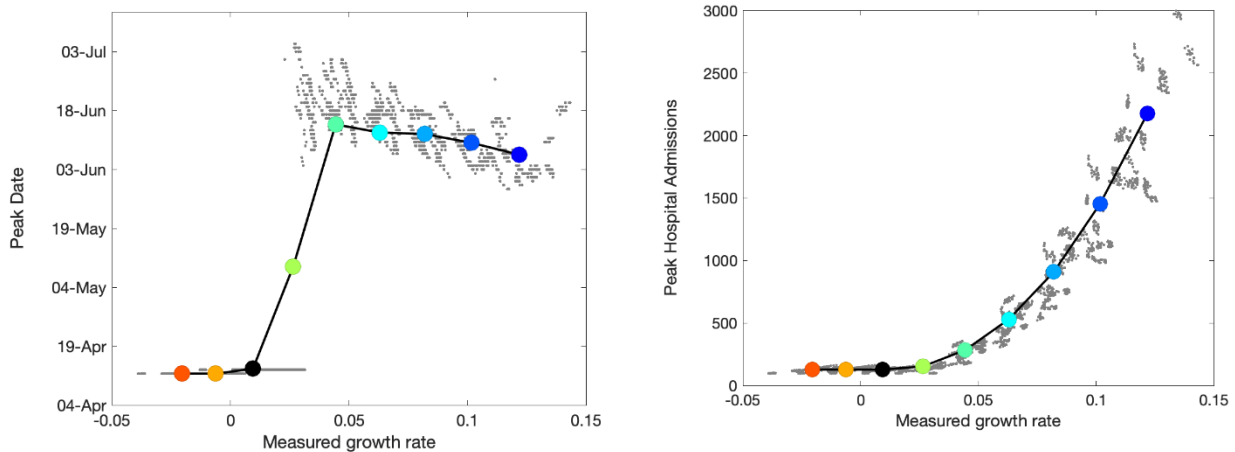
Figure 1.3 Peak date (left panel) and peak height (right panel) in hospital admissions for the range of scenarios considered in Figure 1.2. Grey dots represent the results for individual simulations, coloured dots represent the average for a given parameter set. Default parameters shown in black.

Considering these mean epidemic waves in more quantitative detail, we find that peak height grows non-linearly with the estimated growth rates (Figure 1.3). Of more immediate policy relevance is the time to peak, which informs the period over which positive growth occurs before it is brought under control by the depletion of susceptibles - which is a combined action of vaccination and infection. For low growth rates (less than 0.02 per day which corresponds to an effective *R* below 1.12) there is the potential for the vaccination programme to reverse the early growth. However, for larger growth rates, we expect a substantial wave of infection, which is only brought under control in June after considerable numbers have been admitted to hospital.

This highlights that measurement of and response to the growth rate after Step 2 is vital in terms of the continued relaxation of control measures. Although we expect the growth rate to remain relatively small after Step 2, larger growth rates will not be readily contained simply through the action of vaccination and more stringent methods may be required. Growth rates above 0.03 may necessitate a significant delay before other steps can proceed.

Sensitivity to Vaccine Effectiveness: Step 2 Only
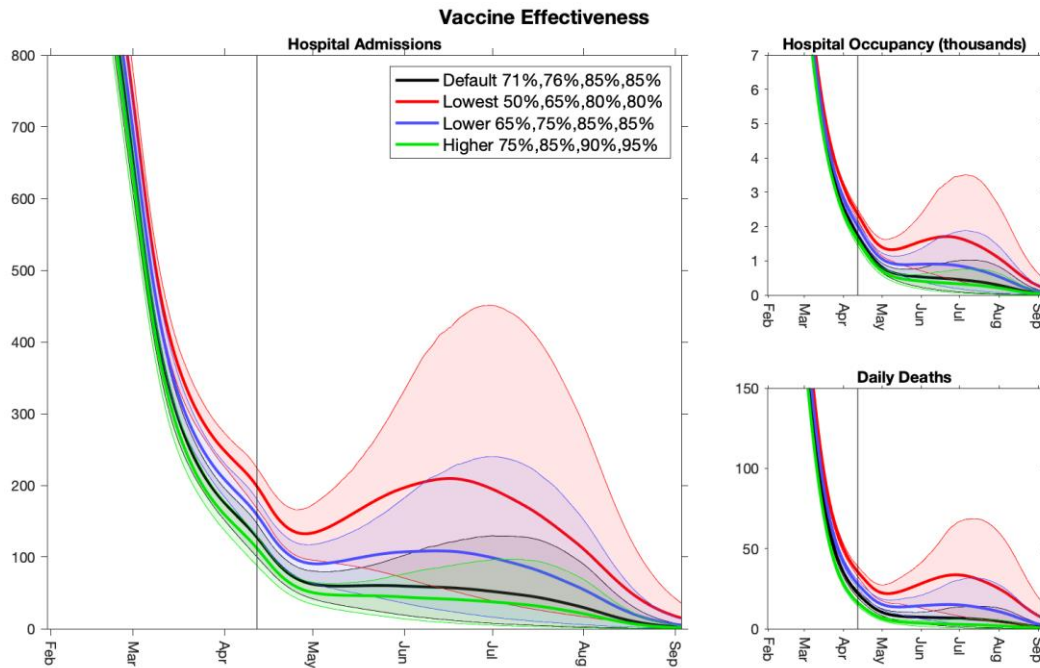
Figure 1.4 Sensitivity of the epidemic curves to vaccine efficacy assumptions.

As described in the introductory material, there is still uncertainty over the efficacy of the vaccine against infection, symptoms, severe disease and death. Some of this uncertainty (especially contradictory evidence from different studies) may in part be due to different study populations; for example much of the Phase 3 trial data is from participants under 65, whereas the real-world data will predominantly be from those over 80. Here we consider four different parameter sets for vaccine efficacy as shown below:

Table of vaccine efficacy after the second dose for the four parameter set considered

| Efficacy against:	Lowest efficacy assumptions	Lower efficacy assumptions	Default assumptions	Higher efficacy assumptions
infection	50	65	71	75
symptoms	65	75	76	85
hospital admission	80	85	90	90
death	80	85	90	95

Even when only Step 2 is considered, vaccine efficacy has a major impact on the size of the outbreak. For the lowest efficacy assumptions (shown in red, which are still within the 95% confidence intervals of many published studies) giving rise to larger numbers of hospital admissions and deaths. Under the default assumptions, and ignoring relaxation Steps 3 and 4, we expect to observe 7000 hospital admissions (CI 2600-13,500) and 1050 deaths (CI 490-1760) from 12th April 2021 until June 2022; whereas this increases to 21,100 (CI 7500-40,600) and 3830 (CI 1500-6870) under the lowest efficacy assumptions.

PART 2. Steps 2, 3 and 4 occur.

