Road Map Scenarios and Sensitivity: Steps 3 and 4

Matt J. Keeling[1,2], Louise Dyson[1,2], Edward Hill[1,2], Sam Moore[1,2], Mike Tildesley[1,2]

1 The Zeeman Institute for Systems Biology & Infectious Disease Epidemiology Research, School of Life Sciences and Mathematics Institute, University of Warwick, Coventry, CV4 7AL, UK.

2 Joint UNIversities Pandemic and Epidemiological Research, https://maths.org/juniper/

Here we consider the likely epidemiological impacts of Steps 3 and 4 of the relaxation roadmap. We use an age-structured model that captures the dynamics within the seven NHS regions of England. The model is matched to data from 30th April 2021, and projections reflect the underlying uncertainty in parameters.

Public Health Conclusions

1. There is considerable uncertainty in the scale and timing of the projected third wave, in part due to the unpredictable nature of human behaviour in response to Steps 3 and 4 of the relaxation roadmap.

2. Maintaining the currently high vaccine uptake and deployment speed is critical to the suppression of the third wave.

3. High transmission after Steps 3 and 4 can precipitate a larger third wave outbreak; a gradual release of restrictions minimises the risk associated with large outbreaks.

4. We expect to observe considerable heterogeneity between regions and local areas in the scale of the third wave, reflecting past exposure and vaccine uptake.

5. Novel variants pose the greatest risk to the relaxation roadmap, although data on their precise characteristics is limited. Detailed surveillance and local surge-testing should greatly reduce this threat, but this is only practical if the third wave remains small. The number of novel variants entering the country is a direct reflection of international travel and the levels of infection in the rest of the world.

Executive Summary

1. We consider the likely epidemiological impacts of Steps 3 and 4 of the relaxation roadmap. This is modelled for the seven NHS regions of England and then the data are combined, although regional heterogeneities are also considered.

2. Four major changes have been made to the model parameters since the previous assessment of the roadmap:
   (a) parameters for Step 2 are now informed by the most recent data.
   (b) 10% seasonality in transmission is included as the default.
   (c) 50% reduction in onward transmission from vaccinated individuals that become infected.
   (d) as part of the sensitivity analysis, a consideration of novel variants with either higher transmission or that can partially escape existing immunity.
   The changes to the default model lead to a smaller third wave than previously predicted.

3. We predict that Step 3 only can lead to a third wave with 9100 (CI 2430-26,400) hospital admissions and 1160 (CI 240-3870) deaths (Fig. 1); Step 3 and 4 combined (generating a higher transmission after 21st June) are projected to generate a larger third wave with 34,900 (CI 10,100-96,400) hospital admissions and 7250 (CI 1450-24,300) deaths (Fig. 6).

4. Under our default parameters, we predict the third wave will generate peak hospital admissions in July and August 2021; however, greater seasonality coupled with less transmission in Step 3 can push the wave into the winter, an effect that is further enhanced by high transmission in Step 4 (Fig. 13). Less relaxation in Step 3 may be highly beneficial in suppressing any summer wave, providing more time to complete the vaccination programme.

5. The size of the third wave is most sensitive to the speed of vaccine deployment, vaccine efficacy and the level of transmission (and hence population-level behaviour) in Step 4 (Fig. 17). These three elements could combine to generate highly optimistic scenarios with 6890 (CI 1540-23,800) hospital admissions over the third wave, or highly pessimistic scenarios with 186,000 (CI 88,200-346,000) hospital admissions (Fig. 18).

6. We predict considerable variation in the size of the third wave in different NHS regions (Fig. 19), primarily due to differences in population level immunity. We expect this to be replicated at finer spatial scales where the heterogeneity in immunity (either due to infection-derived immunity or vaccination) is far larger.

7. England remains extremely vulnerable to novel variants with either higher transmission or that can partially escape existing immunity (Fig. 24). A variant that is 30-40% more transmissible than B.1.1.7 is projected to generate more total hospital admissions than the first wave. Variants that escape immunity (either from infection or vaccination) could generate outbreaks larger than the second wave unless immunity confers a significant degree of protection against severe disease.

8. The models used do not account for multiple factors which could impact the projections: waning immunity after infection or vaccination is ignored, which affects our ability to make long-term predictions; vulnerable risk groups are not explicitly included, all risks are an average for the 5-year age-groups that are modelled; 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; although we have considered the invasion of new variants we have not explicitly accounted for continual imports into England from the rest of world which will be more important when the cases in England are relatively low; 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 or with to address elimination; finally, the model is unable to address either changing patterns in individual behaviour with changes in perceived risk or the finer nuances of control measures, as both of these are translated into a single parameter that captures the impact of NPIs at the population scale.

Methodology and Key Uncertainties

This work uses the model that has been developed in Warwick over the past year [1, 2] and matched to a variety of epidemiological data [3]. The model operates and is fitted to data from the seven NHS regions in England and the three devolved nations, although here we only present results for England (aggregating output from the seven NHS regions). The results of this model have been presented to SPI-M and SAGE on a number of occasions, and the model has been used to examine short-term and medium-term projections as well as reasonable worst-case scenarios. More recently, the model has been extended to include vaccination, initially to investigate priority ordering and subsequently increased in complexity to include two-dose schedules and multiple actions of vaccine protection [2].

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 vaccine has been far higher than anticipated; the brief was to assume that 95% of those in Phase 1 will accept the vaccine, 90% uptake of those aged 30-49 in Phase 2 and 80% uptake of those aged 18-29 - it is also assumed 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.

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 B.1.1.7 variant was the dominant form). We assume that any changes in transmission that occurred following Step 1b on the 29th March 2021 (which is largely concerned with outdoor mixing) or following Step 2 on 12th April 2021 is already captured in parameter estimates. In general, the change in transmission due to these two relaxation steps has been relatively small.

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 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 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 (see Table 1).

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 single mode of action.

The three vaccine efficacies are combined by taking the time-varying weighted average based on the amount of the three vaccines used to date in the UK; and in the ratio 60% (AstraZeneca), 30% (Pfizer), 10% (Moderna) in the future. This leads to a combined efficacy against infection of 60% and 73% after first and second doses; an efficacy against symptoms of 60% and 84% after first and second doses; an efficacy against severe illness and hospitalisation of 80% and 90% after first and second doses; and an

	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] ~95%[E] **80%**
Efficacy against hospital admissions	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%**
Efficacy against onward transmission	49% (38-58%)[H] **50%**	**50%**	38% (21-52%)[H] **40%**	**50%**

Table 1: Vaccine efficacies with citations (A-H) and model-assumed values (bold). Citation are: 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]. H. HOSTED study [8]

efficacy against death of 80% and 90% after first and second doses. These protective effects begin 14 days after each dose of vaccine.

There is now growing evidence that vaccination may reduce onward transmission in those who do still become infected [8]. Here we consider a relatively optimistic assumption, based on the available data, that onward transmission is reduced by approximately 50% for those that become infected after vaccination - note that this is in addition to the reduction that occurs owing to a reduction in infection due to the vaccine.

	Second dose efficacy against				
	Infection	Symptoms	Hospitalisation	Death	Transmission
Default	73%	84%	90%	90%	50%
Lower	65%	80%	85%	85%	50%
Higher	80%	85%	90%	95%	50%

In addition to the default efficacy assumptions outlined above, we also consider sensitivity to these parameters choosing a higher and lower set of efficacies. Vaccine efficacies following the second dose are shown above.
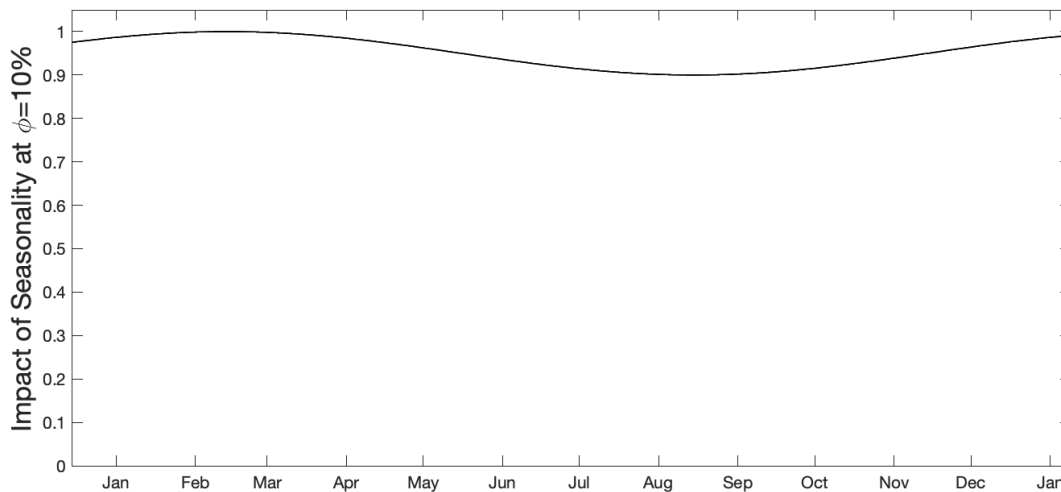
We assume a vaccine deployment schedule with an average of 2.7 million doses per week (from the week commencing 26 April to the week commencing 12 July) and then 2 million doses per week thereafter until second doses are complete. Uncertainty to this roll-out speed is also examined.

2) Controls, timings and estimates of R (excluding immunity). We considered two sets of predictive scenarios: in the first (Part 1) relaxation is stopped after Step 3 on 17th May 2021, 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 3 on 17th May 2021 and Step 4 on 21st June 2021). Both Steps 3 and 4 are envisaged as a proportionate reduction in the level of NPIs control compared to January lockdown levels, relative to levels estimated for early March 2020 (55% for Step 3 and 15% for Step 4). For our default assumptions, R excluding immunity (which captures the impact of controls) increased from approximately 1.29 (CI 1.16-1.39) during the main January-February lockdown, to 1.66 (CI 1.42-1.83) in Step 1 due to school reopening, to 1.88 (CI 1.64-2.1) after Step 2, to 2.41 (CI 2.25-2.57) after Step 3, and finally 3.51 (CI 3.31-3.71) 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 are limited data on this aspect of transmission [9], hence different levels of seasonality are examined in Fig. 12. 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 [9]. We report the level of seasonality (ϕ) as the drop in transmission over the summer relative to the peak in the winter months:

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

Based on available data [9], 10% seasonality would not be an unreasonable assumption, but the value could be larger if good summer weather has a substantive impact on behaviour, reducing indoor mixing. Throughout this document, we have used 10% seasonality ($\phi = 0.1$) as our default assumption.

1 Only Step 3 occurs

We initially assume that only Step 3 of the roadmap takes place and analyse the impact of this relaxation upon hospital admissions, hospital occupancy and daily deaths. The results are summarised in Figs. 1 to 4.
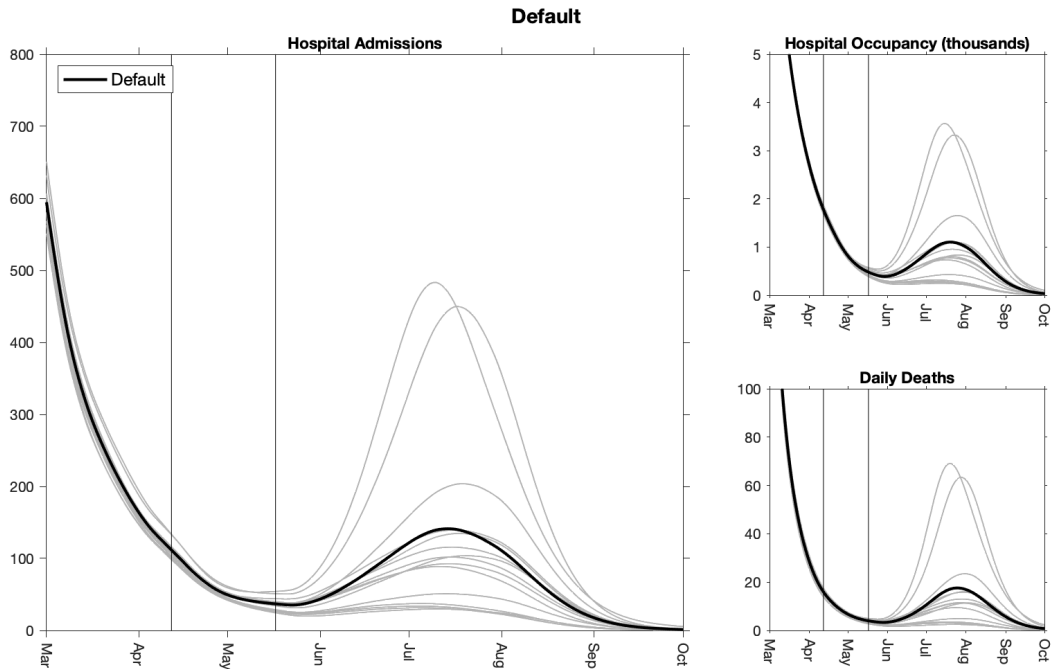
1.1 Default parameters

Fig. 1: Daily Hospital Admissions (left), Hospital Occupancy (top right) and Daily Deaths (bottom right) for England under the default assumptions for the relaxation roadmap. All results are for England only under the default assumptions for the relaxation roadmap. Grey lines show a sample of trajectories, thick black lines are the mean; vertical lines are the dates of Steps 2 and 3.

Using our default parameters, the model predicts a resurgence across all metrics from June to October 2021 (Fig. 1), due to the assumed reduction in control measures (and hence increase in transmission) occurring in Step 3. In this model, R excluding immunity has increased from approximately 1.29 (CI 1.16-1.39) during the main January-February lockdown, to 1.66 (CI 1.42-1.83) due to school reopening, to approximately 1.88 (CI 1.64-2.1) after Step 2 - all based on the historical data; for Step 3 our default assumptions about NPIs means that R excluding immunity increases further to 2.41 (CI 2.25-2.57). Note that values of R excluding immunity above 1 do not necessarily correspond to growth of infection due to the substantial impact of immunity derived from infection and vaccination. In addition, we calculate R excluding immunity at the maximum of the seasonal wave such that it corresponds to the situation during the winter.

