

Quantifying the effect of delaying the second COVID-19 vaccine dose in England: a mathematical modelling study

Natsuko Imai*, Thomas Rawson*, Edward S Knock, Raphael Sonabend, Yasin Elmaci, Pablo N Perez-Guzman, Lilith K Whittles, Divya Thekke Kanapram, Katy A M Gaythorpe, Wes Hinsley, Bimandra A Djaafara, Haowei Wang, Keith Fraser, Richard G FitzJohn, Alexandra B Hogan, Patrick Doohan, Azra C Ghani, Neil M Ferguson, Marc Baguelin, Anne Cori



Summary

Background The UK was the first country to start national COVID-19 vaccination programmes, initially administering doses 3 weeks apart. However, early evidence of high vaccine effectiveness after the first dose and the emergence of the SARS-CoV-2 alpha variant prompted the UK to extend the interval between doses to 12 weeks. In this study, we aimed to quantify the effect of delaying the second vaccine dose in England.

Methods We used a previously described model of SARS-CoV-2 transmission, calibrated to COVID-19 surveillance data from England, including hospital admissions, hospital occupancy, seroprevalence data, and population-level PCR testing data, using a Bayesian evidence-synthesis framework. We modelled and compared the epidemic trajectory in the counterfactual scenario in which vaccine doses were administered 3 weeks apart against the real reported vaccine roll-out schedule of 12 weeks. We estimated and compared the resulting numbers of daily infections, hospital admissions, and deaths. In sensitivity analyses, we investigated scenarios spanning a range of vaccine effectiveness and waning assumptions.

Findings In the period from Dec 8, 2020, to Sept 13, 2021, the number of individuals who received a first vaccine dose was higher under the 12-week strategy than the 3-week strategy. For this period, we estimated that delaying the interval between the first and second COVID-19 vaccine doses from 3 to 12 weeks averted a median (calculated as the median of the posterior sample) of 58 000 COVID-19 hospital admissions (291 000 cumulative hospitalisations [95% credible interval 275 000–319 000] under the 3-week strategy vs 233 000 [229 000–238 000] under the 12-week strategy) and 10 100 deaths (64 800 deaths [60 200–68 900] vs 54 700 [52 800–55 600]). Similarly, we estimated that the 3-week strategy would have resulted in more infections compared with the 12-week strategy. Across all sensitivity analyses the 3-week strategy resulted in a greater number of hospital admissions. In results by age group, the 12-week strategy led to more hospitalisations and deaths in older people in spring 2021, but fewer following the emergence of the delta variant during summer 2021.

Interpretation England's delayed-second-dose vaccination strategy was informed by early real-world data on vaccine effectiveness in the context of limited vaccine supplies in a growing epidemic. Our study shows that rapidly providing partial (single-dose) vaccine-induced protection to a larger proportion of the population was successful in reducing the burden of COVID-19 hospitalisations and deaths overall.

Funding UK National Institute for Health Research; UK Medical Research Council; Community Jameel; Wellcome Trust; UK Foreign, Commonwealth and Development Office; Australian National Health and Medical Research Council; and EU.

Copyright © 2023 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction

The Pfizer–BioNTech COVID-19 vaccine BNT162b2 (tozinameran) and Oxford–AstraZeneca COVID-19 vaccine ChAdOx1 nCoV-19 were approved on Dec 2 and Dec 30, 2020, respectively, in the UK, making the UK the first country to start nationwide COVID-19 vaccination.^{1,2} Vaccines were prioritised for those most at risk of developing severe COVID-19. People residing in care homes and their carers were vaccinated first. Vaccination then proceeded in descending 5-year age groups, also accounting for pre-existing clinical conditions. Initially, the two scheduled doses of each vaccine were

administered 3–4 weeks apart, similar to the schedule used in clinical trials. However, the Joint Committee on Vaccination and Immunisation (JCVI) later recommended delaying the second dose from 3 to 12 weeks after the first dose,³ on the basis of evidence that one vaccine dose provided 70–90% protection against symptomatic disease⁴ and that a higher antibody peak was observed in individuals who received a delayed second dose compared with those who received their second dose at 3 weeks.⁵ The delayed-second-dose strategy allowed the delivery of more first vaccine doses to be prioritised and, thus, high short-term partial