We now consider all four steps the road map takes and analyse the impact of this relaxation upon hospital admissions, hospital occupancy and daily deaths. The results are summarised in Figures 2.1-2.10 below.
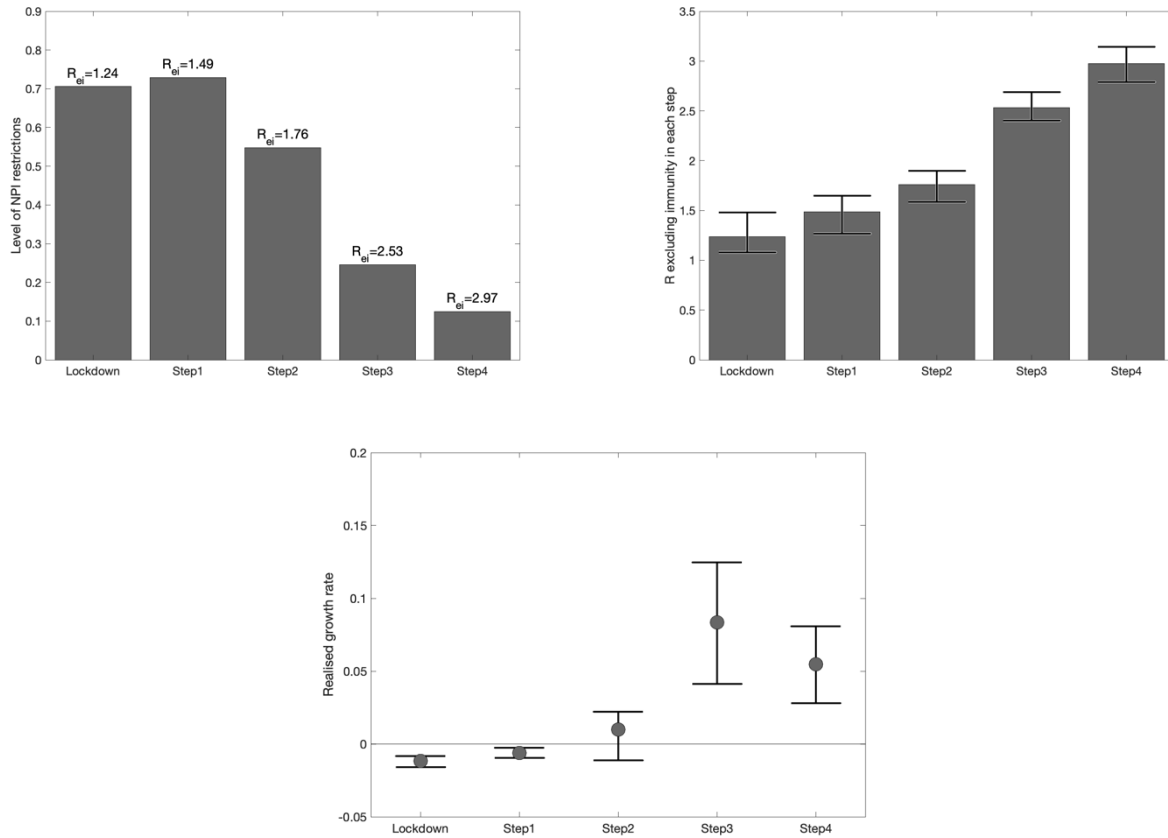
Predictions for Hospital Admissions, Hospital Occupancy & Deaths.
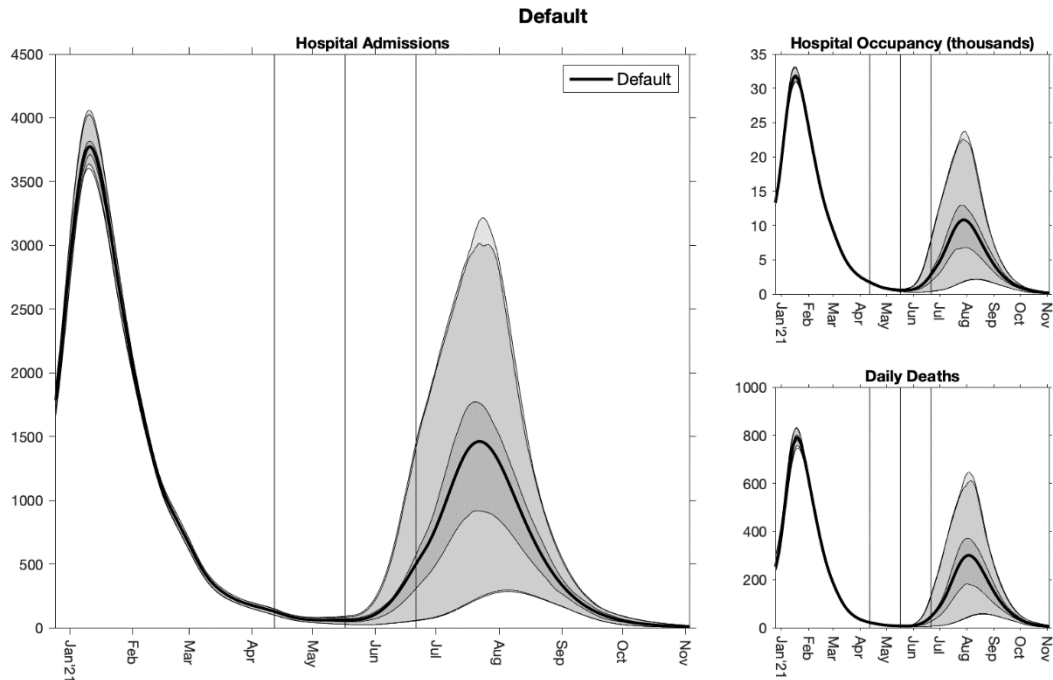
Figure 2.1 Daily Hospital Admissions (left), Hospital Occupancy (top right) and Daily Deaths (bottom right) for England under the default assumptions for the relaxation roadmap. Shaded regions show the 95%, 90% and 50% prediction intervals, while the solid line shows the mean.

Figure 2.1 shows the predicted epidemic waves following the four relaxation steps, focusing on hospital admissions, hospital occupancy and deaths; hospital admissions peak on 23rd July (95% CIs 15 July - 6 August) while deaths peak on 4th August (95% CI 27 July - 21 August). The scale, timing and shape of this wave is driven by two factors: the relaxation (figure 2.2) and the population-level immunity (figure 2.3).

The level of restrictions in lockdown and Step 1 are estimated from the current data, with lockdown measured as an average during January and February, and Step 1 as the most recent level of control. Although we estimate that the level of restrictions is slightly higher (although not statistically significant) in Step 1, this is counteracted by schools re-opening, leading to a higher R value. We note that although we have assumed a reduction in NPI restrictions in each subsequent step (Steps 2-4), which therefore naturally translates to an increase in the reproductive number excluding immunity, the realised growth rate (r) is greatest in Step 3 where the relative change in controls is assumed greatest and which occurs at an earlier time such that there is less population level immunity.

Figure 2.2 Example of the change in NPI restrictions and hence the change in the value of R excluding immunity through different step phases.

Under the default assumptions, we expect to observe 84,400 hospital admissions (CI 20,900-168,000) and 18,600 deaths (CI 4500-36,200) from 12th April 2021 until June 2022. These occur predominantly over the summer months June-September (inclusive) and so could easily be disrupted by patterns of summer mixing (Figure 2.8).
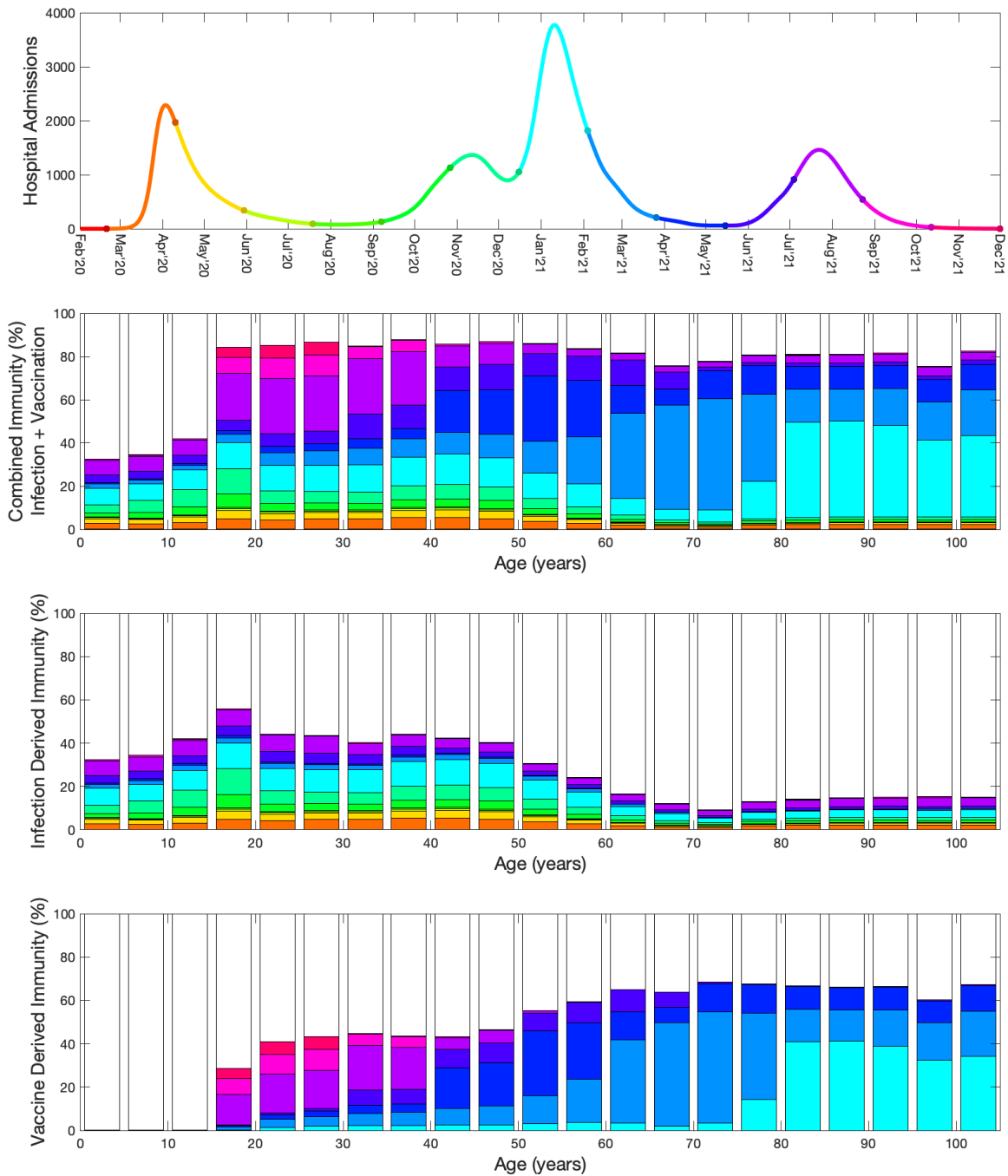
Figure 2.3 Change in immunity through time over thirteen time intervals, represented by different colours. The top graph shows the mean number of daily hospital admissions over time, the centre graph shows the build-up of immunity in the population (from both infection, as well as first and second doses of vaccination), while the lower graphs shows the immunity from infection and vaccination alone.