Under these default assumptions, and ignoring the further relaxations in Step 4, we expect to observe 9100 (CI 2430-26,400) hospital admissions and 1160 (CI 240-3870) deaths from 17th May 2021 until the end of the simulation on 30th June 2022.

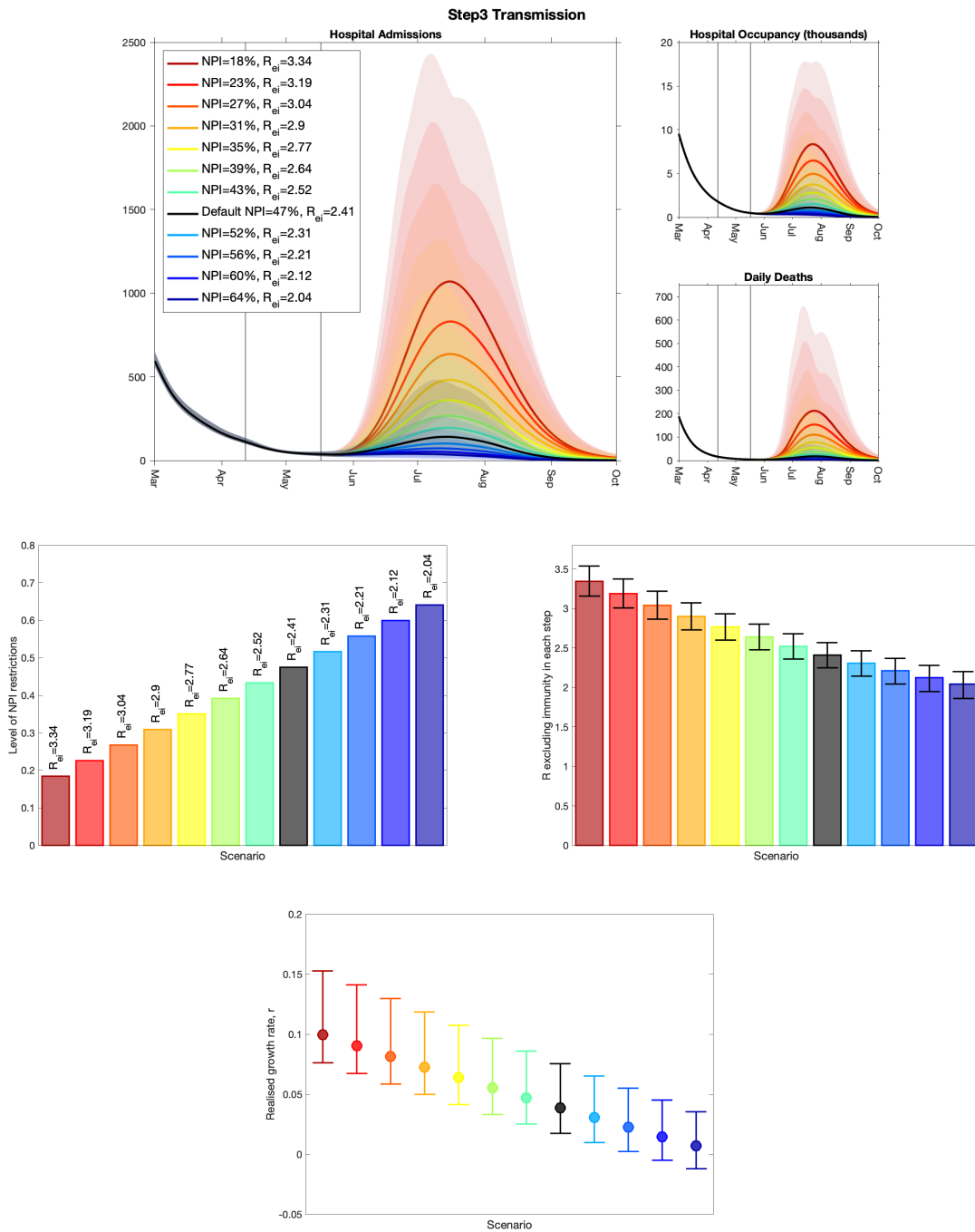## 1.2   Sensitivity to NPI adherence levels

Fig. 2: Top Panels. Daily Hospital Admissions (left), Hospital Occupancy (top right) and Daily Deaths (bottom right) in England for Step 3 of the relaxation roadmap, and considering a range of different adherence levels to non-pharmaceutical interventions (from 18% to 52%). 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 2.04 to 3.34.
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 3. The colour of each bar corresponds with the line colours in the Top Panels, with the default parameters in black.

There is considerable uncertainty concerning how restrictions in Step 3 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 3 (Fig. 2), which lead to mean values of R excluding immunity between 2.04 and 3.34, which translates to mean growth rates between 0.03 and 0.1 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.

Considering these mean epidemic waves in more quantitative detail, we find that peak hospital admissions increases non-linearly with the estimated growth rate (Fig. 3). Of additional policy relevance is the time to peak (after 17th May), 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 R below 1.12), there is the potential for the vaccination programme to reverse any early growth. However, for larger growth rates, we expect a substantial wave of infection, which is only brought under control in July 2021 after considerable numbers have been admitted to hospital.
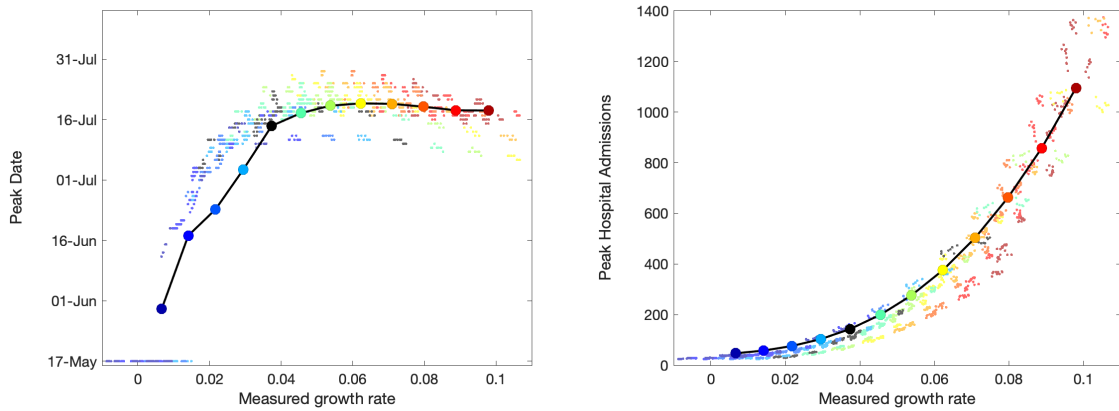

Fig. 3: Peak date (left panel) and peak height (right panel) in hospital admissions for the range of scenarios considered in Fig. 2. Coloured small dots represent the results for individual simulations, coloured large dots represent the average for a given parameter set. Default parameters shown in black.

This highlights that measurement of and response to the growth rate after Step 3 is vital in terms of the continued relaxation of control measures. Although we expect the growth rate to remain relatively contained after Step 3, larger than expected growth rates will not be readily controlled simply through the action of vaccination and more stringent methods may be required.

1.3 Sensitivity to Vaccine Effectiveness: Step 3 Only

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 three different parameter sets for vaccine efficacy (one lower than the default and one higher) as shown below:

Even when only Step 3 is considered, vaccine efficacy has a major impact on the size of the outbreak. The lower efficacy assumptions (shown in red, which are still within the 95% confidence intervals of many published studies) give rise to larger numbers of hospital admissions and deaths (Fig. 4). Under the default assumptions, and ignoring relaxation in Step 4, we expect to observe 9100 (CI 2430-26,400) hospital admissions and 1160 (CI 240-3870) deaths from 17th May until the end of the simulations
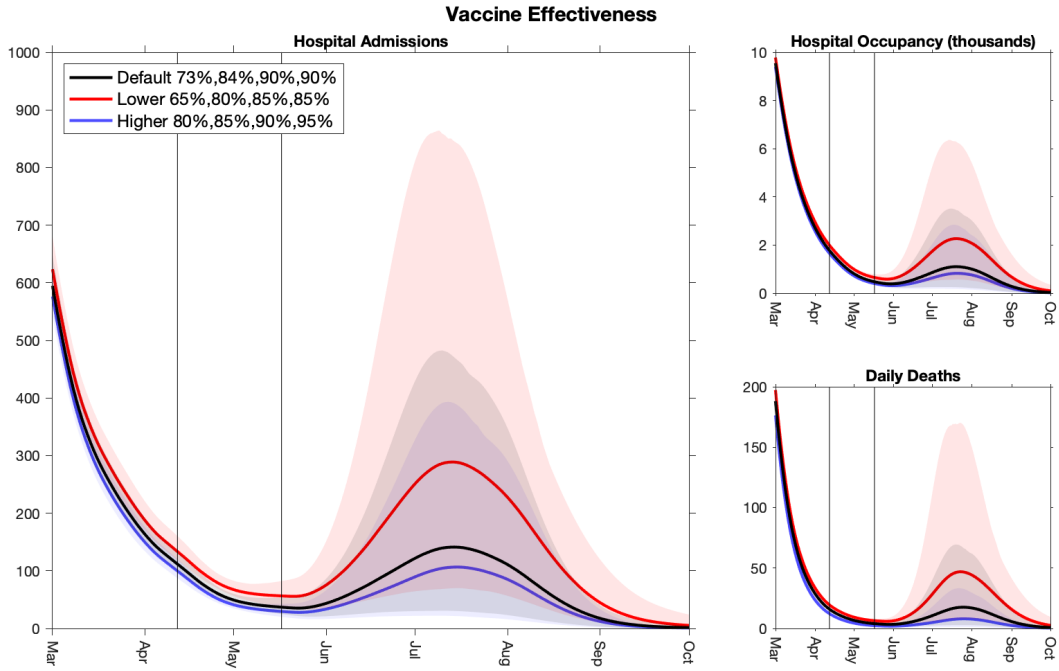
Fig. 4: Daily Hospital Admissions (left), Hospital Occupancy (top right) and Daily Deaths (bottom right) for England showing sensitivity to vaccine efficacy assumptions. Shaded regions show the 95%, 90% and 50% prediction intervals, while the individual thicker lines show the associated means.

	Second dose efficacy against				
	Infection	Symptoms	Hospitalisation	Death	Transmission
Default	73%	84%	90%	90%	50%
Lower	65%	80%	85%	85%	50%
Higher	80%	85%	90%	95%	50%

(30th June 2022); whereas this increases to 18,600 (CI 5270-50,100) and 3030 (CI 628-9660) under the lower vaccine efficacy assumptions, but decreases to 6830 (CI 1750-21,200) and 538 (CI 114-1850) for the more optimistic vaccine efficacy assumptions.

1.4 Summary of Results for Step 3 only.

Here we give the mean (and 95% credible intervals) for four key public health measures calculated over the period 17th May 2021 until 30th June 2022.

Scenario	Total Hospital Admissions	Peak Hospital Admissions	Peak Hospital Occupancy	Total Deaths
Default, $R_{ei} = 2.41$	9100 (2430 - 26,400)	143 (30 - 501)	1150 (390 - 3620)	1160 (240 - 3870)
Higher, $R_{ei} = 3.04$	36,800 (11,600 - 94,200)	663 (196 - 1690)	5060 (1530 - 12,200)	6550 (1490 - 20,600)
Lower, $R_{ei} = 2.04$	3140 (1030 - 9400)	47 (24 - 140)	528 (390 - 1050)	334 (103 - 994)
Higher Vacc Eff	6830 (1750 - 21,200)	108 (22 - 409)	874 (335 - 2940)	538 (114 - 1850)
Lower Vacc Eff	18,600 (5270 - 50,100)	295 (68 - 883)	2300 (553 - 6480)	3030 (628 - 9660)

2 Dynamics including Steps 3 and 4

We now consider all four steps the roadmap takes and analyse the impact of this relaxation upon hospital admissions, hospital occupancy and daily deaths. The results are summarised in Fig. 5 - Fig. 18 below.

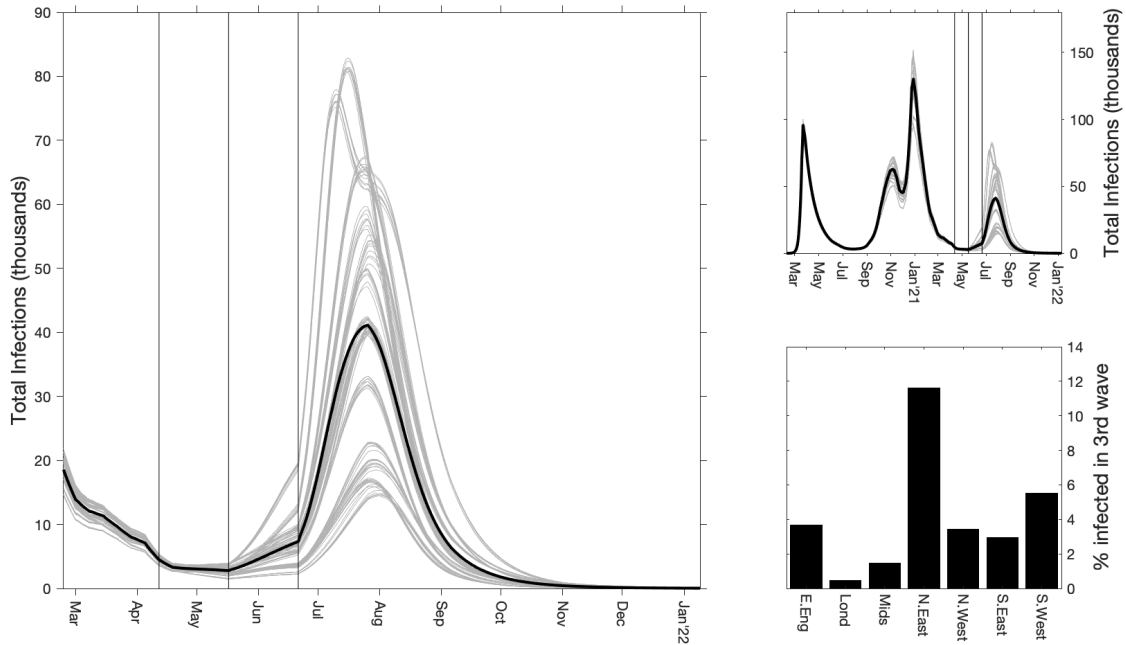### 2.1 Infection, Hospital Admissions, Hospital Occupancy and Deaths.

