Vaccination and non-pharmaceutical interventions for COVID-19: a mathematical modelling study

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Summary

Background The dynamics of vaccination against SARS-CoV-2 are complicated by age-dependent factors, changing levels of infection, and the relaxation of non-pharmaceutical interventions (NPIs) as the perceived risk declines, necessitating the use of mathematical models. Our aims were to use epidemiological data from the UK together with estimates of vaccine efficacy to predict the possible long-term dynamics of SARS-CoV-2 under the planned vaccine rollout.

Methods In this study, we used a mathematical model structured by age and UK region, fitted to a range of epidemiological data in the UK, which incorporated the planned rollout of a two-dose vaccination programme (doses 12 weeks apart, protection onset 14 days after vaccination). We assumed default vaccine uptake of 95% in those aged 80 years and older, 85% in those aged 50–79 years, and 75% in those aged 18–49 years, and then varied uptake optimistically and pessimistically. Vaccine efficacy against symptomatic disease was assumed to be 88% on the basis of Pfizer-BioNTech and Oxford-AstraZeneca vaccines being administered in the UK, and protection against infection was varied from 0% to 85%. We considered the combined interaction of the UK vaccination programme with multiple potential future relaxations (or removals) of NPIs, to predict the reproduction number (R) and pattern of daily deaths and hospital admissions due to COVID-19 from January, 2021, to January, 2024.

Findings We estimate that vaccination alone is insufficient to contain the outbreak. In the absence of NPIs, even with our most optimistic assumption that the vaccine will prevent 85% of infections, we estimate R to be 1·58 (95% credible intervals [CI] 1·36–1·84) once all eligible adults have been offered both doses of the vaccine. Under the default uptake scenario, removal of all NPIs once the vaccination programme is complete is predicted to lead to 21 400 deaths (95% CI 1400–55 100) due to COVID-19 for a vaccine that prevents 85% of infections, although this number increases to 96 700 deaths (51 800–173 200) if the vaccine only prevents 60% of infections. Although vaccination substantially reduces total deaths, it only provides partial protection for the individual; we estimate that, for the default uptake scenario and 60% protection against infection, 48·3% (95% CI 48·1–48·5) and 16·0% (15·7–16·3) of deaths will be in individuals who have received one or two doses of the vaccine, respectively.

Interpretation For all vaccination scenarios we investigated, our predictions highlight the risks associated with early or rapid relaxation of NPIs. Although novel vaccines against SARS-CoV-2 offer a potential exit strategy for the pandemic, success is highly contingent on the precise vaccine properties and population uptake, both of which need to be carefully monitored.

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Introduction

The outbreak of SARS-CoV-2 identified in Wuhan, China, in December, 2019, shaped life in 2020 as a worldwide pandemic emerged.[1] In the UK, the first cases were identified on Jan 31, 2020,[2] with a rapid exponential rise in cases in February and March.[3] The first lockdown began on March 23, 2020, and reversed the growth in infection, although important health metrics such as hospital occupancy and deaths continued to increase for many days.[4] The steady, but spatially heterogeneous, decline in cases continued until August, 2020, when a relaxation of infection control measures and resultant increased mixing precipitated a second wave and, subsequently, a second lockdown in November, 2020. By early December 2020, there were more than 60 000 deaths and 225 000 hospital admissions due to COVID-19 in the UK, and yet it is estimated that less than 20% of the population had been exposed to the virus,[5] suggesting that the outbreak was far from over. Mass vaccination began in the UK on Dec 8, 2020, and offers a potential exit strategy while preventing excessive demands on the health-care system.

In early 2020, more than 50 companies began development of the first vaccines against SARS-CoV-2. Of these, the Pfizer-BioNTech BNT162b2[6] vaccine was first approved for use in the UK on Dec 2, 2020, followed by the Oxford-AstraZeneca vaccine[7] on Dec 20, 2020, and the Moderna vaccine[8] on Jan 8, 2021, although only the

Research in context

Evidence before this study

We searched PubMed, Google Scholar, and *medRxiv* for articles published in English from inception to Feb 15, 2021, with the following search terms: "2019-nCoV", "novel coronavirus", "COVID-19", "SARS-CoV-2" AND "vaccine*" AND "model*". Previous modelling studies have focused on either control by non-pharmaceutical interventions or the optimal deployment of vaccination. However, to our knowledge, a combined analysis of a realistic vaccination programme together with associated relaxation of controls has not been done.

Added value of this study

We combine current knowledge and uncertainty of vaccine characteristics with a mathematical model fitted to epidemiological data from the UK to assess the implications of the planned rollout of a two-dose vaccination programme. We show that under plausible assumptions for efficacy and uptake, the UK is unlikely to reach the herd immunity threshold through vaccination. We predict that only gradual release of non-pharmaceutical interventions coupled with high uptake of a high-efficacy vaccine can prevent subsequent waves of infection.

Implications of all the available evidence

Our study shows that although vaccination of the most vulnerable groups will allow for some relaxation of non-pharmaceutical control measures, this must be done gradually to mitigate large-scale public health consequences.

Pfizer-BioNTech and Oxford-AstraZeneca vaccines were in widespread use in the UK by February, 2021. As of February, 2021, the UK had ordered 457 million doses of vaccines from eight different developers:[8,9] 100 million doses from Oxford-AstraZeneca, 40 million doses from Pfizer-BioNTech, 17 million doses from Moderna, 60 million doses from Novavax, 100 million doses from Valneva, 60 million doses from GSK-Sanofi Pasteur, 30 million doses from Janssen, and 50 million doses from CureVac. This amount is far more than any possible demand from the UK population, but mitigates for potential delays or failures from any single manufacturer. A continuing unknown with the potential vaccines is the degree to which they are effective against transmission, rather than simply preventing symptomatic infection (for further information see the appendix pp 1–2); this is a key uncertainty that we aimed to investigate in this study.

