The impact of accelerated COVID vaccine trials on mortality

A Preprint

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Abstract

1 Abstract

2 Introduction

(this Introduction is copied from here—for the time being please edit in Google Doc) aa The Covid-19 pandemic has had a devastating impact on global health and economies. In the United States and United Kingdom alone, hundreds of thousands of lives were lost in 2020 and 2021. The development and testing of vaccines for Covid-19 progressed at an unprecedented pace, with mass vaccinations beginning in some countries within less than a year from the start of the pandemic.

However, it has been suggested that the vaccines could have been made available even earlier. One proposal for acceleration has been the use of human challenge trials (HCTs) to test for efficacy. HCTs involve intentionally infecting a small group of volunteers with a disease in order to study the efficacy of potential treatments or vaccines. While both ethical and technological barriers to adoption of HCTs are considerable, they have the potential to significantly accelerate the efficacy studies.

In this paper, we aim to quantify the potential benefits of accelerating the approval and distribution of Covid-19 vaccines. While we focus on HCTs, the model we use is generic and applicable to all measures that could have led to earlier use of vaccines.

The potential benefits of accelerating the approval and distribution of vaccines, both in terms of health outcomes and economic impacts, are likely to be significant. In fact, research has suggested that these benefits may be orders of magnitude larger than the costs associated with acceleration (Castillo et al. 2021). Despite this, there has been relatively little research on the impact of speed on vaccination efforts, particularly in terms of epidemiological modeling.

A recent review paper (Więcek, 2022) found only one quantitative estimate of the impact of accelerating testing of vaccines on mortality. This estimate, from Berry et al. (2020), was based on prospective simulations, which overestimated timelines for vaccine field trials and do not have information about the real burden of the Covid-19 pandemic in 2020 and 2021.

We use counterfactual simulations informed by retrospective analysis of data on observed vaccinations, infections, and mortality. This allows us to consider the actual vaccine development timelines. To quantify benefits of speed we consider different acceleration scenarios, estimate the number of vaccinations under each scenario, and then calculate the number of deaths averted, compared to the status quo.

We calculate benefits for two countries, the United States and the United Kingdom. They are large developed countries that were at the front of the queue for vaccine deliveries and therefore would have been likely to benefit from accelerated testing. It's good to contrast these two countries because they had epidemic waves occurring at different times, with different virus strains, and employed different non-pharmaceutical interventions.

Epidemiological modeling simplifies many nuances and may not consider certain factors, such as individual behaviors and responses to public health interventions. Therefore, we also include additional calculations, including both a theoretical model and a back-of-the-envelope calculation which ignores epidemiological spillovers. Additionally, we consider some potential unknowns associated with accelerating vaccine approvals, such as (1) less precise information on efficacy or safety, (2) impact on public confidence in vaccines, (3) the potential for production and distribution constraints to nullify the benefits of accelerated testing.

3 Methods

3.1 Baseline model

To model alternative vaccination timelines, we took an existing compartmental model that simulated the COVID-19 pandemic through 2020 and 2021 including the impact of vaccinations (the "baseline model") and re-ran the simulation freezing all parameters except the vaccination timelines (the "counterfactual models").

The baseline pandemic model used the model behind (Watson et al., 2022a). This model is implemented in open source R packages Squire (Hogan et al., 2021, Walker et al. (2020), Watson et al. (2021)) and SirCOVID (Baguelin et al., 2022). An older version of this model is described in detail in the supplementary material of (Walker et al., 2020), and details of many parameters – again, for an older version of the model – can be found in the supplementary material of (Watson et al., 2022b). Additional incomplete information about the parametrisation of the version of the model we used can be found at COVID-19 LMIC Reports documentation (Watson et al., 2022a), and more up-to-date but less complete model structure can be found in the Nimue documentation (Winskill et al., 2022). Here we will describe the model in broad terms.

The baseline model is an age-stratified SEIRD model. In addition to classifying the population by infection status, the model also classifies people by vaccination status: they may be unvaccinated, vaccinated with 1 dose, vaccinated with 2 doses, vaccinated with 2 doses with waned protection, vaccinated 3 doses and vaccinated with 3 doses with waned protection. People are vaccinated according to vaccination dosage data from Our World in Data (Mathieu et al., 2020) together with a model of vaccine prioritisation. They progress to "waned" classes according to an assumed rate of waning of vaccine-derived immunity, which is itself time and dose-number-dependent. The model accounts for separate modes of vaccine action (infection blocking vs disease blocking), variant-dependent efficacy of vaccine and naturally derived immunity and age-dependent vaccination strategies.

The model assumes homogenous mixing of the population. It models different kinds of infection – "severe" and "non-severe" – which have different age-dependent probabilities of progressing to recovery or death. Individuals who have recovered are assumed to be fully protected by natural immunity for an exponentially random duration duration which is, on average, around 250 days. Individuals who have been vaccinated have different levels of protection at different points in time depending on the dominant strain, and unless they receive additional doeses then protection is considered to have waned after an exponentially random period of time (on average, around 150 days). Vaccinated individuals are also considered to have a reduced likelihood of onward transmission, which also fades when the vaccine protection wanes.

The model features a mix of deterministic parameters and random parameters. We run an ensemble of simulations for each country, sampling the random parameters at the start of each run from pre-defined distributions. The initial number of cases seeding the pandemic in the country and the time series of reproduction numbers of infections in a fully susceptible population R_t is then fit to the observed course of deaths during the time period associated with the simulation.

The distributions of random parameters is given in Table 1. Parameters are sampled from each distribution independently except for the duration of vaccine-derived immunity, which is dependent on vaccine efficacy. 100 sets of parameters are sampled, and epidemic trajectories simulated for each. 95% intervals in our results refer to percentiles among the set of 100 sampled trajectories, so a 95% interval for deaths averted is the pair of numbers given by the 2.5th and the 97.5th percentile of deaths averted among all sampled trajectories. Note that the distributions given here are not exact representations of the models sampling distributions, which involve additional truncation steps.

The model of (Watson et al., 2022a) also samples probabilities of hospitalisation and mechanical ventilation for each trajectory, but these play no role in our analysis not already captured by the infection fatality rate, and so we haven't reported on the relevant parameters here.

Table 1: Distributions from which parameters are sampled. The parameters α_e^P, β_e^P are shape parameters for vaccine platform P with associated dominant strain dependent efficacy e (see text for additional details). The parameters α_d, β_d are shape and rate parameters for distribution of vaccine durations, determined by fitting an antibody decay curve to vaccine efficacies. rescale$(\cdot, f_{min}, f_{med}, f_{max})$ is a function that maps 0 to f_{min}, 0.5 to f_{med} and 1 to f_{max}, linearly interpolating between each. $f_{min}, f_{med}, f_{max}$ are respectively the minimum, median, and maximum estimates of age-adjusted infection fatality.

Parameter	Distribution
Vaccine efficacy V	$V \sim \text{Beta}(\alpha_e^P, \beta_e^P), P \sim U(\{\text{vaccineplatforms}\})$
Vaccine duration D	$\frac{1}{\text{Gamma}(\alpha_d, \beta_d)}$
Infection fatality rate with treatment F	$F = \text{rescale}(X, f_{min}, f_{med}, f_{max}) \quad X \sim \text{Beta}(2, 2)$

Table 2: Vaccine platforms used by each country.

Country	Platforms
USA	mRNA, single dose, subunit
UK	adenovirus, mRNA

The shape parameters α_e^P, β_e^P that appear in Table 1 are the shape parameters associated with a beta distribution with mean μ_e^P and variance 0.005. The mean μ_e^P is determined by estimating the efficacy of each vaccine platform P against each variant (see Table 3). The mean vaccine durations are determined according to models of antibody decay, and are dependent on the sampled vaccine efficacies μ_e^P (Watson et al., 2022a).

We made one change to the model used by (Watson et al., 2022a): by default, vaccination was assumed to reduce onward transmission by 50%, regardless of whether the dose was fresh or waned. We modified this to the schedule shown in Table 4. These represented an average between the estimates of (Eyre et al., 2021) for effectiveness at blocking onward transmission of Alpha and Delta and the estimate of (Tan et al., 2023) for effectiveness of the vaccine at blocking onward transmission of Omicron, as the period of the simulation included both Delta and Omicron waves.

Table 3: Model parameters - central estimates of vaccine efficacy

Vaccine type	Doses	Strain	Protection against infection
mRNA	1	Wild	0.630
mRNA	2	Wild	0.860
mRNA	1	Delta	0.360
mRNA	2	Delta	0.880
mRNA	1	Omicron	0.000
mRNA	2	Omicron	0.136
mRNA	3	Omicron	0.650
Single dose	Full	Wild	0.660
Single dose	Full	Delta	0.500
Adenovirus	Partial	Wild	0.640
Adenovirus	Full	Wild	0.770
Adenovirus	Partial	Delta	0.300
Adenovirus	Full	Delta	0.670
Subunit	Partial	Wild	0.540
Subunit	Full	Wild	0.860
Subunit	Partial	Delta	0.300
Subunit	Full	Delta	0.710

Table 4: Assumed relative transmissibility of infection by vaccinated individuals compared to unvaccinated

Doses	Protection from onward transmission
1 dose (fresh)	27%
2 doses (fresh)	27%
2 doses (waned)	0%
3 doses (fresh)	30%
3 doses (waned stage 1)	10%
3 doses (waned stage 2)	5%

Table 5: Total vaccinations at sample dates

shifted_by	2021-01-01	2021-04-01	2021-07-01
United Kingdom			
Baseline	0	33,337,926	75,688,766
Vaccines 30 days sooner	3,460,361	42,486,427	80,736,395
Vaccines 60 days sooner	14,859,054	57,449,853	86,771,215
Vaccines 90 days sooner	28,042,344	71,663,088	91,140,069
United States			
Baseline	4,521,988	172,124,225	347,123,032
Vaccines 30 days sooner	23,889,241	238,670,399	357,876,350
Vaccines 60 days sooner	56,107,462	289,245,438	372,702,522
Vaccines 90 days sooner	56,107,489	289,245,510	376,955,754

3.2 Vaccine production

To produce counterfactual vaccine dosage timeseries, we suppose that vaccine approcal is brought forward by a number of days (we test approval coming 30, 60 and 90 day sooner). However, if approval is brought forward too much then manufacturers might have a harder time maintaining supply than they would have in the situation that actually played out. We model this by ... (see Tomas' entry in the shared doc)

Plots can currently be found in Vaccine production model

4 Results

4.1 Vaccinations under counterfactual scenarios

Figure 1 shows the cumulative vaccinations for the counterfactual scenarios we investigate. The baseline scenario is the actual vaccination timeline, while the other scenarios are the same timeline but with vaccines administered 30, 60 or 90 days sooner.