Fig. 5: Daily infections including both asymptomatic and symptomatic infections, focusing on the time period of the third wave (left), daily infections over a longer period to compare the three waves (top right) and mean percentage of the regional populations infected in the third wave from 17th May 2021 until the end of the simulations (bottom right). All results are for England only under the default assumptions for the relaxation roadmap. Grey lines show a sample of trajectories, thick black lines are the mean.

Fig. 5 shows the predicted epidemic wave following the four relaxation steps, highlighting the potential variability in the number of infected individuals at a regional scale. Fig. 6 expands this focusing on hospital admissions, hospital occupancy and deaths; hospital admissions peak on 07 August (CI 25 July-14 August) while deaths peak on 17 August (CI 01 August-26 August). The scale, timing and shape of this wave is driven by two factors: the relaxation (Fig. 7) and the population-level immunity (Fig. 8).

The level of restrictions in lock down (measured as an average during January and February 2021) and Steps 1 and 2 are estimated from the current data. 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 growth rate. Step 2, based on the latest data has a growth rate that spans zero, such that there is uncertainty if infection is globally increasing or declining. We assume that NPI restrictions decline further in Steps 3 and 4, which leads to an increase in the reproductive number excluding immunity, and an increase in the realised growth rate (r) also this is influenced by the changing levels of population immunity (Fig. 7).

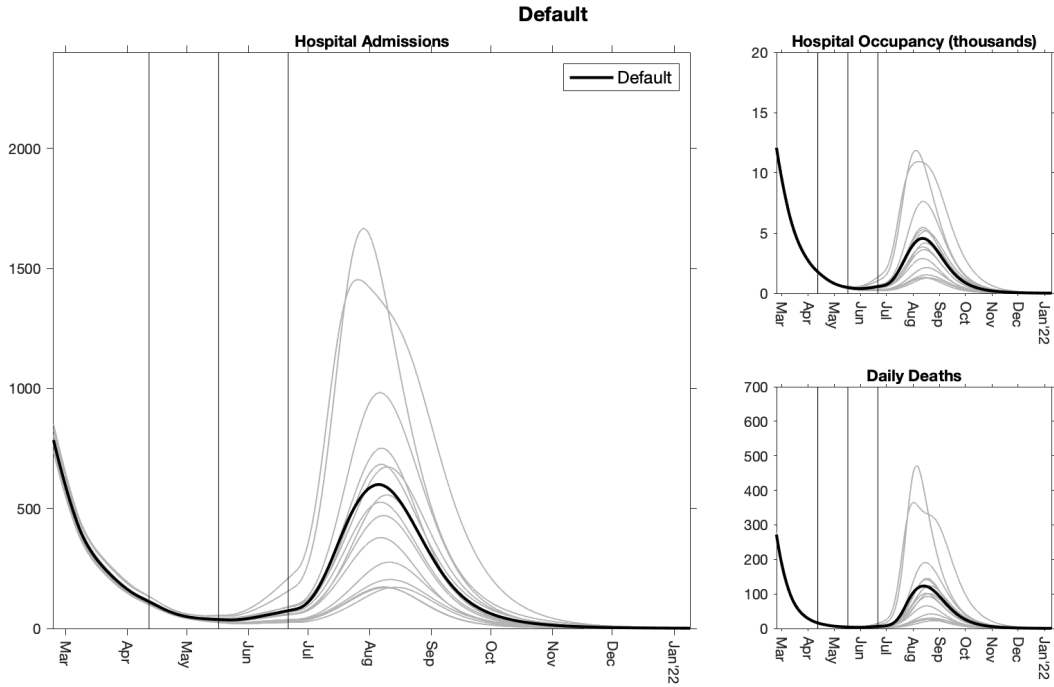Under the default assumptions, we expect to observe 34,900 (CI 10,100-96,400) hospital admissions and

Fig. 6: Daily Hospital Admissions (left), Hospital Occupancy (top right) and Daily Deaths (bottom right) for England under the default assumptions for the relaxation roadmap. Thin grey lines show 15 randomly sampled trajectories, while the thick black line shows the mean; vertical lines are the dates of Steps 2-4.

7250 (CI 1450-24,300) deaths from 17th May 2021 until 30th June 2022. These occur predominantly over the summer months June-September (inclusive) and so could easily be disrupted by different patterns of summer mixing (Fig. 12).

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 3.51 (CI 3.31-3.71). This is larger than observed at the start of the first wave due to the dominance of the B.1.1.7 variant, but smaller than the theoretical maximum due to an assumption of some minimal level of controls being retained. The impact of Step 4 NPI controls is investigated in Fig. 10. 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 (Fig. 8). 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 (Fig. 8 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 (Fig. 8 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.
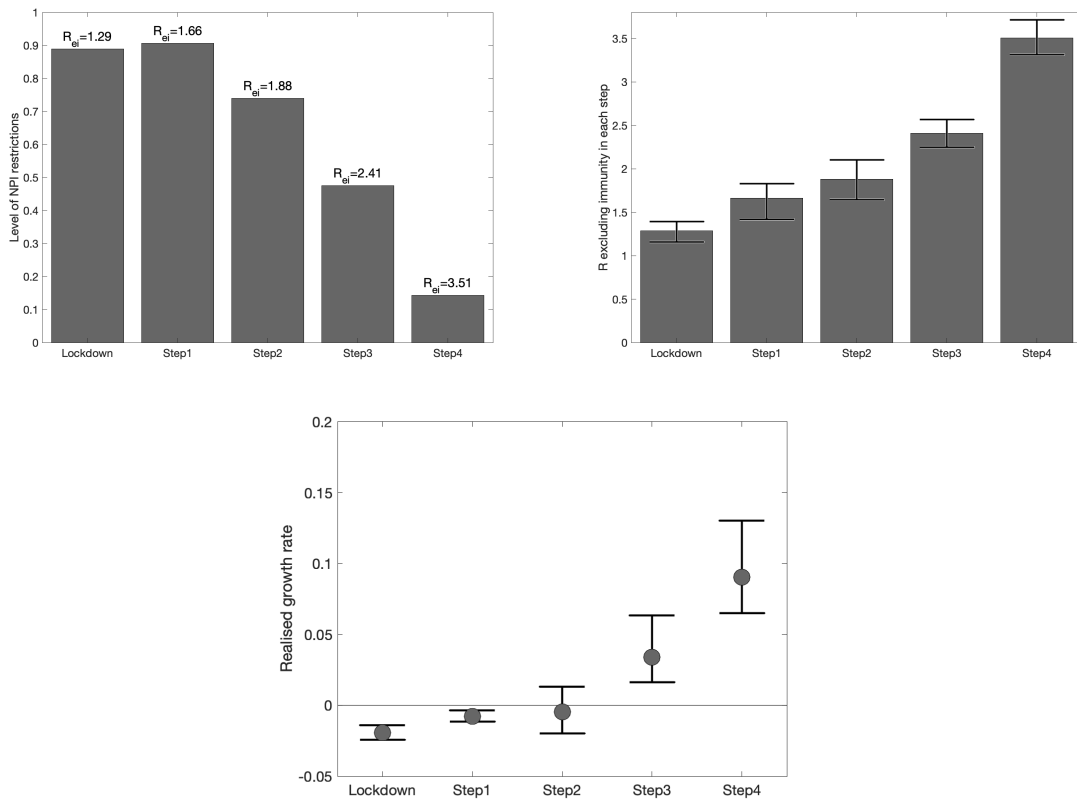
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Fig. 7: Change in NPI restrictions and hence the change in the value of R excluding immunity through different step phases of the default model. This highlights the non-linear dependence of R excluding immunity on the level of NPI restrictions and how population-level immunity is key in translating this to an instantaneous growth rate.
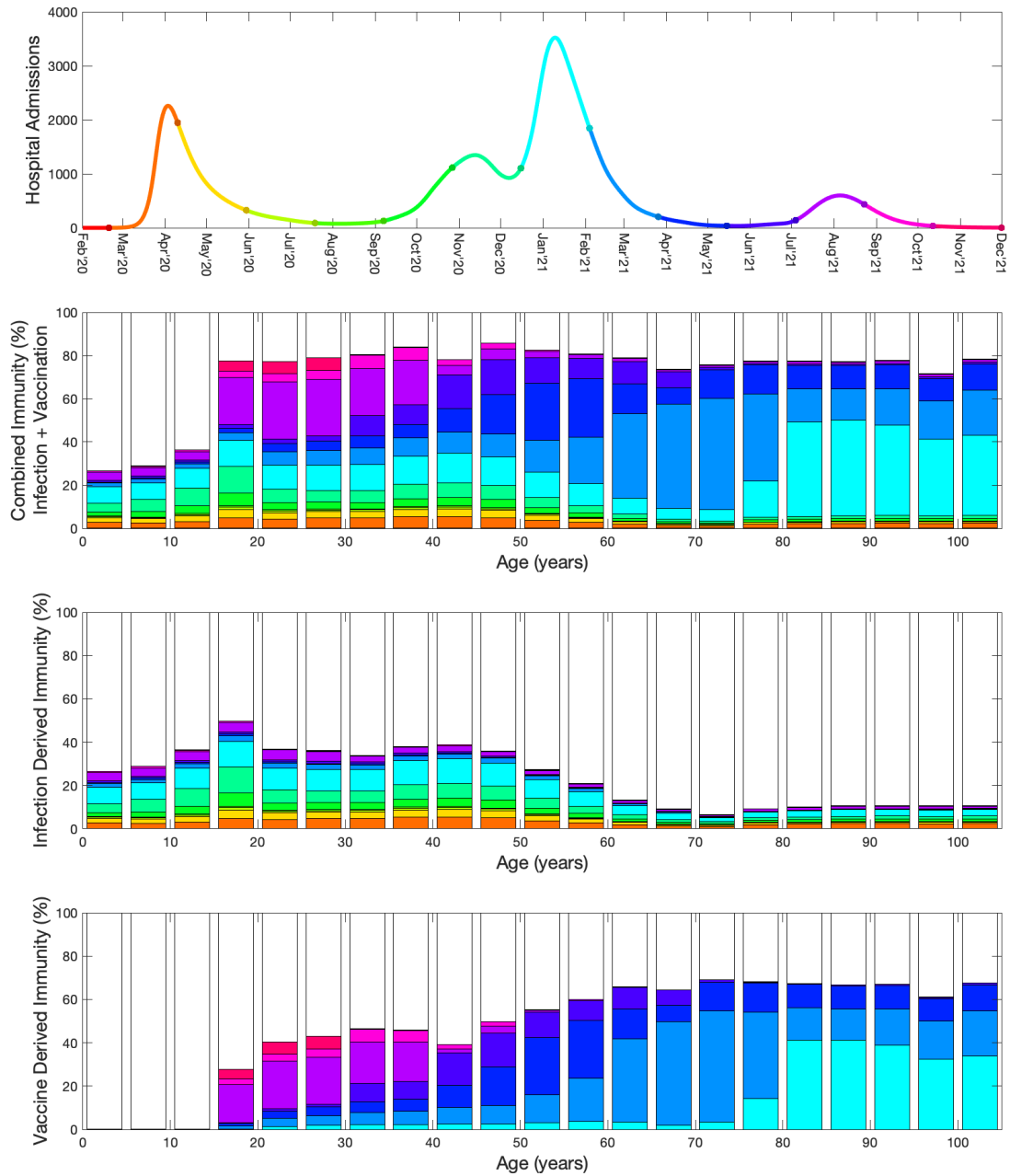
Fig. 8: Change in immunity through time over thirteen time intervals, represented by different colours. The top graph shows the mean number of daily hospital admissions over time, the second row graph shows the build-up of immunity in the population (from both infection, as well as first and second doses of vaccination), while the lower two graphs shows the immunity from infection and vaccination alone, respectively.

