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Supplementary appendix

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SUPPLEMENTARY MATERIAL
Vaccination and Non-Pharmaceutical Interventions: a mathematical modelling study

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10th March 2021

S1 Vaccine Action: assumptions and data

Given the importance of vaccines for controlling the COVID-19 pandemic, it is unsurprising that a large number of manufacturers initiated development of vaccines in early 2020. Many countries, including the UK, pre-ordered doses from multiple manufacturers to off-set the risks of any failures. The UK has over 450 million doses of vaccine on order from 8 different companies [1–3]. As results begin to emerge from phase 3 clinical trials, and from isolated population studies, it is unsurprising that different values for key observations are being reported. Here, we summarise much of the available data as it pertains to our study of vaccination in the UK.

S1.1 Vaccine Action

In many settings (eg childhood immunisation) there is often the simplifying assumption of a single measure of vaccine efficacy [4]. However, the detailed work on SARS-CoV-2 has highlighted that vaccines can impact on multiple elements of infection, transmission and symptoms [5, 6]. Here we define four keys ways in which a vaccine can influence the natural history of infection.

1. *Protection against infection.* The most obvious way in which the vaccine can operate is to prevent (or reduce the risk) of individuals becoming infected. This can either be modelled as a sterilising vaccine (a proportion of vaccinated individuals are fully immune while the remainder are naive) or a leaky vaccine (generating the same reduction in risk for all vaccinated individuals). Current data does not allow us to differentiate between the two assumptions. We use the leaky vaccine assumption.

2. *Protection against symptoms.* This is the most commonly reported aspect of vaccine efficacy and is the most easily measured. However, the concept of symptoms is rather poorly defined; it has differed over time as more symptoms are determined to be associated with SARS-CoV-2 infection, and different clinical trials have used different definitions.

3. *Projection against severe disease.* Potentially the most important action of any COVID-19 vaccine is to prevent severe disease, especially hospital admissions and deaths. Given that these are rare end-points of infection, that most commonly occur in the elderly and vulnerable, there is insufficient power in clinical trials to estimate associated values.

4. *Reduction in onward transmission.* Given that vaccination has been observed to reduce viral load, there may be an additional impact of reducing the scale of onward transmission from those that do become infected. There is no information currently available on preventing onward transmission; ascertaining the magnitude of this effect will require detailed observational studies in closed settings or households.

S1.2 Vaccine efficacy estimates from the literature (as of mid-February 2021)

As of mid-February 2021, there have been a limited number of vaccines that have passed through Phase 3 clinical trials (three have been approved for use in the UK), and none of the trials used standardised measures for efficacy. Efficacy estimates for each vaccine are also subject to change as new data emerges. For a historical record of the publication of relevant clinical trial data over time for candidate vaccines as they progress through the development pipeline, we refer the reader to online living literature reviews that have been produced to curate published data on safety, immunogenicity and efficacy [7].

Given the UK focus of our study, we will concentrate here on the literature pertaining to the Pfizer/BioNtech and Oxford/AstraZeneca vaccines.

Pfizer/BioNtech. The Pfizer/BioNtech vaccine (BNT162b2) is a lipid nanoparticle–formulated, nucleoside-modifiedRNA vaccine that generates an immune response against the SARS-CoV-2 spike protein. The majority of data on the impact of this vaccine comes from the Phase-3 clinical trial [8] and the extensive and early roll out of this vaccine in Israel [9, 10]. From the clinical trial, vaccine efficacy against disease from 2 doses of vaccine was estimated at 95.0% (90.3% - 97.6%). Here, the definition of disease was a positive test for COVID following onset of at least one of the following symptoms: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhoea, or vomiting. There are no data from the clinical trial on reduction in infection, while quoted efficacy following the first dose (52.4%, 29.5%-68.4%) does not account for the 7-14 days necessary to develop partial immunity. Using data for those cases observed between day 15 and 28 after the first dose, efficacy against symptomatic COVID-19 has since been independently estimated by Public Health England as 91% (74% to 97%) [11].

The early data from Israel, where approximately 90% of those over 60 years of age had received at least one dose of the vaccine [10], provides an important picture of the impact of vaccine derived immunity in practice. Chodick *et al.* [9] determined a decrement in SARS-CoV-2 incidence was evident, with a vaccine effectiveness of 51.4% (-7.2% - 78.0%) against SARS-CoV-2 infection 13-24 days after immunisation with the first dose - as measured by positive PCR result following suspected symptoms. Impressively, this vaccine efficacy has already translated into key healthcare benefits, while hospital admissions increased in those under 60 years of age (increasing by 16.1% from 9th January - 6th February 2021), admission in those over 60 years of age declined (a drop of 32.0% in the same time period) [10].

Oxford/Astra Zeneca. The Oxford/Astra Zeneca vaccine (ChAdOx nCoV-1), is a chimpanzee adenoviral vectored vaccine, which also generates immunity against the SARS-CoV-2 spike protein. This vaccine is the main component of the UK vaccination program, since its approval for use for the MHRA on 30th December. Given the short time this has been actively deployed, there is not yet any published population level data, and all efficacy values come from clinical trials [12–14].

Initial work [13] reported a vaccine efficacy against disease of 62.1% (40.1%-75.7%) following two standard doses of the vaccine. A higher efficacy of 90.0% (67.4%-97.0%) was reported for individuals who first received a low dose. Disease was defined as any one of the following symptoms: fever of at least 37·8°C, cough, shortness of breath, and anosmia or ageusia; and was confirmed by nucleic acid amplification test. Estimates of efficacy against infection were obtained in one arm of the trial, where participants provided weekly nose and throat swabs. This generated an estimated efficacy against infection of 46.3% (31.8% - 57.8%) after 1 dose and 55.7% (41.1%-66.7%) after 2 doses.

Subsequent reassessment of the results has shown that individuals with a longer interval (12-weeks) between first and second doses have a higher vaccine efficacy [14]. In this latest work, vaccination (two standard doses given 12 or more weeks apart) is found to reduce symptomatic disease by 81.3% (60.3%-91.2%); while protection following the first dose is estimated as 76.0%

(59.3% - 85.9%) between days 31 and 60. Using the weekly swab tests, it is possible to gain an understanding of reduction in infection (both symptomatic and asymptomatic); the numbers involved are smaller, but generated a level of protection against infection of 63.9% (46.0%-76.9%) after 1 dose and 59.9% (35.8%-75.0%) after the complete 2 doses.

S1.3 Modelling Assumptions

Given the scarcity of information on many aspects of the vaccine, and the ambiguity over the precise definition of a symptomatic case, in our model we capture two main aspects of the action of the vaccine. We model the reduction in infection due to first and second doses of the vaccine (through parameter σ); and we also capture the reduction in severe symptoms leading to hospital admission and death (through parameter z). We do not account for any reduction in onward transmission, beyond the reduction in infection. Similarly, we only capture the reduction in hospital admissions and deaths that are due to the reported reduction in symptomatic infection - although Section S2 examines the sensitivity to this assumption.

The UK vaccination program initially was based around the Pfizer/BioNtech vaccine, but during January 2021 switched to being dominated by the Oxford/Astra Zeneca vaccine – the UK has ordered 100 million doses of the Oxford/Astra Zeneca vaccine compared to 40 million doses of Pfizer/BioNtech vaccine, but the supply of both vaccines is non-uniform. We present our default assumptions concerning vaccine efficacy in Table S1.

Table S1: Action of vaccine model assumptions. Values used in our modelling analysis for the protection against infection (a range of values) and efficacy against severe disease generated following the first and second vaccine dose, respectively.

Protection against infection	1st dose	$1-\sigma_{a,1}/\sigma_{a,0}$	0%, 28%, 48%, 68%
	2nd dose	$1-\sigma_{a,2}/\sigma_{a,0}$	0%, 35%, 60%, 85%
Efficacy against severe disease	1st dose	$1-z_1\sigma_{a,1}/\sigma_{a,0}$	70%
	2nd dose	$1-z_2\sigma_{a,2}/\sigma_{a,0}$	88%

Two other modelling assumptions dominate the impact of vaccination: uptake and speed of delivery. Our default assumption was that the delivery of vaccines matches the Joint Committee on Vaccination and Immunisation (JCVI) priority groups [15]. This was determined by a combination of comorbidity and age, such that the most vulnerable are vaccinated first, which minimises the number of deaths for a given supply of vaccine [16, 17]. The delivery of vaccine from the start of the programme in December 2020 until 10th February 2021 was determined by the available data [18], after which we assumed that the programme can maintain the administration of 2.5 million doses a week. Other alternatives (1.5 million and 4 million doses per week) are explored below.

Data from the UK shows an impressively high uptake of vaccine in the older age-groups. In England, using age group first dose vaccination data reported to 7th February 2021 and 2019 Office for National Statistics (ONS) population estimates [19], more than 90% of those aged 80 years and above (2,588,999 out of an estimated population of 2,836,964) had been vaccinated for COVID-19 with a first dose. For care homes situated in England, 99.4% of eligible care homes had been visited for first dose vaccination and 93.2% of residents of older adult care homes (who had not had COVID-19 in the previous 28 days) had been administered their first vaccine dose [19]. Therefore, for our default uptake we assumed an uptake in those over 80 years old of 95%, whilst for the remainder of the population it is 85%. The vaccine is not currently licensed for those under 18 year of age, and hence they did not form part of our simulated vaccination programme.

S2 Sensitivity to Vaccine Assumptions

The main paper has focused on the uncertainty in how well the vaccine protects against infection. We explore here three other uncertainties in the vaccine behaviour and deployment: (i) protection against hospital admissions and deaths; (ii) speed of vaccine deployment; (iii) vaccine uptake.