Of particular importance for determining the scale of the epidemic wave is the level of NPI controls after Step 4; here we have assumed control measures that generate a reproductive number excluding immunity of 2.97 (CI 2.79-3.14). This is larger than observed at the start of the first wave due to the dominance of the B1.1.7 variant, but smaller than the theoretical maximum due to some moderate level of controls. Further investigation of the impact of Step 4 NPI controls is investigated in Figure 2.4 below. It is worth noting that there is considerable uncertainty in the predictions, with wide 95% credible intervals largely driven by uncertainty in population-level immunity.

Population level immunity is key for long-term control of COVID infections (Figure 2.3). By investigating immunity through time and across age-groups we build a picture of the dynamics. The two observed waves of hospital admissions and the smaller third predicted wave are divided into thirteen time-windows of 50 days each. In the first and second waves (orange and cyan) there is a clear increase in population level immunity (Figure 2.3 lower panels) with most infection in those under 50 and a noticeable peak in those aged 15-19 years. However, during the second wave (cyan) the vaccination programme began, which increased the immunity in older age-groups (Figure 2.3 lower panel). The action of vaccination slowly percolates down the age groups, enhancing the immunity already generated by infection.

We anticipate that the scale of population-level immunity generated by October 2021 may be sufficient to contain infection as long as moderate levels of control are maintained during Step 4.

Sensitivity Analyses.

We now consider several sensitivity analyses to develop a better understanding of the interplay between the relaxation roadmap and key epidemiological and vaccine parameters.

Sensitivity to Final Transmission Level
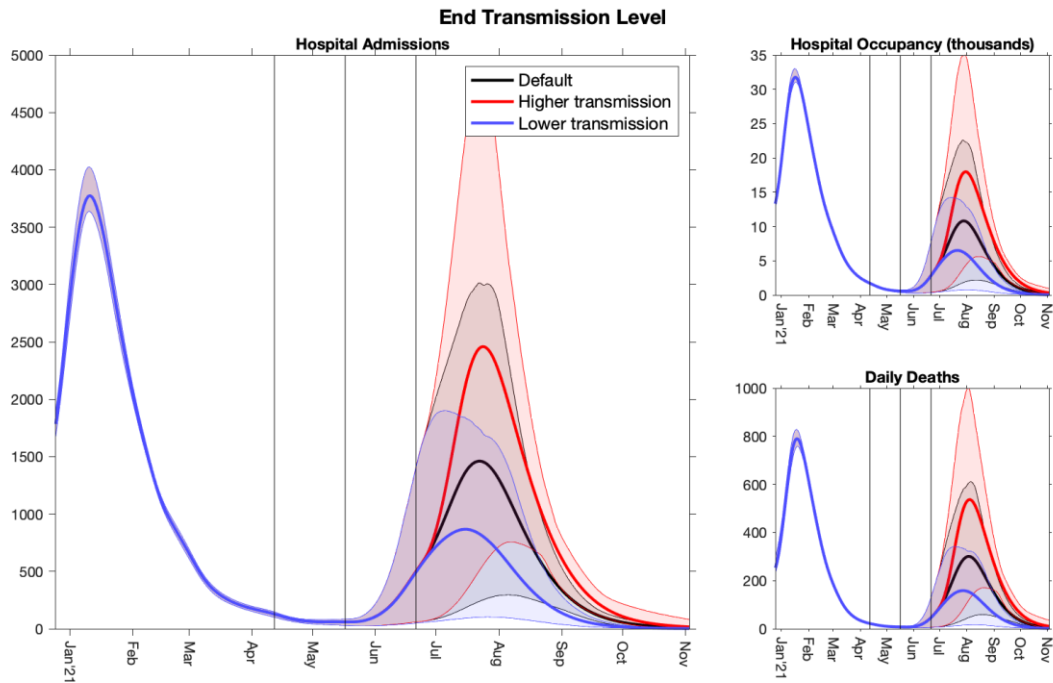
Figure 2.4 Different epidemic waves generated by higher and lower NPI restrictions during Step 4 and hence lower and higher values of R excluding immunity.

We initially focus on the level of NPIs after Step 4, which is one of the key unknowns yet also a key determinant of the size of the resultant wave (Figure 2.4). We again show the default model, for which Step 4 generates an R excluding immunity of 2.97 (CI 2.79-3.14) (Figure 2.5) together with a more optimistic assumption (blue, R excluding immunity 2.53 (CI 2.35-2.70)) and a more pessimistic assumption (red, R excluding immunity 3.51 (CI 3.31-3.70)). Even this most pessimistic assumption is lower than the theoretical maximum of approximately 4.31 due to maintenance of some degree of control.