3 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.
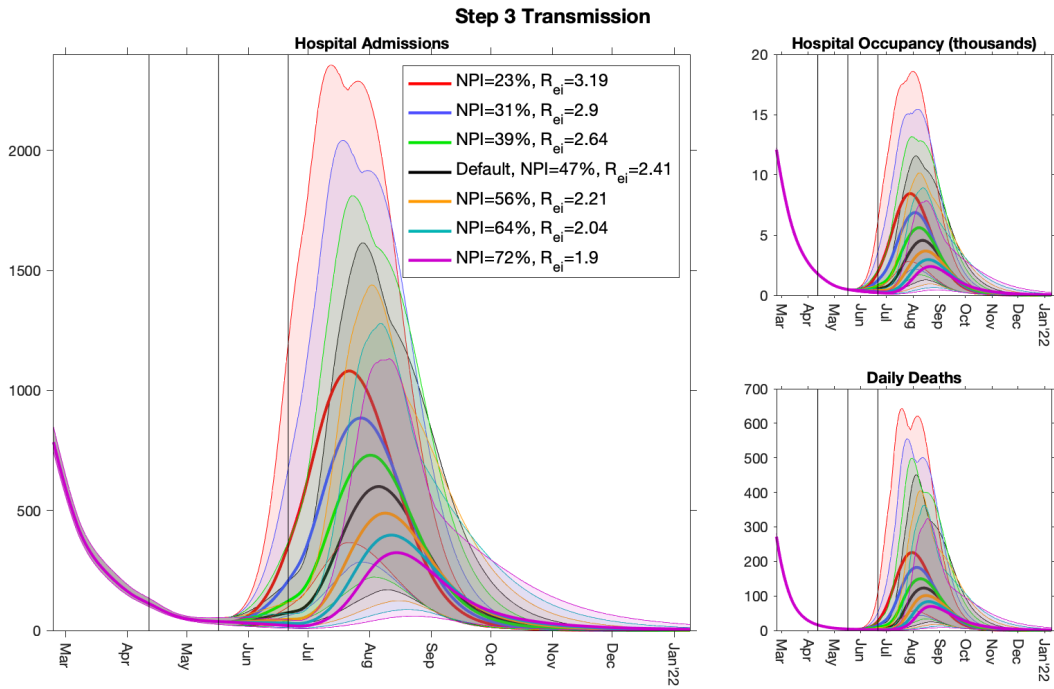
3.1 Sensitivity to Transmission in Step 3

Fig. 9: Different epidemic waves generated by different levels of NPI control (and hence different R excluding immunity values) during Step 3. (Solid lines show the mean, shaded areas are the 95% prediction intervals.)

For a fixed level of control in Step 4 (R excluding immunity of 3.51 (CI 3.31-3.71)) we observe that greater levels of control in Step 3 can generate later and smaller epidemic waves with associated hospital admissions and deaths (Fig. 9). **For the higher levels of NPI control in Step 3, the epidemic wave peaks in late August 2021 but there is a pronounced tail to the third wave which is prolonged into the winter of 2021.** The smaller size of later waves is primarily due to the build-up of population-level immunity through vaccination that occurs during Step 3.

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.

3.2 Sensitivity to Transmission in Step 4

We now 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 (Fig. 10). We again show the default model, for which Step 4 generates an R excluding immunity of 3.51 (CI 3.31-3.71) together with an assumption of greater control (blue, R excluding immunity 2.96 (CI 2.71-3.18)) and an assumption with greater transmission (red, R excluding immunity 4.11 (CI 3.79-4.39)). Even this greater transmission assumption generates
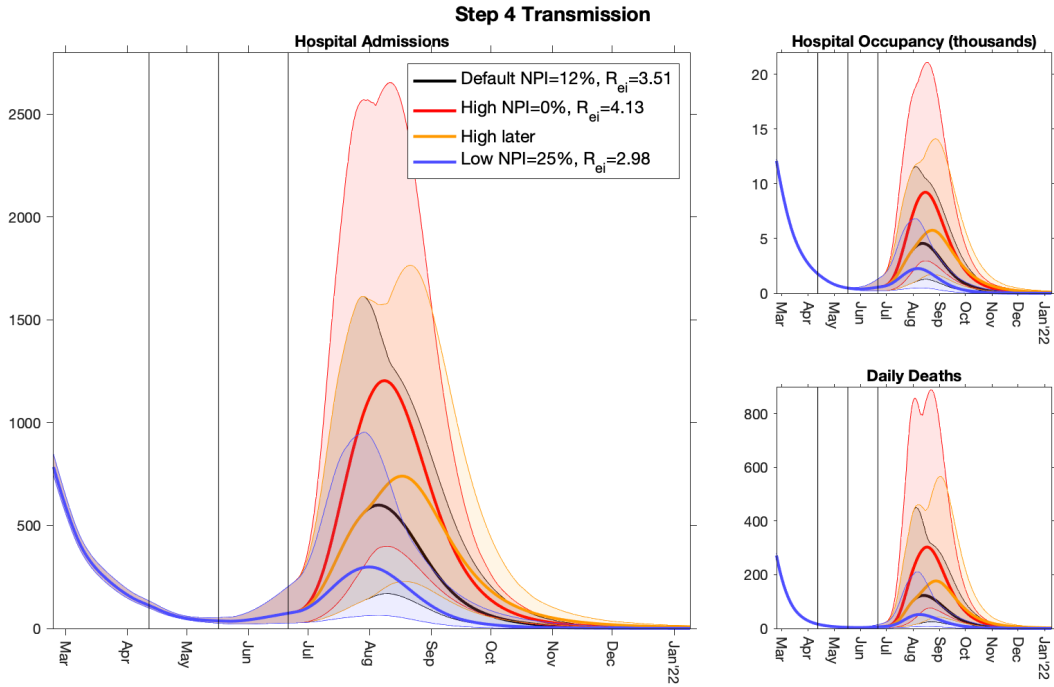
Fig. 10: Different epidemic waves generated by different levels of NPI control (and hence different R excluding immunity values) during Step 4. (Solid lines show the mean, shaded areas are the 95% prediction intervals.)

a lower R excluding immunity than the theoretical maximum of approximately 4.69 (CI 4.31-5.30) due to maintenance of some degree of behavioural change compared to pre-pandemic.

Greater control in Step 4, and hence lower R values, lead to smaller waves of infection with earlier peaks; while less control leads to larger and later waves pushing peak hospital occupancy and deaths into late Autumn. In comparison to the default model where we expect 34,900 (CI 10,100-96,400) hospital admissions and 7250 (CI 1450-24,300) deaths (from 17th May 2021 until the end of the simulations in June 2022), our greater control assumption generates 18,000 (CI 4520-53,400) and 3060 (CI 508-10,800) whereas the greater transmission assumption generates 66,300 (CI 22,400-160,000) and 16,700 (CI 4260-50,400).

We also consider a scenario (shown in orange in Fig. 10) where NPIs hit 12% on the 21st June 2021, as in the default model, but are then relaxed further to 0% five weeks later - equivalent to the high transmission scenario. This delay before complete relaxation of NPIs provides more time for population-level immunity to develop through the on-going vaccination campaign, and generates a wave with 50,500 (CI 15,500-130,000) hospital admissions and 11,800 (CI 2740-37,500) deaths (compared to 66,300 (CI 22,400-160,000) and 16,700 (CI 4260-50,400) if NPIs are relaxed completely on 21st June 2021).

3.3 Sensitivity to Transmission in Steps 3 and 4

To complete this analysis of the impact of the NPIs applied in Steps 3 and 4, and hence the level of transmission, we consider the two-dimensional parameter space defined by the reproductive number excluding immunity in Steps 3 and 4. Here, we have explored a very wide parameter range, which not only captures uncertainty in behaviour during these later Steps, but also demonstrates the possible impacts of a more transmissible variant which would lead to an increase R_{ei}. For each parameter set we compute the total number of infections (both symptomatic and asymptomatic), hospital admissions

and deaths from 17th May 2021 onwards, as well as the peak hospital occupancy and the date of this peak (Fig. 11). In general, high R excluding immunity in both steps generates the largest third waves with the largest number of hospital admissions and deaths. In contrast, later epidemic peaks occur when the transmission in Step 3 is low, but transmission in Step 4 is high.
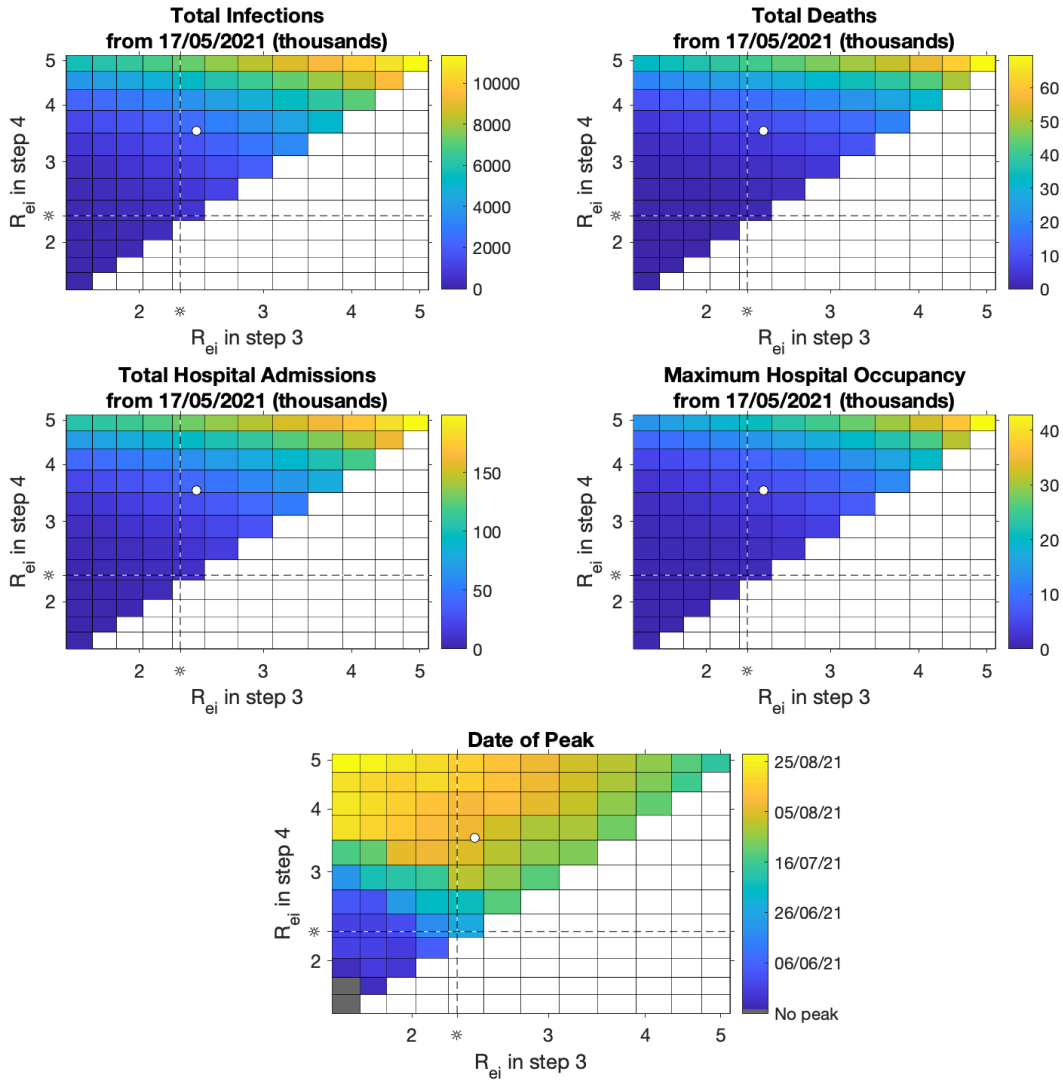

Fig. 11: Impact of different levels of NPI and hence different R excluding immunity (R_{ei}) in Steps 3 and 4. Note that total infections, hospital admissions and deaths, and maximum hospital occupancy are all shown in thousands and are measured from 17 May 2021. The peak date corresponds to when the peak hospital occupancy occurs; squares in grey are when the maximum occupancy occurs on 17th May. The white dot corresponds to the default parameters used elsewhere in the paper, while the dashed horizontal and vertical lines correspond to the value of R excluding immunity estimated for Summer 2020. (Calculations are performed over a uniform grid of NPI values for Steps 3 and 4, which convert to a non-linear scale for R excluding immunity.)
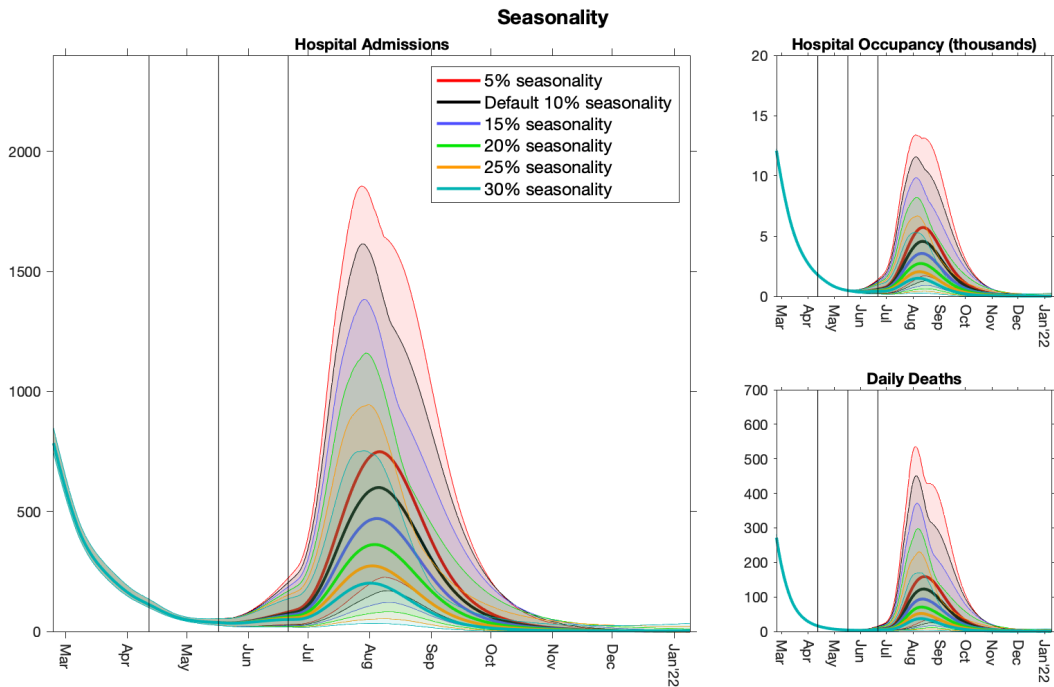
3.4 Sensitivity to Seasonality

Fig. 12: Impact of seasonality (measured as the relative drop in transmission at the lowest point compared to the peak) on the infection dynamics. (Solid lines show the mean, shaded areas are the 95% prediction intervals.)