Lancet Public Health 2023; 8: e174–83

Published Online
February 9, 2023
[https://doi.org/10.1016/S2468-2667\(22\)00337-1](https://doi.org/10.1016/S2468-2667(22)00337-1)

*Contributed equally

Medical Research Council
Centre for Global Infectious
Disease Analysis, Jameel
Institute, School of Public
Health, Imperial College
London, London, UK
(N Imai PhD, T Rawson DPhil,
E S Knock PhD, R Sonabend PhD,
Y Elmaci MSc,
P N Perez-Guzman MD,
L K Whittles PhD,
D T Kanapram PhD,
K A M Gaythorpe PhD,
W Hinsley PhD,
B A Djaafara MRes, H Wang MSc,
K Fraser PhD, R G FitzJohn PhD,
A B Hogan PhD, P Doohan PhD,
Prof A C Ghani PhD,
Prof N M Ferguson DPhil,
M Baguelin PhD, A Cori PhD);
National Institute for Health
Research Health Protection
Research Unit in Modelling
Methodology, Imperial College
London, UK Health Security
Agency, London School of
Hygiene & Tropical Medicine,
London, UK (E S Knock,
Prof N M Ferguson, M Baguelin,
A Cori); Department of
Computer Science, Technische
Universität Kaiserslautern,
Kaiserslautern, Germany
(R Sonabend); Engineering
Department, University of
Cambridge, Cambridge, UK
(R Sonabend); School of
Population Health, University
of New South Wales, Sydney,
NSW, Australia (A B Hogan);
Department of Infectious
Disease Epidemiology, Faculty
of Epidemiology and
Population Health, London
School of Hygiene & Tropical
Medicine, London, UK
(M Baguelin)

Correspondence to:
Dr Anne Cori, Medical Research
Council Centre for Global
Infectious Disease Analysis,
Jameel Institute, School of Public
Health, Imperial College London,
London W2 1PG, UK
a.corii@imperial.ac.uk

Research in context

Evidence before this study

We searched MEDLINE via PubMed from database inception to June 10, 2022, for relevant literature on the effect of COVID-19 vaccine dosing intervals, with no language restrictions, using the following search terms: (COVID-19) AND (vaccin*) AND (dose OR dosing) AND (delay OR interval) AND (quant* OR assess* OR impact). Of 382 studies identified, 12 were prospective assessments of optimal vaccination strategies, exploring trade-offs between vaccine mode of action, vaccine effectiveness, coverage, and availability. Only two studies retrospectively assessed the effects of different vaccination intervals. One assessed the optimal timing during the epidemic to switch to an extended dosing interval, and the other assessed all-cause mortality and hospitalisation risk between two dosing groups.

Added value of this study

We use a data synthesis approach combining real-world evidence from multiple data sources to retrospectively quantify the short-to-medium-term effect of extending the COVID-19 vaccine dosing interval from the manufacturer-recommended 3 weeks to 12 weeks in England. This decision to change the

interval was controversial at the time. Retrospective evaluations of key interventions are essential to assess and improve current and future strategic decisions around COVID-19 vaccination, particularly in light of upcoming booster programmes and the potential for new variants to emerge, and to ensure lessons learned are quantified and documented.

Implications of all the available evidence

Our study shows that rapidly providing partial (single-dose) vaccine-induced protection to a larger proportion of the population was successful in reducing hospitalisations and deaths due to COVID-19 in the first 9 months of the vaccination programme in England. This result was enabled by adaptation of guidelines in light of emerging evidence. Overall, published studies show that optimal vaccination strategies are highly dependent on vaccine availability, coverage, and effectiveness, as well as risk factors for infection and severity. However, they highlight the important role mathematical modelling can play in prospectively or retrospectively assessing different control options in a given context, particularly where detailed data are available.

protection for as many people as possible, which was important in the context of the SARS-CoV-2 alpha (B.1.1.7) variant of concern emerging at the time.