See Online for appendix

Vaccination against SARS-CoV-2 provides multiple unique challenges that are not encountered by many other vaccination programmes. Most of the experience about vaccination programmes is based on childhood vaccines, where the aim is simply to achieve high uptake in each birth cohort and associated boosters. To date, the seasonal influenza programme represented the largest annual delivery of vaccinations in the UK,[10] but seasonal influenza immunisation is proactive (beginning before many cases arise), the influenza season is of relatively short duration, and the reproduction ratio for seasonal influenza is lower than for SARS-CoV-2.[11] By contrast, for SARS-CoV-2, there is a race between infection and vaccination; infection can grow exponentially, whereas vaccination rates are inherently restricted by supply and logistics. However, the infection rate can be reduced by various non-pharmaceutical interventions (NPIs) while a vaccine is targeted to sections of the population where it will have the greatest impact.[12] Therefore, the future of SARS-CoV-2 control is dependent, in complex non-linear ways, on the initial prevalence of infection, the strength of NPIs and the rate of growth or decay of infection, the speed with which the vaccine can be rolled out, the targeting and uptake of the vaccine, and vaccine characteristics. The uncertainties and interactions between these components necessitate the use of mathematical models to quantify and optimise the effects of vaccination on the COVID-19 pandemic.[12–14]

Here, we present an age-structured mathematical model, fitted to various UK epidemiological data, to forecast the dynamics of COVID-19 in 2021 and beyond based on multiple scenarios of NPI relaxation and vaccine characteristics. These model results provide possible bounds on the expected number of deaths and hospitalisations, thus providing important policy insights into the interaction between continued NPIs and the ongoing vaccination programme. We aimed to capture the risk-structured delivery programme for the UK and focus on the consequences of relaxing NPIs, and consider the individual risks and how these are mitigated by vaccination.

Methods

Epidemiological model and fitting

In this mathematical modelling study, we adapted an existing age-structured and regionally structured model of SARS-COV-2 dynamics that had been matched to UK data[15] for the seven National Health Service regions of England and the three devolved nations (Scotland, Wales, and Northern Ireland). The model is extended to include the consequences of changes to NPIs, the spread of the B.1.1.7 variant, and vaccination (for the full description of the model and mathematical equations see appendix pp 15–22). The model is matched to the historical pattern of daily deaths, hospital admissions and occupancy, intensive care unit (ICU) occupancy, and the proportion of population-level PCR swab tests (known in the UK as pillar 2 tests) that are positive, and reliably captures the scale of the first and second waves of the pandemic; the same epidemiological quantities are forecast into the future. In matching to the available

UK data, our prediction of daily deaths due to COVID-19 corresponds to deaths within 28 days of a positive COVID test, which might therefore be an underestimate of the true value. Incorporating simple immunity due to vaccination into this model showed that prioritising the oldest age groups and most vulnerable people would lead to the greatest reduction in deaths.[12] In this study, we increased the realism of the vaccination dynamics, including the anticipated speed of vaccine rollout across the population and the need to administer two doses.

We used a two-dose model to simulate the effect of vaccination in both reducing infection (and hence onward transmission) and reducing symptomatic disease (detailed in appendix pp 1–3). We assumed that delivery of the second dose would be prioritised over new first doses, with an interval of 84 days (12 weeks) between doses, in line with UK policy.[16] In the absence of detailed vaccine-specific information on how efficacy changes over time since vaccination, we assume a simple stepped efficacy that scales according to the assumed final vaccine efficacy, as follows: from the first dose to day 14, zero efficacy; from day 14 to second dose on day 84, 80% of final vaccine efficacy; from day 84 to day 98, 80% of final vaccine efficacy; and from day 98 onwards, final vaccine efficacy is achieved (appendix p 16).

We assumed that both previous infection and vaccination grant long-lasting immunity to SARS-CoV-2 variants circulating in the UK. Therefore, the model ignores the potential invasion or emergence of other variants where the vaccine might offer less protection, and ignores the effects of waning of immunity, which might become important over longer timescales.

Model scenarios

A key issue is that models cannot forecast the strength of NPIs that will be imposed in the future and the level of support (and therefore adherence to NPIs) from the general population. Therefore, we are forced to simulate a range of scenarios that might bound future behaviour. We optimistically assumed that in the short term (with precise dates depending on the scenario modelled) controls would be sufficient to keep infection levels declining; our fit to historical data estimated that during the lockdown from January to February, 2021, the reproduction number (R) has been approximately 0·77 (95% credible intervals [CI] 0·75–0·80, but with considerable regional variation). Control measures are then relaxed in our model at various times (February, 2021, April, 2021, or January, 2022) and declined either immediately or over a period of 5 months, 8 months, 10 months, or 14 months; under these changes we predict how daily deaths and hospital admissions are affected by NPIs and the vaccination programme.

Vaccination schedules for SARS-CoV-2 in the UK are not precisely determined over long timescales, although the immediate priority order has been defined.[17] We implemented an accelerating delivery programme in our model that approximated the anticipated rollout of SARS-CoV-2 vaccination in the UK, and follows the priority ordering: 1 million doses of Pfizer-BioNTech vaccine across December, 2020; 1 million doses per week from the start of January, 2021, increasing to 2 million doses per week by February, 2021, using a mixture of Pfizer-BioNTech and Oxford-AstraZeneca vaccines, and 2·5 million doses per week from the start of February, 2021, until vaccine completion using a mixture of vaccines.