S2.1 Greater protection against hospital admissions and deaths

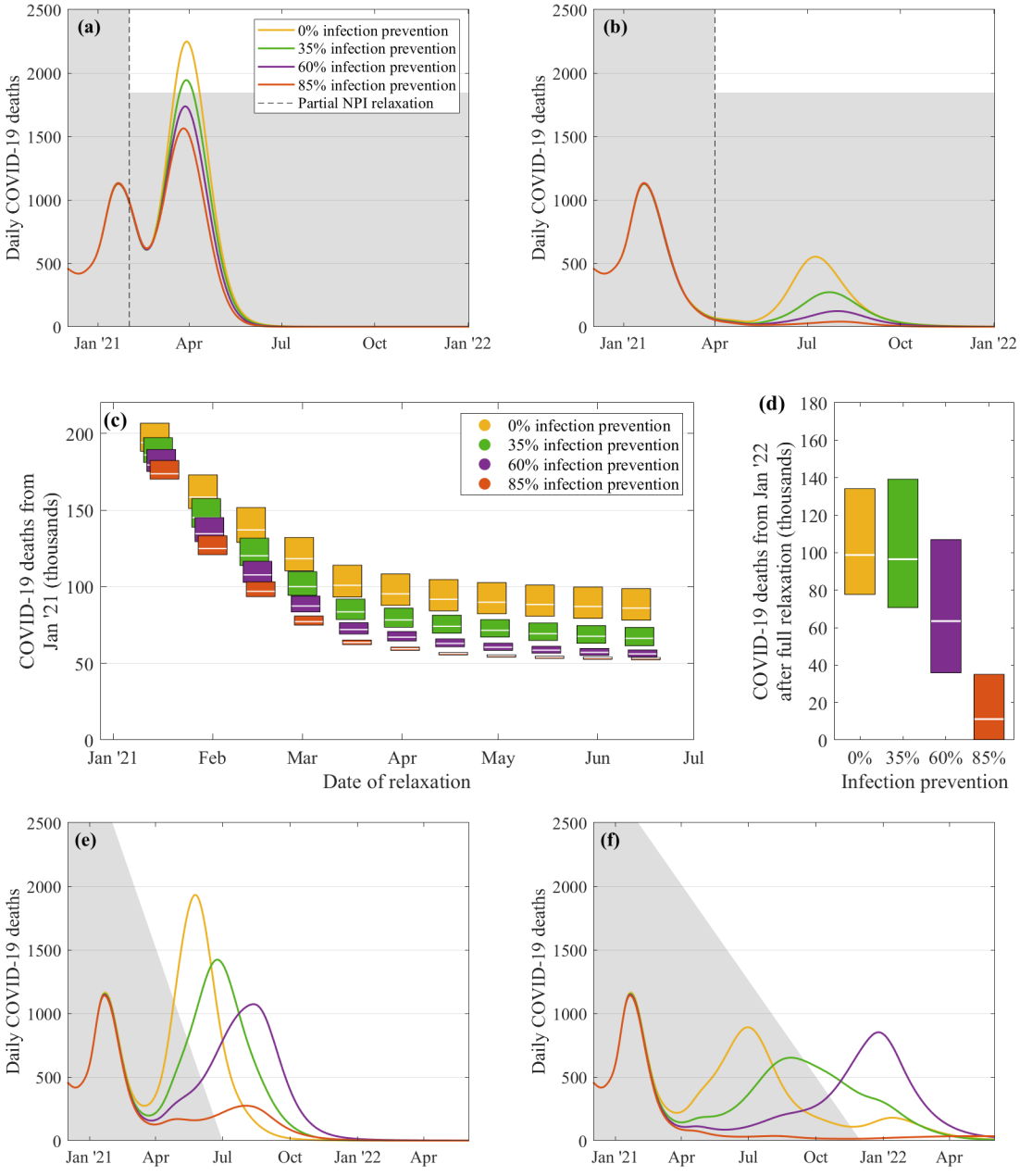

Figure S1: Predicted daily deaths in the UK following the start of an immunisation program and relaxation or removal of NPIs. This is a re-working of Figure 2 from the main paper, but including a higher efficacy against disease (94% rather than 88% after two doses).

We made the cautious assumption in the main paper that the level of protection against hospital admission or deaths was comparable to that reported against symptomatic illness (88%). Here we consider a much higher level of protection (94% as a weighted average between the two vaccines used in the UK), effectively halving the risk of hospitalisations and deaths following symptomatic infection in the vaccinated population.

Although this has halved the deaths in the vaccinated population, the absolute change has been relatively modest as following early release of controls there is still an appreciable fraction of the vulnerable population that have not received two doses of vaccine. The greatest impact is seen when the protection against infection is low (0%) as that is when many vaccinated individuals become infected so the action of disease blocking is greatest (Figure S1).

S2.2 Changes to vaccine deployment

Our default assumption has been that the UK can administer 2.5 million doses of vaccine per week (approximately 386 thousand per day). This is highly contingent on supply of the vaccine - hence we consider a more pessimistic scenario in which only 1.5 million doses of vaccine can be given each week (Figure S2). We also consider a more optimistic scenario of 4 million doses a week, in line with government targets (Figure S3).

Slower deployment of vaccination (1.5 million doses a week) has the greatest impact on the time taken to reach a given level of population immunity (Figure S2, bottom left), with vaccination still on-going in early 2022. Here the biggest impact is when the vaccine is highly effective in protecting against infection, this is because a slower deployment has the greatest impact on the reproductive number (R) when the vaccine confers this form of protection.

The converse is true for a more rapid deployment of vaccine; for example in Figure S3b we clearly see that the greater population immunity achieved by May 2021 has a substantial impact on the epidemics when protection against infection is high. The exception to this rule is moderate protection against infection (35%) and gradual release of NPIs (Figure S3e and f) where lower early cases in April-October 2021 leads to a more pronounced outbreak later - although the total number of deaths remains lower for faster deployment.

S2.3 Summary

In summary, greater protection from the vaccine (Figure S1) has a more marked effect on the total number of deaths than speed of vaccination (Figures S2 and S3). However, more rapid deployment of the vaccine has a greater impact on the epidemic peak if controls are relaxed early.

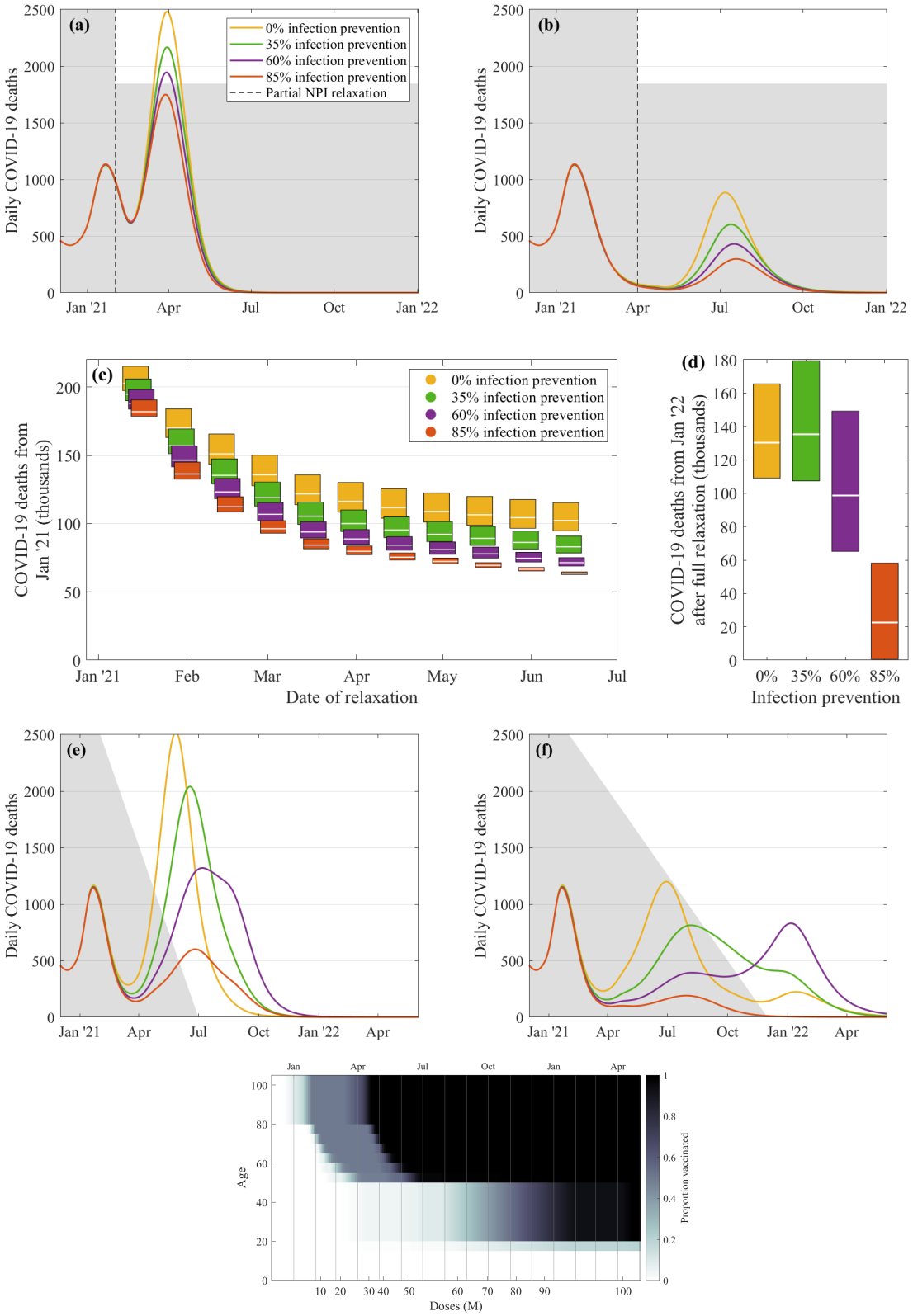

Figure S2: Scheduling and impact of vaccine uptake. Predicted daily deaths in the UK following the start of an immunisation program and relaxation or removal of NPIs. This is a re-working of Figures 1 and 2 from the main text, except it is assumed that the roll-out of vaccination is far slower with only 1.5 million doses administered each week.