This strategy received criticism, citing the lower protection offered to people at highest risk from the disease by delaying the second dose, the limited evidence to support this change from trial protocols, and concerns of partial vaccination accelerating the emergence of vaccine-evading variants of concern.^{6,7} However, prompted by vaccine shortages and the emergence of the alpha variant, several countries, including Canada,⁸ Denmark,⁹ Norway,¹⁰ India,¹¹ and South Africa,¹² also extended the time between doses. Previous studies have explored the potential impact and optimisation of mass vaccination schedules under different assumptions regarding vaccine effectiveness, vaccine mode of action, waning immunity, and use of non-pharmaceutical interventions.^{13,14} These studies showed that more hospitalisations and deaths could be prevented under a delayed-second-dose strategy, but results were sensitive to vaccine effectiveness assumptions and vaccine mechanisms, underscoring the importance of continued non-pharmaceutical interventions.^{15–17} Quantifying the effect of interventions is crucial to evaluating the success of an epidemic response, allowing decision makers to improve and inform ongoing and future interventions.

The aims of the current study were to retrospectively assess the effect of delaying the second vaccine dose in England and to examine what the epidemic trajectory in terms of COVID-19 hospitalisations, deaths, and

SARS-CoV-2 infections would have looked like if a 3-week interval had been maintained.

Methods

Study population and data sources

We used data on daily COVID-19 hospital admissions, bed occupancy, deaths, and positive and negative PCR test results for individuals aged 25 years or older in each of the seven National Health Service (NHS) regions in England. All data were collected by the UK Government's Department of Health and Social Care as part of surveillance activities and were shared with us or are publicly available. Population-level data on the prevalence of positive PCR tests from the Real-time Assessment of Community Transmission (REACT) study,¹⁸ prevalence of SARS-CoV-2 antibody positivity based on serological data, the daily number of SARS-CoV-2 variant tests identified as delta (B.1.617.2) or non-delta in the variant and mutation dataset from the UK Health Security Agency, and the daily number of first and second vaccine doses received by age and vaccine type, as reported by the NHS, were also aggregated at the NHS regional level. All data were fully anonymised, and some were further aggregated for statistical disclosure purposes (appendix 1 p 5).

Ethics permission was sought for the study through the standard ethical review processes of Imperial College London (London, UK), and was approved by the university's research governance and integrity team (Imperial College Research Ethics Committee reference 21IC6945). Patient consent was not required as the

See Online for appendix 1

research team accessed fully anonymised data only, which were collected as part of routine public health surveillance activities by the UK Government.

Epidemiological model and fitting

We used a previously described susceptible–exposed–infectious–removed stochastic transmission model¹⁹ which reliably captures the age-specific scale and timing of the SARS-CoV-2 pandemic in England in 2021²⁰ to examine the effect of vaccination between Dec 8, 2020, when vaccination started, and Sept 13, 2021, just before the introduction of booster doses in England, which are not considered in this study (figure 1). This period was marked by the transition (in May–June, 2021) from alpha to delta as the dominant SARS-CoV-2 variant in the UK population.

We modelled the population by English NHS region and by 5-year age bands (from 0–4 years to 75–79 years), with a single category for people aged 80 years and older, a category for care-home workers, and a category for care-home residents.¹⁹ We represented individuals according to their infection status, modelling infected individuals in the community and in hospitals, with detailed clinical pathways, vaccination status, and SARS-CoV-2 variants (figure 1; appendix 1 p 4). We fit a two-variant model to multiple data sources for each NHS region (appendix 1 pp 47–48), explicitly capturing the emergence of the delta variant (appendix 1 p 48). The delta variant is seeded at a region-specific date determined by the model fit. We used Bayesian evidence synthesis inference, allowing all data sources to jointly inform the model in a single robust statistical framework²¹ and examined daily and cumulative infections, hospital admissions, and deaths. Further methodological detail is available in appendix 1 (pp 3–39).

We modelled vaccine roll-out, including dosing interval, as reported by the NHS. Thus, the actual average dosing interval might differ slightly from reported guidelines. We refer to this as the 12-week strategy.

Vaccine effectiveness against infection, symptomatic disease, hospitalisation, death, and onward transmission for each variant was informed by UK-based effectiveness studies.^{22–25} We assumed the first dose to be effective 21 days after administration, with no protection beforehand, and the second dose to reach full effectiveness 7 days after administration, with a stepwise change in the individual vaccine protection at these changepoints (appendix 1 p 8). Our baseline analysis assumes the same vaccine effectiveness under the 12-week and 3-week strategies and no waning after the first dose, regardless of dosing interval.