Throughout, we assumed a default scenario of 95% uptake of first and second doses in care homes and those over 80 years of age, in line with current observations;[18] uptake drops to 85% for those aged 50–79 years, and decreases further to 75% for those aged 18–49 years. As per current UK vaccination plans, we did not consider the vaccination of those younger than 18 years. For the UK population of around 66 million people, around 3·3 million are older than 80 years, 21 million are between 50 and 79 years, and 27 million are younger than 50 years but older than 18 years,[19] and hence eligible for vaccination. In practice, vaccination is also likely to be highly correlated within households and sociodemographic groups,[20] which will weaken the population-scale effect of any protection against infection induced by the vaccine. We assumed that doses might be given to either susceptible or recovered individuals with equal probability, but such doses would only have an impact on the susceptible population.

Vaccine efficacy against disease was assumed to be high (in keeping with preliminary reports[6,7])—94% during the earliest phase when just the Pfizer-BioNTech vaccine is used, dropping to 88% as a weighted mean when the Oxford-AstraZeneca vaccine is also used (appendix pp 2–3). The role of vaccines in preventing infection, and hence onward transmission, is less clear. Data from the Oxford-AstraZeneca trial have provided an initial understanding of vaccine capability to reduce infection (both symptomatic and asymptomatic), with a reported mean efficacy after one dose of 67% (95% CI 49–79).[21] At the time of writing data were not available for other COVID-19 vaccines. Therefore, we consider four different assumptions for protection against SARS-CoV-2 infection: 0%, 35%, 60%, and 85%, which we assumed operates by preventing primary infection. Disease efficacy considers both protection against infection and the reduction of severe symptoms if infection does occur (appendix p 3).

Output analysis

We simulated infection dynamics from February, 2020, matched to the observed pattern of daily cases, hospitalisations, and deaths until the end of January, 2021, and output the daily hospital admissions and deaths due to COVID-19 in the UK until Jan 1, 2024, assuming the continuation of the vaccination programme until completion. The end date ensured that, under the

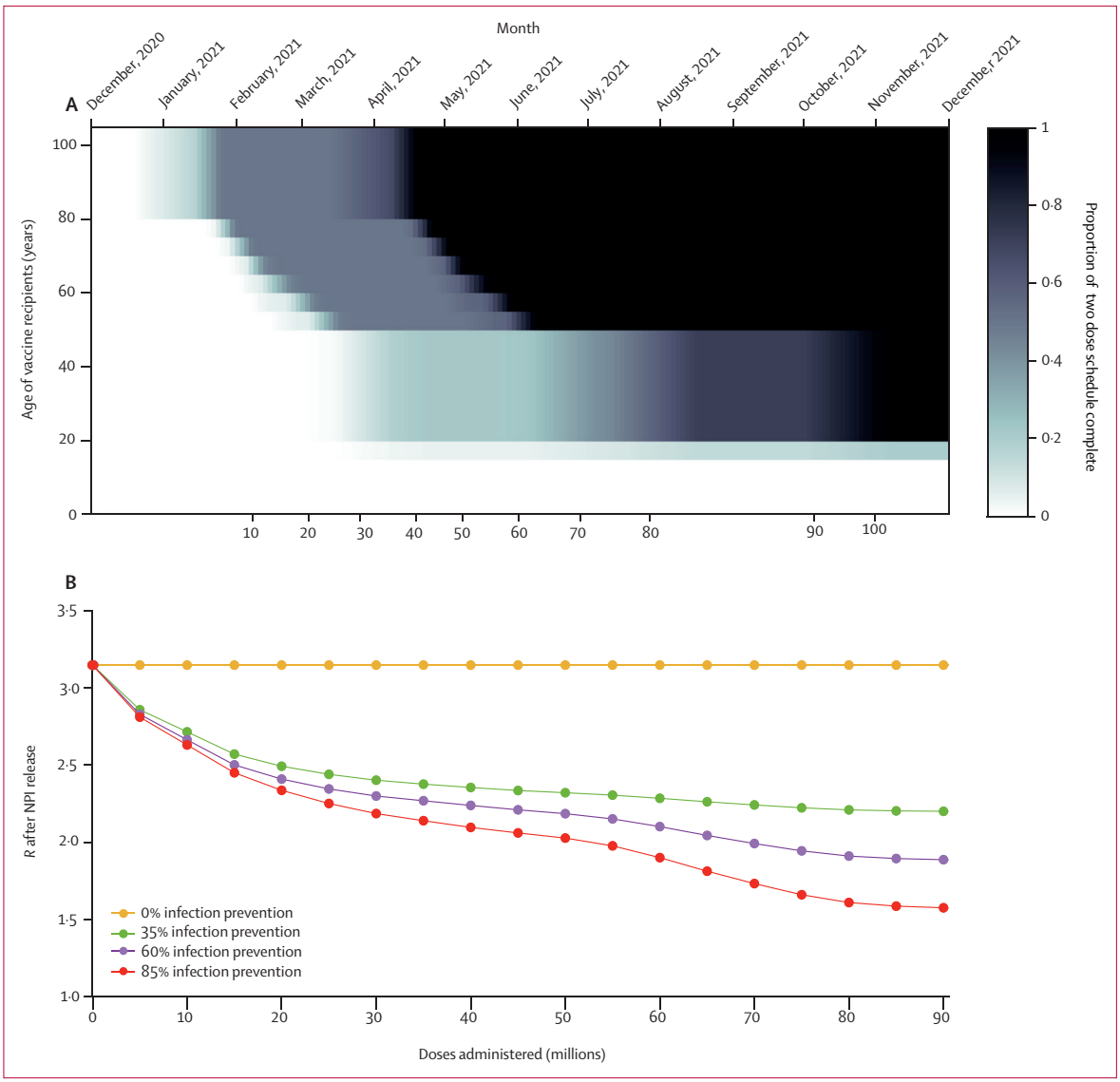

Figure 1: **Scheduling and impact of vaccine uptake**
(A) Assumed vaccine uptake over time, showing the number of vaccines given to each age group relative to the theoretical maximum when each person receives two doses. The non-linear spacing in the total number of doses occurred due to our assumption that an 84-day separation between first and second doses would be maintained throughout the entirety of the vaccination programme. (B) Estimated *R* for a given number of administered vaccine doses, ignoring any additional increase in immunity from natural infection (after Jan 29, 2021) and excluding any effect on contact patterns resulting from NPIs. Other values of R_0 would introduce a relative scaling of the predictions. NPIs=non-pharmaceutical interventions. *R*=effective reproduction number.