Table 5 shows the actual vaccinations administered on 2021-01-01, 2021-04-01 and 2021-07-01 alongside the administration numbers for the counterfactual scenarios we investigage.

```
## The following `from` values were not present in `x`: Counterfactual scenario
```

4.2 Impact of counterfactual vaccination scenarios

Table 6 shows the number of deaths averted by each counterfactual scenario. The number of deaths averted is calculated as the difference between the number of deaths under the baseline scenario and the number of deaths under the counterfactual scenario. The number of deaths averted is shown as the average number of deaths averted, as well as the interval that contains 95% of simulation trajectories (see Section Methods for details on how simulation trajectories are sampled). The number of deaths averted is also shown as the average number of deaths averted per 10,000 people in each country.

```
## Warning: Using `all_of()` outside of a selecting function was deprecated in tidyselect 1.2.0.
```

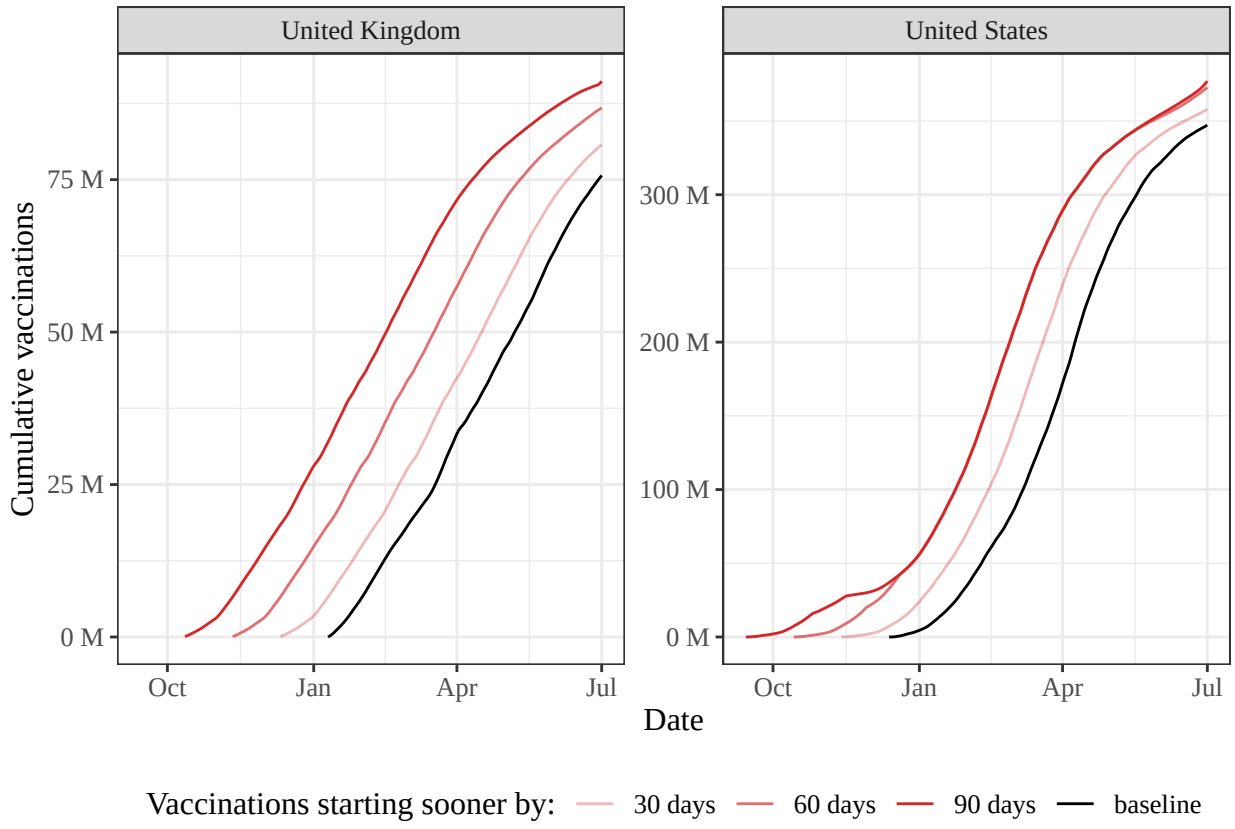

Figure 1: DJ4 Cumulative vaccine counterfactuals

```
## i See details at <https://tidyselect.r-lib.org/reference/faq-selection-context.html>
## This warning is displayed once every 8 hours.
## Call ‘lifecycle::last_lifecycle_warnings()‘ to see where this warning was generated.

## The following ‘from‘ values were not present in ‘x‘: Counterfactual scenario, Deaths averted, Deaths
```

Figure 2 shows the number of deaths per day under each counterfactual scenario compared to the baseline. Also shown is the interval containing 95% of the counterfactual simulation trajectories. Figure @ref{cumulative-deaths} shows cumulative deaths under the baseline and counterfactual scenarios.

5 Discussion

5.1 Placeholder for commentary on main results

5.2 Subsequent infection waves

While our main results present the number of deaths averted up to July 2021, we simulated the counterfactual scenarious up until the end of 2021. The longer timeline includes an additional wave of infections in both the US and the UK. Our model shows much more uncertainty over the effect of earlier vaccination timelines for this second wave of infections in the United States. In this country, the 95% interval of simulation traces ranges from 228 000 lives saved to 90 000 extra deaths. The UK, on the other hand, shows much less variation in the impact of earlier timelines on the number of deaths in the second wave.

There are numerous ways that altering the timing of vaccinations can alter the pandemic trajectory for subsequent waves of infection. Effects that enter into our model are: 1. Earlier vaccine administration means that people will experience waning vaccine protection earlier, which could make them vulnerable

Table 6: DJ5 Averted deaths

counterfactual_label	delta_deaths	delta_deaths_perpop	baseline_cumulative_deaths_avg	delta_deaths_perreported
United Kingdom to April 2021				
30 days sooner	5,682 [4,250; 9,361]	0.85 [0.63; 1.40]	140486	0.04
60 days sooner	16,024 [13,351; 25,544]	2.39 [1.99; 3.81]	140486	0.11
90 days sooner	26,942 [23,165; 35,453]	4.02 [3.45; 5.29]	140486	0.19
United Kingdom to July 2021				
30 days sooner	5,959 [4,655; 9,242]	0.89 [0.69; 1.38]	143115	0.04
60 days sooner	17,900 [14,991; 26,488]	2.67 [2.23; 3.95]	143115	0.13
90 days sooner	29,616 [25,497; 36,711]	4.41 [3.80; 5.47]	143115	0.21
United Kingdom to Jan 2022				
30 days sooner	10,290 [8,657; 14,397]	1.53 [1.29; 2.15]	174302	0.06
60 days sooner	38,221 [32,957; 41,018]	5.70 [4.91; 6.11]	174302	0.22
90 days sooner	56,926 [51,235; 59,932]	8.49 [7.64; 8.93]	174302	0.33
United States to April 2021				
30 days sooner	17,343 [2,871; 37,637]	0.52 [0.09; 1.14]	643041	0.03
60 days sooner	54,609 [13,318; 104,973]	1.65 [0.40; 3.17]	643041	0.08
90 days sooner	78,091 [29,336; 138,458]	2.36 [0.88; 4.18]	643041	0.12
United States to July 2021				
30 days sooner	33,093 [12,630; 48,999]	1.00 [0.38; 1.48]	684646	0.05
60 days sooner	80,747 [32,170; 122,491]	2.44 [0.97; 3.70]	684646	0.12
90 days sooner	102,180 [47,565; 150,268]	3.08 [1.43; 4.53]	684646	0.15
United States to Jan 2022				
30 days sooner	57,879 [-34,415; 126,631]	1.75 [-1.04; 3.82]	978291	0.06
60 days sooner	153,618 [-30,648; 258,929]	4.63 [-0.92; 7.81]	978291	0.16
90 days sooner	240,451 [96,025; 311,001]	7.25 [2.90; 9.38]	978291	0.25

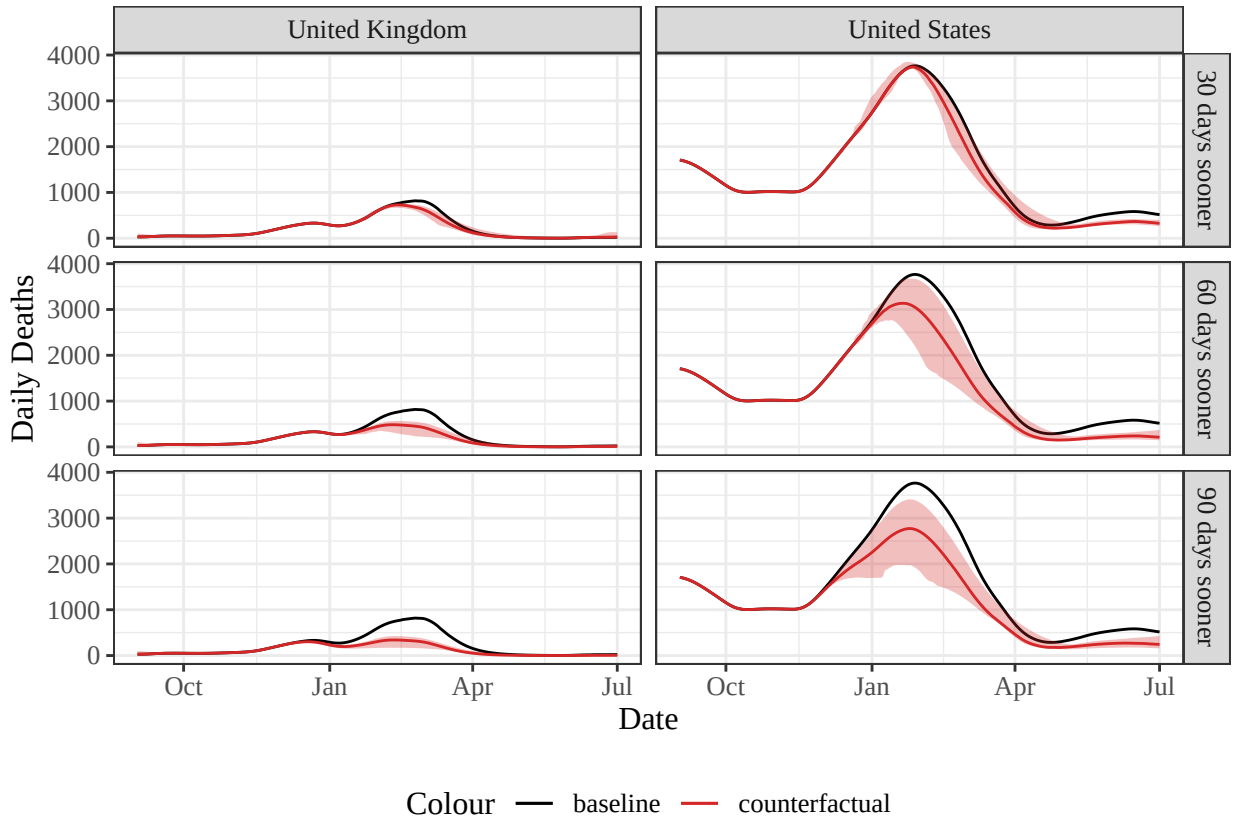

Figure 2: DJ6 Daily deaths per scenario

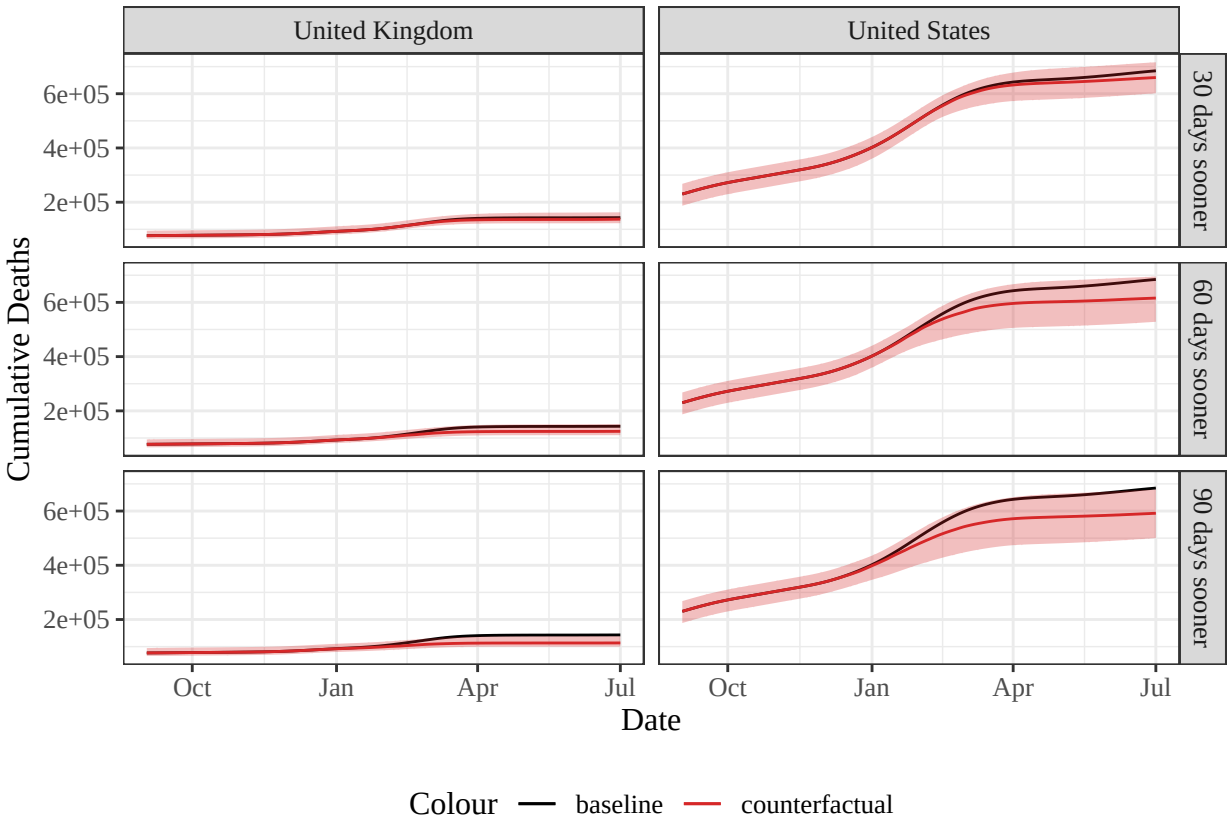

Figure 3: Cumulative deaths per scenario

if this waning coincides with a peak in infections (this is expected to increase infections at later dates) 2. Earlier vaccine administration can reduce the total number of infections immediately following the vaccination campaign, leading to fewer people having naturally acquired immunity at later dates (this is expected to increase infections at later dates) 3. Earlier vaccine administration can reduce the number of people infected at the start of a followup wave of infections (this is expected to increase the time taken to reach an infection peak and reduce the overall number of infections) 4. Earlier vaccine administration goes together with earlier administration of booster doses, so people may be *more* protected at followup waves due to having recently received a booster (this is expected to reduce the overall number of infections)