However, we allowed for waning of infection-induced protection and vaccine-induced protection (after the second dose only), imperfect cross-protection between variants, and a fitted increased severity of the delta variant relative to the alpha variant.²⁶ We assumed that infection-induced immunity against the same

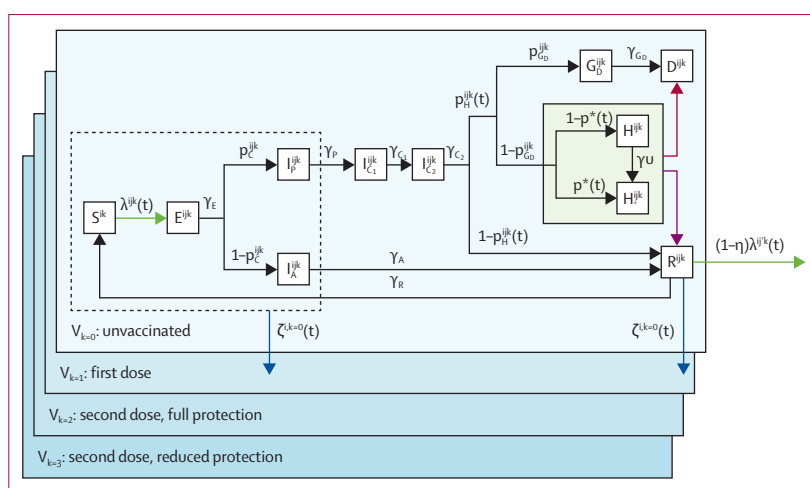


Figure 1: Flow diagram showing an overview of the extended susceptible–exposed–infectious–removed transmission model

Blue arrows represent relevant flows in vaccination strata, dark red and purple in hospital pathways, and green in SARS-CoV-2 variant compartments. See appendix 1 for the full diagram with flows describing SARS-CoV-2 variants, vaccination status, and hospital pathways (p 4), and definitions of all variables and parameters (pp 17, 35). S=susceptible. E=exposed. I_A =infected, asymptomatic. I_C =presymptomatic infectious. I_C =symptomatic, infectious. I_C =symptomatic, not infectious. H=hospitalised. G =severe disease, leading to death (at home). D=deceased (as a result of COVID-19). R=recovered. i =age or care-home group (5-year age bands from 0–4 years to 75–79 years; ≥ 80 years age group; care-home worker; and care-home resident). k =SARS-CoV-2 variant (alpha, delta, or alpha:delta [ie, infected with delta after a previous infection with alpha]). k =vaccination stratum (0, 1, 2, 3). V_k =in vaccination stratum k . $\lambda(t)$ =force of infection at time t . γ =rate of disease progression. p_c =probability of being symptomatic, given infected. p_h =probability of severe disease requiring hospitalisation, given symptomatic disease. p_{ω} =probability of death for severe symptomatic cases outside of hospital. p^* =probability of COVID-19 diagnosis confirmed before admission to hospital. η =probability of being protected against infection with the SARS-CoV-2 delta variant for those recovered from infection with the SARS-CoV-2 alpha variant. $\zeta(t)$ =rate of movement between vaccination strata.

SARS-CoV-2 variant wanes following an exponentially distributed duration with a mean of 6 years.²⁷ To model waning of vaccine-induced protection, we assumed individuals who had received two vaccine doses moved to a reduced-protection (ie, waned) compartment after, on average, 24 weeks. We fitted vaccine effectiveness in the second-dose and reduced-protection compartments, for all vaccines and disease outcomes, to the time-varying vaccine effectiveness previously estimated by Andrews and colleagues^{22,24} (figure 2; appendix 1 pp 11–13).

Assessing the potential effect of alternative vaccination schedules

We explored a counterfactual scenario with a 3-week interval between doses (referred to as the 3-week strategy) to assess the effect of increasing the vaccine dosing interval to 12 weeks (12-week strategy) on the epidemic trajectory. To account for the limited vaccine supply, we assumed that the total (first and second dose) daily number of vaccines administered matched that reported by the NHS. Doses were then distributed between first and second doses according to the dosing interval in the respective scenario (figure 3A). We compared the reported numbers and age distribution of hospital admissions between the fitted 12-week strategy and the counterfactual 3-week strategy.