Greater control in Step 4, and hence lower R values, lead to smaller and earlier waves of infection; while less control leads to larger and later waves pushing hospital occupancy and deaths into late Autumn. In comparison to the default model where we expect 84,400 (CI 20,900-168,000) and 18,600 (CI 4500-36,200) hospital admissions and deaths, our more optimistic assumption generates 53,600 (CI 8800-118,000) and 10,600 (CI 1600-23,800), whereas the more pessimistic assumption generates 129,000 (CI 53,100-224,800) and 30,500 (CI 13,300-50,300).
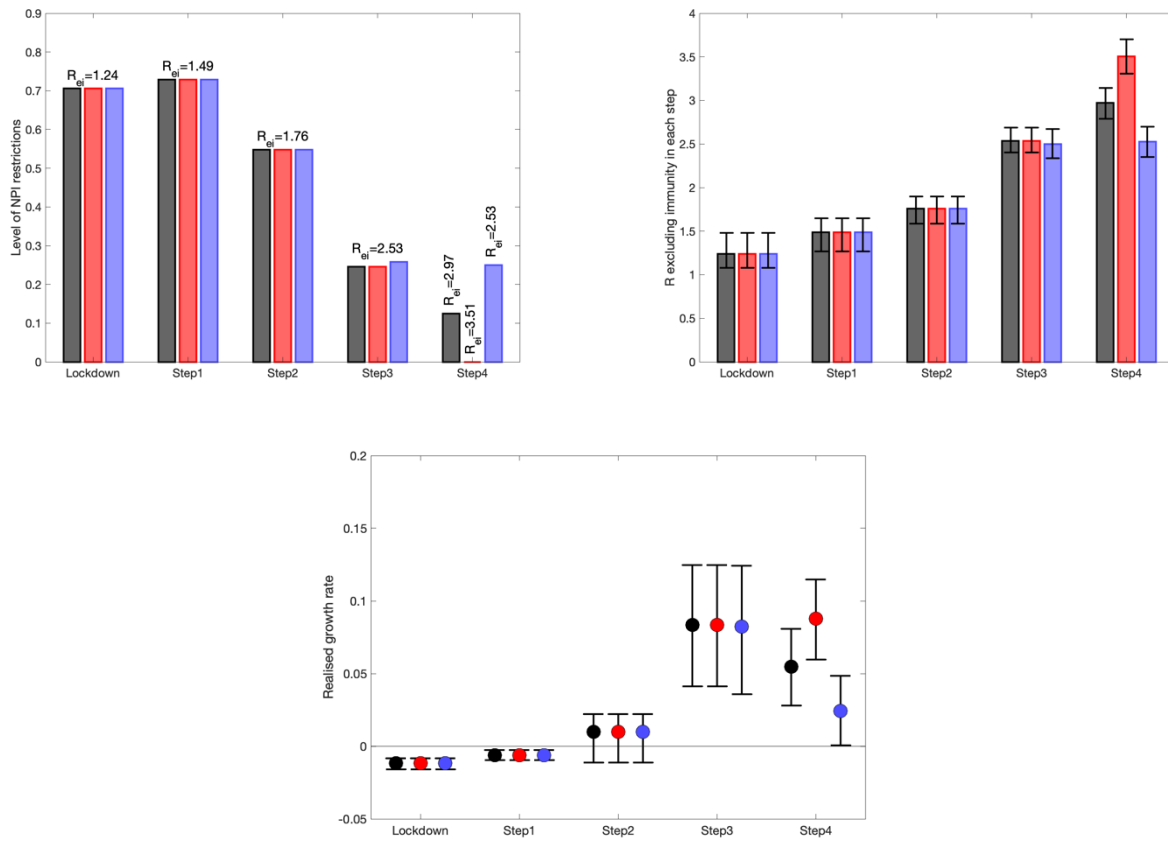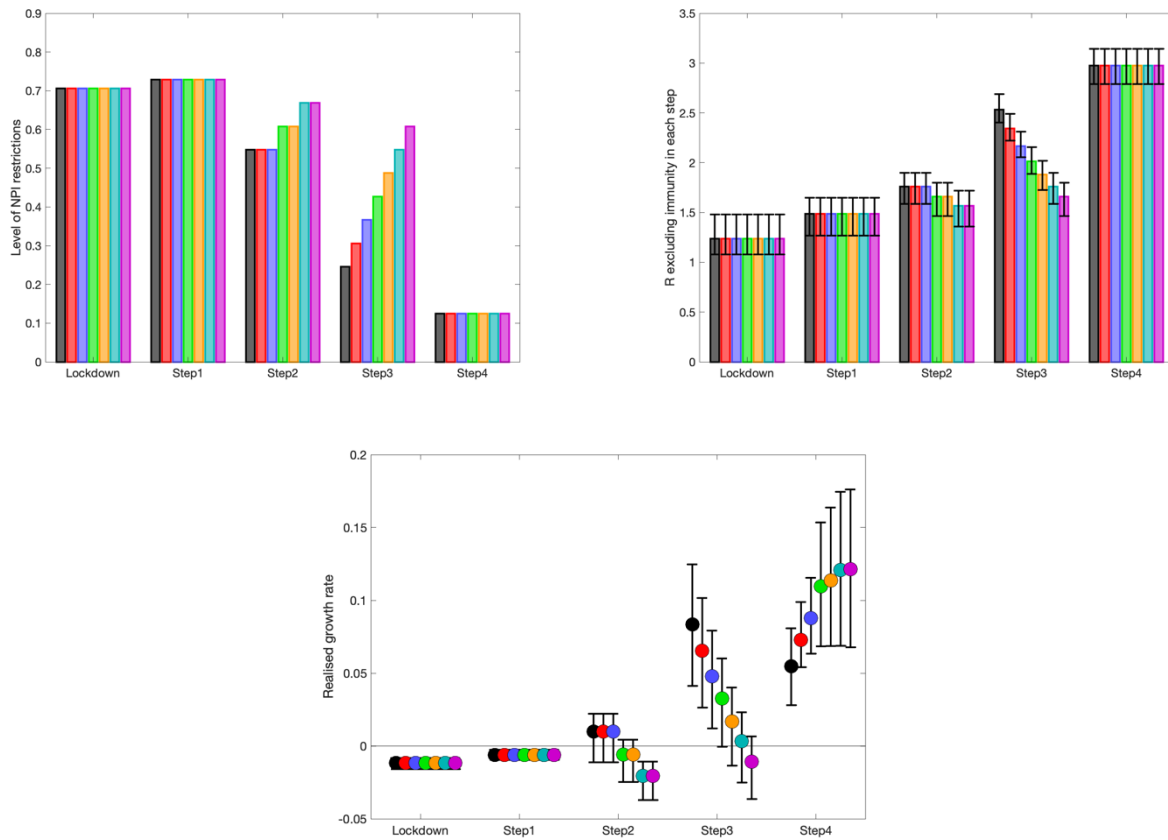
Figure 2.5 Example of the change in NPI restrictions and hence the change in the value of R excluding immunity through different step phases.

Sensitivity to Transmission in Steps 2 and 3
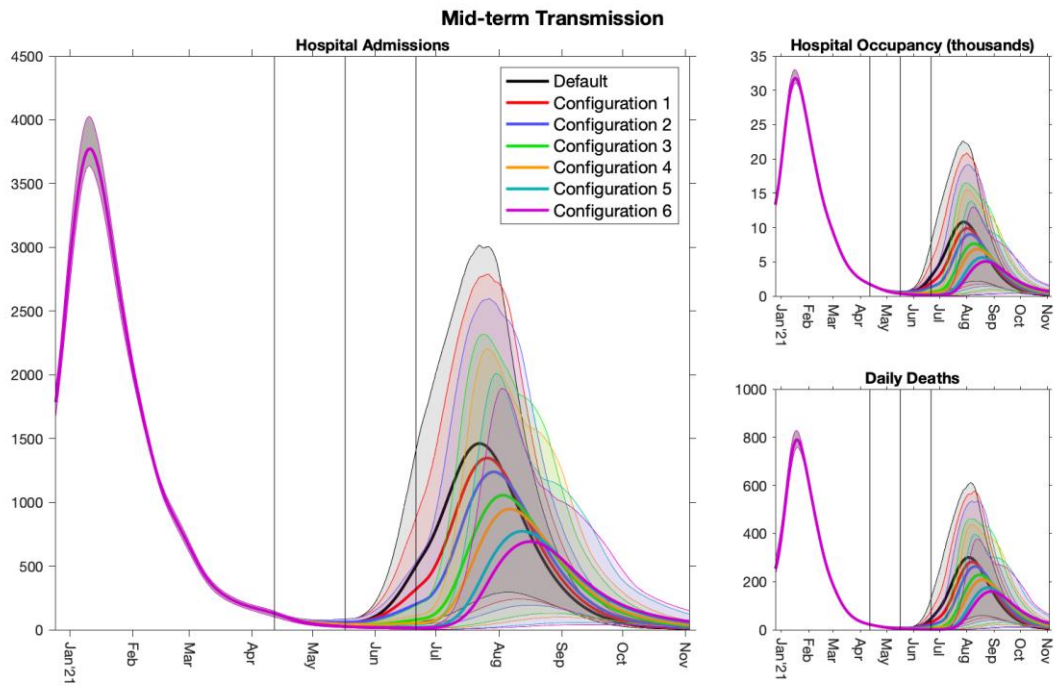
Figure 2.6 Different epidemic waves generated by different levels of NPI control (and hence different R excluding immunity values) during Steps 2 and 3.

Figure 2.7 The change in NPI restrictions and hence the change in the value of R excluding immunity and the realised growth rate through different step phases.

For a fixed level of control in Step 4 (R excluding immunity of 2.97) we observe that greater levels of control in Steps 2 and 3 can generate later and smaller epidemic waves (with associated hospital admissions and deaths). The smaller size of later waves is primarily due to the build-up of population-level immunity through vaccination.

Predicting the level of control in any given step is challenging due to the lack of available behavioural data on similar sets of restrictions and the potential difference between how relaxation of measures is treated by the public. Any of the epidemics shown is therefore plausible, with a significant spread in both magnitude and timing.

Maintaining tighter control in Step 3 clearly has substantial advantages, leading us to conclude that this may be one of the key public-health messages.