Earlier vaccine administration may also lead to behaviour change, which is not captured by our model. The effect of behaviour change downstream of vaccination is also hard to predict. If earlier vaccination leads to fewer infections in deaths at a given point in time, and as a result people relax social distancing behaviour, then our model might overestimate short-term infections and deaths in the early vaccination scenario (though people would of course be benefiting from reduced social distancing). At the same time, such a situation would lead to a higher rate of natural immunity, which could reduce the impact of a subsequent infection wave.

We hypothesise that differences between the US and the UK that lead to the divergent results may be: - Booster doses were much more popular in the UK than in the US. On Jan 1 2022 50.5% of the UK population had received booster doses compared to 23.4% of the US population (Mathieu et al., 2020) - Our model predicts that in the short run, earlier vaccinations suppress the level of infections in the UK more than they do in the US.

To test the hypothesis that differential booster doses explain some of the difference, we ran a simulation where the rate of booster doses in the US was counterfactually adjusted so that the coverage of booster doses in both the US and UK were equal on Jan 1 2022 (to achieve this, we rougly doubled the booster dose coverage in the US). The results are in Supplementary Table 8. We note that this counterfactual doesn't

drastically reduce the uncertainty over long run deaths averted in the US, suggesting that the differences between the US and the UK estimates are driven by something other than differences in booster adoption.

While we show that earlier vaccinations have large benefits to mortality in infections waves occurring close to the vaccination campaign, and our best guess is that earlier vaccinations yield large benefits to mortality overall, we are substantially less certain of the latter conclusion. Due to uncertainty about the effects of early vaccination on followup waves, we are substantially uncertain about the overall size and sign of the mortality benefit for COVID-19. Furthermore, future pandemics (or even followup waves of COVID-19) are going to differ from the period we studied, and the overall benefits of accelerated vaccinations are likely to be sensitive to these differences.

5.3 Sensitivity to modelling assumptions

We explored various alternative model configurations in order to assess the sensitivity of our conclusion to modelling assumptions. Compared to a hypothetical ideal model that yields correct counterfactual assessments, the model we employ is likely to differ in a number of ways: - It may differ structurally. We might anticipate some structural differences - for example, overdispersion in the distribution of contact rates is not captured by our model, but overdispersion in this distribution was typically found to be high (Endo et al., 2020). However, there may be other structural differences that we do not anticipate - The assumed distributions of input parameters may differ in our model and in the hypothetical ideal

Both of these differences mean that the fitted values of R_t are also likely to differ between our model and the hypothetical ideal, and hence they may yield substantially different assessments of counterfactual scenarios. If it turns out that counterfactual assessments are very sensitive to input parameter values, then we might conclude that our estimates are likely to differ substantially from the "true" counterfactual. Because of the prospect of structural differences, this is true even if we have done a very good job of estimating parameters. If our results are robust to variation of parameters within a reasonable range, then if we believe that our model is capable of yielding a good approximation to the ideal for some "reaonsable" parameter choices, we should also think our counterfactual assessments are a good approximation to ideal counterfactual assessments.

We assess the impact of three different parameter estimates on our overall results. To do this, we examine the average conclusion from the model runs featuring the top and bottom deciles of each of the following parameters: - The average infection-blocking efficacy of one and two doses of the vaccine - The average duration for protection due to one and two doses of the vaccine - The average duration of protection due to natural immunity

In both countries, the estimates of deaths averted showed little sensitivity to the estimated duration of natural immunity (Supplementary Table 11. The estimates of deaths averted in the UK was *also* relatively insensitive to the estimated vaccine efficacy, though the estimate in the US was more sensitive to this value (it is worth noting that in the case of the US the model explored captured a wider range of variation in vaccine efficacy) - see Supplementary Table 9. Note that for long-run estimates of deaths averted in the US (up to Jan 2022), higher estimates of vaccine efficacy were associated with much greater uncertainty over the number of deaths averted. This may be due to the fact that, given a more effective vaccine, waning immunity will have a larger impact on the end results.

The estimate of long-run deaths averted in the US was extremely sensitive to the estimated duration of vaccine derived immunity, with a difference of 14 days in this parameter estimate yielding long-run estimates of deaths averted that ranged from 32 255 to *negative* 11 456 (that is, 11 456 extra deaths) for a 30 day advance in the vaccination schedule. Notably, short estimates of vaccine duration were also associated with extreme decreases in the uncertainty over the number of deaths averted. Note that the short run estimates of deaths averted (up to July 2021) were robustly positive, but were also substantially more uncertain for longer estimates of the duration of vaccine protection.

Our model is already very uncertain about the effect of earlier vaccinations on the second infection wave in the US. However, the high sensitivity of this figure to the estimated duration of vaccine-derived protection offers an extra reason to be unsure that the model is providing us with an accurate assessment of the counterfactual impacts on this timescale.

We also run an identical analysis to our main analysis, except with a model fit to reported numbers of COVID-19 deaths instead of COVID-19 deaths estimated from excess mortality. The results are reported in Supplementary Table 7 and Supplementary Figure 4. This method yields larger estimates of deaths averted than our main method, particularly up to July 2021 where the estimates are close to the 95th percentile

estimate for the main method. This is in spite of the fact that the total estimated number of deaths under this method is somewhat lower than under the excess mortality method.

6 Conclusion

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A Sensitivity

A.1 Baseline fit to reported deaths instead of excess deaths

```
## The following ‘from‘ values were not present in ‘x‘: Counterfactual scenario, Deaths averted, Deaths
```

A.2 Counterfactual scenario: what if US had doubled the rate of booster uptake?

```
## The following ‘from‘ values were not present in ‘x‘: Counterfactual scenario, Deaths averted, Deaths
```

Table 7: Averted deaths calculated on the basis of a model fit to reported deaths

counterfactual_label	delta_deaths	delta_deaths_perpop	baseline_cumulative_deaths_avg	delta_deaths_perreported
United Kingdom to April 2021				
30 days sooner	5,682 [4,250; 9,361]	0.85 [0.63; 1.40]	140486	0.04
60 days sooner	16,024 [13,351; 25,544]	2.39 [1.99; 3.81]	140486	0.11
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60 days sooner	38,221 [32,957; 41,018]	5.70 [4.91; 6.11]	174302	0.22
90 days sooner	56,926 [51,235; 59,932]	8.49 [7.64; 8.93]	174302	0.33
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60 days sooner	54,609 [13,318; 104,973]	1.65 [0.40; 3.17]	643041	0.08
90 days sooner	78,091 [29,336; 138,458]	2.36 [0.88; 4.18]	643041	0.12
United States to July 2021				
30 days sooner	33,093 [12,630; 48,999]	1.00 [0.38; 1.48]	684646	0.05
60 days sooner	80,747 [32,170; 122,491]	2.44 [0.97; 3.70]	684646	0.12
90 days sooner	102,180 [47,565; 150,268]	3.08 [1.43; 4.53]	684646	0.15
United States to Jan 2022				
30 days sooner	57,879 [-34,415; 126,631]	1.75 [-1.04; 3.82]	978291	0.06
60 days sooner	153,618 [-30,648; 258,929]	4.63 [-0.92; 7.81]	978291	0.16
90 days sooner	240,451 [96,025; 311,001]	7.25 [2.90; 9.38]	978291	0.25

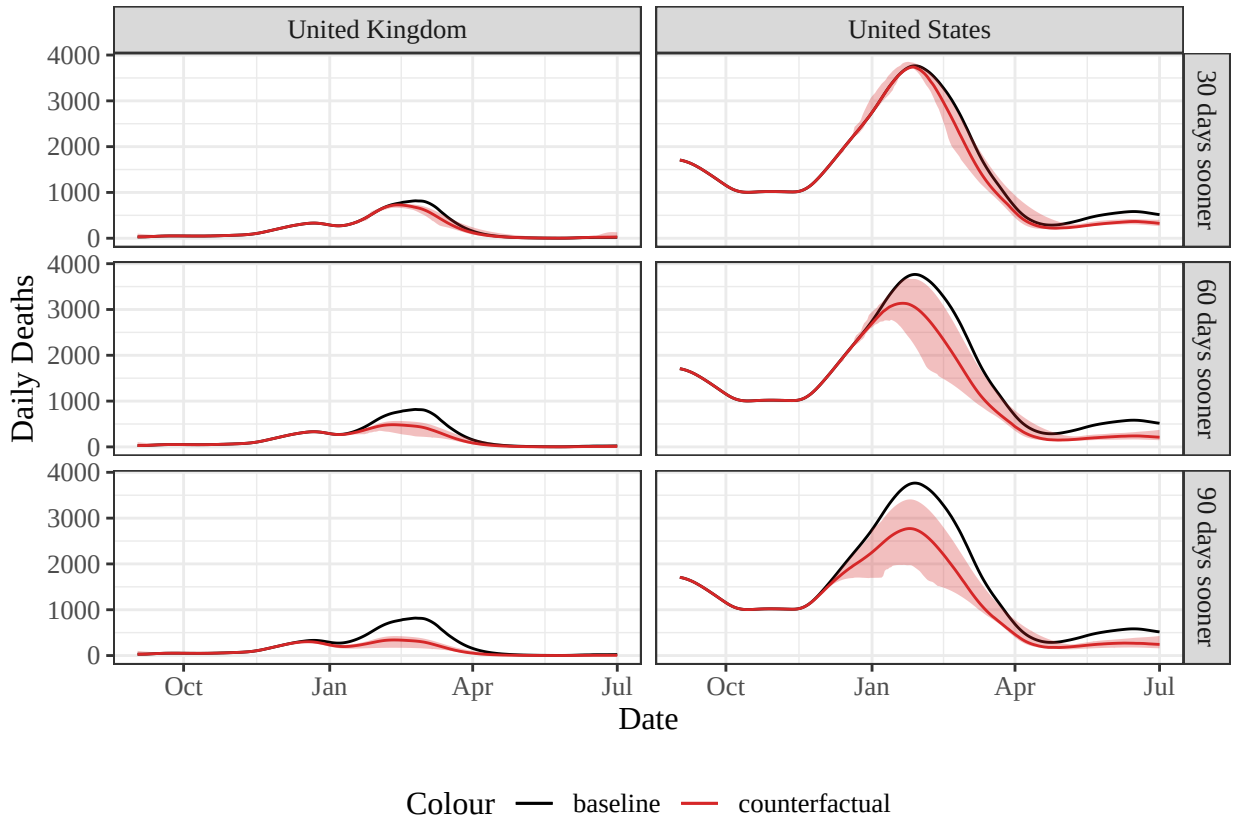

Figure 4: DJ6 Daily deaths per scenario

Table 8: How would US outcomes change if boosters were adopted at twice the actual rate?