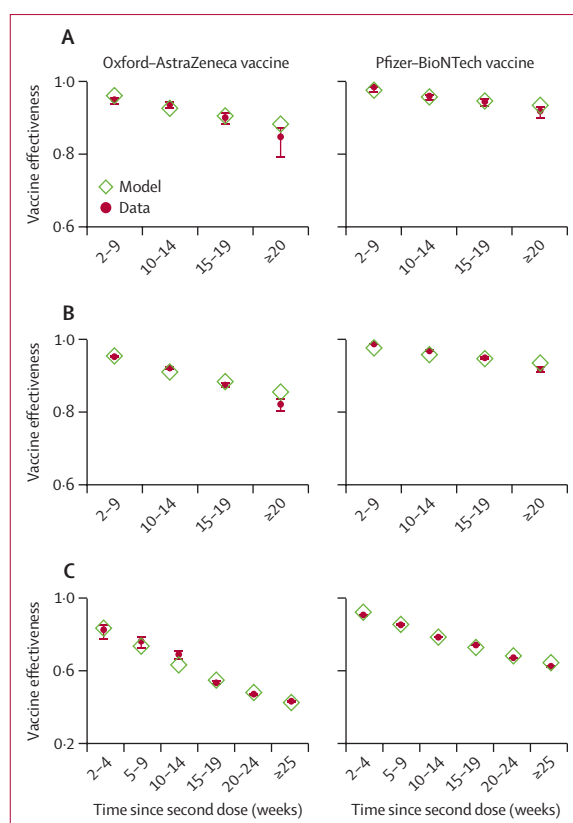


Figure 2: Vaccine effectiveness against the SARS-CoV-2 delta variant over time following the second dose of COVID-19 vaccine

Vaccine effectiveness is shown separately for the Oxford–AstraZeneca vaccine (ChAdOx1 nCoV-19; left column) and the Pfizer–BioNTech vaccine (BNT162b2, tozinameran; right column), and for three outcomes: death (A), severe disease (B), and mild disease or infection (C). We assumed the same protection against infection and mild disease. The graphs show data and uncertainty ranges representing vaccine effectiveness estimates from Andrews and colleagues' study,²⁴ and points corresponding to our model assumptions. We assumed that the Moderna vaccine has the same vaccine effectiveness as BNT162b2. Note: the x-axis differs in the bottom row. Corresponding data for the SARS-CoV-2 alpha variant are provided in appendix 1 (p 11).

We estimated the time-varying transmission rate (β) by fitting the model to data up to Sept 13, 2021, capturing the effect of changing restrictions and behaviours (appendix 1 pp 36–37, 49; appendix 2), and used these estimated β values to simulate the 3-week strategy.

Sensitivity analyses

We ran sensitivity analyses to assess the effect of assumptions on vaccine effectiveness and waning of vaccine-induced protection on our results (appendix 1 p 40). First, we accounted for uncertainty in vaccine effectiveness when a 3-week interval is used. Our baseline counterfactual assumes identical vaccine effectiveness between the 3-week and 12-week interval scenarios; however, second-dose vaccine effectiveness could be lower after a shorter dosing interval.²⁹ We explored two scenarios in which vaccine effectiveness is higher and lower than our baseline assumption when a

3-week interval is assumed. Second, to account for general uncertainty in vaccine effectiveness against the delta variant, we ran analyses for a range of vaccine effectiveness values. Third, we considered uncertainty in the waning of vaccine-induced immunity by running analyses with varying vaccine effectiveness in the reduced-protection compartment after the second dose. Fourth, we accounted for uncertainty in the timing of vaccine-induced waning immunity by testing a longer mean waning time, considering that the shorter (3-week) dosing interval might affect the mean duration of waning after the second dose. Fifth, we considered uncertainty in the waning of immunity following the first dose. As waning of vaccine effectiveness after the first dose is not explicitly modelled, the first-dose vaccine effectiveness values used represent the mean vaccine effectiveness afforded across the 12 weeks between doses. A shorter dosing interval could plausibly increase the mean vaccine effectiveness after the first dose because of reduced waning after the first dose. Thus, we considered a scenario in which first-dose vaccine effectiveness was increased in the 3-week interval counterfactual. Finally, we assessed the potential effect of immediate vaccine-induced protection after the first dose as an extreme assumption on time to effectiveness.