Sensitivity to Seasonality
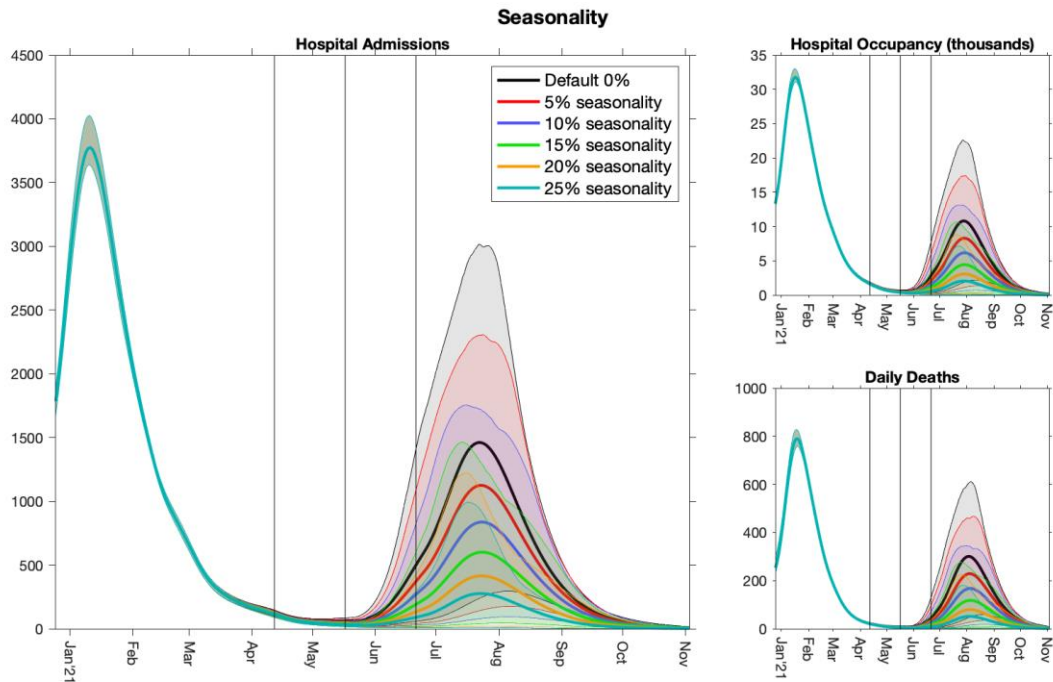
Figure 2.8 Impact of seasonality (measured as the relative drop in transmission at the lowest point compared to the peak) on the infection dynamics.

Seasonality is seen to have a substantial impact on the outbreak after Step 4. Estimates from Baker *et al* (2020)[8] 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.

10% seasonality, which is a plausible estimate for what may be expected in the UK could reduce the peak number of hospital admissions by 44% (CI 30-67%) compared to the default model without seasonality, and reduces the total number hospitalised in the third wave by 43% (CI 32-63%).

We find that squashing of the peak by imposing high seasonality does not lead to a displaced outbreak later in the year. This is due to the high degree of vaccine derived immunity that will have developed in the population by this point, such that by November England is likely to be close to herd immunity - dependent on the level of control in Step 4. In addition, the August trough in transmission is well-placed to suppress this relaxation wave.

**Sensitivity to Vaccine Roll-out speed**
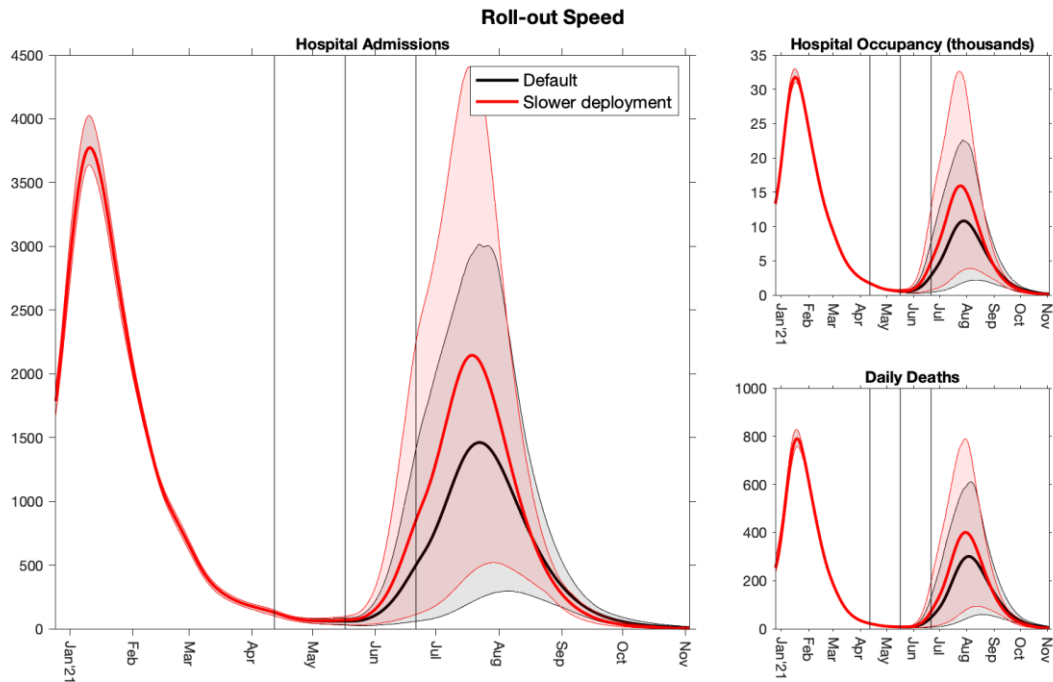
Figure 2.9 The impact of a slower vaccine roll-out speed (red) which has fewer vaccinations being delivered in the second half of May compared to the default assumption.

As expected, a slightly slower vaccine roll-out programme leads to a larger epidemic wave, as less population immunity will have developed by the time Steps 3 and 4 are enacted. However, given that there is relatively little difference between the two prescribed roll-out speeds (around 7% over 20 weeks), the difference between the two epidemic profiles is surprisingly large.

This suggests that maintaining high delivery of vaccine over the entire period is key and small drops in supply could generate significant changes in hospital admissions as lower population level immunity is amplified by the associated greater growth rate.

Sensitivity to Vaccine Effectiveness
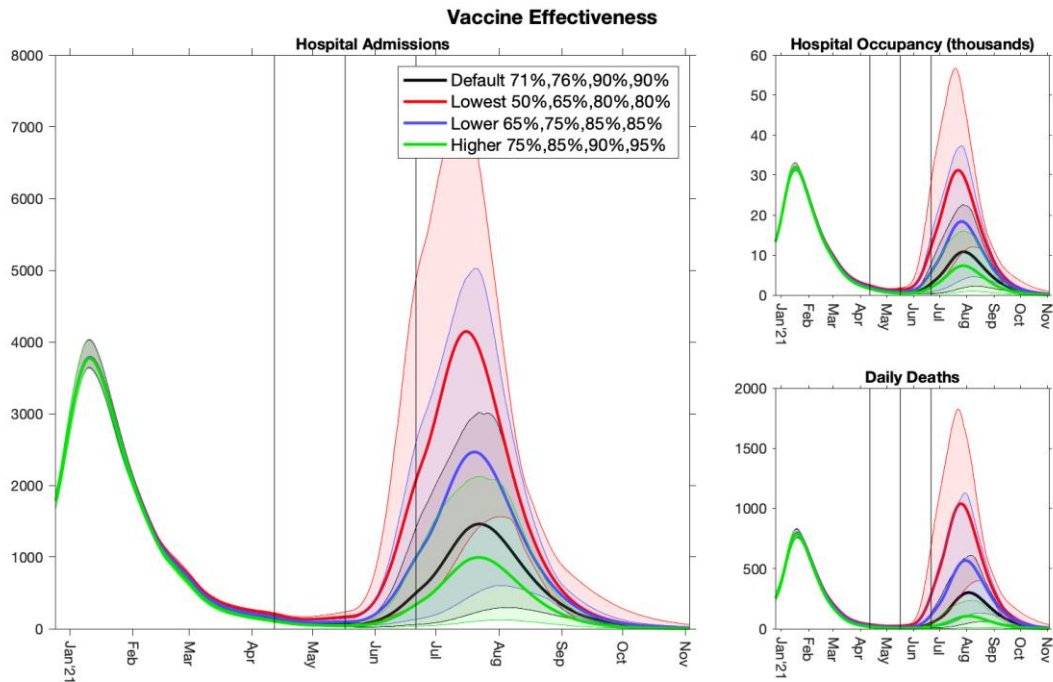
Figure 2.10 Sensitivity of the epidemic curves to vaccine efficacy assumptions.