counterfactual_label	delta_deaths	delta_deaths_perpop	baseline_cumulative_deaths_avg	delta_deaths_perreported
United Kingdom to April 2021				
30 days sooner	5,682 [4,250; 9,361]	0.85 [0.63; 1.40]	140486	0.04
60 days sooner	16,024 [13,351; 25,544]	2.39 [1.99; 3.81]	140486	0.11
90 days sooner	26,942 [23,165; 35,453]	4.02 [3.45; 5.29]	140486	0.19
United Kingdom to July 2021				
30 days sooner	5,959 [4,655; 9,242]	0.89 [0.69; 1.38]	143115	0.04
60 days sooner	17,900 [14,991; 26,488]	2.67 [2.23; 3.95]	143115	0.13
90 days sooner	29,616 [25,497; 36,711]	4.41 [3.80; 5.47]	143115	0.21
United Kingdom to Jan 2022				
30 days sooner	10,290 [8,657; 14,397]	1.53 [1.29; 2.15]	174302	0.06
60 days sooner	38,221 [32,957; 41,018]	5.70 [4.91; 6.11]	174302	0.22
90 days sooner	56,926 [51,235; 59,932]	8.49 [7.64; 8.93]	174302	0.33
United States to April 2021				
30 days sooner	17,343 [2,871; 37,637]	0.52 [0.09; 1.14]	643041	0.03
60 days sooner	54,609 [13,318; 104,973]	1.65 [0.40; 3.17]	643041	0.08
90 days sooner	78,091 [29,336; 138,458]	2.36 [0.88; 4.18]	643041	0.12
United States to July 2021				
30 days sooner	33,093 [12,630; 48,999]	1.00 [0.38; 1.48]	684646	0.05
60 days sooner	80,747 [32,170; 122,491]	2.44 [0.97; 3.70]	684646	0.12
90 days sooner	102,180 [47,565; 150,268]	3.08 [1.43; 4.53]	684646	0.15
United States to Jan 2022				
30 days sooner	57,879 [-34,415; 126,631]	1.75 [-1.04; 3.82]	978291	0.06
60 days sooner	153,618 [-30,648; 258,929]	4.63 [-0.92; 7.81]	978291	0.16
90 days sooner	240,451 [96,025; 311,001]	7.25 [2.90; 9.38]	978291	0.25