assumption of no waning immunity, the epidemic will have died out and no further deaths will occur.

Our calculation of *R* was computed from the predicted growth rate of infection, assuming the complete release of all NPIs and for a given number of doses administered. The calculation of *R* assumed protection against infection afforded by the vaccine but ignored any increase in immunity from infection after January, 2021. We considered hospital admissions and deaths from Jan 1, 2021, to Jan 1, 2024, and either showed the number of daily deaths and admissions or the summed total over this period. In a final piece of analysis, we calculated how the number of daily deaths was distributed between four groups: individuals that have yet to be offered the vaccine (predominately comprising younger age groups that were not eligible to receive the vaccine at that point in time), those who were eligible but because of health reasons or personal beliefs remained unvaccinated, those who had received one dose so far, and those that received both doses. This analysis was done with the assumption that vaccination offers 60% protection against infection, although the qualitative findings are insensitive to this assumption.

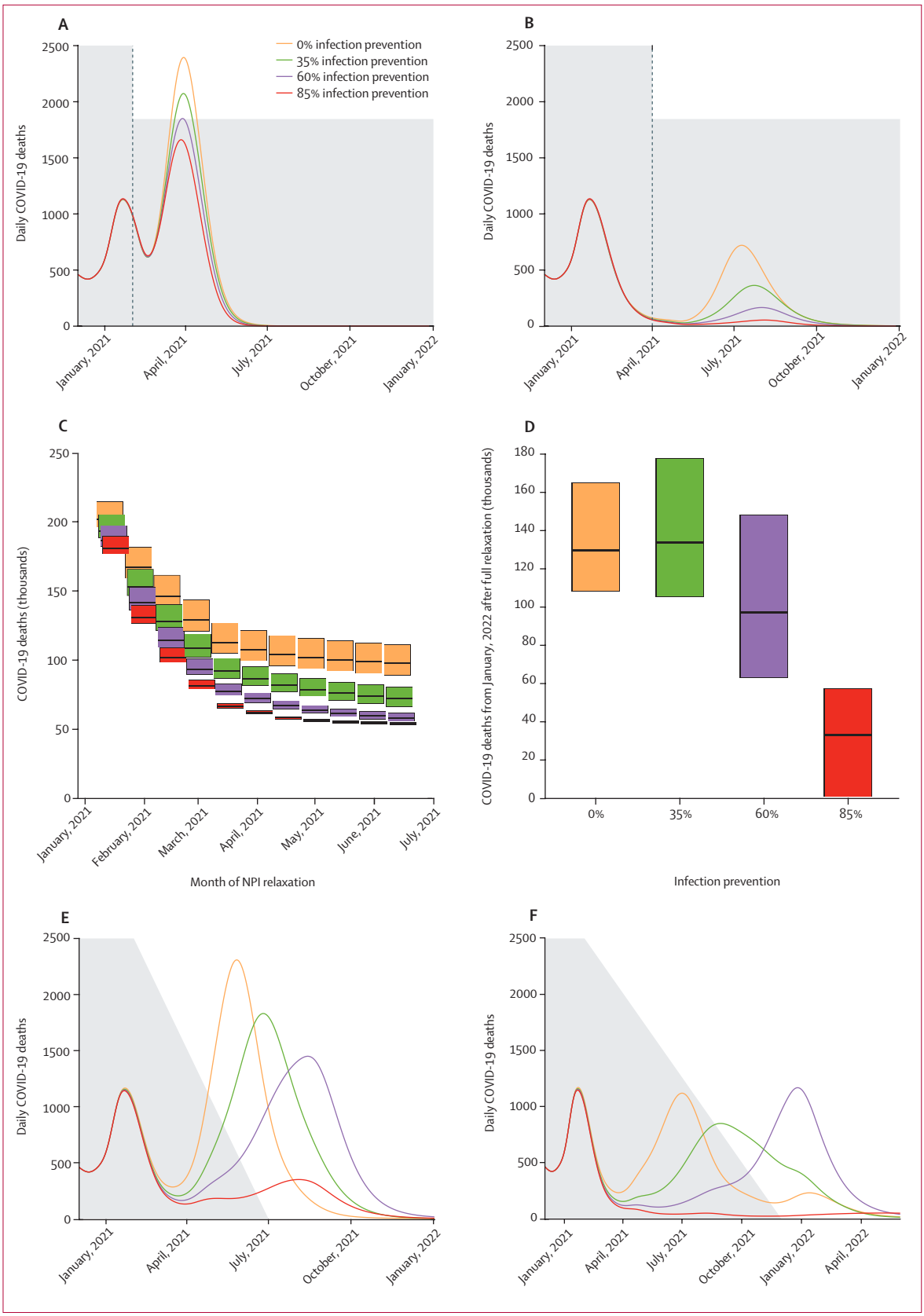

***Figure 2*: Predicted daily deaths from COVID-19 in the UK after the start of an immunisation programme and relaxation or removal of NPIs**