As we described in the introductory material, there is still considerable uncertainty over the efficacy of the vaccine against infection, symptoms, severe disease and death. Some of this uncertainty (especially contradictory evidence from different studies) may in part be due to different study populations; for example, much of the Phase 3 trial data is from participants under 65, whereas the real-world data will predominantly be from those over 80. Here we consider four different parameter sets for vaccine efficacy as shown below:

Table of vaccine efficacy after the second dose for the four parameter set considered

Efficacy against:	Lowest efficacy assumptions	Lower efficacy assumptions	Default assumptions	Higher efficacy assumptions
infection	50	65	71	75
symptoms	65	75	76	85
hospital admission	80	85	90	90
death	80	85	90	95

Vaccine efficacy has a major impact on the size of the outbreak, with the lowest efficacy assumptions (which are still within the 95% confidence intervals of many published studies) giving rise to very large numbers of hospital admissions and deaths. **Under the default assumptions, we expect to observe 84,400 hospital admissions (CI 20,900-168,000) and 18,600 deaths (CI 4500-36,200) from 12th April 2021 until June 2022; whereas this increases to 226,300 (CI 111,200-364,800) and 59,900 (CI 30,100-93,300) under the lowest efficacy assumptions.**

## Sensitivity to Vaccine Uptake in 18-50 year olds

Throughout we have assumed that the vaccine uptake will remain high in all age-groups, in particular we assumed 90% uptake in the Phase 2 vaccination programme which targets individuals aged 18 to 49. Here we consider sensitivity to this assumption by considering a range of uptake values for this lower age group.
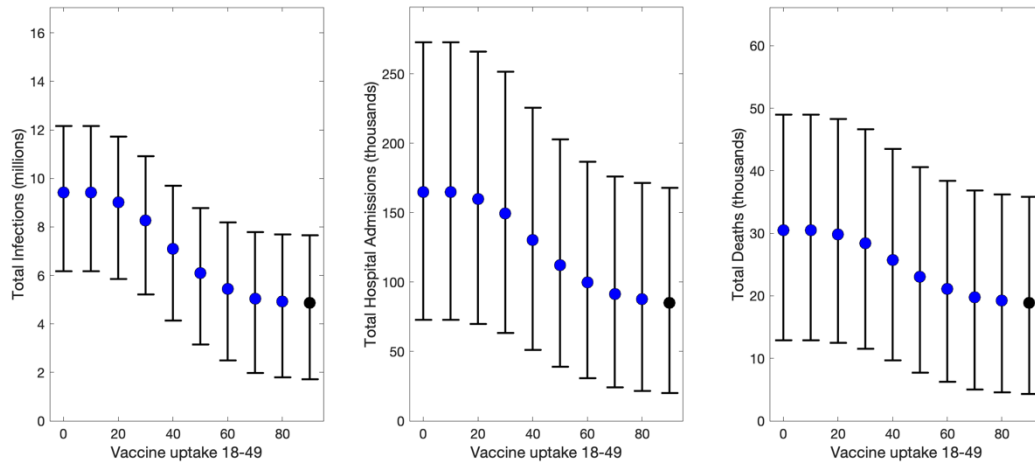
Figure 2.11 The mean and credible intervals for the total number of infections, hospital admissions and deaths over the third wave of the epidemic (from 12th April 2021 until June 2022). The y-scale is set such that the default model (black, 90%) is at the same height in all three graphs, showing that the greatest variation is in those requiring hospital admission.

As expected, lower uptake in the 18-49 year olds leads to higher number of cases, hospital admissions and deaths. However, the pattern is sigmoidal with relatively shallow gradients for either high or low uptake.

Proportion of hospital admissions and deaths that have been vaccinated.
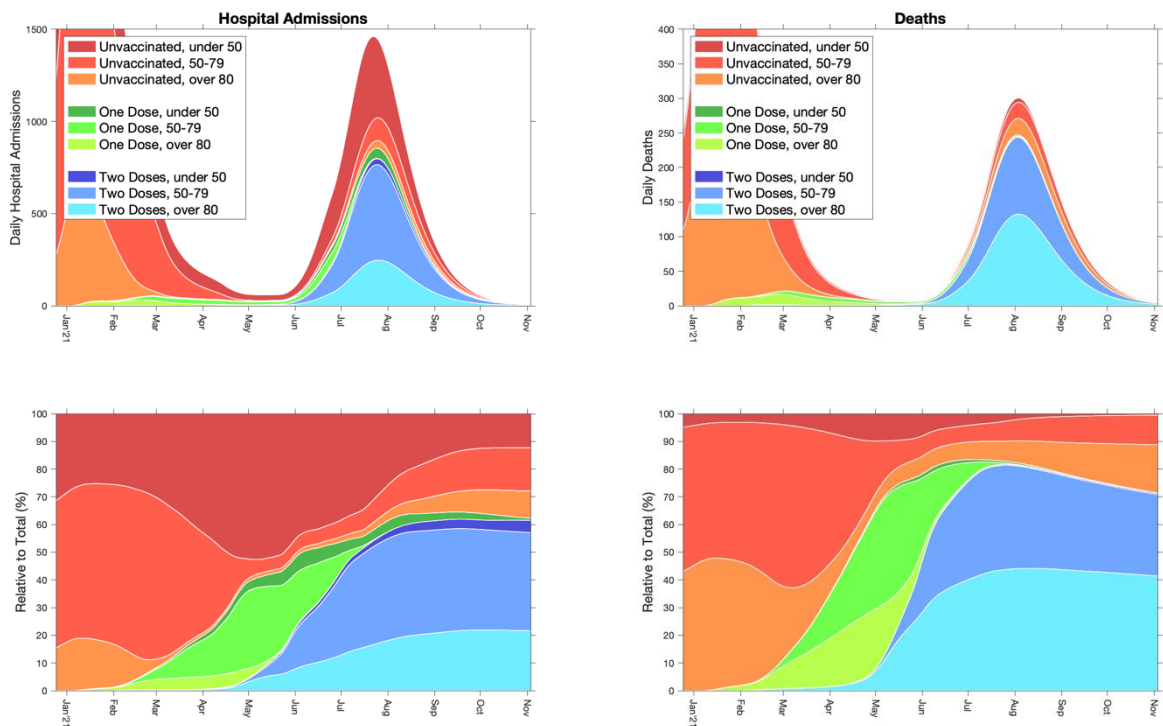
Figure 2.12 Distribution of ages and vaccination states throughout the relaxation wave. Those that have not been vaccinated are in red, those receiving one dose are in green and those that have received two doses are in blue. Darker colours correspond to younger age groups. Results for both hospital admission and deaths are shown.

Examining the constituent components within the relaxation wave is important for understanding the action of the vaccine and where to focus public health efforts. The top panels show the components of the relaxation wave over time: those that have not been vaccinated are in red, those receiving one dose are in green and those that have received two doses are in blue. Darker colours correspond to younger age groups (under 50) while the lighter colours correspond to the older age groups (above 80).

The relaxation wave in both hospital admission and deaths is dominated by those that have already received two doses of the vaccine, comprising around 60% and 70% of the wave respectively.

This dominance can be attributed to the high levels of uptake in the most at-risk age groups, such that vaccine failures account for more serious illness than unvaccinated individuals. If the vaccine generates a higher efficacy against severe illness than in our default model (cf green line in Figure 2.10), then both the relative and absolute size of the blue regions would decrease.

Regional Variation

The COVID-19 outbreak in England has been characterised by regional fluctuations superimposed on the general waves of infection. The South West has consistently had relatively low numbers of cases, hospitalistions and deaths; the North West dominated the early growth of the second wave while London has often shown more dramatic rise and decline than the rest of the country. We expect this pattern to continue for the relaxation wave, and expect some spatial patterns to be amplified by heterogeneity in vaccine uptake.