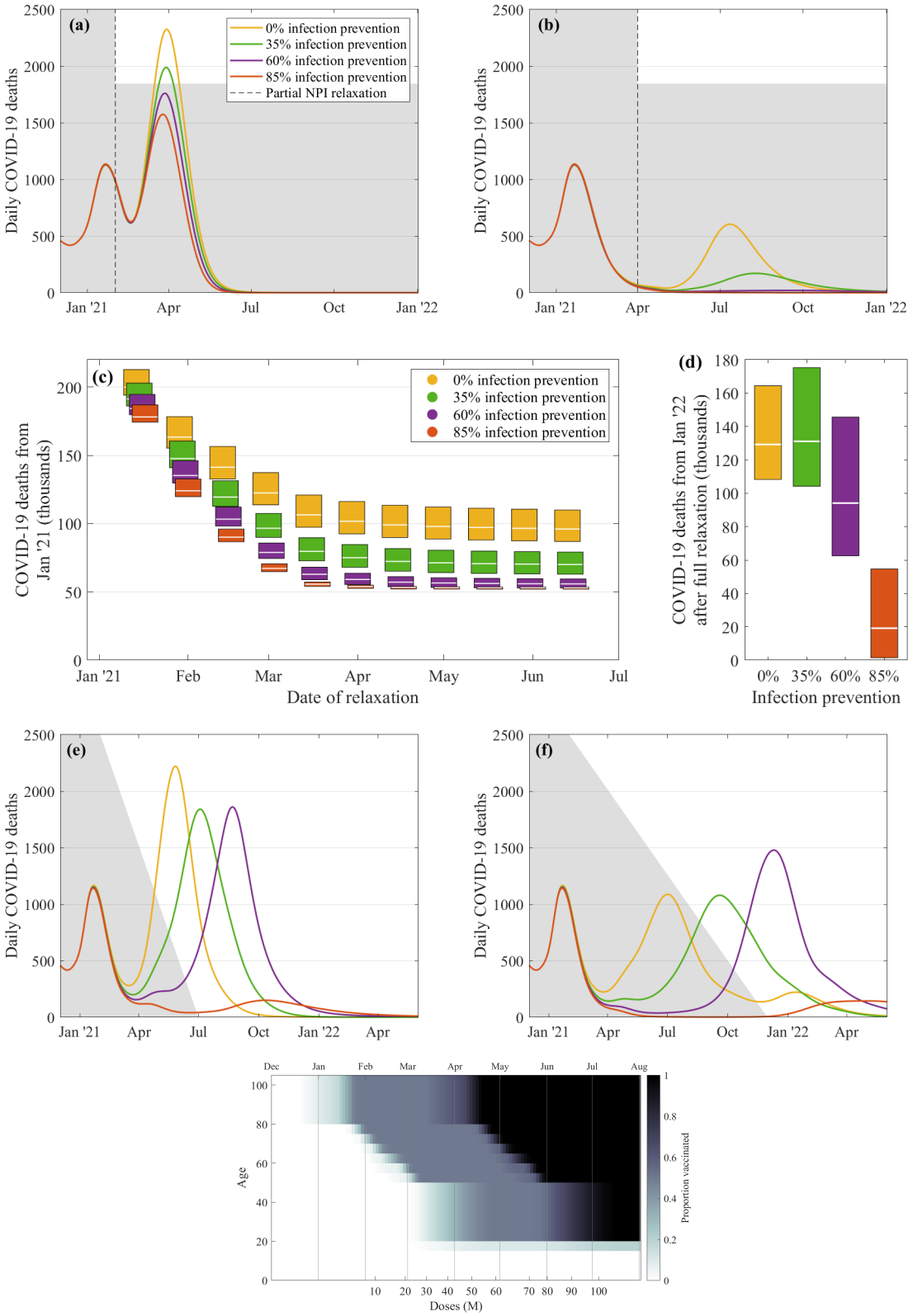

Figure S3: Scheduling and impact of vaccine uptake. Predicted daily deaths in the UK following the start of an immunisation program and relaxation or removal of NPIs. This is a re-working of Figures 1 and 2 from the main text, except it is assumed that the roll-out of vaccination is far quicker achieving 4 million doses administered each week.

S2.4 Changes to vaccine uptake

Obtaining high vaccine uptake is critical for the success of any vaccine campaign. In a scenario in which the herd immunity threshold is not reached, uptake is even more important as the only means of protecting the most vulnerable. In the UK we have had tremendous success in reaching an extremely high percentage of those over 80 years old; and our default assumption is for slowly declining uptake in younger cohorts. In the main paper we used a more optimistic and pessimistic assumption (Figure 2c and d) to consider long-term behaviour. Here we show the dynamics that arise from these two assumptions.

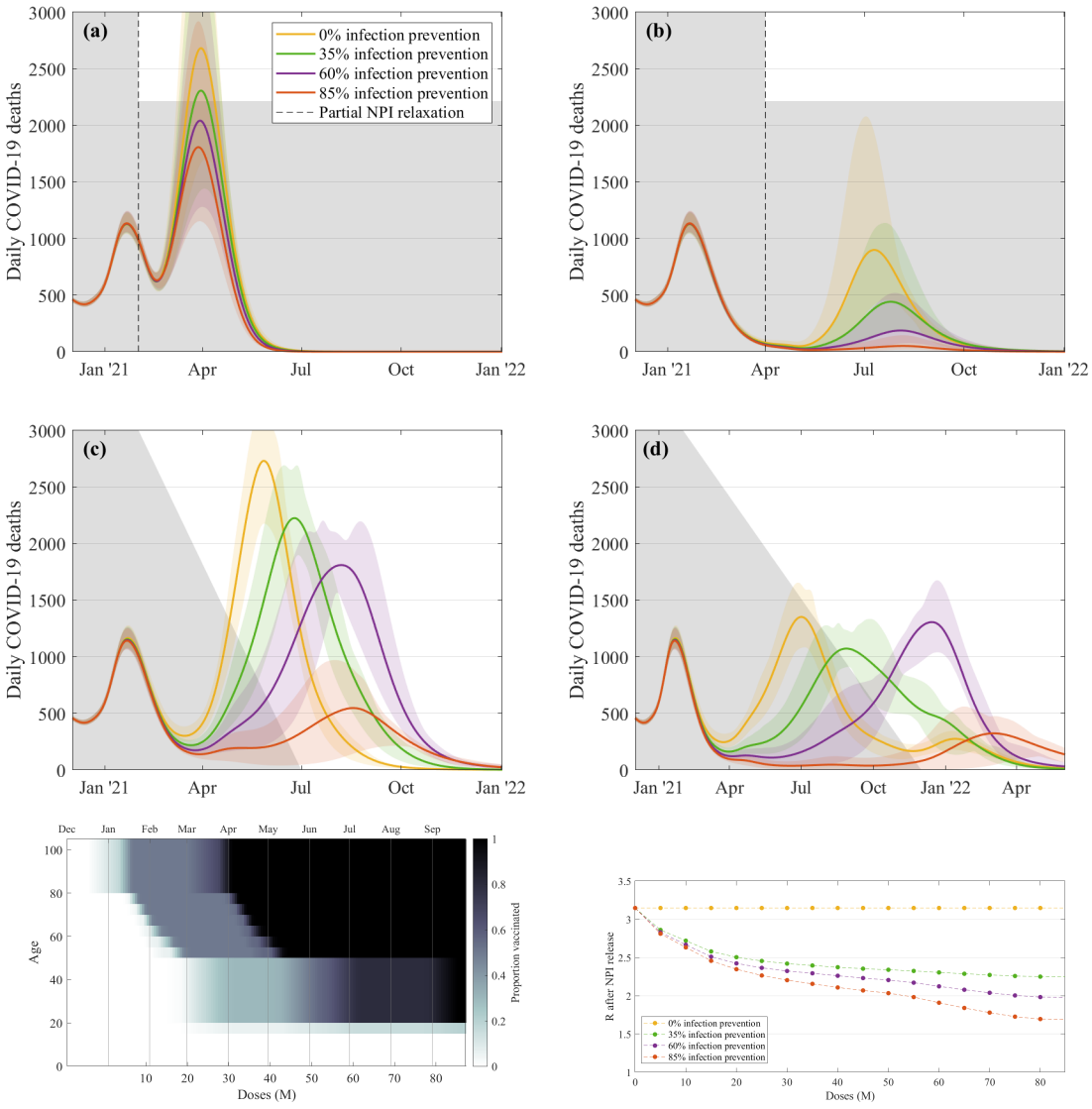

Figure S4: Scheduling and impact of pessimistic vaccine uptake. Predicted daily deaths in the UK following the start of an immunisation program and relaxation or removal of NPIs. This is a re-working of Figures 1 and 2 from the main text, except it assumes the pessimistic uptake levels used to generate Figures 2c and 2d (90% in the over 80's, 80% in those 50-79, and 70% in those 18-49).

As expected, lower uptake levels generate large epidemic waves, that generally occur earlier as NPIs are gradually released (Figure S4). higher levels of uptake take slightly longer to achieve complete coverage in any one priority group, but suppress the scale of future epidemic waves (Figure S5). A comparison between the default, optimistic and pessimistic uptakes in terms of total deaths is shown in the main text Figure 2c and d.