Shading indicates the level of NPIs implemented. (A, B) The effect of relaxing current NPI measures down to those implemented in early September, 2020. The dashed line indicates the point of partial NPI relaxation—February, 2021, in panel A and April, 2021, in panel B. (C, D) The total effect (cumulative deaths) of different patterns of releasing NPIs. The central black bar represents the default uptake scenario, whereas the upper and lower edges of the box correspond to the pessimistic and optimistic uptake scenarios. Panel C follows the pattern in panels A and B, reducing NPIs to September, 2020, levels at a given date and calculating the number of deaths due to COVID-19 from Jan 1, 2021. Panel D keeps all NPIs in place until January, 2022, such that the vaccination programme is complete and then models the effect of complete removal of all controls. (E, F) Correspond to gradual reduction in NPIs from their maximum in January, 2021, until removal of all control measures. Results of all figure panels are the mean of 500 simulations that explore the inferred parameter values, and totals are calculated until Jan 1, 2024. NPIs=non-pharmaceutical interventions.

	0% infection prevention	35% infection prevention	60% infection prevention	85% infection prevention
February, 2021, partial release				
Default uptake	166 100 (119 900–267 900)	152 000 (110 400–250 500)	140 700 (104 300–228 600)	130 100 (99 500–203 100)
Pessimistic uptake	180 500 (130 800–290 000)	164 400 (119 300–270 800)	151 200 (111 700–246 700)	138 500 (105 400–217 800)
Optimistic uptake	159 500 (115 200–257 200)	146 600 (106 700–241 000)	136 300 (101 400–220 500)	126 900 (97 400–197 100)
April, 2021, partial release				
Default uptake	106 800 (75 100–178 400)	85 800 (62 200–145 700)	71 300 (56 100–111 300)	61 400 (53 100–79 900)
Pessimistic uptake	120 200 (82 800–203 800)	94 000 (65 900–165 600)	75 100 (57 400–123 200)	62 200 (53 500–82 400)
Optimistic uptake	99 800 (71 200–164 400)	81 700 (60 600–135 200)	69 600 (55 600–105 600)	61 300 (53 100–79 400)
June, 2021, partial release				
Default uptake	98 100 (69 300–164 600)	73 100 (55 000–125 500)	58 900 (50 800–80 900)	53 900 (49 600–57 900)
Pessimistic uptake	111 300 (76 900–190 200)	81 000 (57 900–146 000)	61 700 (51 900–92 200)	54 200 (49 800–58 200)
Optimistic uptake	90 800 (65 000–150 200)	68 800 (53 500–113 800)	57 600 (50 300–74 900)	53 800 (49 600–57 900)

Data are means and 95% credible intervals. Three different timings of partial release are considered, bringing the level of non-pharmaceutical interventions to the levels observed in early September, 2020. Three different assumptions about vaccine uptake are considered: default 95%, 85%, and 75%; pessimistic 90%, 80%, and 70%; and optimistic 95%, 90%, and 85% in those aged 80 years and older, 50–79 years, and 18–49 years, respectively.

Table 1: **Model projections of deaths due to COVID-19 in the UK between Jan 1,2021, and Jan 1, 2024.**

	0% infection prevention	35% infection prevention	60% infection prevention	85% infection prevention
Default uptake	129 300 (102 600–154 800)	133 200 (91 100–189 800)	96 700 (51 800–178 900)	21 400 (1480–57 600)
Pessimistic uptake	164 900 (134 500–190 600)	177 700 (129 100–235 700)	147 800 (89 000–235 000)	57 100 (23 000–111 500)
Optimistic uptake	108 700 (84 600–132 200)	105 800 (68 500–160 300)	63 251 (29 397–137 198)	1030 (300–17 500)

Means and 95% credible intervals are shown. Strict non-pharmaceutical interventions remain in place until Jan 1, 2022, and then are completely released, by which time all adults over 18 years of age have been offered the vaccine. Three different assumptions about vaccine uptake are considered: default 95%, 85%, and 75%; pessimistic 90%, 80%, and 70%; and optimistic 95%, 90%, and 85% in those aged 80 years and older, 50–79 years, and 18–49, respectively.

Table 2: **Model projections of deaths from COVID-19 in the UK between Jan 1, 2022, and Jan 1, 2024**

All results shown, including the estimated *R*, daily deaths, and daily hospital admissions, represent the mean of 500 simulations that explore the inferred posterior parameter space determined by matching to the historical pattern of deaths, hospital admissions and occupancy, ICU occupancy, and the proportion of pillar 2 tests that are positive; credible intervals for the predictions are shown in the appendix (pp 11–12).

Sensitivity analysis

Our primary sensitivity analyses are to the level of protection against SARS-CoV-2 infection (either 0%, 35%, 60%, or 85%) and the scenarios for the relaxation of NPIs over time.

In addition to the default assumptions of vaccine uptake by different age groups (95%, 85%, and 75%), we also did sensitivity analysis using an optimistic scenario of increased uptake to 95%, 90%, and 85%, and a pessimistic scenario with decreased uptake to 90%, 80%, and 70%, in the age groups 80 years and older, 50–79 years, and 18–49 years, respectively.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Although efficacy against disease is of immediate benefit in protecting individuals against developing severe symptoms, it is the protection against infection from vaccination that leads to a reduction in the intrinsic growth rate and *R*. For the counterfactual scenario of zero protection against infection, we estimate *R* to be constant at 3·15 (95% CI 2·93–3·37) regardless of the numbers of vaccine doses administered, which is higher than in the first pandemic wave because of increased prevalence of the B.1.1.7 variant in the UK,[22] but is reduced from its theoretical maximum (estimated to have a basic reproduction number of 4·31, 95% CI 3·91–4·80) due to natural infection generating an increase in population-level immunity up to January, 2021 (figure 1). When protection against infection is high (85%), vaccination can generate a substantial decline in *R*, although insufficient to drive *R* below 1 for our default assumptions about vaccine uptake. Even when all second doses have been administered, we predict that *R*=1·58 (95% CI 1·36–1·83) for 85% protection against infection, with higher *R* values for less protective vaccines.