Seasonality is seen to have a substantial impact on the outbreak after Step 4. Estimates from Baker *et al.* [9] 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. Here we take 10% as our baseline assumption, but note that higher levels of seasonality lead to suppressed summer waves.

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 October/November 2021 England is likely to be close to herd immunity - dependent on the level of control in Step 4. In addition, the August seasonal trough in transmission rate is well-placed to suppress this relaxation wave without substantially shifting the peak.

In the default analysis (and much of the sensitivity analysis), we predict the main third wave of hospital admissions will occur during the summer of 2021 triggered by the increase in transmission in Steps 3 and 4. However, it is conceivable that with additional seasonality and alternative assumptions about transmission in Steps 3 and 4, the summer wave can be pushed into the winter - although in this case waning immunity is likely to play a larger role.

To investigate the timing of the third wave, we project the dynamics forwards for different combinations of seasonality (see Fig. 12) and NPIs in Step 3 (which generates different values of R excluding immunity, see Fig. 9). For each parameter combination, we determine the expected number of hospital admissions over time (see Fig. 13, subplots on left and right); these hospital admission times are then stacked for each parameter set to show the distribution of cases throughout the year May 2021 to May 2022. If the box associated with a particular set of seasonality and Step 3 NPIs is more blue

then those admissions happen later, whereas a more red box represents admissions happening earlier. This analysis is performed for both the default level of NPIs in Step 4 (R excluding immunity 3.51 (CI 3.31-3.71), Fig. 13, top) and for the higher level of transmission in Step 4 (R excluding immunity 4.11 (CI 3.79-4.39), Fig. 13, bottom). High seasonality and low transmission in Step 3 suppress the summer wave, whereas high transmission in Step 4 means that the peak transmission in the winter months is high allowing a subsequent wave.
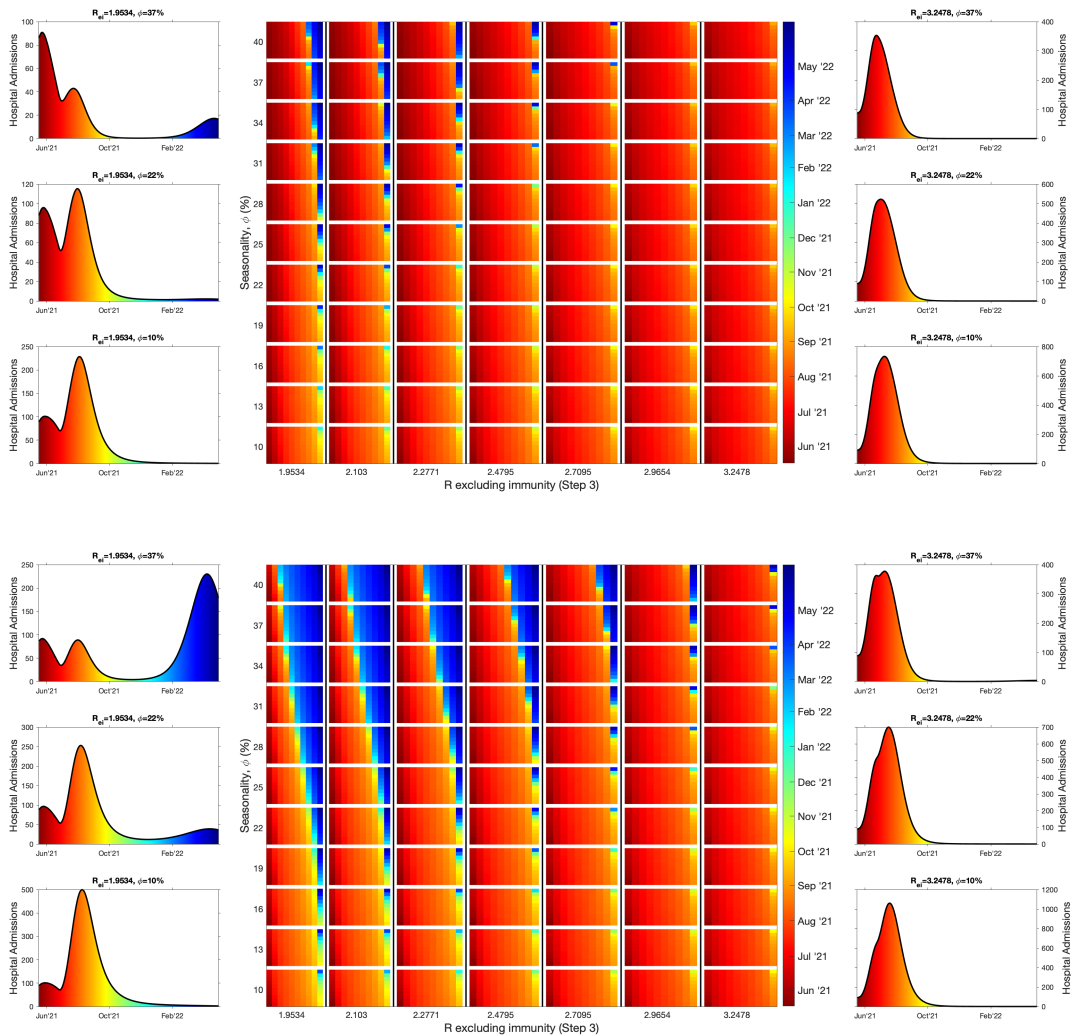

Fig. 13: The effect of NPIs in Step 3 (which generates an R excluding immunity value) and seasonality on the timing of hospital admissions for the next year (May 2021 - May 2022), shown here for **default assumptions about transmission in Step 4 (top) and for higher transmission assumptions in Step 4**. Hospital admissions in the summer are coloured reds and yellows, whereas hospital admissions in the autumn and winter are greens and blues. Subplots to the left and right show example mean outbreaks for different parameter combinations, note the different y-scales.

This analysis shows that it is possible to generate a small summer wave and a larger wave later in the winter, but this only occurs for a small set of parameters. A resurgence in the winter may also be promoted by waning immunity, although rates of waning immunity are expected to be sufficiently slow for this not to have a major impact.

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3.5 Sensitivity to Vaccine Roll-out Speed

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. Here we have considered roll-out speeds that are 10% or 20% faster or slower than the default. Slower speeds lead to a larger change in the epidemic size than faster roll-outs.
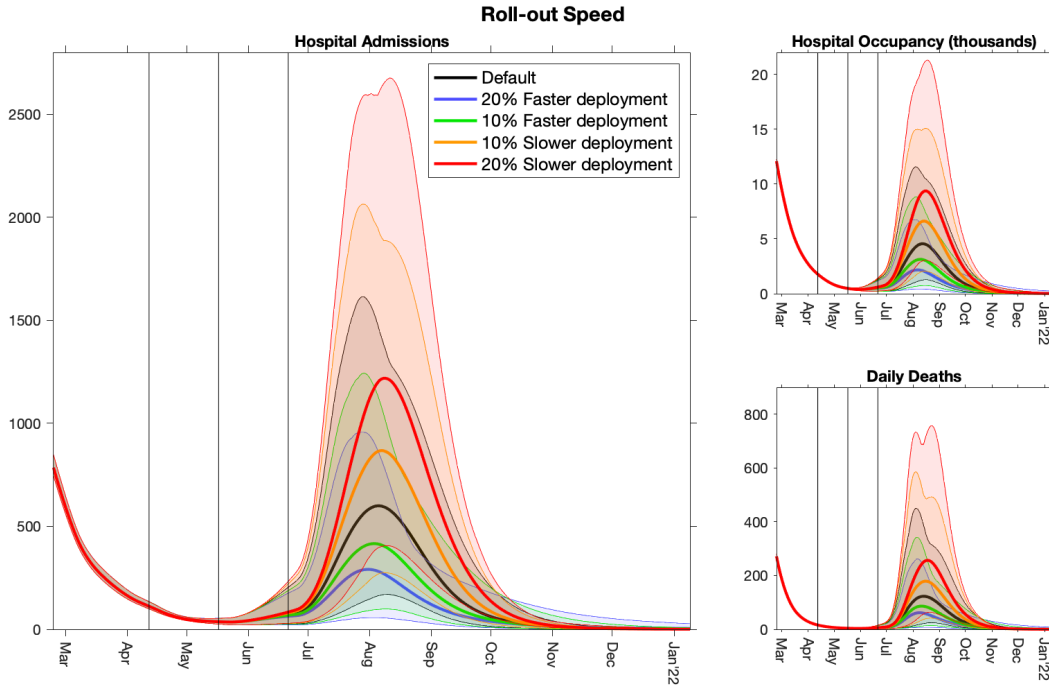

Fig. 14: The impact of vaccine roll-out speed being faster (blue/green) or slower (orange/red) than the default schedule. (Solid lines show the mean, shaded areas are the 95% prediction intervals.)

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.

3.6 Sensitivity to Vaccine Effectiveness

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 are from participants under 65, whereas the real-world data will predominantly be from those over 80. Here we consider three different parameter sets for vaccine efficacy as shown below:

	Second dose efficacy against				
	Infection	Symptoms	Hospitalisation	Death	Transmission
Default	73%	84%	90%	90%	50%
Lower	65%	80%	85%	85%	50%
Higher	80%	85%	90%	95%	50%

Vaccine efficacy has a major impact on the size of the outbreak, with the lower efficacy assumptions (which are still within the 95% confidence intervals of many published studies) giving rise to very large
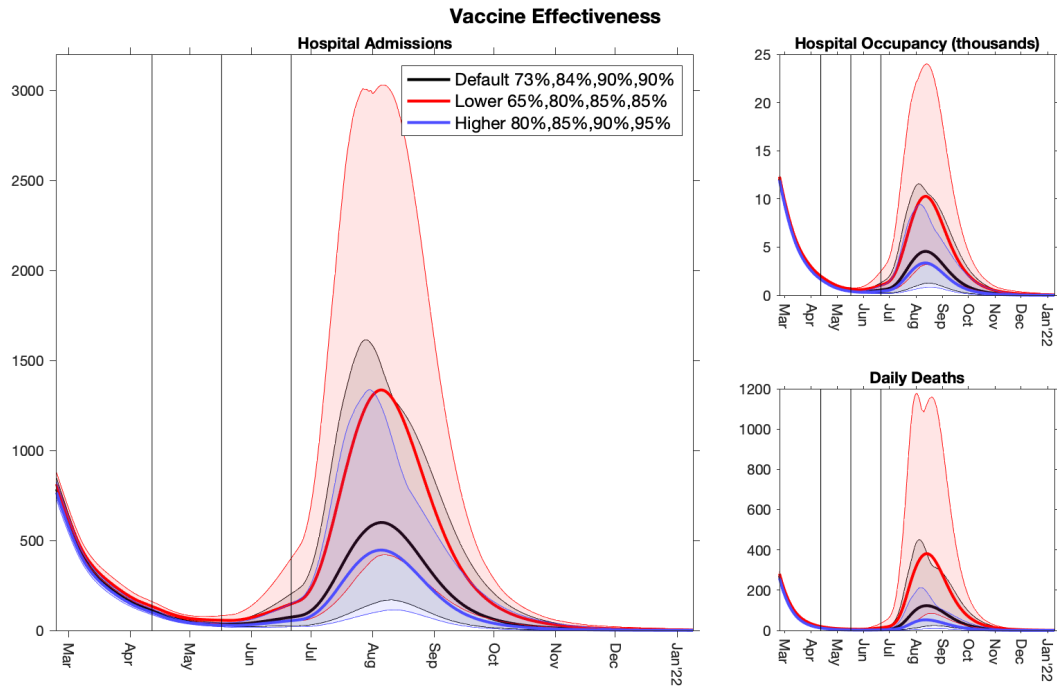
Fig. 15: Sensitivity of the epidemic curves to vaccine efficacy assumptions, showing the impact of both higher efficacy (blue) and lower efficacy (red). (Solid lines show the mean, shaded areas are the 95% prediction intervals.)

numbers of hospital admissions and deaths. Under the default assumptions, we expect to observe 34,900 (CI 10,100-96,400) hospital admissions and 7250 (CI 1450-24,300) deaths from 17th May 2021 until the end of the simulations; this increases to 77,200 (CI 25,700-189,000) and 21,500 (CI 5020-67,600) under the lower vaccine efficacy assumptions and decreases to 25,400 (CI 6920-73,000) and 3030 (CI 548-10,400) under the higher vaccine efficacy assumptions

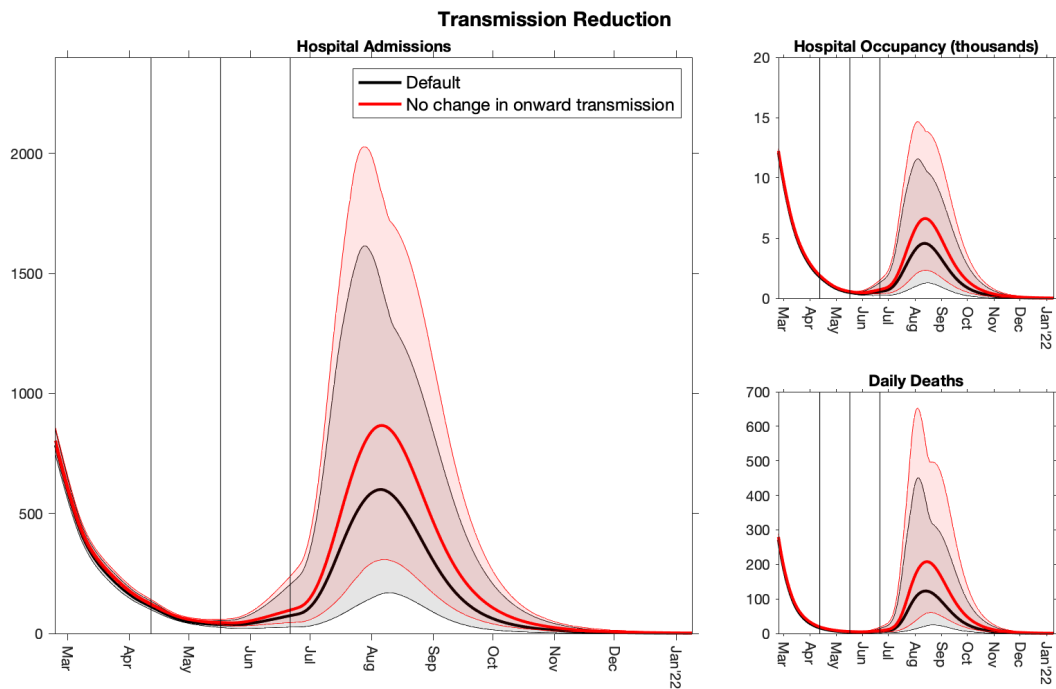## 3.7 Sensitivity to Reduction in Transmission after Vaccination

Fig. 16: Epidemic waves generated by removing the reduction in onward transmission due to vaccination (red), compared to the default assumption (black). In this alternative formulation onward transmission from vaccinated individuals is the same as transmission from unvaccinated individuals. (Solid lines show the mean, shaded areas are the 95% prediction intervals.)