A.3 Sensitivity to parametric estimates

```
## The following ‘from‘ values were not present in ‘x‘: Counterfactual scenario, Deaths averted, sensit
## The following ‘from‘ values were not present in ‘x‘: Counterfactual scenario, Deaths averted, sensit
## The following ‘from‘ values were not present in ‘x‘: Counterfactual scenario, Deaths averted, sensit

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## The following ‘from‘ values were not present in ‘x‘: Counterfactual scenario, Deaths averted, sensit
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## The following ‘from‘ values were not present in ‘x‘: Counterfactual scenario, Deaths averted, sensit
## The following ‘from‘ values were not present in ‘x‘: Counterfactual scenario, Deaths averted, sensit
## The following ‘from‘ values were not present in ‘x‘: Counterfactual scenario, Deaths averted, sensit

## Warning: Removed 209 rows containing missing values (‘geom_line()‘).
## Removed 209 rows containing missing values (‘geom_line()‘).
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B Vaccine production model

Figure 15 shows the assumptions we made about the achievable production when vaccines were approved to be used 30, 60 and 90 days earlier.

Figures 16 and @rel{fig:prod-cap-usa} show our assumptions about the maximum number of vaccines that could be produced each day if vaccines were approved 30, 60 and 90 days earlier.

Table 9: Sensitivity to average vaccine efficacy against infection (VEI)

counterfactual_label	sensitivity_value_avg	delta_deaths	delta_deaths_perpop	baseline_cumulative_deaths_avg	delta_death
UK to April 2021					
30 days sooner	0.27	5,427 [4,730; 6,421]	0.81 [0.71; 0.96]	138248	
30 days sooner	0.47	6,373 [5,240; 7,244]	0.95 [0.78; 1.08]	133936	
60 days sooner	0.27	15,387 [14,162; 17,731]	2.29 [2.11; 2.64]	138248	
60 days sooner	0.47	17,665 [15,618; 19,046]	2.63 [2.33; 2.84]	133936	
90 days sooner	0.27	25,371 [24,364; 28,164]	3.78 [3.63; 4.20]	138248	
90 days sooner	0.47	28,046 [26,325; 29,582]	4.18 [3.92; 4.41]	133936	
UK to July 2021					
30 days sooner	0.27	5,734 [5,058; 6,640]	0.85 [0.75; 0.99]	140544	
30 days sooner	0.47	6,620 [5,575; 7,497]	0.99 [0.83; 1.12]	136056	
60 days sooner	0.27	17,066 [15,874; 18,665]	2.54 [2.37; 2.78]	140544	
60 days sooner	0.47	18,706 [17,287; 20,048]	2.79 [2.58; 2.99]	136056	
90 days sooner	0.27	28,057 [26,771; 29,984]	4.18 [3.99; 4.47]	140544	
90 days sooner	0.47	29,596 [28,923; 31,097]	4.41 [4.31; 4.64]	136056	
UK to Jan 2022					
30 days sooner	0.27	9,839 [9,164; 10,442]	1.47 [1.37; 1.56]	171721	
30 days sooner	0.47	11,110 [10,091; 12,431]	1.66 [1.50; 1.85]	167174	
60 days sooner	0.27	37,569 [36,286; 39,384]	5.60 [5.41; 5.87]	171721	
60 days sooner	0.47	37,063 [35,884; 39,538]	5.53 [5.35; 5.89]	167174	
90 days sooner	0.27	55,523 [54,261; 58,576]	8.28 [8.09; 8.73]	171721	