Upon relaxation of control measures we predict waves of infection and associated deaths, although these are reduced by increased levels of vaccine derived immunity in the population. Early, modest relaxation of NPIs

(February 2021; figure 2A), matched to the levels observed in early September, 2020 (when *R* was between 1·2 and 1·6 across the seven English National Health Service regions and the three devolved nations without the B.1.1.7 variant in predominant circulation), generates a wave of infection and associated deaths even under our most optimistic assumptions (corresponding to a vaccine that blocks 85% of infection). Later relaxation of NPIs (April 2021; figure 2B), in conjunction with a vaccine that generates moderate levels of protection against infection, enhances the chance of accruing additional population immunity and generating a smaller subsequent wave.

To consider sensitivity to vaccine uptake, we analysed the total number of deaths due to COVID- 19 predicted by the model from Jan 1, 2021, to Jan 1, 2024 (figure 2C; ie, the areas under the curves in figure 2A, B). Even in these scenarios, when some degree of NPIs remained (at the level observed in early September, 2020), the abrupt change from a high to lower strength of control could precipitate an epidemic wave. The scale of this wave and the resulting total number of deaths is driven by the date of the relaxation, the level of protection against infection, and the uptake of vaccine in the population (table 1). Although early relaxation leads to the largest number of total deaths, for relaxation times beyond April, 2021, it is the level of protection against infection that has the greatest effect. The lower limit of these totals (around 50 000) is dominated by deaths in January and February, 2021.

If we wait until January, 2022, to completely lift all restrictions, such that the entire adult population have been offered two doses of vaccine, we still generally predict a substantial outbreak upon relaxation with a large number of associated deaths (appendix p 11 shows the associated dynamics over time; figure 2D, table 2). Even with 85% protection against infection, the sudden release of all restrictions is predicted to generate an infection wave leading to 21 400 deaths (95% CI 1480–57 600). This finding is unsurprising given that vaccination alone is unable to drive *R* below 1 (figure 1B). The only exception is an optimistic vaccine uptake assumption together with a high (85%) degree of protection against infection, when subsequent COVID-19 deaths remain low but not zero, generating a mean of 1030 deaths (95% CI 300–17 500). When the vaccine offers no protection against infection, removing NPIs triggers an uncontrolled wave of infection in which only those successfully immunised (around 88% efficacy in the 65% of the entire population that receive the vaccine) will be protected against severe disease, hence the predicted number of deaths is large (129 300, 95% CI 102 600–154 800). However, the relationship between these parameters and predicted deaths is highly non-linear and even when protection against infection is 60%, the predicted number of deaths from the post-relaxation wave of infection is 96 700 (95% CI 51 800–178 900).

The modelled stepwise release of all NPIs generates an overshooting wave of infection (figure 2A, B); a more

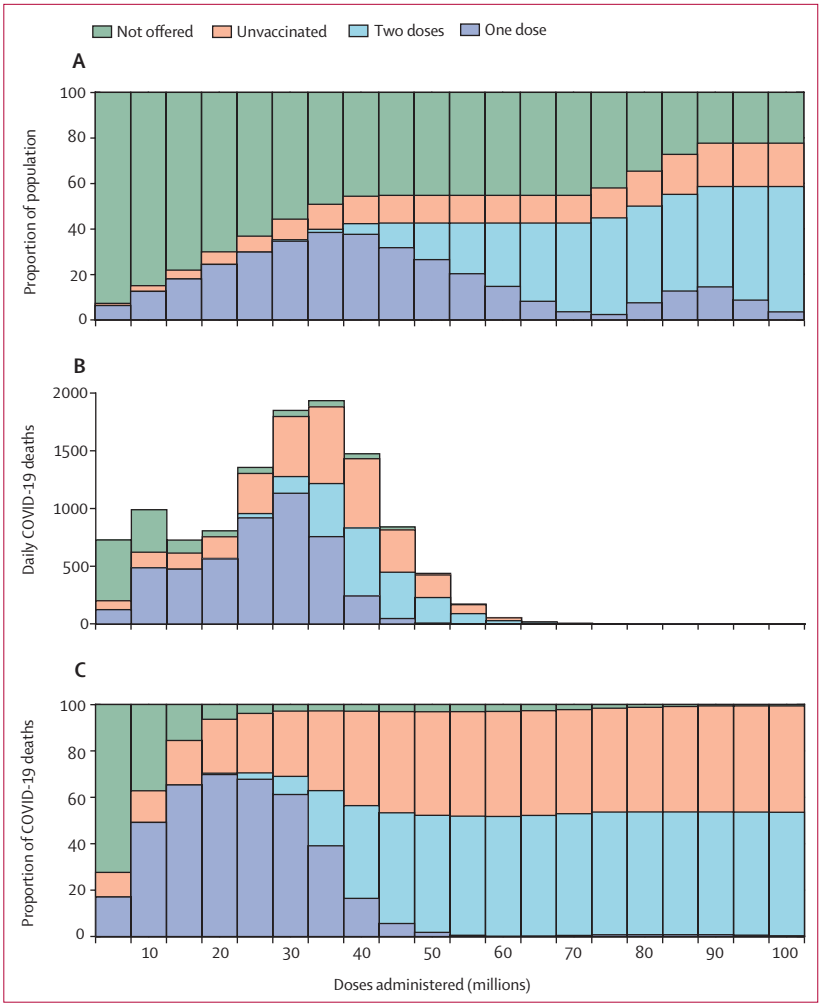

Figure 3: **Characterisation of disease dynamics in terms of vaccine status as a function of the number of doses delivered so far**