In two simple exploratory analyses, we considered longer-term SARS-CoV-2 dynamics beyond the end of the study period based on extreme scenarios (appendix 1 pp 65–67).

Analyses were conducted in R version 4.1.0 (see appendix 1 p 46 for full details of package versions).

Role of the funding source

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

Results

From Dec 8, 2020, to Sept 13, 2021, use of the 12-week interval between first and second doses adopted in the UK led to a greater number of individuals receiving their first vaccine doses than would have been possible using the 3-week interval. As of Sept 13, 2021, 40 410 555 first doses were administered with use of the 12-week interval, compared with 38 962 837 first doses administered in the counterfactual 3-week scenario. With a 3-week interval between doses, fewer individuals would receive their first vaccine dose, but the roll-out of second doses would start sooner for individuals identified as being at highest risk of severe disease (ie, the oldest individuals and those living in care homes; figure 3A).

Our model effectively captures national COVID-19 daily hospital admissions by age in our study period (figure 3B; appendix 1 p 47).¹⁹ The 3-week strategy led to a higher peak number of daily hospital admissions during the delta variant wave, with 2030 hospitalisations (95% credible interval 1690–2360) on July 22, 2021, in our baseline

See Online for appendix 2

scenario (compared with the observed 827 hospitalisations in the 12-week scenario; figure 3B). Under the 3-week strategy, we estimated 291 000 (275 000–319 000) cumulative hospitalisations and 64 800 (60 200–68 900) deaths between Dec 8, 2020, and Sept 13, 2021, compared with 233 000 (229 000–238 000) hospitalisations (figure 3C) and 54 700 (52 800–55 600) deaths under the 12-week strategy over the same period. Additionally, more infections occurred under the 3-week (16 400 000 [15 200 000–19 200 000]) than the 12-week strategy (12 700 000 [11 100 000–16 000 000]; appendix 1 p 70).

Cumulative COVID-19 hospitalisations were greater under the 3-week than the 12-week strategy up to Sept 13, 2021 (figure 3C), with a more apparent difference between strategies from late May, 2021, following the emergence of the delta variant. This difference stabilised in September as, under the 3-week strategy, the epidemic peaked and then declined much faster than in the observed 12-week strategy because of rapid depletion of the number of susceptible individuals.

The greater number of hospitalisations estimated under the counterfactual 3-week strategy was driven by fewer individuals overall benefiting from full or partial vaccine-induced protection. For example, by early April 2021, 7·7 million fewer individuals had any level (one or two doses) of vaccine-induced protection under the 3-week than the 12-week strategy. This pattern persisted in April and May, 2021 (figure 4A), and the gap subsequently narrowed from June, 2021, onwards.

The number of individuals with reduced protection after the second dose was higher throughout the study period under the 3-week than the 12-week strategy: vaccine protection under the 3-week strategy had already started to wane in some individuals by March, 2021 (appendix 1 p 55). This number increased over time, with 10 million people under the 3-week and 7 million under the 12-week strategy having reached at least 24 weeks post second dose by the beginning of July, 2021 (appendix 1 p 56). This consistently higher level of reduced protection in the 3-week strategy was due to the prioritisation of fully vaccinating (with second doses) each eligible age group before the next group became eligible (appendix 1 p 14). Throughout the study period, we found a lower proportion of individuals at risk of infection at each timepoint (figure 4B) and from June, 2021 onwards a lower risk, through vaccination, of hospitalisation if infected (figure 4C) in the 12-week than the 3-week vaccination strategy. In the 3-week strategy, although the oldest age groups (at highest risk of severe disease) received greater protection earlier, the population-level risk of severity was still higher than in the 12-week strategy (figure 4C).

We estimated the age distribution of hospitalisations to remain broadly similar under both vaccination strategies (appendix 1 p 56), with most hospitalisations in the older age groups (figure 5).