Considering the default parameters, we find that London and the Midlands have by far the smallest relaxation waves – despite London having a slightly lower vaccine uptake. This is attributable to the larger proportion of the population infected in previous waves leading to greater immunity within the population (Figure 2.13). By a similar reasoning, the South West has a relatively large relaxation wave due to its lower level of population-level immunity to date.
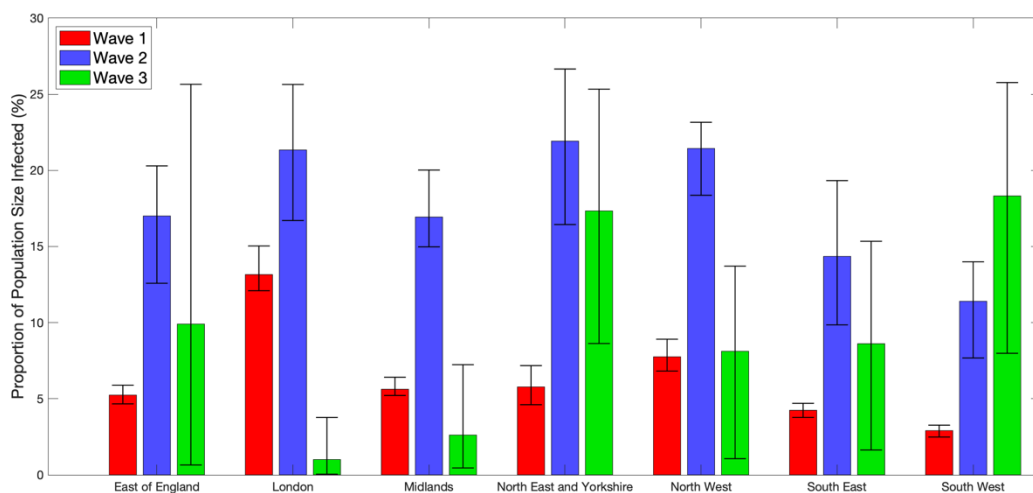
Figure 2.13 The estimated size of the Wave 1 (Feb-Aug 2020), Wave 2 (Sept 2020-Mar 2021) and Wave 3 (Apr 2021 onwards). London, which is estimated to have the largest combination of waves 1 and 2 has the smallest predicted relaxation wave, while the South West which is estimated to have the smallest combination of previous waves has the relatively largest third wave.

Variation in vaccine uptake at a smaller spatial scale is much more pronounced than at a regional scale, with some LTLAs only achieving 60-70% uptake in their oldest residents (although such estimates are potentially affected by the errors in estimating the number of residents within an area). Such low-uptake regions could potentially become local hot-spots of infection, driving small scale waves of infection.

Variants

We have assumed throughout that prior infection gives perfect protection against future infections (with no waning of immunity) and that the efficacy of the vaccinations is maintained. The UK is currently dominated by the B.1.1.7 variant, and the vaccines in use have good efficacy against this variant.

The potential for novel variants that evade vaccine immunity or infection-acquired immunity could significantly change the results shown here. In particular, preliminary evidence indicates that the AstraZeneca vaccine may have reduced efficacy against B1.351, with efficacy against mild to moderate disease estimated as 10.4% (95% CI, −76.8 to 54.8)[9]. While it is hoped that the vaccines may be more efficacious at preventing severe disease from B.1.351, there are currently no estimates of this efficacy. Similarly, there is limited evidence regarding the protection of either the Pfizer vaccine or prior infection with B.1.1.7 against B.1.351, although studies show reduced neutralization titers from Pfizer and AstraZeneca vaccinees and convalescent sera[10,11].

In a worst-case scenario, with low existing immunity against B.1.351, importation of this variant into the UK could lead to a large wave of infection and morbidity. There is again limited evidence regarding the relative transmissibility of B.1.351 compared to B.1.1.7 (in the same population); however, even if B.1.351 is less transmissible the lower associated immunity could provide a significant competitive advantage leading to a wave of B.1.351 infection.

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[9] Madhi, Shabir A., et al. "Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B. 1.351 Variant." New England Journal of Medicine (2021).

[10] Planas, Delphine, et al. "Sensitivity of infectious SARS-CoV-2 B. 1.1. 7 and B. 1.351 variants to neutralizing antibodies." bioRxiv (2021).

[11] Zhou, Daming, et al. "Evidence of escape of SARS-CoV-2 variant B. 1.351 from natural and vaccine induced sera." Cell (2021).

APPENDIX: FURTHER SENSITIVITY ANALYSES

As an (semi-) independent check on the results, a distinct branch of the model code was used to predict the impact of the relaxation roadmap using relaxation parameters that were tied to previous dates in the outbreak. The results of this alternative approach are in broad agreement with the results above, although the default assumption of slightly more control in Step 3 (equated to Summer 2020) pushes the outbreak to slightly later in the year.

In the central scenario (Figure 3.1) it is assumed that the situation following Step 3 will be similar to that seen last summer, where the level of NPIs was at its most relaxed level since the start of the UK epidemic. Prior steps are scaled intermediary to this and the effect of full lockdown seen before the 8th of March 2021. The effect of reopening of schools is also included in the first stage of the model.

It is expected that remaining levels of caution will mean that pre-Covid behaviour will not immediately resume following the removal of enforced interventions at Step 4 of the roadmap, but rather a low level of impact from social behaviour will continue to be seen for some time to come, gradually reducing over time. To model this we consider, in the central scenario, an NPI impact at one quarter of the summer 2020 level immediately after step 4, gradually decreasing to a very minimal level by the 1st of December 2021.

Due to the high level of behavioural uncertainty, particularly influenced by lockdown fatigue and perceived reduction in risk following vaccination, alongside the central assumptions we also consider scenarios with greater/lesser increases in mixing across Steps 1-3 (Figures 3.1-3.3) as well as a possible higher level of remaining caution at half the summer 2020 level following Step 4 (Figure 3.5) or complete return to pre-Covid normality following the roadmap completion (Figure 3.4).

In each scenario, alongside the default vaccine efficacies, we also consider the effects of more or less optimistic vaccine parameters, in line with the lower and higher assumptions in the efficacy sensitivity section, as well as slower rollout speed scenario. Results here are presented in terms of daily hospitalisations, with other disease indicators following similar trends.

Across all scenarios it is apparent that the highest variability is in the uncertainty regarding vaccine effect, with this having a significantly greater impact than rollout speed, making the difference in most cases between a significant further wave of infection and relatively minimal further disease impact. Due to the continued level of uncertainty in vaccine effect, it seems wise to continue to proceed with NPI relaxation cautiously.

In all scenarios considered, the bulk of the relaxation wave is generally associated with Step 4. Looking at Figures 3.1-3.3 it may be seen that sensitivity to the first three steps of the roadmap has only a minor impact on any subsequent wave of infection, with more cautious first steps producing slightly lower and later peaks than less cautious ones. A much greater difference can be seen between Figures 3.4 and 3.5. Here we see a significant impact resulting from the public response following the final stage of the relaxation. Immediate disregard to any caution is seen to cause significant further infection, while a more significant tail off period results in only very minimal further disease impact.

Results

Plots showing daily hospitalisations across the period of the whole roadmap projected into 2022 under different assumptions regarding the level of NPI compliance. The scale of NPI restrictions and hence the level of mixing within each step is represented by the grey shading. The purple lines

show default efficacy assumptions, while the yellow and green lines represent the higher and lower efficacy assumptions previously detailed. Solid lines represent the expected vaccine delivery speed, while the dotted lines represent the slower rollout scenario.
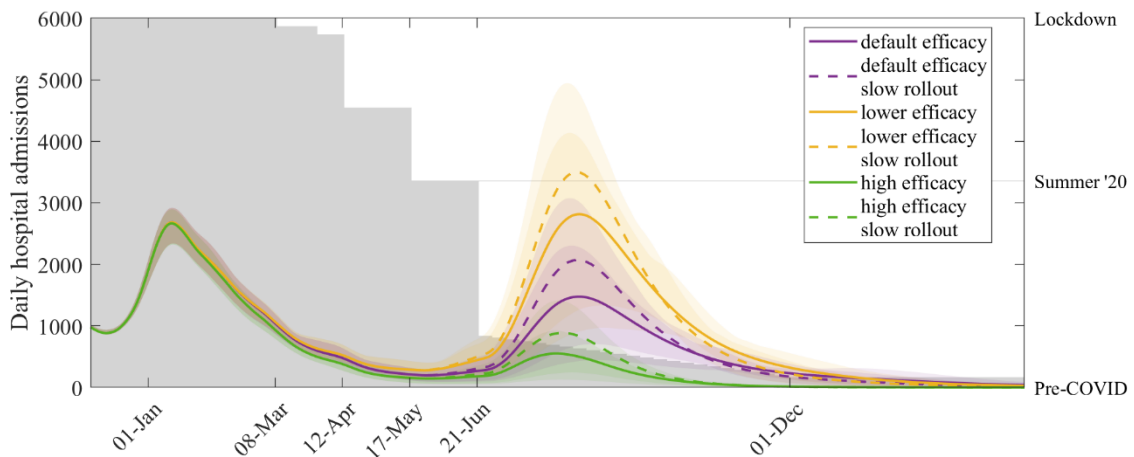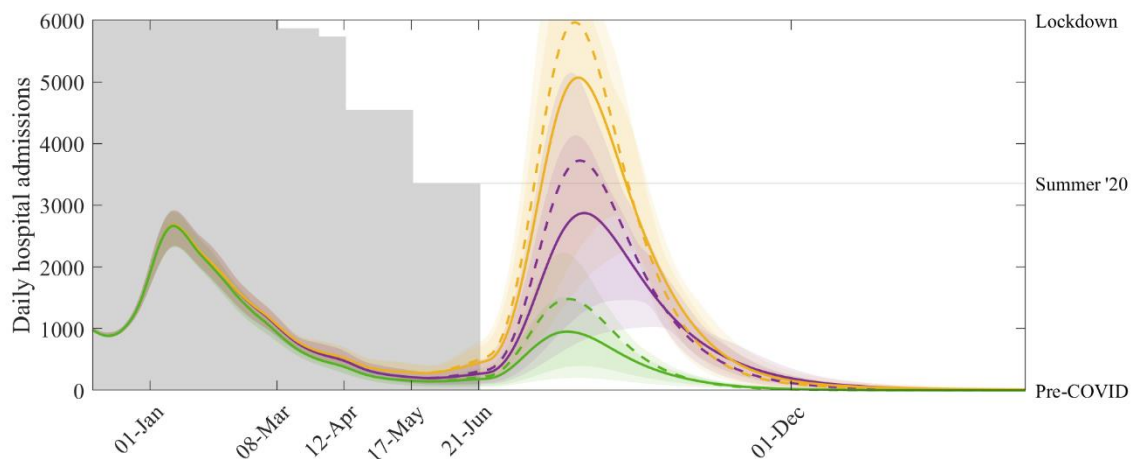