Since the previous examination of the roadmap (before Step 2), we have now included the observation that onward transmission from those infected but vaccinated may be reduced by around 50%. Here we assess the impact of that assumption, by comparing the default model with one in which those infected after vaccination have the same transmission potential as unvaccinated individuals (Fig. 16).

3.8 Combined Sensitivity

Here we consider all the sensitivities examined so far and their impact on the number of hospital admissions from 17th May 2021 until 30th June 2022 (Fig. 17). Three main drivers of lower hospital admissions are clearly identified: greater control (and hence lower transmission) in Step 4; higher vaccine efficacy; and faster speed of vaccine roll-out. The first and third of these can clearly be influenced by policy decisions, but will also depend on population behaviour. The remaining driver depends on data being accrued on vaccine efficacy within the population, and will depend (in part) on the ratio of vaccine types used over the next few months. In principle these three elements could combine to generate an even smaller third wave (Fig. 18 left, with 6890 (CI 1540-23,800) hospital admissions during the third wave from 17th May 2021 until the end of simulations) or a considerably larger wave (Fig. 18 right, with 186,000 (CI 88,200-346,000) hospital admissions).
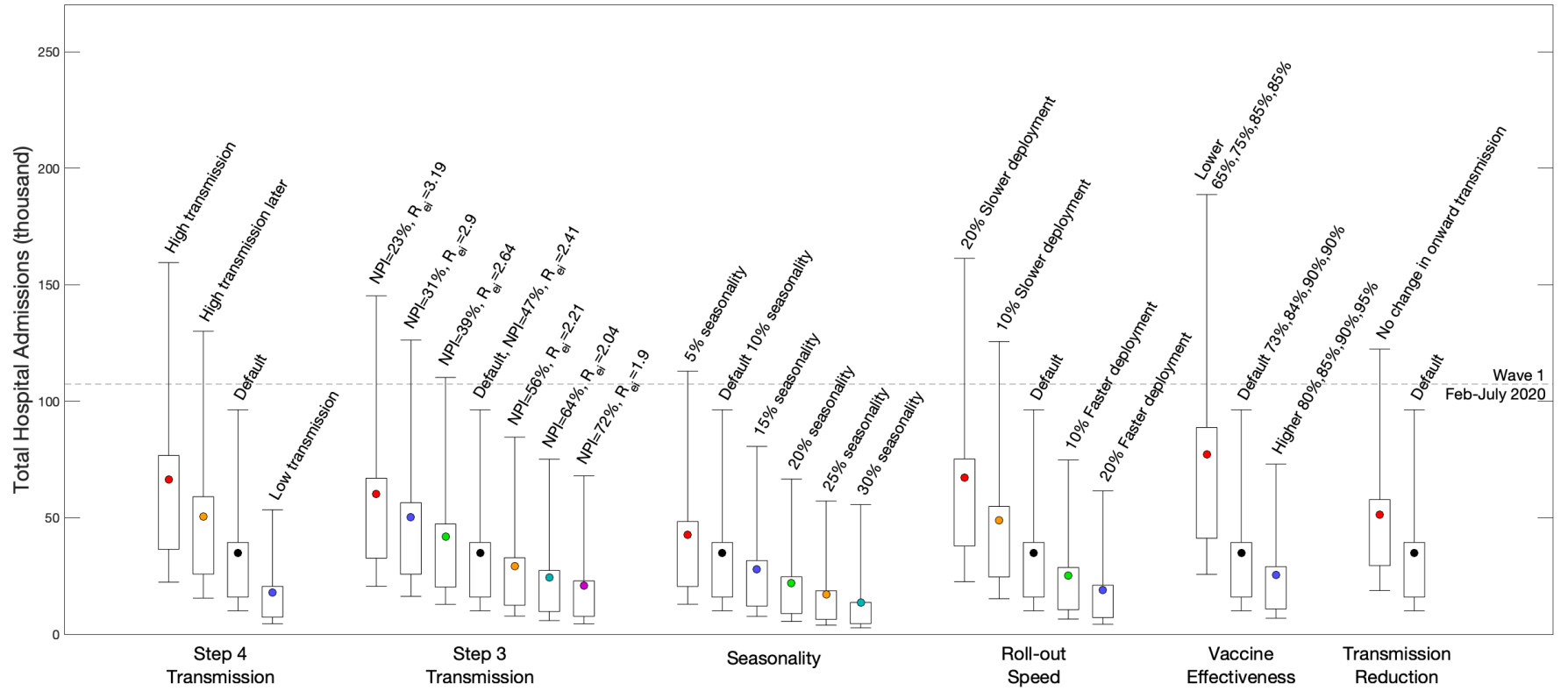
Fig. 17: Comparison of all the uncertainties investigated, showing their impact on the total number of hospital admissions from 17th May 2021 until the end of June 2022. Dots show the mean values, while the box and whisker plots show the interquartile and 95% prediction intervals.
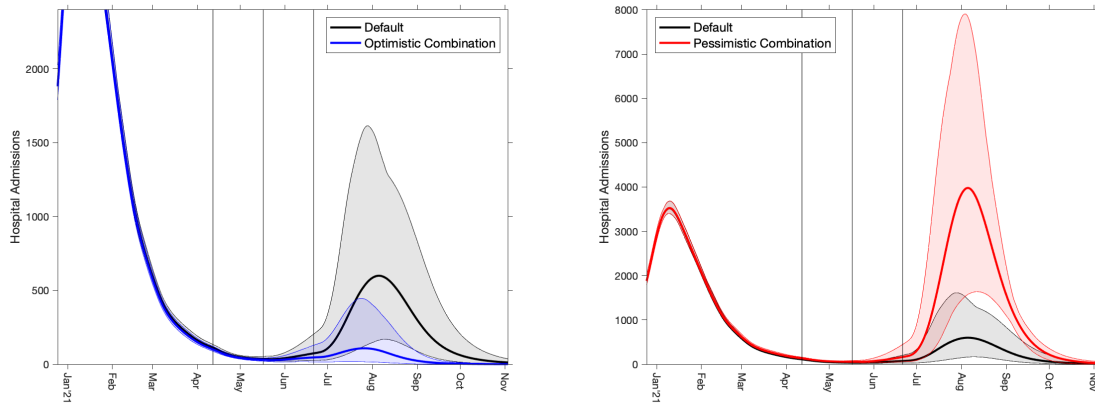
Fig. 18: Hospital admissions using combinations of roll-out speed, vaccine efficacy and reduced onward transmission that either suppress the third wave (left: optimistic combination, lower transmission in Step 4, 20% faster vaccine deployment and higher vaccine efficacy assumptions) or lead to a large third wave (right: pessimistic combination, higher transmission in Step 4, 20% slower vaccine deployment and lower vaccine efficacy assumptions). Note the very different y-scales on the two graphs. (Solid lines show the mean, shaded areas are the 95% prediction intervals.)

3.9 Summary of Results for Steps 3 and 4

Here we give the mean (and 95% credible intervals) for four key public health measures calculated over the period 17th May 2021 until 30th June 2022.

Scenario	Total Hospital Admissions	Peak Hospital Admissions	Peak Hospital Occupancy	Total Deaths
Default, $R_{ei} = 2.41$	34,900 (10,100 - 96,400)	621 (169 - 1640)	4640 (1270 - 11,700)	7250 (1450 - 24,300)
Step 3, $R_{ei} = 3.19$	60,200 (20,600 - 145,000)	1100 (364 - 2400)	8560 (2780 - 18,900)	12,700 (3280 - 38,400)
Step 3, $R_{ei} = 2.04$	20,800 (4470 - 68,000)	350 (57 - 1160)	2530 (432 - 8010)	4420 (615 - 17,400)
Step 4, $R_{ei} = 4.11$	66,300 (22,400 - 160,000)	1230 (398 - 2710)	9350 (2940 - 21,600)	16,700 (4260 - 50,400)
Step 4, $R_{ei} = 4.11$ delayed	50,500 (15,500 - 130,000)	759 (226 - 1810)	5840 (1700 - 14,400)	11,800 (2740 - 37,500)
Step 4, $R_{ei} = 2.96$	18,000 (4520 - 53,400)	308 (62 - 976)	2310 (475 - 6960)	3060 (508 - 10,800)
20% seasonality	22,000 (5510 - 66,600)	380 (79 - 1190)	2810 (599 - 8340)	4230 (704 - 15,400)
20% slower rollout	67,100 (22,600 - 161,000)	1240 (403 - 2740)	9490 (3000 - 21,800)	14,300 (3600 - 43,400)
20% faster rollout	19,000 (4310 - 61,500)	301 (53 - 982)	2220 (408 - 6920)	3890 (576 - 15,000)
Higher Vacc Eff	25,400 (6920 - 73,000)	471 (113 - 1360)	3470 (844 - 9560)	3030 (548 - 10,400)
Lower Vacc Eff	77,200 (25,700 - 189,000)	1360 (417 - 3100)	10,400 (3140 - 24,500)	21,500 (5020 - 67,600)
Pessimistic combination	186,000 (88,200 - 346,000)	4050 (1610 - 8020)	31,100 (12,600 - 61,700)	68,000 (24,100 - 169,000)
Optimistic combination	6890 (1540 - 23,800)	110 (20 - 461)	872 (339 - 3240)	673 (111 - 2720)

4 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, hospitalisations and deaths; the North West dominated the early growth of the second wave while London has often shown a more dramatic rise and decline in cases 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.

For 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 (Fig. 19).
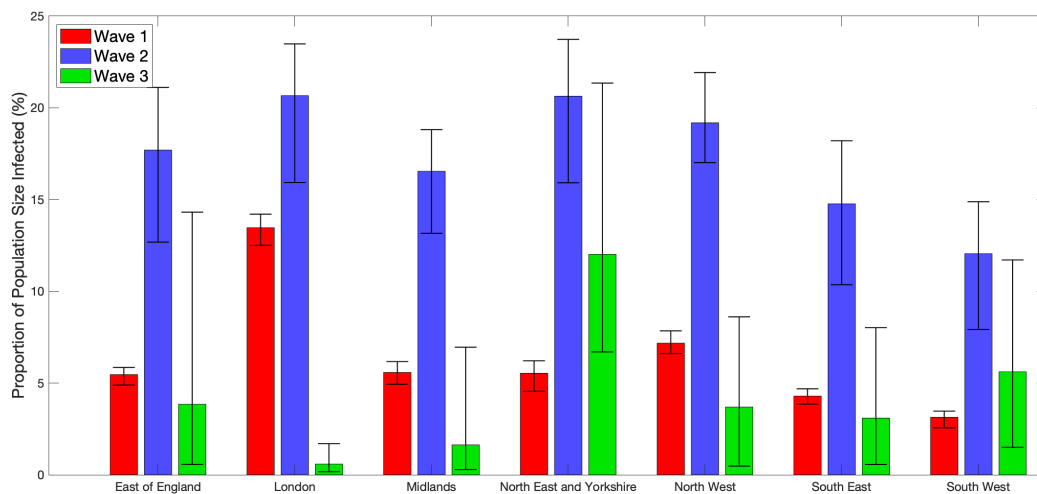

Fig. 19: The estimated proportion of the regional population infected in Wave 1 (Feb-Aug 2020), Wave 2 (Sept 2020-Mar 2021) and Wave 3 (May 2021 onwards). London, which is estimated to have the largest combined levels of cumulative infection during waves 1 and 2 has the smallest predicted relaxation wave.

Variation in vaccine uptake at a smaller spatial scale is much more pronounced than at a regional scale, with some LTLAs only achieving 70-80% 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.

We therefore expect the third wave to be extremely heterogeneous both at the regional and finer spatial scales, reflecting vaccine uptake and population level immunity.

5 Variants of Concern

We consider three different scenarios of a variant successfully invading the UK in early March 2021, but in very low numbers. To understand the role that NPIs play in controlling these novel variants, we consider a situation in which relaxation is halted at Step 2, one in which only Steps 2 and 3 occur (compare to Fig. 1), and one in which relaxation proceeds through Steps 2 to 4 (compare to Fig. 6). In general, the majority of the third wave of infection (from June 2021 onwards) in these scenarios is attributable to the novel variant. We assume that the VoC has been introduced to England at very low levels on 15th March 2021 (at one infection per NHS region), and it grows from this small seeding.