90 days sooner	0.47	56,787 [55,585; 58,099]	8.47 [8.29; 8.66]	167174	
US to April 2021					
30 days sooner	0.14	4,082 [3,075; 6,632]	0.12 [0.09; 0.20]	635148	
30 days sooner	0.41	17,653 [14,031; 26,425]	0.53 [0.42; 0.80]	662076	
60 days sooner	0.14	19,790 [14,257; 30,879]	0.60 [0.43; 0.93]	635148	
60 days sooner	0.41	56,229 [46,530; 81,381]	1.70 [1.40; 2.45]	662076	
90 days sooner	0.14	44,124 [31,110; 63,930]	1.33 [0.94; 1.93]	635148	
90 days sooner	0.41	80,087 [68,910; 116,119]	2.42 [2.08; 3.50]	662076	
US to July 2021					
30 days sooner	0.14	14,504 [12,505; 16,224]	0.44 [0.38; 0.49]	675941	
30 days sooner	0.41	33,653 [30,213; 40,510]	1.02 [0.91; 1.22]	704935	
60 days sooner	0.14	38,058 [32,168; 47,456]	1.15 [0.97; 1.43]	675941	
60 days sooner	0.41	82,538 [73,567; 103,780]	2.49 [2.22; 3.13]	704935	
90 days sooner	0.14	59,995 [47,934; 77,224]	1.81 [1.45; 2.33]	675941	
90 days sooner	0.41	104,871 [95,126; 134,613]	3.16 [2.87; 4.06]	704935	
US to Jan 2022					
30 days sooner	0.14	55,656 [17,713; 106,927]	1.68 [0.53; 3.23]	969868	
30 days sooner	0.41	88,322 [-33,457; 132,496]	2.66 [-1.01; 4.00]	998900	
60 days sooner	0.14	141,521 [92,629; 208,627]	4.27 [2.79; 6.29]	969868	
60 days sooner	0.41	212,058 [-32,299; 266,664]	6.40 [-0.97; 8.04]	998900	
90 days sooner	0.14	231,248 [218,112; 263,030]	6.98 [6.58; 7.93]	969868	
90 days sooner	0.41	274,313 [117,271; 316,884]	8.27 [3.54; 9.56]	998900	

Table 10: Sensitivity to duration of vaccine acquired immunity (DVI)

counterfactual_label	sensitivity_value_avg	delta_deaths	delta_deaths_perpop	baseline_cumulative_deaths_avg	delta_death
UK to April 2021					
30 days sooner	145	5,375 [4,268; 7,518]	0.80 [0.64; 1.12]	153920	
30 days sooner	153	6,969 [5,250; 9,378]	1.04 [0.78; 1.40]	131665	
60 days sooner	145	15,531 [13,389; 21,591]	2.32 [2.00; 3.22]	153920	
60 days sooner	153	18,496 [15,166; 24,903]	2.76 [2.26; 3.71]	131665	
90 days sooner	145	26,132 [24,144; 31,447]	3.90 [3.60; 4.69]	153920	
90 days sooner	153	28,627 [25,344; 34,263]	4.27 [3.78; 5.11]	131665	
UK to July 2021					
30 days sooner	145	5,668 [4,819; 7,471]	0.85 [0.72; 1.11]	157154	
30 days sooner	153	7,191 [5,528; 9,249]	1.07 [0.82; 1.38]	133700	
60 days sooner	145	17,222 [16,261; 22,697]	2.57 [2.42; 3.38]	157154	
60 days sooner	153	19,386 [16,539; 25,948]	2.89 [2.47; 3.87]	133700	
90 days sooner	145	29,427 [27,676; 33,051]	4.39 [4.13; 4.93]	157154	
90 days sooner	153	29,970 [27,529; 35,780]	4.47 [4.10; 5.33]	133700	
UK to Jan 2022					
30 days sooner	145	9,938 [9,414; 12,296]	1.48 [1.40; 1.83]	188809	
30 days sooner	153	12,020 [10,682; 14,462]	1.79 [1.59; 2.16]	165021	
60 days sooner	145	37,896 [33,292; 39,590]	5.65 [4.96; 5.90]	188809	
60 days sooner	153	38,801 [33,389; 40,639]	5.78 [4.98; 6.06]	165021	
90 days sooner	145	56,607 [53,429; 58,586]	8.44 [7.96; 8.73]	188809	