Figure 3.1: Central scenario – NPI controls (and hence transmission) following step 3 here is assumed similar to that at the most relaxed period seen last summer. Prior steps are scaled intermediary to this and the effect of full lockdown seen before the 8th of March 2021. NPI restrictions are assumed to be one quarter of the summer 2020 level immediately after step 4, gradually decreasing to a very minimal level by the 1st of December 2021.
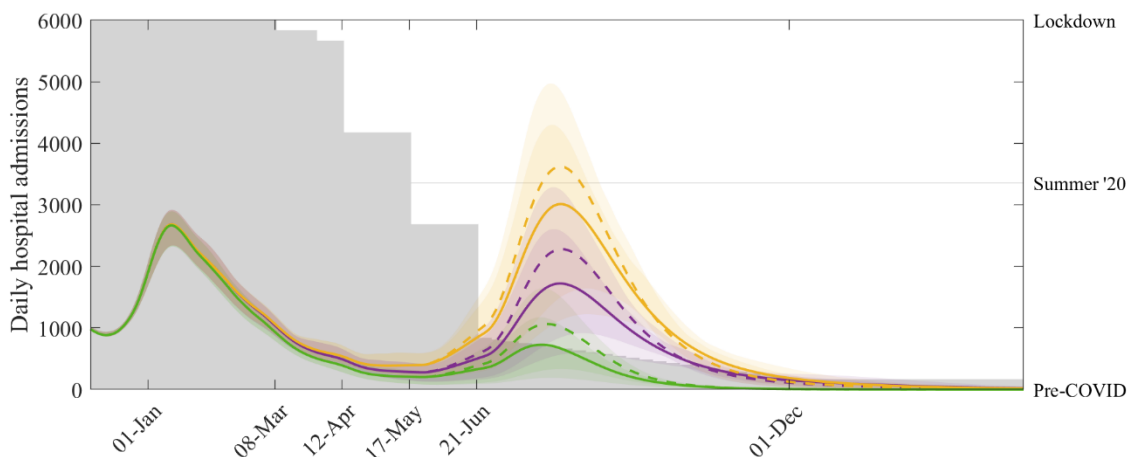

Figure 3.2: Larger steps 1-3 – NPI controls following step 3 here is assumed at 80% of that at the most relaxed period seen last summer (hence there is greater transmission than the default scenario). Prior steps are scaled intermediary to this and the effect of full lockdown seen before the 8th of March 2021. NPI restrictions are assumed to be one quarter of the summer 2020 level immediately after step 4, gradually decreasing to a very minimal level by the 1st of December 2021.
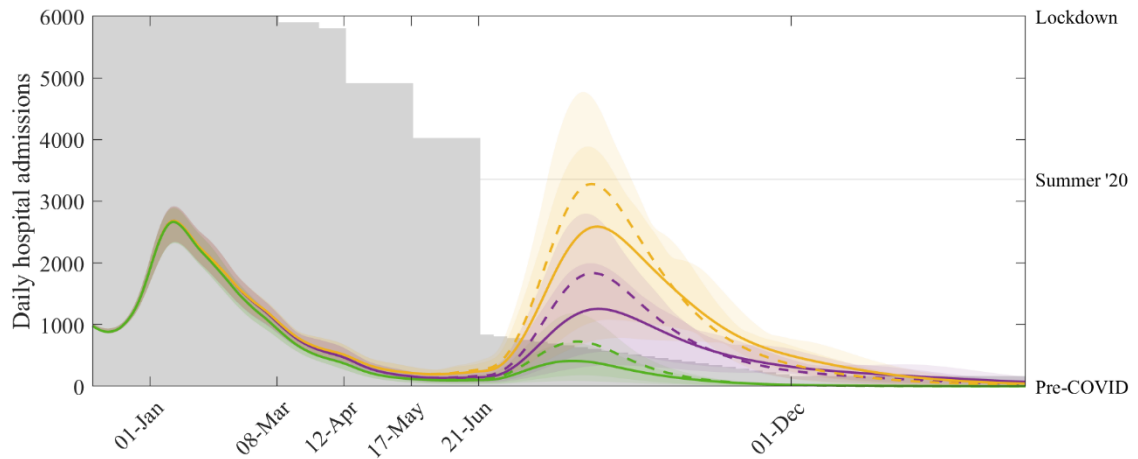
Figure 3.3: Smaller steps 1-3 – NPI controls following step 3 here is assumed at 120% of that at the most relaxed period seen last summer (hence there is less transmission than the default scenario). Prior steps are scaled intermediary to this and the effect of full lockdown seen before the 8th of March 2021. NPI restrictions are assumed to be one quarter of the summer 2020 level immediately after step 4, gradually decreasing to a very minimal level by the 1st of December.

Figure 3.4: Low final caution – NPI controls (and hence transmission) following step 3 here is assumed similar to that at the most relaxed period seen last summer. Prior steps are scaled intermediary to this and the effect of full lockdown seen before the 8th of March 2021. Transmission is taken to reflect a full return to pre-Covid behaviour following step 4.
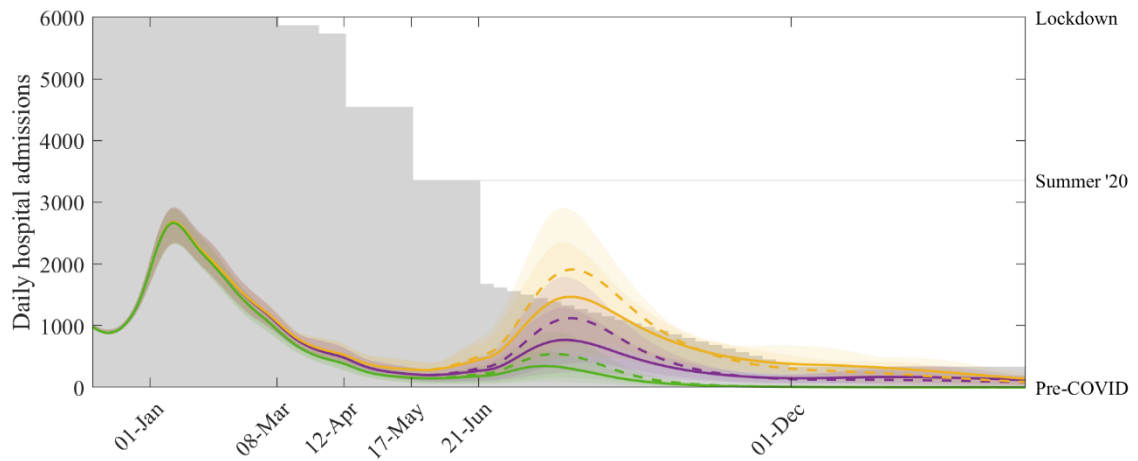
Figure 3.5: High final caution – NPI controls (and hence transmission) following step 3 here is assumed similar to that at the most relaxed period seen last summer. Prior steps are scaled intermediary to this and the effect of full lockdown seen before the 8th of March 2021. Transmission is taken at one half of the summer 2020 level immediately after step 4, gradually decreasing to a very minimal level by the 1st of December 2021.