In the first three scenarios, the new variant has the same transmission rate as B.1.1.7, but is able to partially overcome existing immunity (although we assume infection with the novel variant confers complete immunity to both B.1.1.7 and the new variant); in the fourth example we assume complete cross immunity and similar levels of protection by vaccination, but consider a new variant that is able to transmit more rapidly.
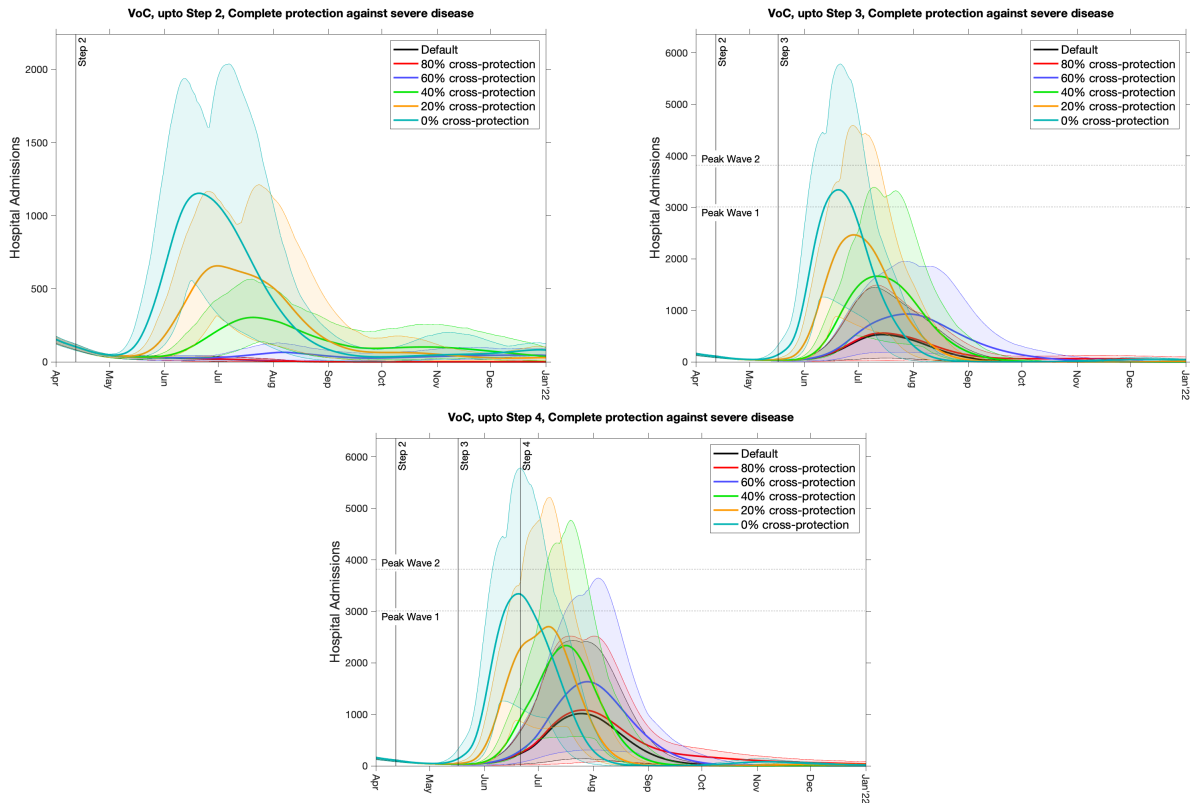
5.1 Complete protection against severe disease

Fig. 20: Projected hospital admissions for a novel variant that can partially overcome existing immunity, but where the subsequent risks of severe disease are effectively zero. The three figures show the impact of stopping the relaxation roadmap at Step 2, continuing only to Step 3 or completing Step 4. Lines are labelled by the amount of cross-protection against infection. Note that the three figures have axes on different scales.

Here we consider a variant that can partially escape immunity from previous infection, which we label as cross-protection against infection, and can partially escape immunity from vaccination, labelled as efficacy from vaccination against infection (Fig. 20). Individuals who are infected with the novel variant, and were previously immune, have a reduced chance of showing symptoms (reduced to 20%); the

risk of severe illness (in terms of hospital admissions or deaths) is reduced to zero for re-infection or is reduced by 90% for those with vaccine-derived immunity (comparible to the 90% vaccine efficacy assumed elsewhere in this work for B.1.1.7). These levels of protection are summarised in the table below:

Parameter set	Cross-protection against			Efficacy from vaccination against		
	Infection	Hospital Admission	Death	Infection	Hospital Admission	Death
1	80%	100%	100%	58%	90%	90%
2	60%	100%	100%	44%	90%	90%
3	40%	100%	100%	29%	90%	90%
4	20%	100%	100%	15%	90%	90%
5	0%	100%	100%	0%	90%	90%

In these new-variant models, additional hospital admissions and deaths, beyond those predicted in the default model, arise through greater community transmission (of the new variant) and hence infection of individuals that are not protected by the vaccine or infection-derived immunity.

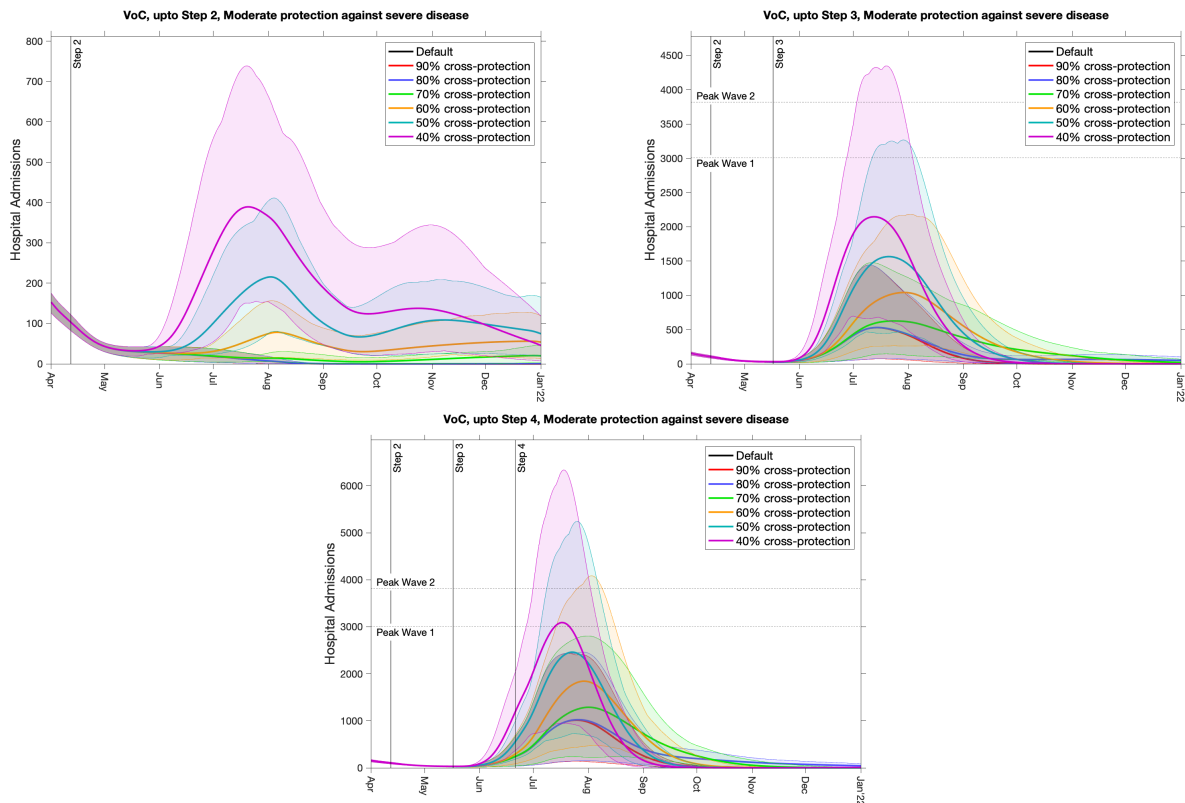## 5.2 Moderate protection against severe disease

Fig. 21: Projected hospital admissions for a novel variant that can partially overcome existing immunity, but where the subsequent risks of severe disease are substantially reduced. The three figures show the impact of stopping the relaxation roadmap at Step 2, continuing only to Step 3 or completing Step 4. Lines are labelled by the amount of cross-protection against infection. Note that the three figures have axes on different scales.

In the second scenario (Fig. 21), the novel variant again has the same transmission rate as B.1.1.7, and again can partially escape immunity from previous infection or vaccination; here we vary cross protection between 0 and 60%. Individuals who are infected with the novel variant, and were previously immune, have a reduced chance of showing symptoms (reduced to 20%, as in the scenario above), but now reduced chance of requiring hospital treatment (reduced to 20% compared to infection of naive individuals) and of mortality (reduced to 10% compared to infection of naive individuals) conditional

on being infected . Therefore, while the novel variant can partially overcome existing immunity, the public health implications are reduced.

Parameter set	Cross-protection against			Efficacy from vaccination against		
	Infection	Hospital Admission	Death	Infection	Hospital Admission	Death
1	90%	98%	99%	66%	89%	89%
2	80%	96%	98%	58%	87%	89%
3	70%	94%	97%	51%	86%	88%
4	60%	92%	96%	44%	84%	87%
5	50%	90%	95%	37%	83%	86%
6	40%	88%	94%	29%	81%	86%

In this example, the additional amount of severe disease (compared to Section 5.1) leads to **substantially** larger waves of hospital admission and mortality (compared to Fig. 20) despite the fact the the levels of cross-protection and vaccine efficacy remains high.
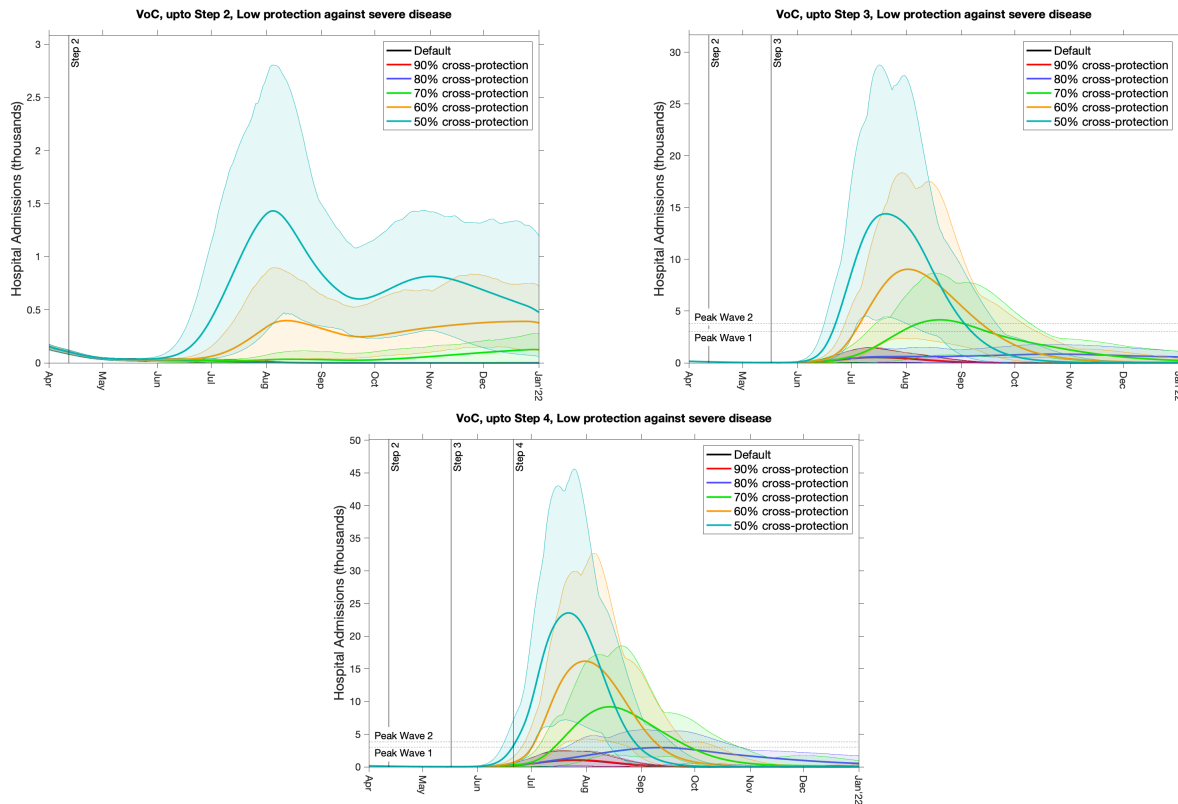
5.3 Low protection against severe disease

Fig. 22: Projected hospital admissions for a novel variant that can partially overcome existing immunity, but where the subsequent risks of severe disease are only slightly reduced. The three figures show the impact of stopping the relaxation roadmap at Step 2, continuing only to Step 3 or completing Step 4. Lines are labelled by the amount of cross-protection against infection. Note that the three figures have axes on different scales, and that here we plot thousands of hospital admissions.

The third scenario (Fig. 22) is similar to the first two, in that the novel variant has the same transmission rate as B.1.1.7 and can partially overcome existing immunity. However, we now assume that the protection offered by this previous immunity is far weaker, such that the chance of showing symptoms is only reduced to 90%, the chance of requiring hospital treatment is only reduced to 80% and the chance of mortality is only reduced to 70%, compared to infection of naive individuals. As such the

public health consequences of this variant are more extreme, even for the same level of underlying levels of novel-variant infection.