90 days sooner	153	56,960 [51,594; 59,709]	8.49 [7.69; 8.90]	165021	
US to April 2021					
30 days sooner	138	3,940 [2,992; 4,609]	0.12 [0.09; 0.14]	642759	
30 days sooner	152	23,149 [14,745; 37,299]	0.70 [0.44; 1.13]	640167	
60 days sooner	138	19,294 [14,349; 22,769]	0.58 [0.43; 0.69]	642759	
60 days sooner	152	70,860 [47,764; 104,348]	2.14 [1.44; 3.15]	640167	
90 days sooner	138	43,375 [30,901; 50,992]	1.31 [0.93; 1.54]	642759	
90 days sooner	152	98,626 [69,021; 142,471]	2.98 [2.08; 4.30]	640167	
US to July 2021					
30 days sooner	138	14,324 [13,399; 15,232]	0.43 [0.40; 0.46]	684378	
30 days sooner	152	37,968 [30,615; 48,862]	1.15 [0.92; 1.47]	681210	
60 days sooner	138	38,188 [34,217; 40,849]	1.15 [1.03; 1.23]	684378	
60 days sooner	152	94,644 [74,504; 122,458]	2.86 [2.25; 3.69]	681210	
90 days sooner	138	60,193 [50,825; 66,743]	1.82 [1.53; 2.01]	684378	
90 days sooner	152	119,355 [94,951; 156,333]	3.60 [2.86; 4.72]	681210	
US to Jan 2022					
30 days sooner	138	62,656 [46,195; 102,124]	1.89 [1.39; 3.08]	977973	
30 days sooner	152	18,527 [-50,342; 99,203]	0.56 [-1.52; 2.99]	975237	
60 days sooner	138	154,505 [125,477; 201,908]	4.66 [3.79; 6.09]	977973	
60 days sooner	152	87,687 [-69,999; 224,621]	2.65 [-2.11; 6.78]	975237	
90 days sooner	138	236,004 [217,415; 257,023]	7.12 [6.56; 7.75]	977973	
90 days sooner	152	197,209 [91,484; 281,985]	5.95 [2.76; 8.51]	975237	

Table 11: Sensitivity to duration of naturally acquired immunity (DNI)

counterfactual_label	sensitivity_value_avg	delta_deaths	delta_deaths_perpop	baseline_cumulative_deaths_avg	delta_death
UK to April 2021					
30 days sooner	159	4,916 [4,018; 6,087]	0.73 [0.60; 0.91]	159017	
30 days sooner	334	5,994 [4,451; 7,515]	0.89 [0.66; 1.12]	144237	
60 days sooner	159	14,942 [12,609; 17,425]	2.23 [1.88; 2.60]	159017	
60 days sooner	334	16,964 [13,794; 21,611]	2.53 [2.06; 3.22]	144237	
90 days sooner	159	25,881 [22,876; 28,237]	3.86 [3.41; 4.21]	159017	
90 days sooner	334	27,568 [23,496; 31,494]	4.11 [3.50; 4.69]	144237	
UK to July 2021					
30 days sooner	159	5,352 [4,503; 6,385]	0.80 [0.67; 0.95]	164645	
30 days sooner	334	6,252 [4,698; 7,466]	0.93 [0.70; 1.11]	146577	
60 days sooner	159	17,341 [15,154; 19,032]	2.59 [2.26; 2.84]	164645	
60 days sooner	334	18,161 [14,829; 22,720]	2.71 [2.21; 3.39]	146577	
90 days sooner	159	29,657 [26,966; 31,194]	4.42 [4.02; 4.65]	164645	
90 days sooner	334	29,406 [25,132; 33,099]	4.38 [3.75; 4.93]	146577	
UK to Jan 2022					
30 days sooner	159	9,850 [9,177; 10,883]	1.47 [1.37; 1.62]	196046	
30 days sooner	334	10,480 [8,542; 12,408]	1.56 [1.27; 1.85]	178125	
60 days sooner	159	39,733 [37,748; 41,074]	5.92 [5.63; 6.12]	196046	
60 days sooner	334	38,199 [32,889; 39,587]	5.69 [4.90; 5.90]	178125	
90 days sooner	159	58,636 [56,027; 60,416]	8.74 [8.35; 9.01]	196046	