We compare in Figure S6 the results from Figure S4, Figure S5, and the default results shown

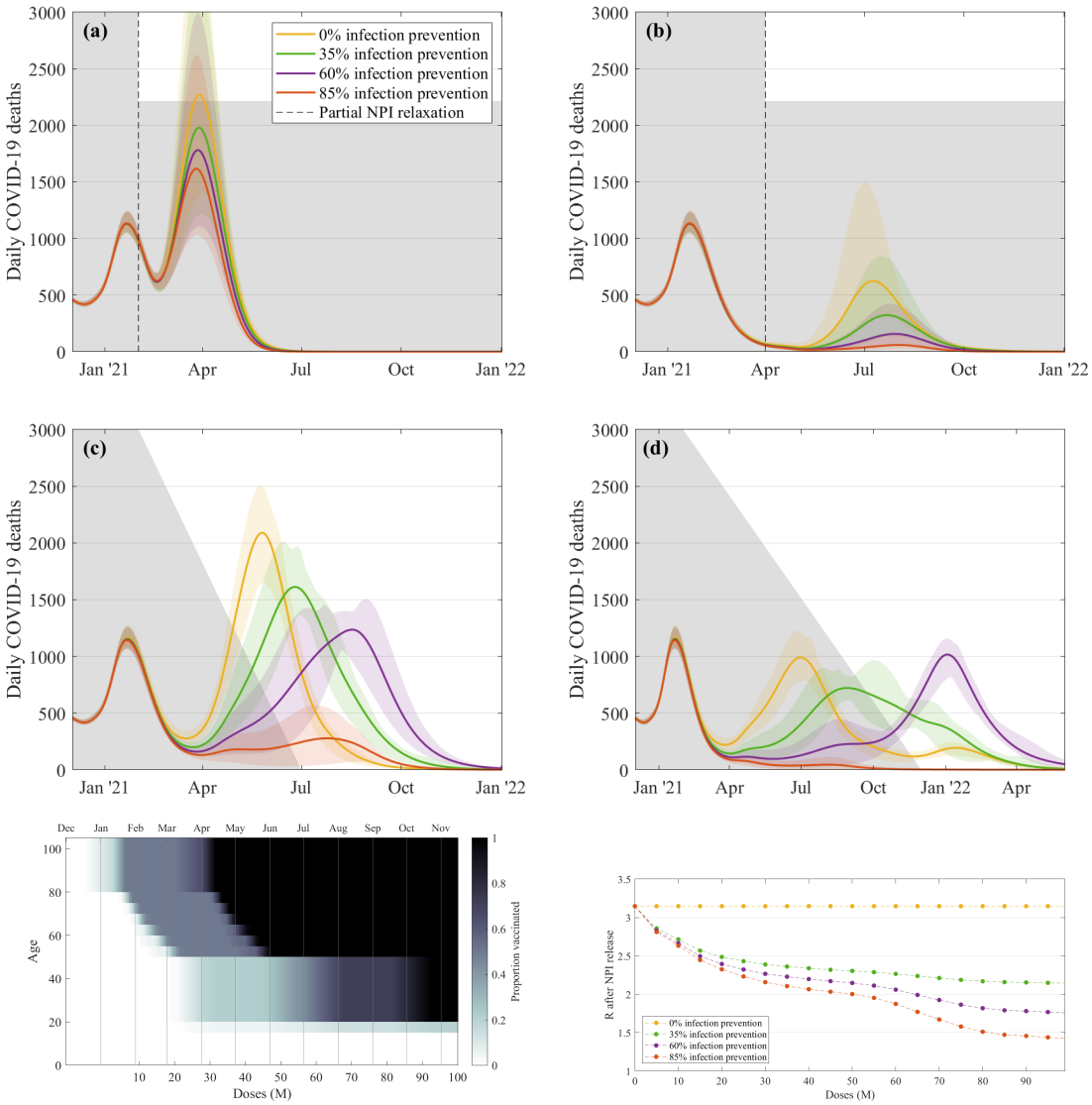

Figure S5: Scheduling and impact of optimistic vaccine uptake. Predicted daily deaths in the UK following the start of an immunisation program and relaxation or removal of NPIs. This is a re-working of Figures 1 and 2 from the main text, except it assumes the optimistic uptake levels used to generate Figures 2c and 2d (95% in the over 80's, 90% in those 50-79, and 85% in those 18-49).

in Figure 2 of the main text. We illustrate the impact of protection against infection, the timing and pattern of NPI relaxation and vaccine uptake, in terms of total deaths from COVID-19 from January 2021 onwards (until the infection goes extinct). The level of protection against infection is clearly the dominant characteristic; although of the variables that are more easily controlled the uptake generally has the highest impact.

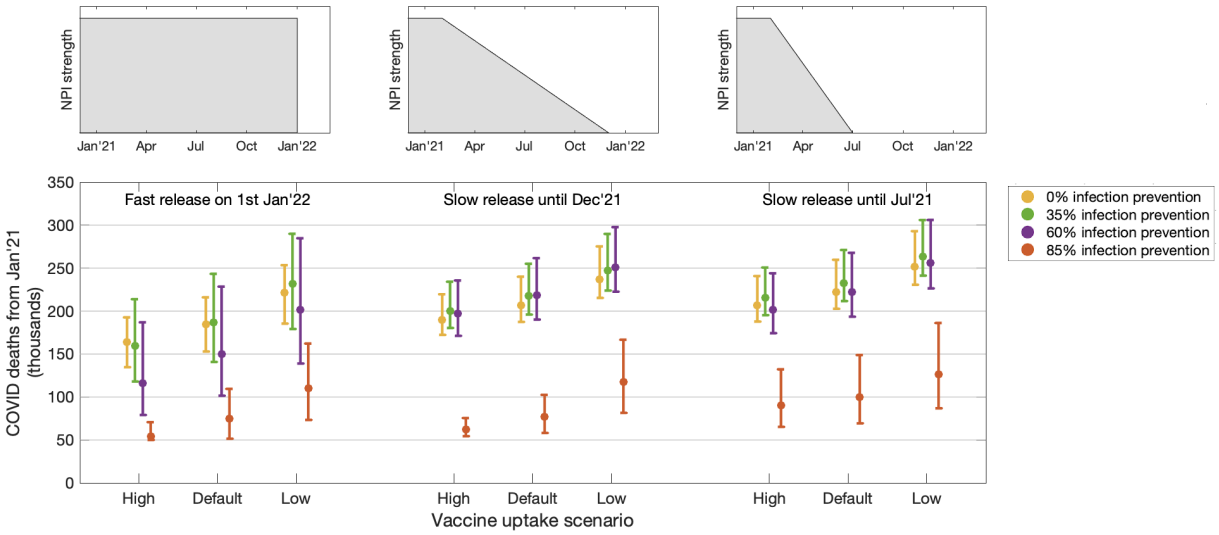

Figure S6: Summary of simulations from Figure S4, Figure S5, and Figure 2 of the main text. Results show the mean and 95% confidence intervals for the number of COVID-19 deaths from January 2021 until January 2024, sufficiently long so that the disease has died out due to our assumption of long-lasting immunity.

Finally, we considered the impact of extending the existing schedule to include children over 12 years of age; adding six years to the current guidelines. This adds approximately 30 million doses to the vaccination schedule (Figure S7), but only generates a modest reduction in R following release of NPIs. It is clear that vaccinating teenage children adds relatively little to the control of infection once older adults have been vaccinated.

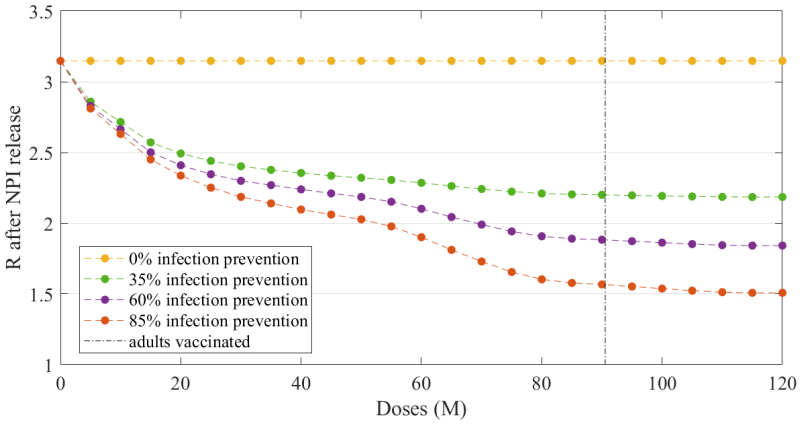

Figure S7: Impact of vaccine uptake (including children over 12 years of age) on R. Estimated effective reproduction number R for a given number of administered vaccine doses, including the vaccination of children (doses 90 million - 120 million). This should be compared to Figure 1b in the main text. R is calculated ignoring any additional increase in immunity from natural infection (after 29th January 2021) and excluding any impact on contact patterns due to non-pharmaceutical interventions.

S3 Extensions to NPI assumptions

In the main text we focused on a few chosen scenarios that illustrate the range of plausible behaviours, and only considered COVID-19 related deaths. Here, we show some other representative scenarios and the impact on the number of hospitalisations under all of these cases. We also display the 95% credible intervals, as defined by the variability in inferred parameters; these shaded regions contain 95% of all simulations at every point in time. We note that any one prediction will not necessarily follow the upper or lower bound, these are envelopes that contain predictions that may wander both above and below the mean.