Parameter	Cross-protection against			Efficacy from vaccination against		
set	Infection	Hospital Admission	Death	Infection	Hospital Admission	Death
1	90%	92%	93%	66%	84%	85%
2	80%	84%	86%	58%	78%	80%
3	70%	76%	79%	51%	72%	75%
4	60%	68%	72%	44%	67%	70%
5	50%	60%	65%	37%	61%	64%

5.4 Complete protection against all infection, but higher transmission

In the final scenario (Fig. 23), immunity (either due to vaccination or natural infection) still holds, but the variant has a higher transmission rate (cf when B.1.1.7 spread across the UK). Vaccine efficacy against infection and severe disease is assumed to be the same as B.1.1.7. The rate of transmission is measured relative to the observed transmission of B.1.1.7.
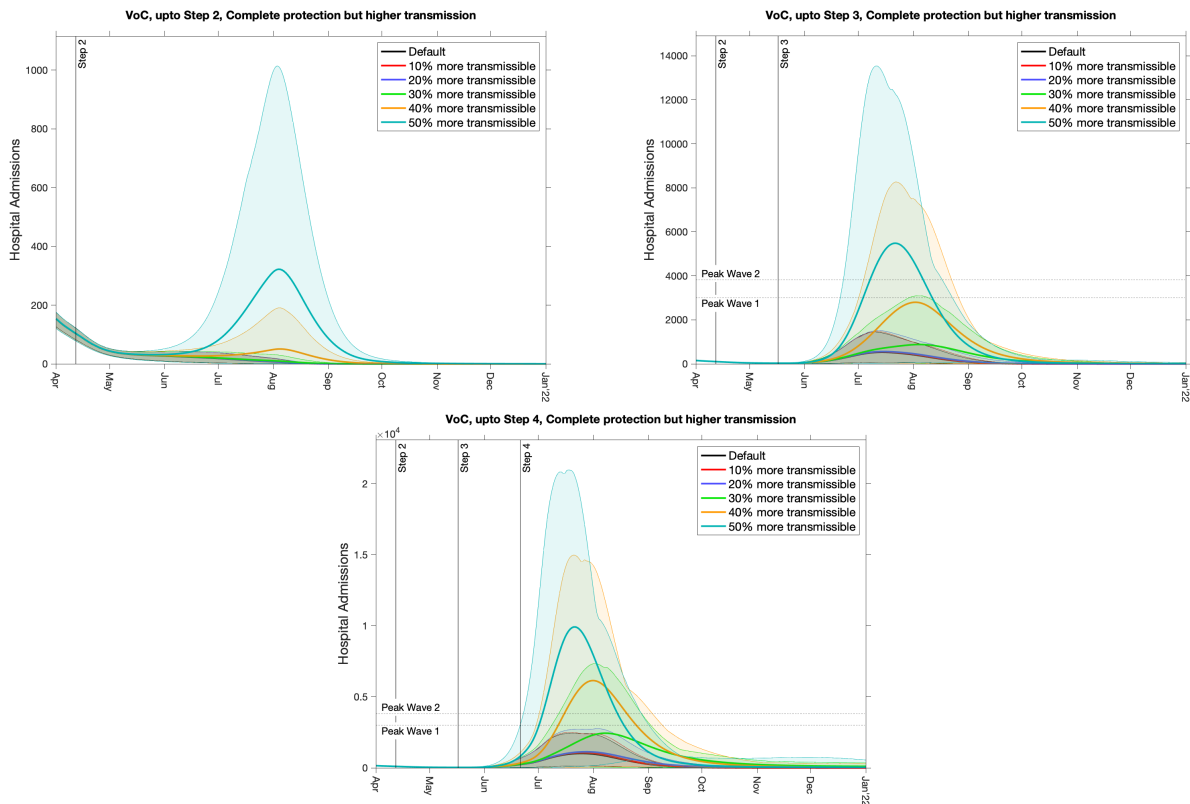

Fig. 23: Projected hospital admissions for a novel variant with higher transmission rates. The three figures show the impact of stopping the relaxation roadmap at Step 2, continuing only to Step 3 or completing Step 4. Note that the three figures have axes on different scales.

5.5 Combined VoC Sensitivity

Here we show the means, inter-quartile ranges and 95% prediction intervals for the number of hospital admissions from 17th May 2021 until the end of the simulations in June 2022. This is shown for each of the scenarios considered above (Figs. 20 to 23) and for scenarios in which relaxation is halted after Step 2, continues to Step 3 only, or where relaxation continues through to Step 4.
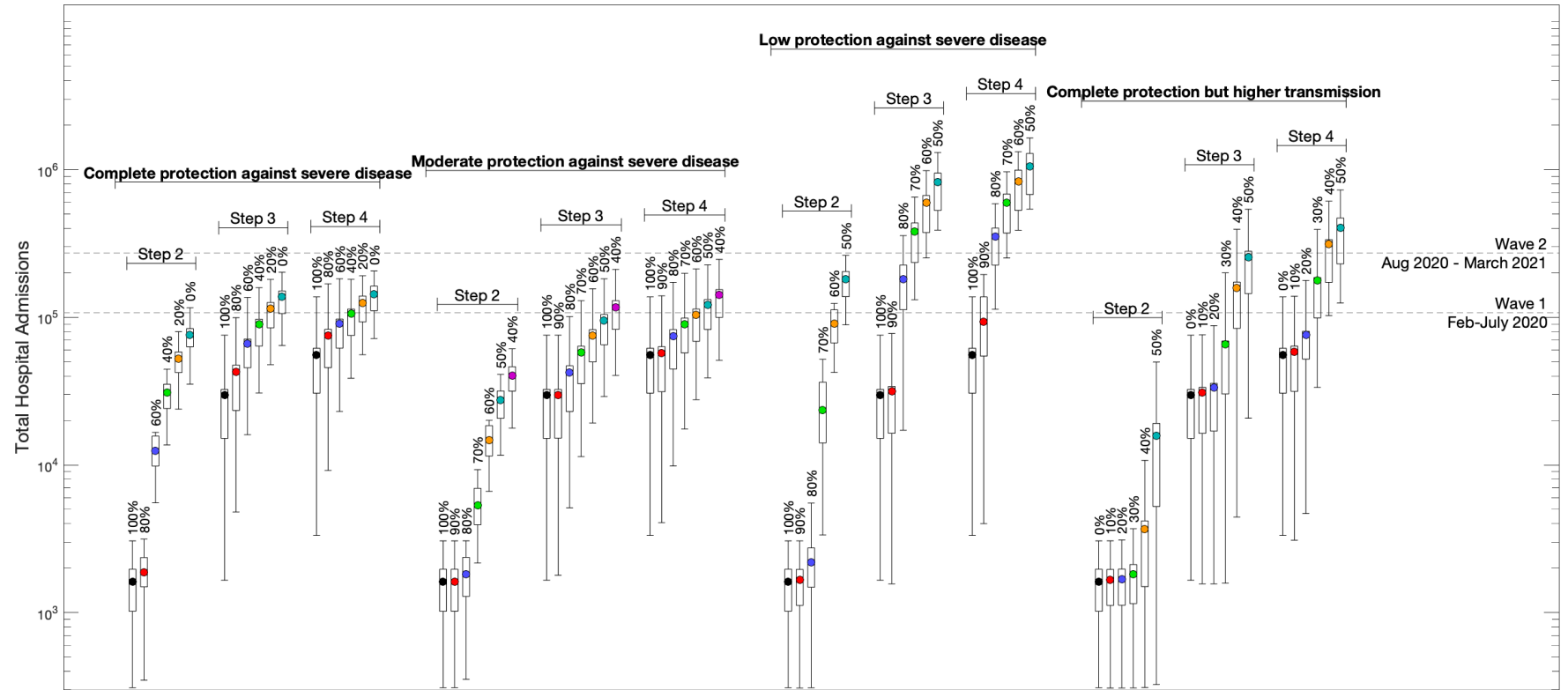
Fig. 24: Comparison of all the uncertainties investigated for VoC, showing their impact on the total number of hospital admissions from 17th May 2021 until the end of June 2022. Points and box and whisker plots are labelled by the amount of cross-protection against infection for the first three scenarios and by the amount of additional transmission for the fourth scenario.

Variants that can escape existing immunity and where this past immunity has a limited impact on severe disease are of the greatest immediate concern, leading to large waves of infection even when the relaxation is curtailed at Step 2 (Fig. 24), and can generate third waves that without additional control measures are larger than the second wave. In the longer term, while new vaccines may be developed in response to immune-escape variants, variants with higher transmission may require higher levels of control (through vaccination and NPIs) into the future. Assuming that the relaxation roadmap continues into Step 4, the estimated total number of hospital admissions from a third wave associated with a novel variant exceeds that observed in the first wave for: 30% cross immunity in the complete protection model (Fig. 20); 50% cross immunity in the moderate protection model (Fig. 21); 80% cross immunity in the low protection model (Fig. 22); and for a model with 30% greater transmission but no vaccine escape (Fig. 23).

5.6 Data under-pinning VoC assumptions

There is extremely limited data on vaccine efficacy and cross protection. Genomic data from India suggests that B.1.617 may have a competitive advantage over other variants (including B.1.1.7) potentially due to a higher transmission rate, although there is an expectation that current vaccines may offer protection; in this respect B.1.617 may be closest to the situation examined in Section 5.4. In contrast B.1.351 (often known as the South African variant) is considered to be no more transmissible than B.1.1.7 but may be able to partially escape immunity from vaccination or natural infection; in this respect B.1.351 may be closest to the situation examined in Sections 5.1-5.3.

One element that is relatively well described is the potential increase in variants throughout England. Fig. 25 shows the weekly trend in S-gene positive samples identified from Pillar 2 PCR sampling of symptomatic individuals. We fully recognise that not all S-gene positive samples are variants of concern, but feel that this rapid data stream has merit in identifying recent trends, and note that an increasing proportion of sequenced S-gene positive samples are now found to be variants of concern. We also note that surge testing in potential hot-spots may introduce substantial biases to these patterns and that some of the trends could reflect increasing number of S-gene positive variants entering the country with limited community transmission. This bias is reduced in our data by considering only individuals reporting symptoms, although surge testing could still provoke biases through increased public concern in these areas leading to symptomatic individuals being more likely to request a test. Nevertheless, the pattern is of considerable concern.
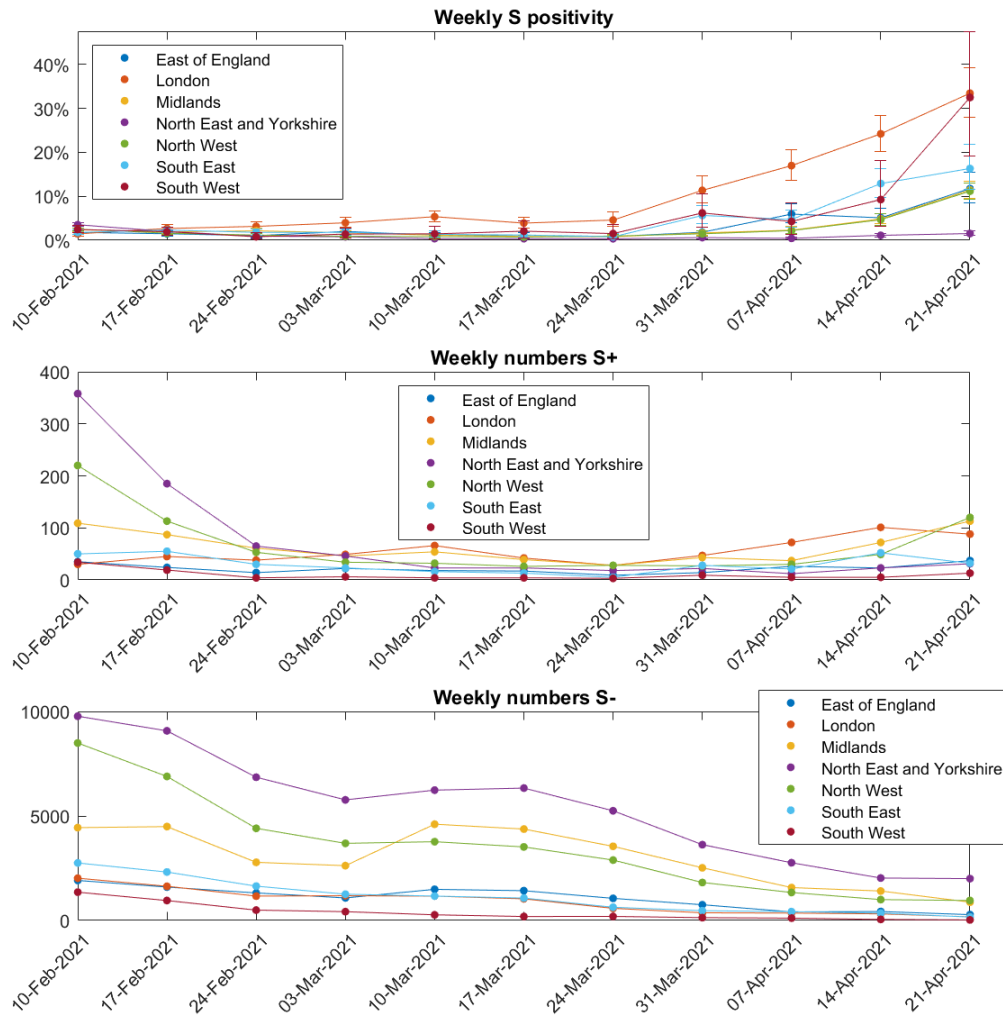
Fig. 25: Data from Pillar 2 testing of individuals reporting symptoms, showing the percentage of S-gene positive samples (top, with 95% CIs) and well as the absolute number of S-gene positive (middle) and S-gene negative (bottom) samples each week across the seven NHS regions in England.

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