90 days sooner	334	56,438 [51,713; 58,377]	8.41 [7.71; 8.70]	178125	
US to April 2021					
30 days sooner	154	4,835 [3,299; 30,054]	0.15 [0.10; 0.91]	643587	
30 days sooner	332	19,865 [2,971; 35,840]	0.60 [0.09; 1.08]	645924	
60 days sooner	154	23,267 [15,383; 88,573]	0.70 [0.46; 2.67]	643587	
60 days sooner	332	61,340 [13,860; 100,165]	1.85 [0.42; 3.02]	645924	
90 days sooner	154	51,145 [33,690; 120,901]	1.54 [1.02; 3.65]	643587	
90 days sooner	332	83,271 [30,046; 130,545]	2.51 [0.91; 3.94]	645924	
US to July 2021					
30 days sooner	154	14,936 [12,895; 43,725]	0.45 [0.39; 1.32]	685320	
30 days sooner	332	34,911 [13,312; 47,968]	1.05 [0.40; 1.45]	687215	
60 days sooner	154	41,492 [33,818; 110,267]	1.25 [1.02; 3.33]	685320	
60 days sooner	332	86,026 [33,892; 119,086]	2.60 [1.02; 3.59]	687215	
90 days sooner	154	67,209 [52,416; 138,908]	2.03 [1.58; 4.19]	685320	
90 days sooner	332	106,555 [49,702; 144,420]	3.21 [1.50; 4.36]	687215	
US to Jan 2022					
30 days sooner	154	53,782 [18,880; 106,617]	1.62 [0.57; 3.22]	979316	
30 days sooner	332	47,054 [1,464; 117,121]	1.42 [0.04; 3.53]	981602	
60 days sooner	154	144,804 [92,245; 216,414]	4.37 [2.78; 6.53]	979316	
60 days sooner	332	149,676 [42,686; 244,012]	4.52 [1.29; 7.36]	981602	
90 days sooner	154	240,412 [220,909; 280,083]	7.25 [6.66; 8.45]	979316	
90 days sooner	332	243,531 [169,952; 294,245]	7.35 [5.13; 8.88]	981602	

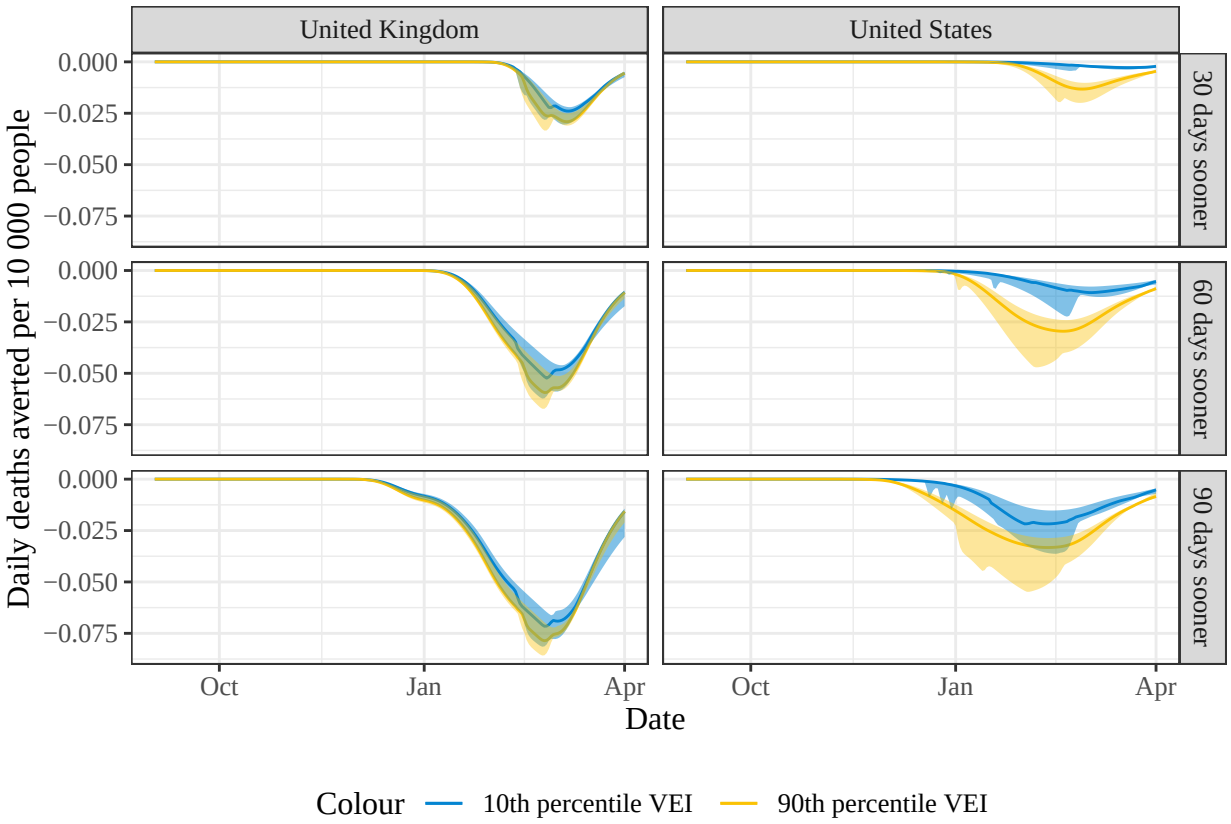

Figure 5: DJ6 Daily deaths per scenario, sensitivity to vaccine duration

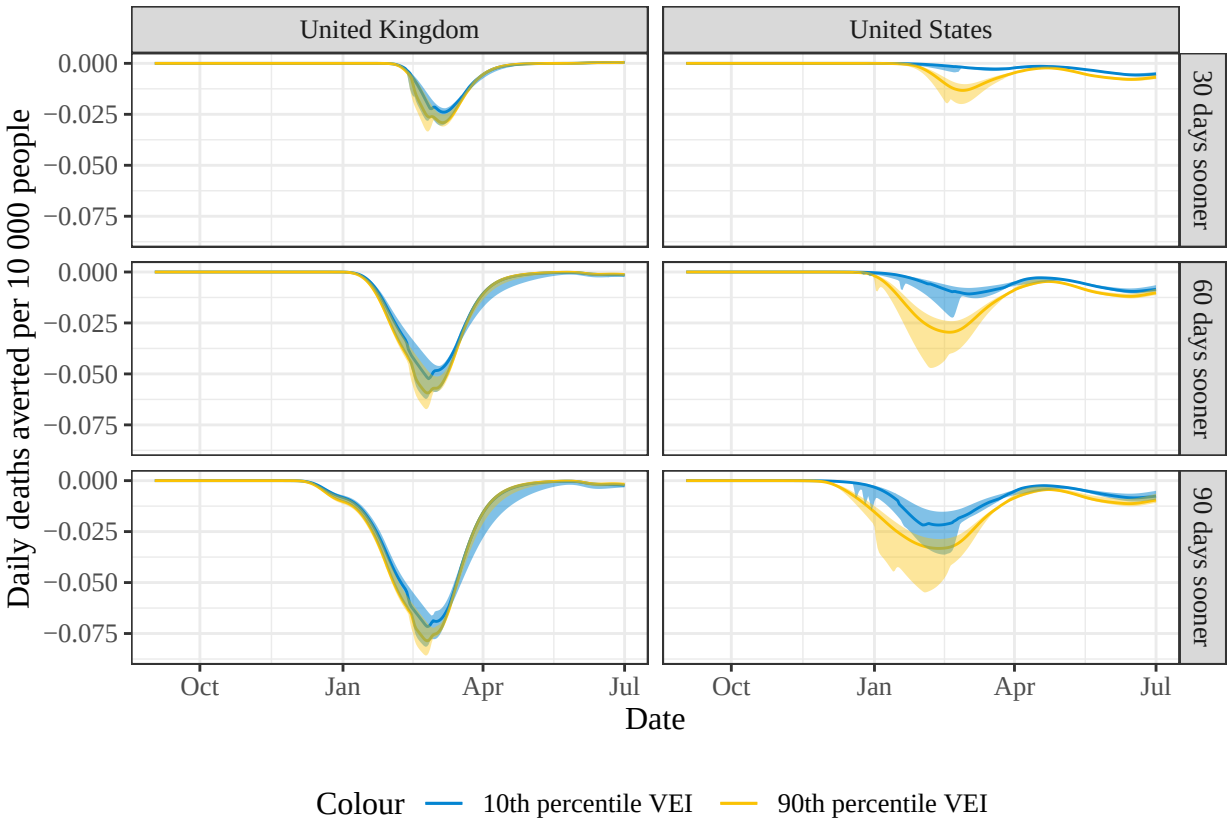

Figure 6: DJ6 Daily deaths per scenario, sensitivity to vaccine duration

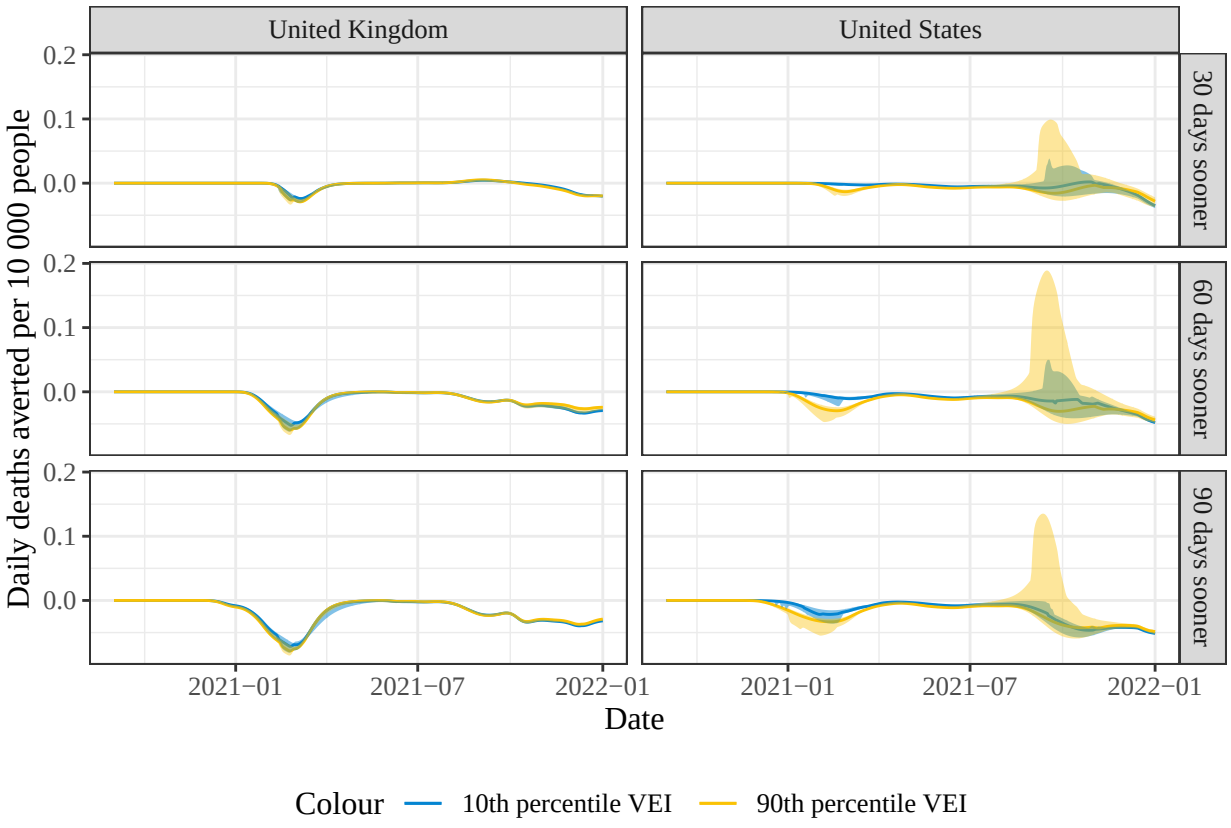

Figure 7: DJ6 Daily deaths per scenario, sensitivity to vaccine duration

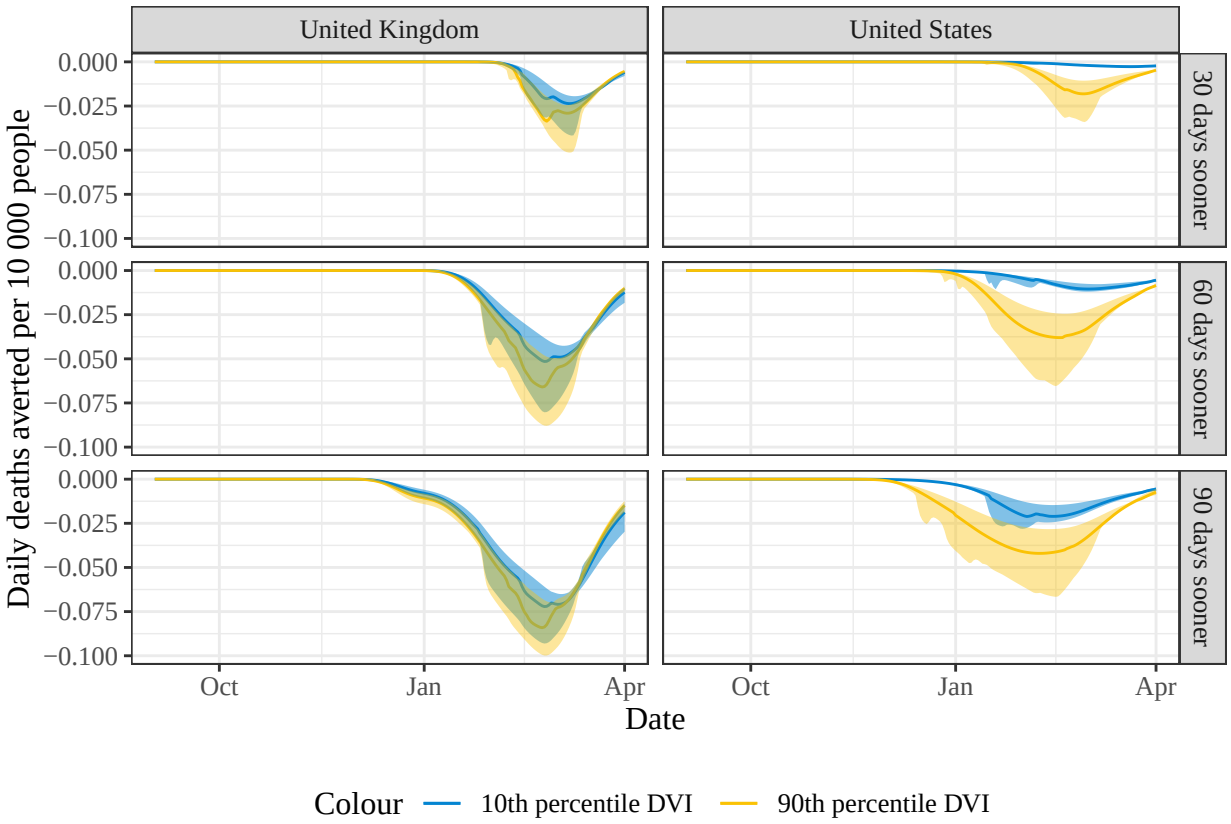

Figure 8: DJ6 Daily deaths per scenario, sensitivity to vaccine efficacy

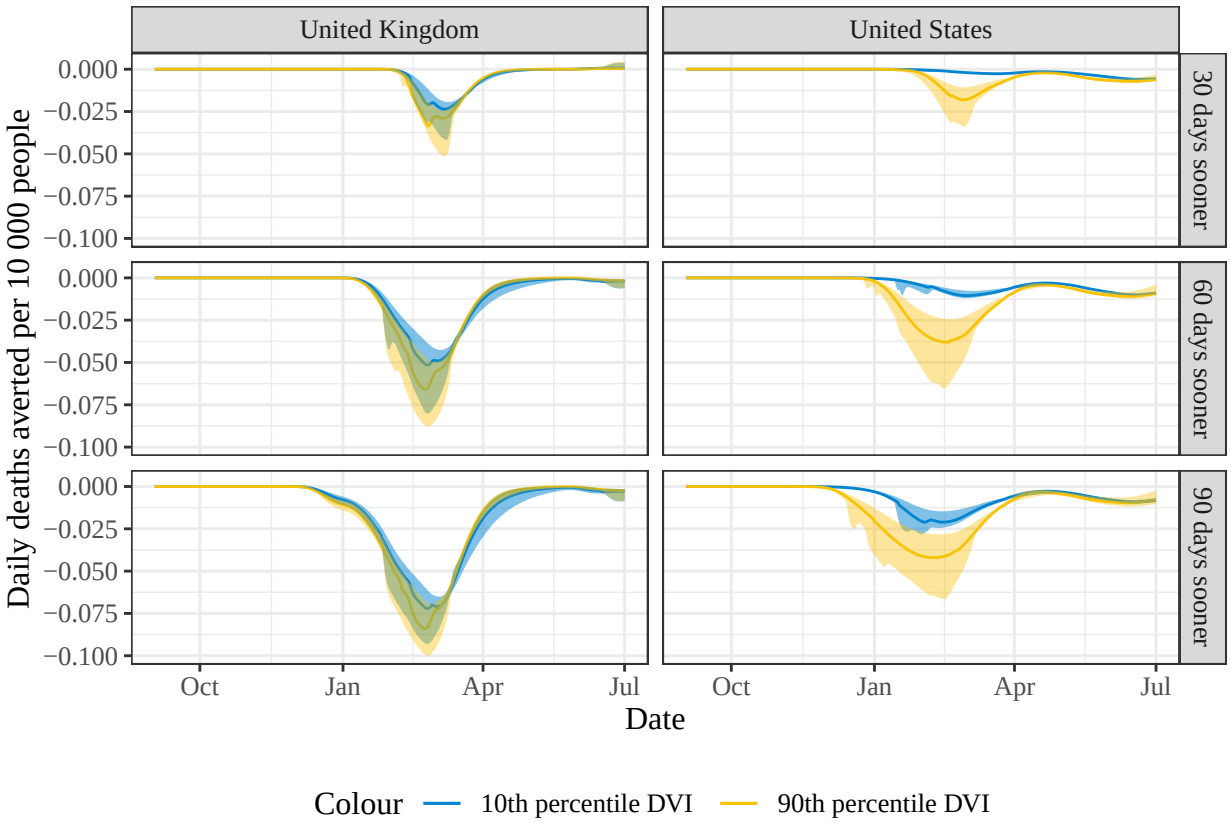

Figure 9: DJ6 Daily deaths per scenario, sensitivity to vaccine efficacy

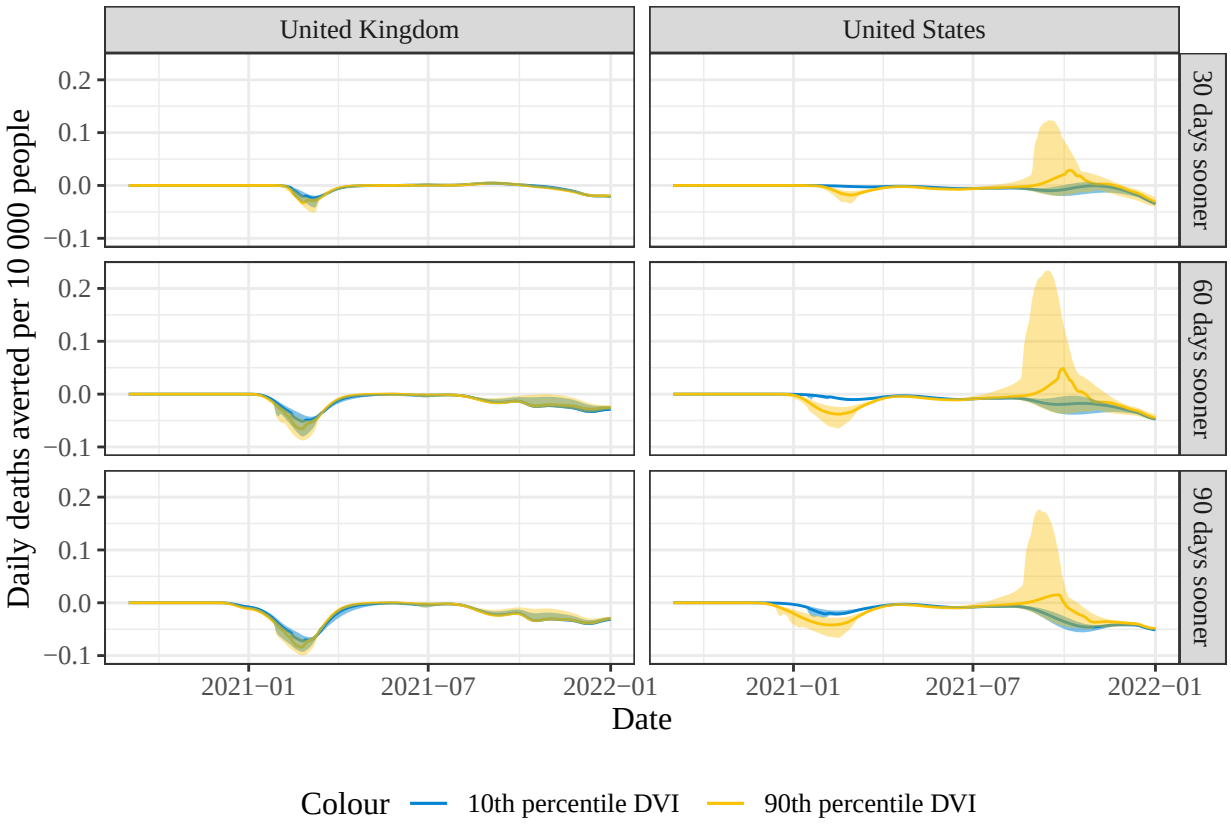

Figure 10: DJ6 Daily deaths per scenario, sensitivity to vaccine efficacy

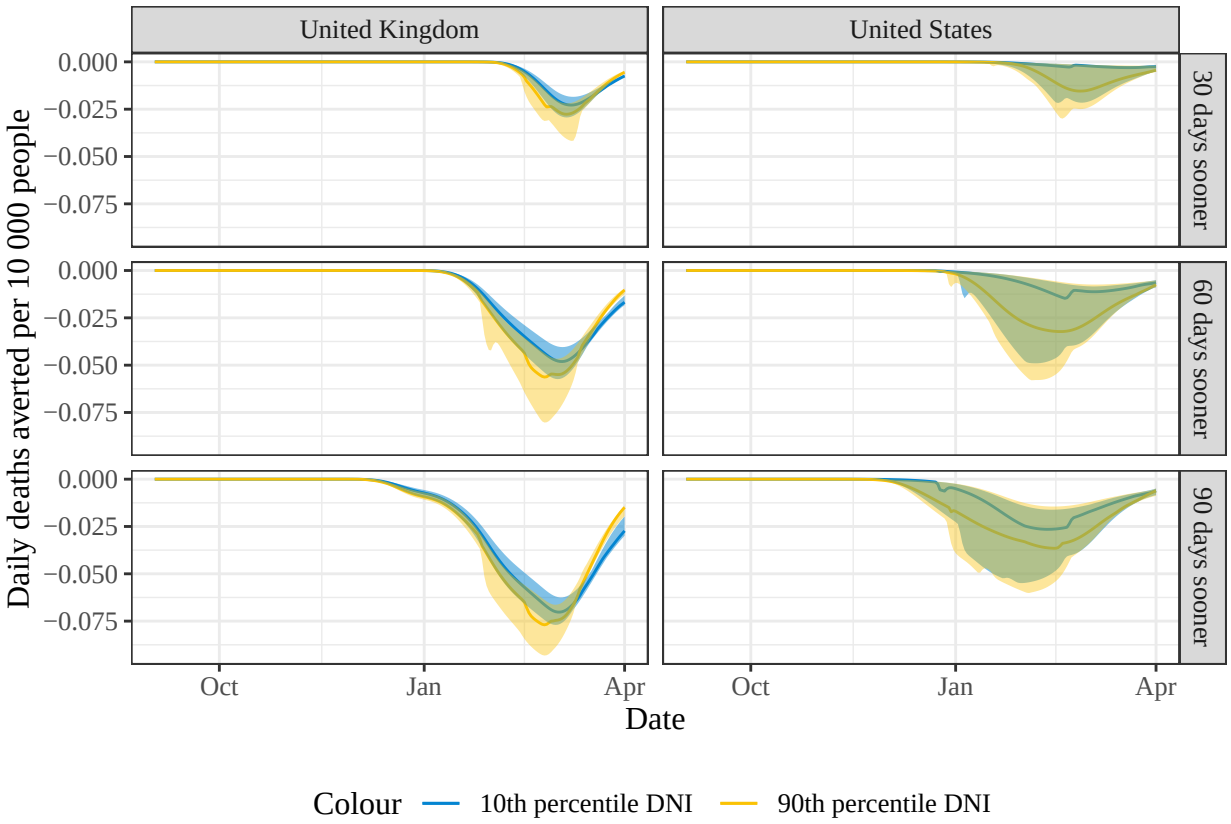

Figure 11: DJ6 Daily deaths per scenario, sensitivity to natural immunity duration

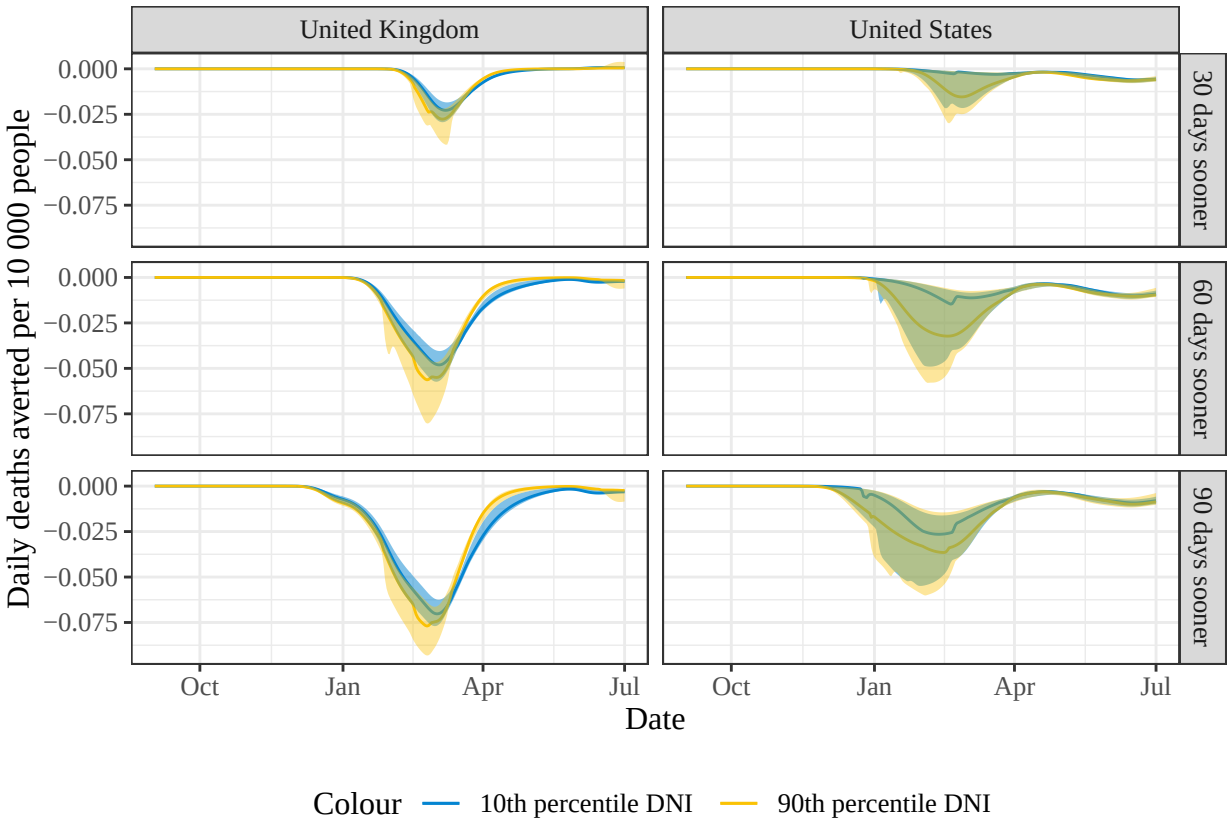

Figure 12: DJ6 Daily deaths per scenario, sensitivity to natural immunity duration

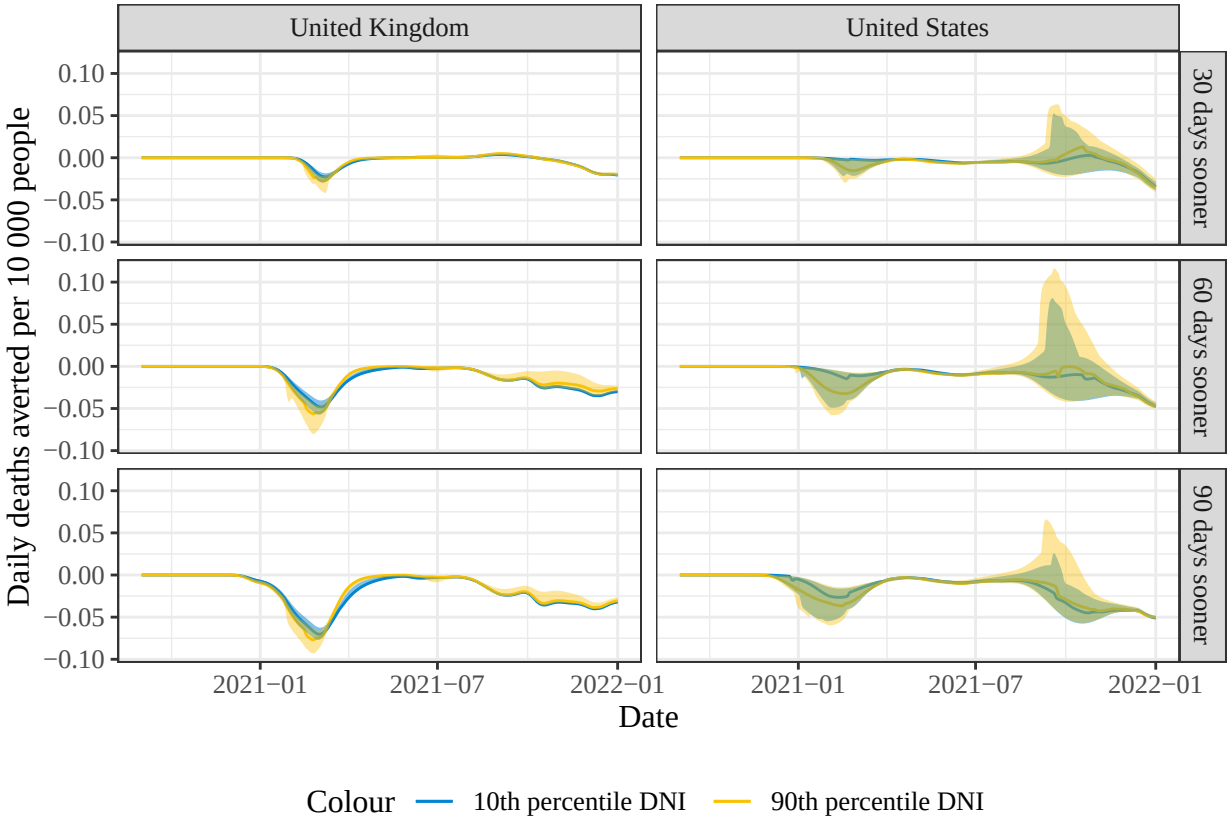

Figure 13: DJ6 Daily deaths per scenario, sensitivity to natural immunity duration

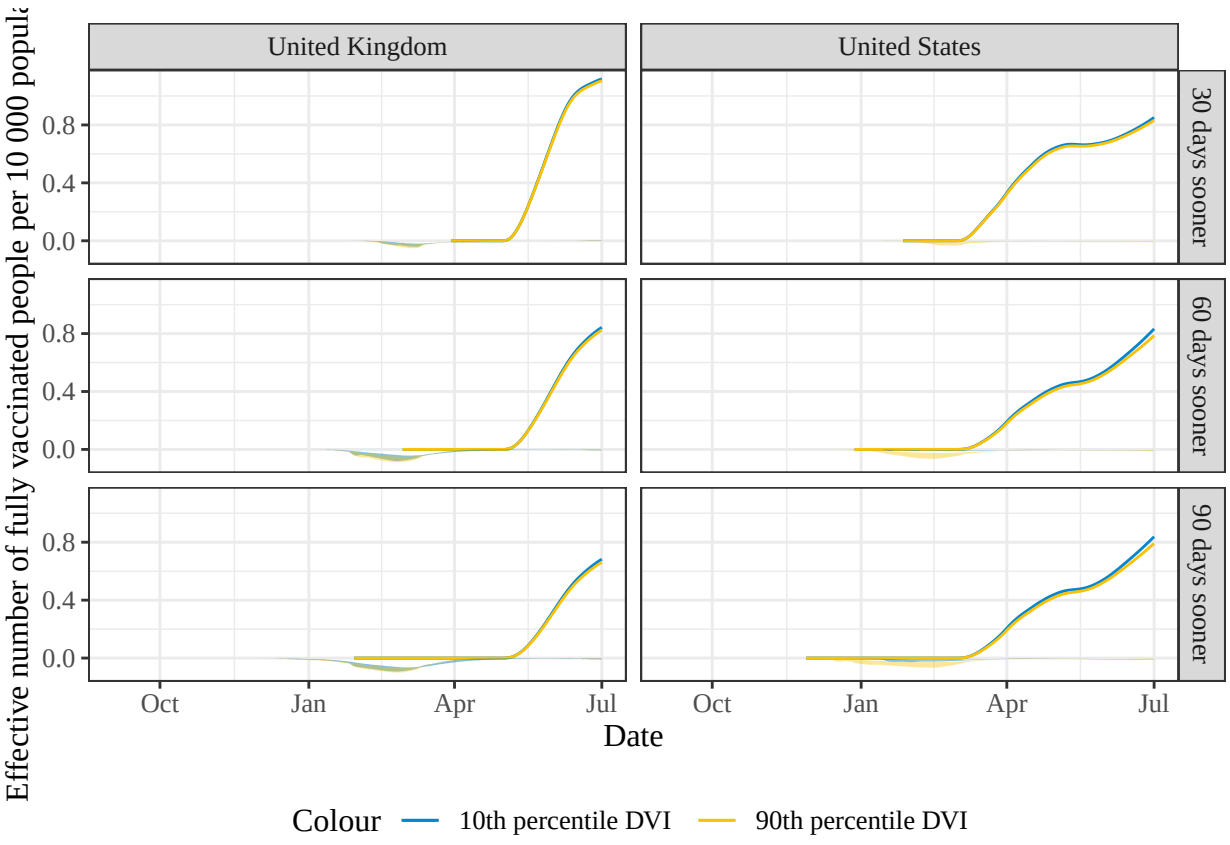

Figure 14: Vaccinated, sensitivity to vaccine duration

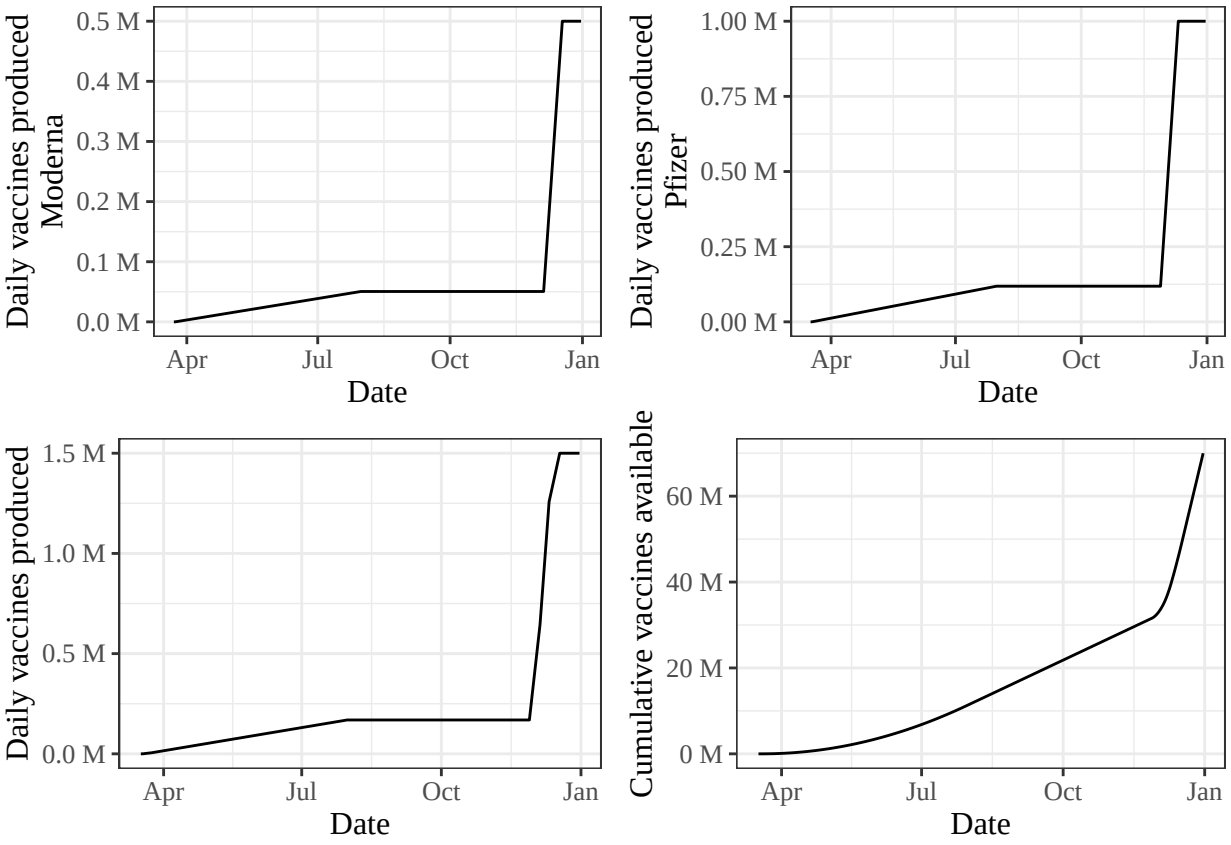

Figure 15: DJ9 Vaccine production assumptions

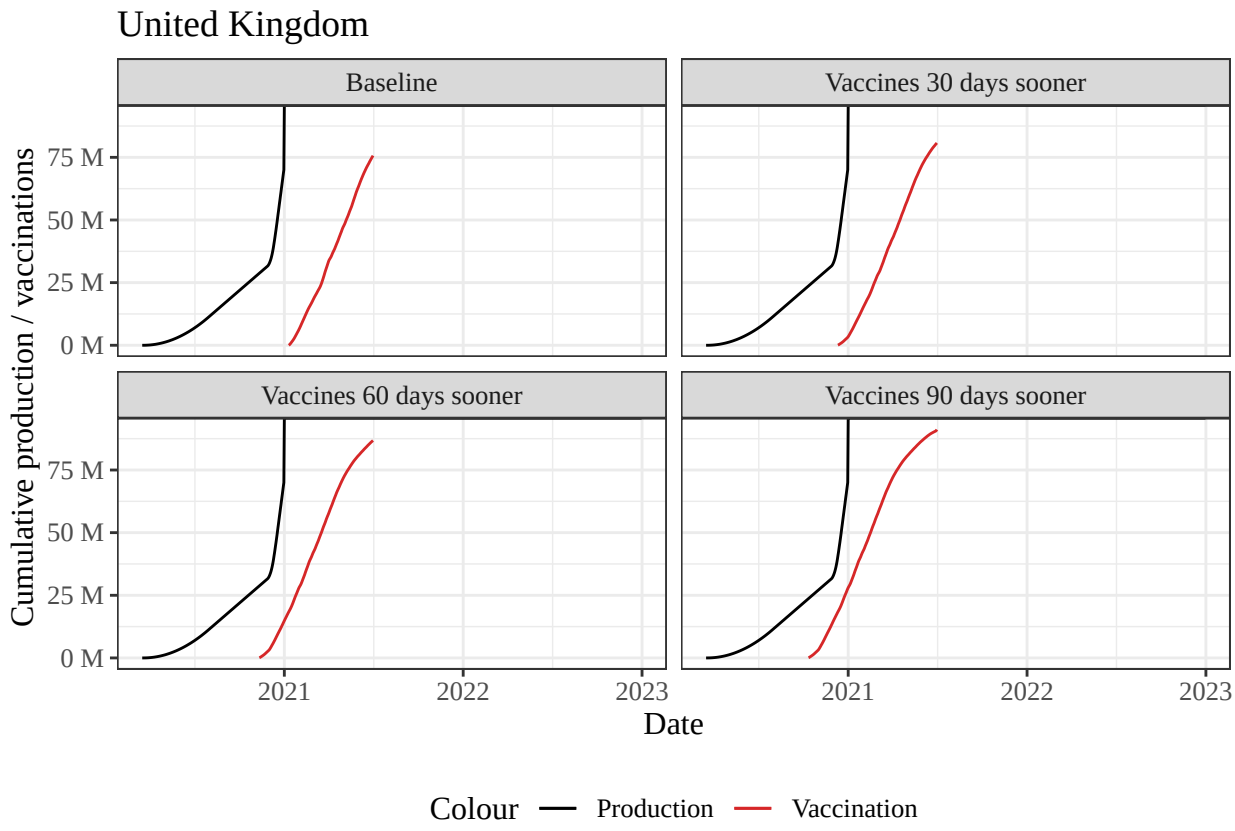

Figure 16: DJ10 Limits from production UK

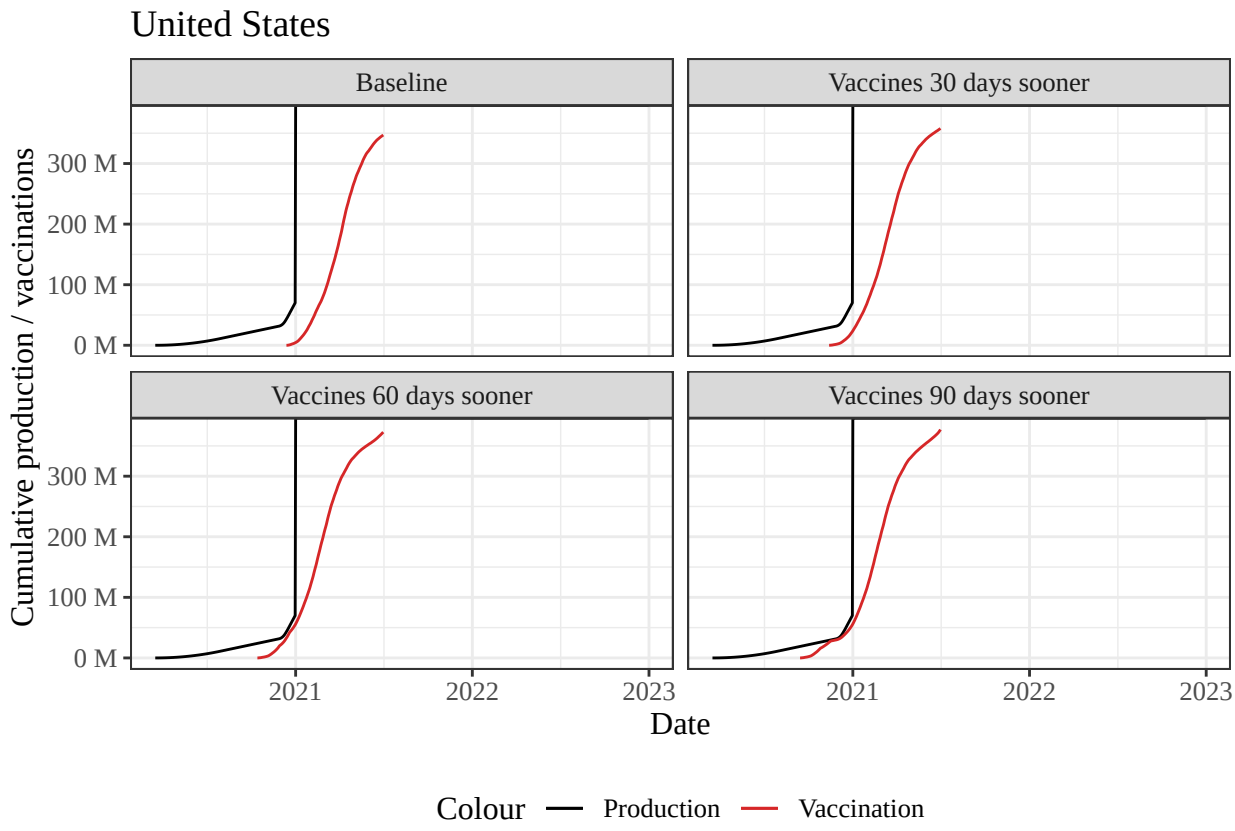

Figure 17: DJ10 Limits from production UK