S3.1 Alternative Step-wise NPI relaxation

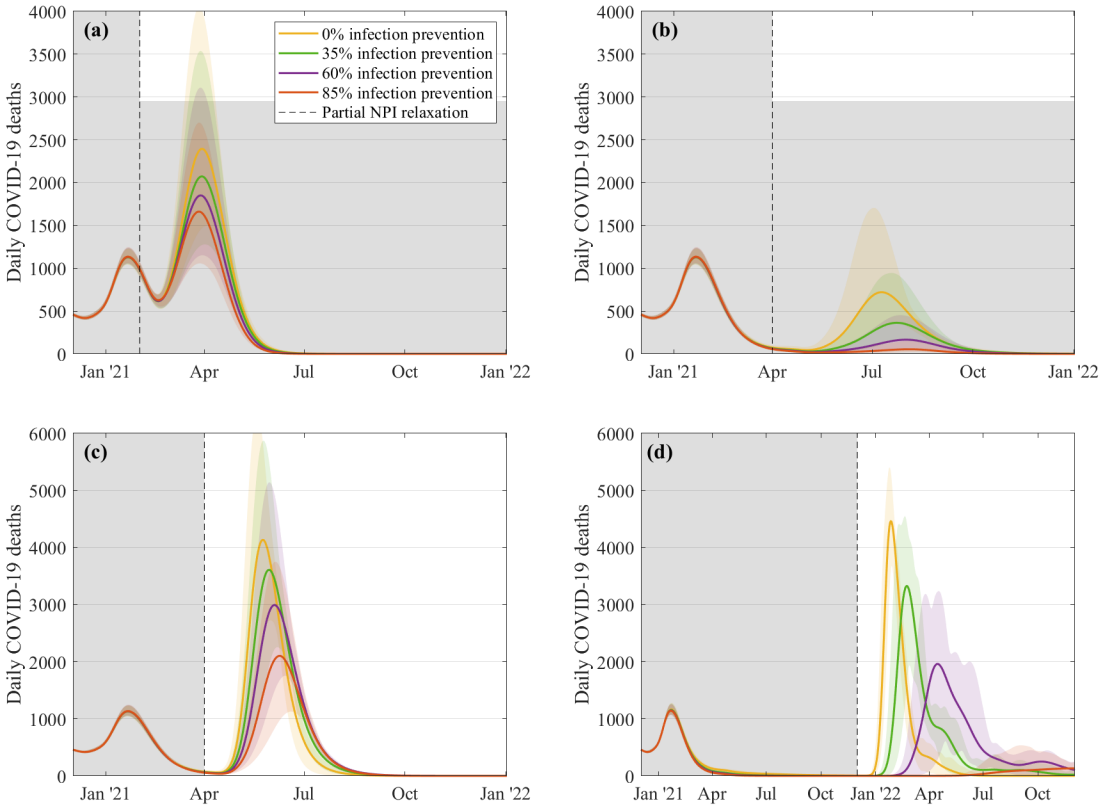

Figure S8: Predicted daily deaths in the UK following the start of an immunisation program and relaxation or removal of NPIs. Panels **(a)** and **(b)** show the effect of partial NPI measures down to those seen in early September 2020 (generating $R \sim 1.2 - 1.6$ dependent on the region and level of the new variant) from February or April 2021 respectively. These are the same as Figure 2(a) and (b) in the main text, and are included for comparison. Panels **(c)** and **(d)** show the complete removal of all NPI measures (leading to $R \sim 2.4 - 3.4$ with the B.1.1.7 variant and partial population immunity) from either April or December 2021. Shaded regions show the 95% credible intervals.

We extend the graphs shown in the main paper (Figure 2(a,b)), to consider the partial relaxation or complete release of non-pharmaceutical interventions (NPIs). Moderate relaxation of NPIs to a level seen in early September 2020 (Figure S8(a,b)) can lead to a sustained wave of deaths. Later relaxation leads to smaller waves, as more individuals have been vaccinated, with the smallest waves occurring if there is also strong infection-blocking capabilities (Figure S8(b), green line). Similarly, complete removal of NPIs in April 2021 or December 2021 (Figure S8(c,d)) generates the highest waves of infection with very large numbers of deaths. Again, only late release on controls and a strong infection-blocking vaccine can mitigate the worst effects. We stress that as hospitalisations and deaths increased we would expect both national legislation and emergent behaviour to limit the spread, so these predictions should be considered as extreme worse-case scenarios.

S3.2 Alternative Gradual NPI-relaxation

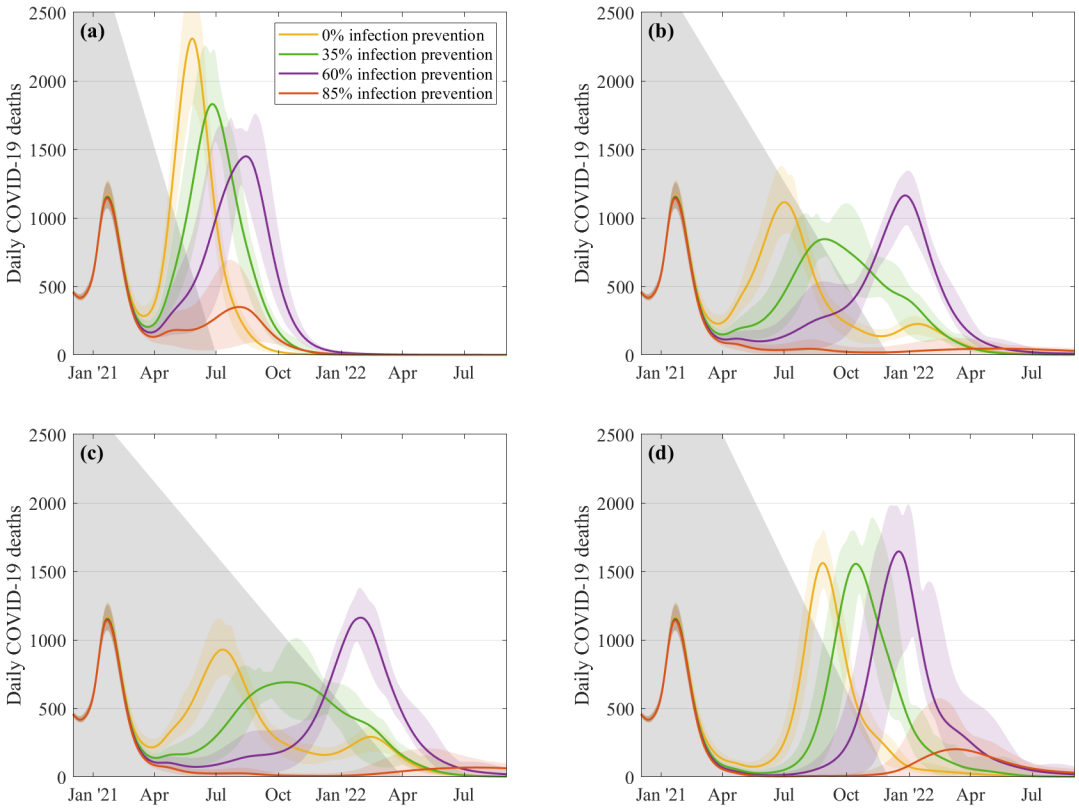

Figure S9: Effect of gradual relaxation of NPI measures on deaths across the UK following the start of vaccination. In panels **(a)-(d)** different relaxation scenarios are shown with NPIs reduced linearly from December levels down to complete release over different time periods represented by the height of the grey shading. Panels (a) and (b) are the same as Figure 2(e) and (f) from the main paper, and are shown for comparison. Shaded regions show the 95% credible intervals.

We complement the graphs shown in the main paper (Figure 2(d,e)), with other temporal profiles of NPI relaxation; in all cases NPIs drop steadily from their value estimated in mid-January 2021 to zero. Figure S9(e) summarises the combined impact of relaxation and protection against infection. For a given set of vaccine characteristics, we obtained the greatest benefit from a long slow release of NPIs (Figure S9(c)), whereas a rapid early release (Figure S9(a)) is predicted to cause the most deaths. In general there are minimal differences between vaccines with low protection against infection (0% compared to 35%), and it is only for the highest protection against infection of 85% that deaths are substantially reduced.

S4 Impact of Vaccination and NPI-release on Hospital Admissions

Although in this paper we have used deaths due to COVID-19 as our primary measure of vaccine impact, hospital admissions remain a key issue of public health concern due to the excessive demands they may place on the health care system. Figures S10 and S11 replot the outbreaks from Figures S8 and S9 (which include the scenarios examined in the main text, Figure 2) but show hospital admissions rather than deaths - although the broad patterns remain similar.