(A) Composition of the entire population. (B) Number of daily deaths due to COVID-19. (C) Proportion of COVID-19 deaths. For all panels, we display simulations assuming: 95%, 85% and 75% uptake for those ≥80 years, aged 50–79 years, and aged 18–49, respectively; 60% protection against infection; and with a moderate reduction in NPIs at the start of February, 2021. Results are the mean of 500 simulations that explore the inferred parameter values.

gradual release of restrictions could mitigate these effects (figure 2E, F). At 85% protection against infection, even partial release of NPIs in February, 2021 (figure 2A), generates an infection wave that peaks at 1670 (95% CI 1000–3400) deaths per day, whereas complete relaxation over 5 months (figure 2E) or 10 months (figure 2F) leads to waves that peak at 430 (0–910) and 46 (5–180) respectively. Therefore, a slow release of NPIs might offer a realistic compromise, allowing a degree of relaxation but maintaining low case numbers if the vaccine confers a high level of protection against infection (figure 2F).

The precise dynamics and outcomes are contingent on the assumed intrinsic *R* before the relaxation of NPIs, which in this study is around 0·77 (95% CI 0·75–0·80) after a tight lockdown in early 2021. Other values for this quantity will change the precise curves but would not

change the qualitative conclusions. We observed similar patterns if we examined the number of daily admissions to hospital (appendix pp 13–14), with a third wave predicted if NPIs are relaxed too early or if the vaccine has a restricted effect on infection and onward transmission.

Although we predominantly focused on the population-level consequences of the vaccination programme, an important question is what is the proportion of vaccinated individuals who become severely ill and die with COVID-19 (figure 3). From 0–30 million doses and 70–90 million doses, the number of individuals who have not been offered the vaccine declines linearly, reflecting our assumption of a constant supply of vaccine and progression through the vaccine priority groups,[17] while those who are unvaccinated but in eligible age groups and those who have received one vaccine dose increase linearly. In the interim (between 30–55 million doses) and later periods (after 90 million doses) the priority switches to giving second doses (figure 3A).

Since the existing vaccination strategy targets the most vulnerable people first,[17] early deaths are dominated by high-risk individuals who have been vaccinated and received just one dose (figure 3B)—in this group vaccine efficacy against disease is assumed to be 70% (appendix p 3). By the time 15 million doses have been administered, less than 15% of all deaths are in those who have not been offered the vaccine (figure 3B, C). Once 30 million doses have been administered, around 60% of all deaths are expected to be in those who have been vaccinated (figure 3C). Over the simulated epidemic between Jan 1, 2021, until Jan 1, 2024, we predict that 48·3% (95% CI 48·1–48·5) and 16·0% (15·7–16·3) of deaths will be in individuals who have had one or two doses of the vaccine, respectively. Although at the individual level we assumed that two doses of vaccine would reduce the risk of mortality by 88% (appendix p 3), given the high proportion of vulnerable individuals receiving the vaccine, deaths are inevitably dominated by vaccine failures (that did not generate immunity).

Discussion

In this study, we show that vaccines that provide both high efficacy against disease and a substantial amount of protection against infection offer a means of eventually relaxing controls without a large subsequent wave of hospital admissions and deaths. Our conclusions rely on the vaccine characteristics, but also on vaccine uptake in the population—in particular, the most vulnerable people who require protection against disease—but also in the general population, if protection against infection is to generate high levels of population immunity. In practice, vaccine uptake is likely to be regionally and socio-demographically correlated.[23,24] Such correlations could lead to pockets of high susceptibility in the population, which could act as locations of small-scale outbreaks and reduce the effect of population immunity.[25] Vaccine uptake might vary over time as the perceived risk varies,[26,27] with high levels of hospital admissions and deaths likely to generate a greater demand for the vaccine. We expect there to be a complex four-way interaction between levels of infection, NPI policy, NPI adherence, and vaccine uptake.[28] Therefore, from a public health perspective, it is crucial to understand the drivers of vaccine uptake and vaccine hesitancy[29] to identify groups that might have lower than average uptake and plan accordingly.

Early relaxation of NPIs, before sufficient immunity has been established, would precipitate a large wave of infection, with resultant hospital admissions and deaths. A similar effect is predicted from any final release of NPIs if the herd immunity threshold has not been achieved. Even with high levels of vaccine uptake, a substantial fraction of the population needs to be immunised to prevent large subsequent waves of infection, implying that strong NPIs would still be required even when phase 1 of the vaccination programme (offering vaccine to all people older than 50 years) is complete to avoid surges in infection. A more measured approach, in which NPIs are gradually released over a period of many months, has advantages over sudden changes to controls but still might not mitigate the worst effects. Calculating the effects on health services due to subsequent waves of infection is complex and dependent on both the volume and peak of hospital admissions. Similarly, although a rapid relaxation of NPIs might give rise to a similar expected number of deaths as a prolonged epidemic under a gradual release of NPIs, a more prolonged outbreak with a lower peak prevalence provides a far greater opportunity for future interventions to be effective and places less stress on the health-care system. Throughout this study, we focused on COVID-19 related deaths, matching the common UK definition as death within 28 days of a positive COVID test. However, other measures, such as excess deaths, might give a more robust picture of the true effect of SARS-CoV-2, but these often have a substantial delay between deaths and reporting. We stress that if hospital occupancy and deaths increased to excessive levels because of changes in NPIs, we would expect both national legislation and emergent behaviour to limit spread.[30] Therefore, our scenarios represent a pessimistic view of measures in response to a worsening outbreak.