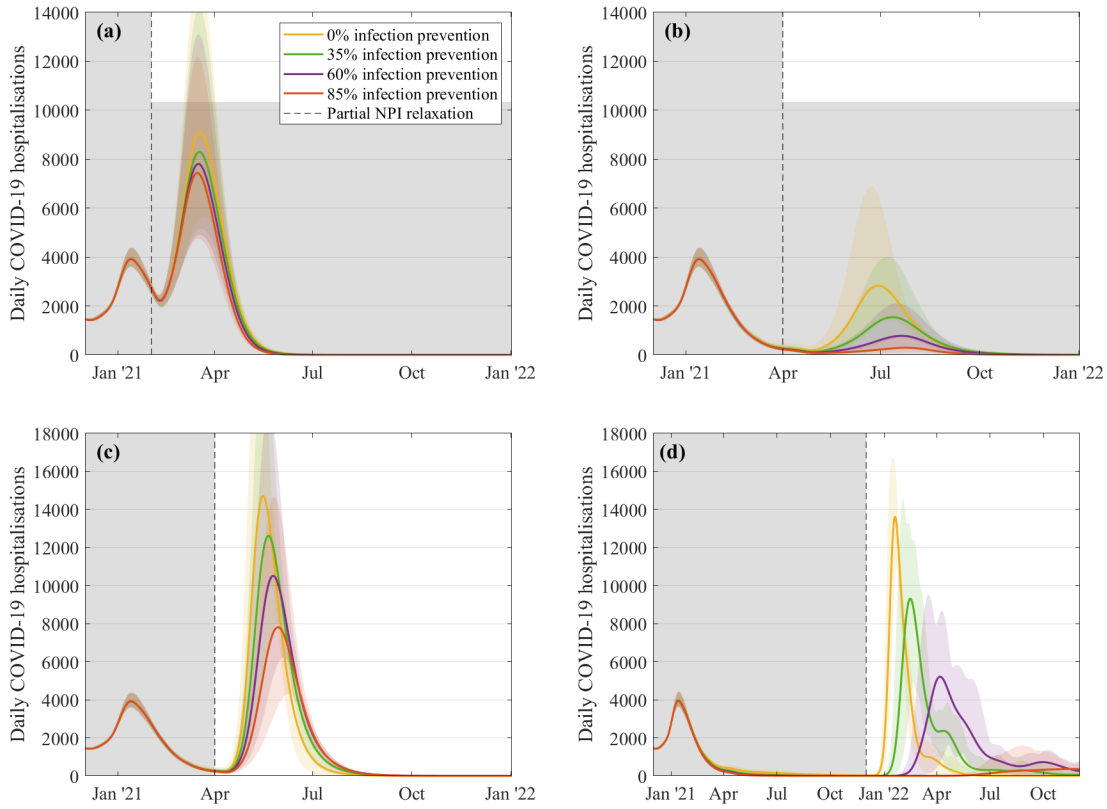

Figure S10: Predicted daily hospitalisations in the UK following the start of an immunisation program and relaxation or removal of NPIs. Panels **(a)** and **(b)** show the effect of partial NPI measures down to those seen in early September 2020 (generating $R \sim 1.2 - 1.6$ dependent on the region and level of the new variant) from February or April 2021 respectively, while panels **(c)** and **(d)** show the complete removal of all NPI measures (leading to $R \sim 2.4 - 3.4$) from either April or December 2021.

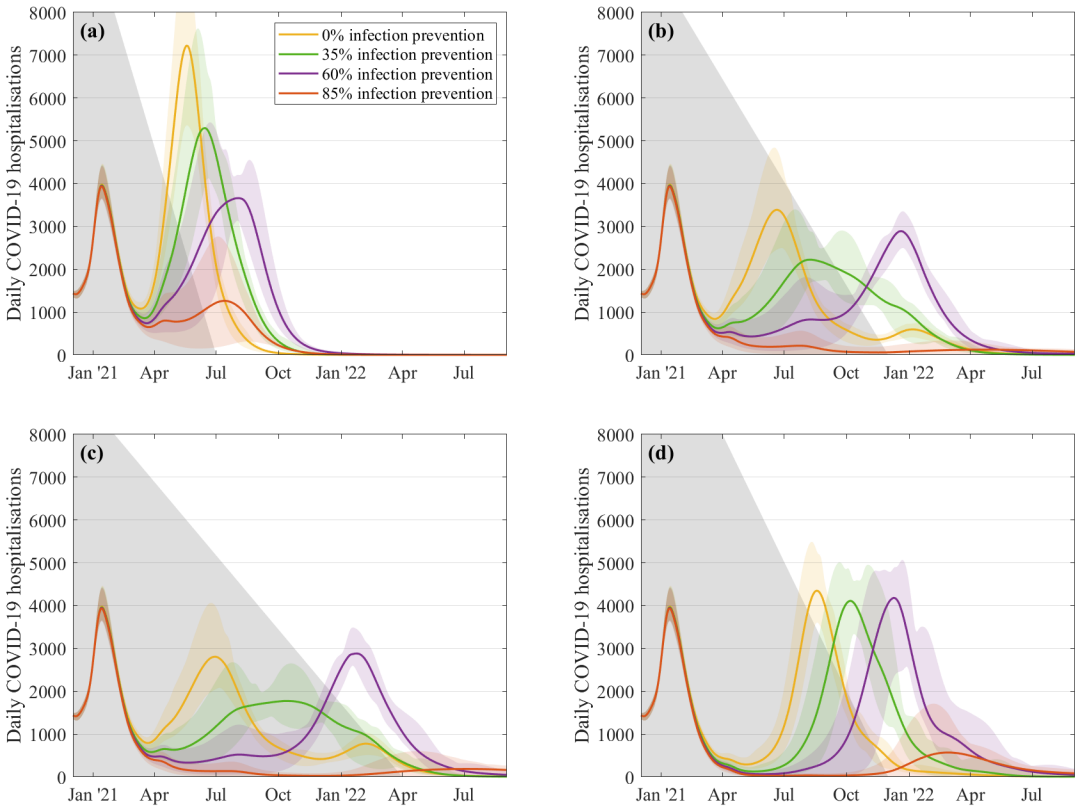

Figure S11: Effect of gradual relaxation of NPI measures on hospital admissions across the UK following the start of vaccination. In panels **(a)-(d)** different relaxation scenarios are shown with NPIs reduced linearly from December levels down to complete release over different time periods represented by the height of the grey shading.

S5 The Mathematical Model

Here we present the basic model formulation that underpins the age-structured predictions of COVID-19 dynamics in the UK (Figure S12), and how the parameters of this model have been inferred from the available data. We used a compartmental age-structured model, developed to simulate the spread of SARS-CoV-2 within ten regions of the UK (seven regions in England: East of England, London, Midlands, North East & Yorkshire, North West, South East and South West; and the devolved nations: Northern Ireland, Scotland and Wales) [20], with parameters inferred to generate a fit to deaths, hospitalisations, hospital occupancy and serological testing [21]. The model population is stratified by age, with force of infection determined by the use of an age-dependent (who acquires infection from whom) social contact matrix for the UK [22, 23]. Additionally, we allow susceptibility and the probabilities of becoming symptomatic, being hospitalised and the risk of dying to be age dependent; these are matched to UK outbreak data. Finally, we account for the role of household isolation, by separating primary and secondary infections within a household (more details may be found in [20]). This allows us to capture household isolation by preventing secondary infections from playing a further role in onward transmission. Model parameters were inferred on a regional basis using regional time series of recorded daily hospitalisation numbers, hospital bed occupancy, ICU occupancy and daily deaths [21].

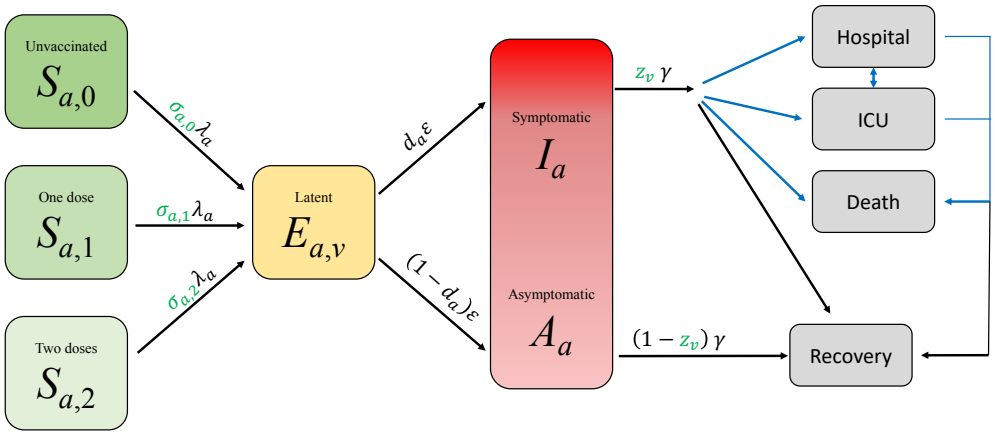

Figure S12: Representation of the basic model states and transitions. Black arrows show key epidemiological transitions while blue arrows show movements to observable states. Parameters in green show the action of vaccine on infection and probability of disease. In this graphic representation we have not separated the symptomatic and asymptomatic infections, to better illustrate that these compartments are somewhat ambiguous and depend on precise definitions being used at the time.

S5.1 Model description

We first show the underlying system of equations that account for the transmission dynamics, including symptomatic and asymptomatic transmission, household saturation of transmission and household quarantining. The population is stratified into multiple compartments: individuals may be susceptible (S), exposed (E), infectious with symptoms (I), or infectious and either asymptomatic or with very mild symptoms (A). Asymptomatic infections are assumed to transmit infection at a reduced rate given by τ. To some extent, the separation into symptomatic (I) and asymptomatic (A) within the model is somewhat artificial as there are a wide spectrum of symptom

severities that can be experienced.

We let superscripts denote the first infection in a household (F), a subsequent infection from a symptomatic household member (SI) and a subsequent infection from an asymptomatic household member (SA). A fraction (H) of the first detected cases (necessarily symptomatic) in a household are quarantined (QF), as are all their subsequent household infections (QS) - we ignore the impact of household quarantining on the susceptible population as the number in quarantine is assumed small compared with the rest of the population. The recovered class is not explicitly modelled, although it may become important once we have a better understanding of the duration of immunity. We omitted natural demography and disease-induced mortality in the formulation of the epidemiological dynamics.

We extended the model formulation to capture a range of vaccination scenarios. We modelled two vaccination classes for individuals where it has been 14 days since they received their first and second dose of the vaccine; the 14-day delay allows partial immunity to develop (Figure S13). We included these within the S and E class by adding an additional vaccination subscript for the number of doses received; hence $S_{a,0}$ corresponds to susceptible unvaccinated individuals while $S_{a,2}$ corresponds to those that received their second dose of vaccine at least 14 days ago.

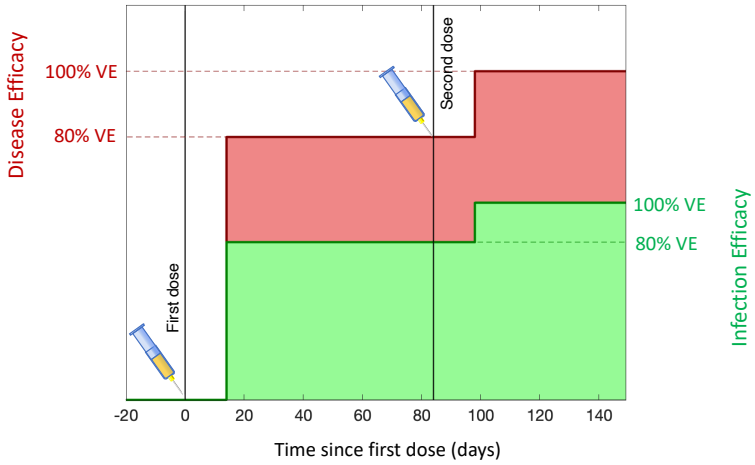

Figure S13: Dynamics of vaccine efficacy within an individual. 14 days after the first dose partial efficacy is developed, and 14 days after the second dose efficacy is raised to its maximum value. We highlight two forms of efficacy: efficacy against severe symptomatic disease (red) which is captured by the parameter z within the model; and protection against infection (green) which prevents all infection and acts on parameter σ.