Although we know that vaccines offer considerable protection against disease for the individual, at the population level we still expect a substantial proportion of deaths to be in people that have received one or two doses of the vaccine. The precise proportions are a function of vaccine uptake in those most at risk—increasing vaccine uptake reduces the number of deaths but increases the contribution of vaccinated individuals to the overall proportion of deaths. There is a strong influence of how well the vaccine protects against severe disease; greater efficacy against the most severe disease will again reduce the number of deaths and will also decrease the proportions associated with vaccinated individuals. At present, much of the available data for vaccine efficacy is generated from

younger age groups (below 65 years old), requiring assumptions to be made regarding the relative effectiveness in older people (over 80 years old who suffer the greatest burden of severe disease). Were the vaccine to be less efficacious in older people, this would result in a relatively higher number of deaths and an increase in the proportion of deaths associated with vaccinated individuals.

As of January, 2021, multiple vaccine manufacturers had published peer-reviewed articles to present the findings of their phase 3 trials.[6,7,31] These publications have been used to provide approximate parameters for this model-based study, but many questions have not been quantitatively addressed. Therefore, several key vaccine parameters within the model are based on parsimonious assumptions, and we identify the following three limitations that require additional experimental or observational data to refine model assumptions. First, as explained throughout this paper, determining whether the vaccine prevents infection is key for the development of population immunity, and hence the role of vaccination in long-term control of COVID-19. In the case of the Oxford-AstraZeneca vaccine, initial estimates of efficacy against infection have been obtained from one group of a clinical trial in which participants provide weekly nose and throat swabs, with evidence of the effectiveness of the vaccine against preventing infection substantially greater than zero.[21] There is the potential for the vaccine to further reduce viral shedding from vaccinated individuals, reducing onward transmission, but this is likely to be difficult to measure in a real-world setting. Second, we assumed that efficacy against disease applies equally across the entire spectrum of disease, but if the vaccine offers greater protection against the most severe disease this will reduce our predictions for hospital admissions and deaths. Finally, we expect efficacy to vary with age and between risk groups and incorporating such heterogeneity into models is key for more robust predictions. With the number of clinical and observational trials in progress, these efficacy estimates are emerging from a rapidly changing field, with the estimated ranges of efficacy for each vaccine subject to revision as new data emerge. To that end, online living literature reviews have been produced to curate published data on safety, immunogenicity, and efficacy.[32] Throughout this paper, we assumed a 14-day delay from vaccination to developing protection. Evidence suggests that some level of immunity might occur as early as 7 days after vaccination with the Pfizer vaccine,[6] although the delay might be longer for the Oxford-AstraZeneca vaccine or in older individuals. Our cautious assumption does not qualitatively change the infection dynamics, as it is equivalent to imposing a slight delay (7-day) in vaccine delivery.

Over longer timescales, the possibilities of waning immunity and virus mutation might influence these predictions. Waning immunity, either of naturally derived immunity or immunity induced from vaccination, might necessitate seasonal vaccination programmes against SARS-CoV-2, protecting the most vulnerable people in a similar manner to seasonal influenza vaccination.[33] We are lacking in our fundamental understanding of SARS-CoV-2 epidemiology, in particular whether subsequent infections have the same severity as primary infections, as well as quantitative estimates of the duration of protection. Both elements can be factored into the prediction mechanisms developed here, but without detailed evidence, such long-term forecasts are speculation. More data would also be required to include potential seasonal changes in transmission rates, which might affect the shape of predicted epidemics but are unlikely to change broad patterns for the total number of deaths or individuals requiring hospital treatment. Furthermore, careful monitoring of viral mutations will be needed to detect whether specific variants are associated with antigenic escape from vaccine-acquired immunity (as of February, 2021, the mutation with the strongest evidence of causing antigenic change was E484K, with variants containing the E484K mutation being of particular concern, such as the B.1.351 lineage[34]). In a population with high vaccine-derived immunity, vaccine-escape variants are likely to outcompete the original variants, becoming widespread and necessitating updated vaccines to improve protection.

Effective vaccines with high uptake are likely to be an essential element in the long-term control and potential elimination of COVID-19. However, experience with other diseases has shown that elimination is difficult and generally requires a targeted multi-strategy approach.[35] The same is likely to be true for SARS-CoV-2, with eradication unlikely to be feasible in the short-term and requiring a global perspective. Although mass vaccination will inevitably reduce R and disease prevalence, other measures, such as intensive test, trace, and isolate strategies, will be needed to target pockets of infection. Maintaining low levels of infection is likely to be key to the success of test, trace, and, isolate strategies[36] and in reducing the risk of vaccine escape.[37] Ultimately, whether we achieve eradication of SARS-CoV-2 is likely to depend on the long-term natural history of the infection and the public health importance attached to this goal.

Contributors

Data analysis and visualisation was led by SM, who programmed the model with help from EMH and MJK. All authors interpreted the findings, contributed to writing the manuscript, and approved the final version for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

SM reports grants from the National Institute for Health Research (NIHR), outside the submitted work. EMH reports grants from the Medical Research Council (MRC), during the conduct of the study, and is a member of the UK Government's Scientific Pandemic Influenza Group on Modelling, Operational subgroup (SPI-M). MJT reports grants from the MRC and UK Research and Innovation (UKRI), during the conduct of the study, and is a member of SPI-M. LD reports grants from the MRC and UKRI, during the conduct of the study, and is a member of SPI-M. MJK reports grants from the NIHR, MRC, and UKRI, during the conduct of the study, and is a member of SPI-M and the Joint Committee on Vaccination and Immunisation.

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