The full equations are given by

$$\begin{aligned}
\frac{dS_{a,0}}{dt} &= -\left(\lambda^F_{a,0}+\lambda^{SI}_{a,0}+\lambda^{SA}_{a,0}+\lambda^Q_{a,0}\right)\frac{S_{a,0}}{N_a} - V_{a,1}(t)S_{a,0},\\
\frac{dS_{a,1}}{dt} &= V_{a,1}(t)S_{a,0} - \left(\lambda^F_{a,1}+\lambda^{SI}_{a,1}+\lambda^{SA}_{a,1}+\lambda^Q_{a,1}\right)\frac{S_{a,1}}{N_a} - V_{a,2}(t)S_{a,1},\\
\frac{dS_{a,2}}{dt} &= V_{a,2}(t)S_{a,1} - \left(\lambda^F_{a,2}+\lambda^{SI}_{a,2}+\lambda^{SA}_{a,2}+\lambda^Q_{a,2}\right)\frac{S_{a,2}}{N_a}\\
\frac{dE^F_{1,a,v}}{dt} &= \lambda^F_{a,v}\frac{S_{a,v}}{N_a} - M\varepsilon E^F_{1,a,v}, \qquad v\in\{0,1,2\}\\
\frac{dE^{SI}_{1,a,v}}{dt} &= \lambda^{SI}_{a,v}\frac{S_{a,v}}{N_a} - M\varepsilon E^{SI}_{1,a,v},\\
\frac{dE^{SA}_{1,a,v}}{dt} &= \lambda^{SA}_{a,v}\frac{S_{a,v}}{N_a} - M\varepsilon E^{SA}_{1,a,v},\\
\frac{dE^{Q}_{1,a,v}}{dt} &= \lambda^{Q}_{a,v}\frac{S_{a,v}}{N_a} - M\varepsilon E^{Q}_{1,a,v},\\
\frac{dE^X_{m,a,v}}{dt} &= M\varepsilon E^X_{m-1,a,v} - M\varepsilon E_{m,a,v}, \qquad X\in\{F,SI,SA,Q\}\\
\frac{dI^F_{a,v}}{dt} &= d_a(1-H)M\varepsilon E^F_{M,a,v} - \gamma I^F_{a,v},\\
\frac{dI^{SD}_{a,v}}{dt} &= d_a M\varepsilon E^{SI}_{M,a,v} - \gamma I^{SI}_{a,v},\\
\frac{dI^{SU}_{a,v}}{dt} &= d_a(1-H)M\varepsilon E^{SA}_{M,a,v} - \gamma I^{SA}_{a,v},\\
\frac{dI^{QF}_{a,v}}{dt} &= d_a H M\varepsilon E^F_{M,a,v} - \gamma I^{QF}_{a,v},\\
\frac{dI^{QS}_{a,v}}{dt} &= d_a H M\varepsilon E^{SA}_{M,a,v} + d_a\varepsilon E^Q_{a,v} - \gamma I^{QS}_{a,v},\\
\frac{dA^F_{a,v}}{dt} &= (1-d_a)M\varepsilon E^F_{M,a,v} - \gamma A^F_{a,v},\\
\frac{dA^S_{a,v}}{dt} &= (1-d_a)M\varepsilon (E^{SI}_{M,a,v}+E^{SA}_{M,a,v}) - \gamma A^S_{a,v},\\
\frac{dA^Q_{a,v}}{dt} &= (1-d_a)M\varepsilon E^Q_{M,a,v} - \gamma A^Q_{a,v},
\end{aligned}$$

Here we have included M latent classes, giving rise to an Erlang distribution for the latent period, while the infectious period was exponentially distributed. Throughout we have taken $M=3$.

The forces of infection which govern the non-linear transmission of infection obey:

$$\begin{aligned}
\lambda^F_{a,v} &= \beta_{nV}(t)\sigma_{a,v}\sum_{b,v}\left(I^F_{b,v}+I^{SI}_{b,v}+I^{SA}_{b,v}+\tau(A^F_{b,v}+A^S_{b,v})\right)\beta^N_{ba},\\
\lambda^{SI}_{a,v} &= \beta_{nV}(t)\sigma_{a,v}\sum_{b,v} I^F_{b,v}\beta^H_{ba},\\
\lambda^{SA}_{a,v} &= \beta_{nV}(t)\sigma_{a,v}\tau\sum_{b,v} A^F_{b,v}\beta^H_{ba},\\
\lambda^{Q}_{a,v} &= \beta_{nV}(t)\sigma_{a,v}\sum_{b,v} D^{QF}_{b,v}\beta^H_{ba},
\end{aligned}$$

where β^H represents household transmission and $\beta^N=\beta^S+\beta^W+\beta^O$ represents all other transmission locations, comprising school-based transmission (β^S), work-place transmission (β^W) and

transmission in all other locations (β^O). These matrices are taken from Prem *et al.* [23] to allow easy translation to other geographic settings, although other sources such as POLYMOD [22] could be used. $\beta_{nV}(t)$ is a time-varying term that captures the increase in the B.1.1.7 variant in the UK and its generally higher rate of transmission (approximately 50% higher than the original). The temporal component of this term is derived from a higher-dimensional framework that models both the original and new variant as separate epidemic processes.

Two key parameters, together with the transmission matrix, govern the age-structured dynamics: σ_a corresponds to the age-dependent susceptibility of individuals to infection (as we assume the probability associated with transmission from an infected individual to a susceptible contact to be constant with respect to age, we also absorb that quantity into the σ_a parameters); d_a the age-dependent probability of displaying symptoms (and hence potentially progressing to more severe disease). Both of these are also modified by the vaccine status, such that those that have received one or two doses of vaccine have a lower risk of infection and a lower risk of developing symptoms. The action of vaccine on the parameter σ captures the protection against infection aspect of the vaccine, while the action on d captures the efficacy against disease (Figure S13). We also define τ as the reduced transmission from asymptomatic infections compared to symptomatic infections; given the probability of displaying symptoms is less in the younger age groups, this parameter shapes the role of younger ages in onward transmission.

We require our model to capture both individual level quarantining of infected individuals and isolation of households containing identified cases. In a standard ODE framework this level of household structure is only achievable at large computational expense [24, 25]. Thus, we instead made a relatively parsimonious approximation to achieve a comparable effect.

We assume that all within household transmission originates from the first infected individual within the household (denoted with a superscript F, or QF if they become quarantined). This allows us to assume that secondary infections within a household in isolation (denoted with a superscript QS or Q) play no further role in any of the transmission dynamics. As a consequence, high levels of household isolation can drive the epidemic extinct, even if within household transmission is high – an effect not achievable with the standard SEIR-type modelling approach. This improved methodology also helps to capture to some degree household depletion of susceptibles (or saturation of infection), as secondary infections in the household are incapable of generating additional household infections.

S5.2 Capturing social distancing

We obtained age-structured contact matrices for the United Kingdom from Prem et al. [23]. We used these contact matrices to provide information on normal levels of household transmission (β^H_{ab}, with the subscript ab corresponding to transmission from age group a against age group b), school-based transmission (β^S_{ab}), work-place transmission (β^W_{ab}) and transmission in all other locations (β^O_{ab}).

We assume that any instigated non-pharmaceutical interventions (patterns of social-distancing or lockdown measures) leads to a reduction in the work, school and other matrices while increasing the strength of household contacts. Any given level of non-pharmaceutical interventions (NPIs), captured by the parameter ϕ between zero and one, therefore scales the four transmission matrices between their normal values (when $\phi = 0$) and their value under the most severe lockdown ($\phi = 1$).

We infer the level of NPIs as a slowly varying parameter in the MCMC processes on a weekly basis. In turn, the weekly value of ϕ allows us to calculate the growth rate r (and hence the reproductive number R) by an eigenvalue approach.

S5.3 Parameter Inference

As with any model of this complexity, there are multiple parameters that determine the dynamics. Some of these are global parameters and apply for all geographical regions, with others used to capture the regional dynamics. Some of these parameters are matched to the early outbreak data (including the resultant age-distribution of infection), however the majority are inferred by an MCMC process (Table S2).

Table S2: Key model parameters and their source. Mean values and 95% credible intervals are shown where appropriate; values of ϕ^R and hence H^R vary systematically over time due to changes in control measures so only the 95% credible intervals are given.

Parameter	Description	Source	Value
$V_{a,1}(t)$, $V_{a,2}(t)$	Time varying rate at which individuals in age group a receive their first or second dose of vaccine	Assumptions based on UK vaccination supply	
β	Age-dependent transmission, split into household, school, work and other	Matrices from Prem *et al.* [23]	
γ	Recovery rate, changes with τ, the relative level of transmission from undetected asymptomatics compared to detected symptomatics	Fitted from early age-stratified UK case data to match growth rate and R_0	0.52 (0.37-1.0)
d_a	Age-dependent probability of displaying symptoms (and hence being detected), changes with α and τ	Fitted from early age-stratified UK case data to capture the age profile of infection.	see figure S14
$\sigma_{a,v}$	Age-dependent and vaccine status dependent susceptibility, changes with α and τ	Fitted from early age-stratified UK case data to capture the age profile of infection.	see figure S14
H^R	Household quarantine proportion $= 0.8\phi_R$	Can be varied according to scenario	0.23-0.58 (see ϕ)
N_a^R	Population size of a given age within each region	Office for National Statistics	
ε	Rate of progression to infectious disease ($1/\varepsilon$ is the duration in the exposed class).	MCMC	0.31 (0.23-0.35)
α	Scales the degree to which age-structured heterogeneity is due to age-dependent probability of symptoms ($\alpha = 0$) or age-dependent susceptibility ($\alpha = 1$)	MCMC	0.26 (0.06-0.41)
τ	Relative level of transmission from asymptomatic compared to symptomatic infection	MCMC	0.25 (0.10-0.41)
ϕ^R	Regional relative strength of the lockdown restrictions; scales the transmission matrices. Can also be varied according to scenario.	MCMC	see figure S14
σ^R	Regional modifier of susceptibility to account for differences in level of social mixing	MCMC	1.0 (0.48-1.78)
D_S^R	Regional scaling for the mortality probability $P_a(\text{Death}\|\text{Symptomatic})$)	MCMC	1.0 (0.43-1.51)
H_S^R	Regional scaling for the hospitalisation probability $P_a(\text{Hospitalised}\|\text{Symptomatic})$)	MCMC	1.0 (0.72-1.34)
I_S^R	Regional scaling for the ICU probability $P_a(\text{ICU}\|\text{Symptomatics})$)	MCMC	1.0 (0.59-1.73)
$\beta_{nV}(t)$	Increase in transmission due to B.1.1.7 variant	MCMC	see figure S14

We would highlight that the parameters of α and τ are key in determining age-structured behaviour and are therefore essential in quantifying the role of school children in transmission [26]. We argue that a low τ and a low α are the only combination that are consistent with the growing body of

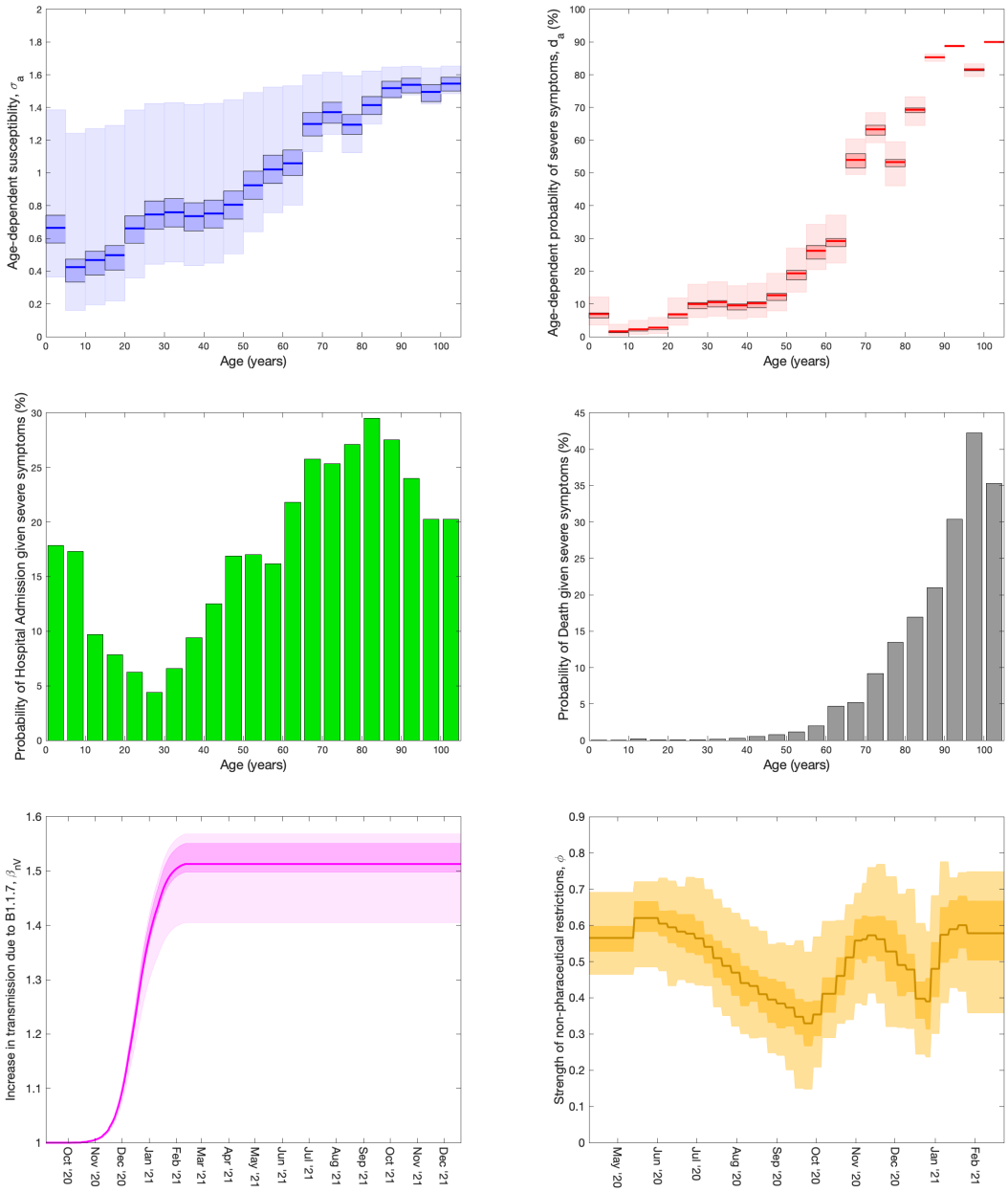

Figure S14: Key age and time dependent parameters. Here we show: **(top left)** age-dependent susceptibility (blue, from MCMC); **(top right)** age-dependent probability of symptoms (red, from MCMC); **(middle left)** probability of hospital admission conditional on symptoms (green); **(middle right)** probability of death conditional on symptoms (grey); **(bottom left)** relative increase in transmission rate due to the spread of new variant B.1.1.7 (pink, from MCMC); and **(bottom right)** the strength of non-pharmaceutical interventions (mustard, from MCMC). Those values that are inferred from the MCMC process show the 95% (light shading) and 50% credible intervals (dark shading) and the mean value (line).

data suggesting that levels of seroprevalence show only moderate variation across age-ranges [27], yet children are unlikely to display major symptoms, suggesting their role in transmission may be lower than for other respiratory infections [28, 29].

Throughout the current epidemic, there has been noticeable heterogeneity between the different regions of England and between the devolved nations. In particular, London is observed to have a large proportion of early cases and a relatively steeper decline in the subsequent lock-down than the other regions and the devolved nations. In our model this heterogeneity is captured through three regional parameters (D_S^R, H_S^R and I_S^R) which act on the heterogeneous population pyramid of each region to generate key observables.

S5.4 Public Health Measurable Quantities

The main model equations focus on the epidemiological dynamics, allowing us to compute the number of symptomatic and asymptomatic infectious individuals over time. However, these quantities are not directly measured - and even the number of confirmed cases (the closest measure to symptomatic infections) is highly biased by the testing protocols at any given point in time. It is therefore necessary to convert infection estimates into quantities of interest that can be compared to data. We considered seven such quantities which we calculated from the number of new symptomatic infections on a given day $I_{a,v}^d$.

1. **Hospital Admissions:** An age-dependent fraction of symptomatic individuals are assumed to need hospital treatment (figure S14), with a distributed lag (L_H) between infection and hospitalisation. This is modified by the vaccine efficacy against disease, governed by the parameter z_v for individuals that have received v doses of vaccine. As such:

$$\text{Total Hospital Admissions}(d) = \sum_{D,a,v} L_H(d-D) I_{a,v}^D z_v.$$

2. **ICU Admissions:** Similarly, an age-dependent fraction of symptomatic individuals are assumed to need treatment in an Intensive Care Unit. This is modified by the vaccine efficacy against disease, government by the parameter z_v for individuals that have received v doses of vaccine. This quantity is not a quantity that is generally reported in the UK, and therefore we cannot match our model predictions to this data source.

3. **Hospital Beds Occupied:** By convolving hospital admissions with the distributions of lengths of stay, we can estimate the number of hospital beds occupied.

4. **ICU Beds Occupied:** Though ICU admission data are not routinely collected in the UK and so cannot form part of our estimation process, the number of ICU beds occupied is recorded and our predictions are fitted to available data. By convolving the estimated ICU admissions with the distributions of lengths of stay in ICU, we generated estimates for the number of ICU beds occupied.

5. **Number of Deaths:** Mortality is assumed to occur to a fraction of symptomatically infected individuals, with the probability of mortality dependent upon age (figure S14), and occurring after a distributed lag. This is modified by the vaccine efficacy against disease, governed by the parameter z_v for individuals that have received v doses of vaccine.

6. **Proportion of Pillar 2 positives:** Given that the raw number of detected cases in any region is substantially influenced by the number of tests conducted, we consider the proportion of pillar 2 tests that are positive as a less biased figure. We assume that those symptomatically infected with COVID-19 compete with individuals suffering symptoms from other infections for the available testing capacity. This leads to proportion of pillar 2 tests that are positive being a saturating function of the number of symptomatic infections, with a single scaling parameter.

We compared these model predictions to the data by assuming that the true numbers are drawn from a negative binomial distribution with the model value as the mean, while the true proportions (Pillar 2 positives) are from a beta-binomial. Further details regarding this and the estimation of R from fitting the model to data may be found in Keeling *et al.* [21], although due to the rapidity with which new data streams become available this earlier work did not include the use of Pillar 2 testing data.

A sample version of the ODE code and parameters can be obtained at: https://github.com/sammoore25/Vaccination-and-Non-Pharmaceutical-Interventions-a-mathematical-modelling-study

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