During the study period, the 12-week strategy led to more individuals being partially protected for longer

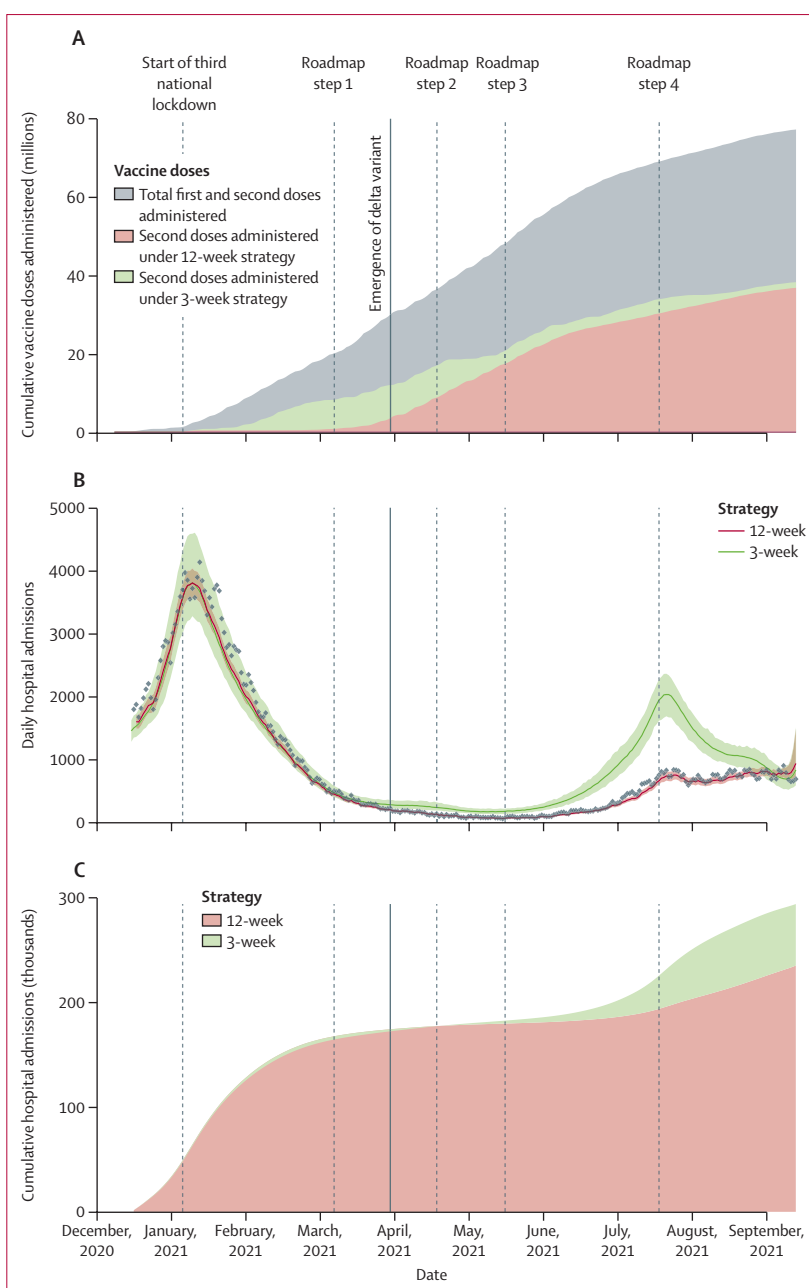


Figure 3: COVID-19 vaccine doses administered and epidemic trajectory in England

Results are shown for central vaccine effectiveness and waning assumptions (see appendix 1 pp 57–64 for sensitivity analyses results). The vertical dashed lines indicate each step of the UK Government's roadmap out of lockdown,²⁸ in which non-pharmaceutical interventions were lifted in a stepwise manner: step 1, schools reopened, outdoor gatherings of no more than six people allowed; step 2, non-essential retail opened; step 3, outdoor gatherings up to 30 people allowed, indoor gatherings up to 6 people allowed; step 4, no limits on social contact. The vertical solid line shows the time when the delta variant emerged. (A) Cumulative vaccine doses administered between Dec 8, 2020, and Sept 13, 2021. (B) Daily hospital admissions. Points show the data, lines represent the median model fit under the 12-week strategy and median of the simulated daily hospital admissions under the counterfactual scenario assuming a 3-week delay between vaccine doses. Shaded areas are 95% credible intervals. Uncertainty is greater for the 3-week scenario, which was explored through unconstrained simulations, than for the 12-week fit, which was obtained by particle filtering and is thus more constrained by the data (see appendix 1 pp 4–5 for methods). (C) Cumulative hospital admissions over time under the 12-week and 3-week strategies.

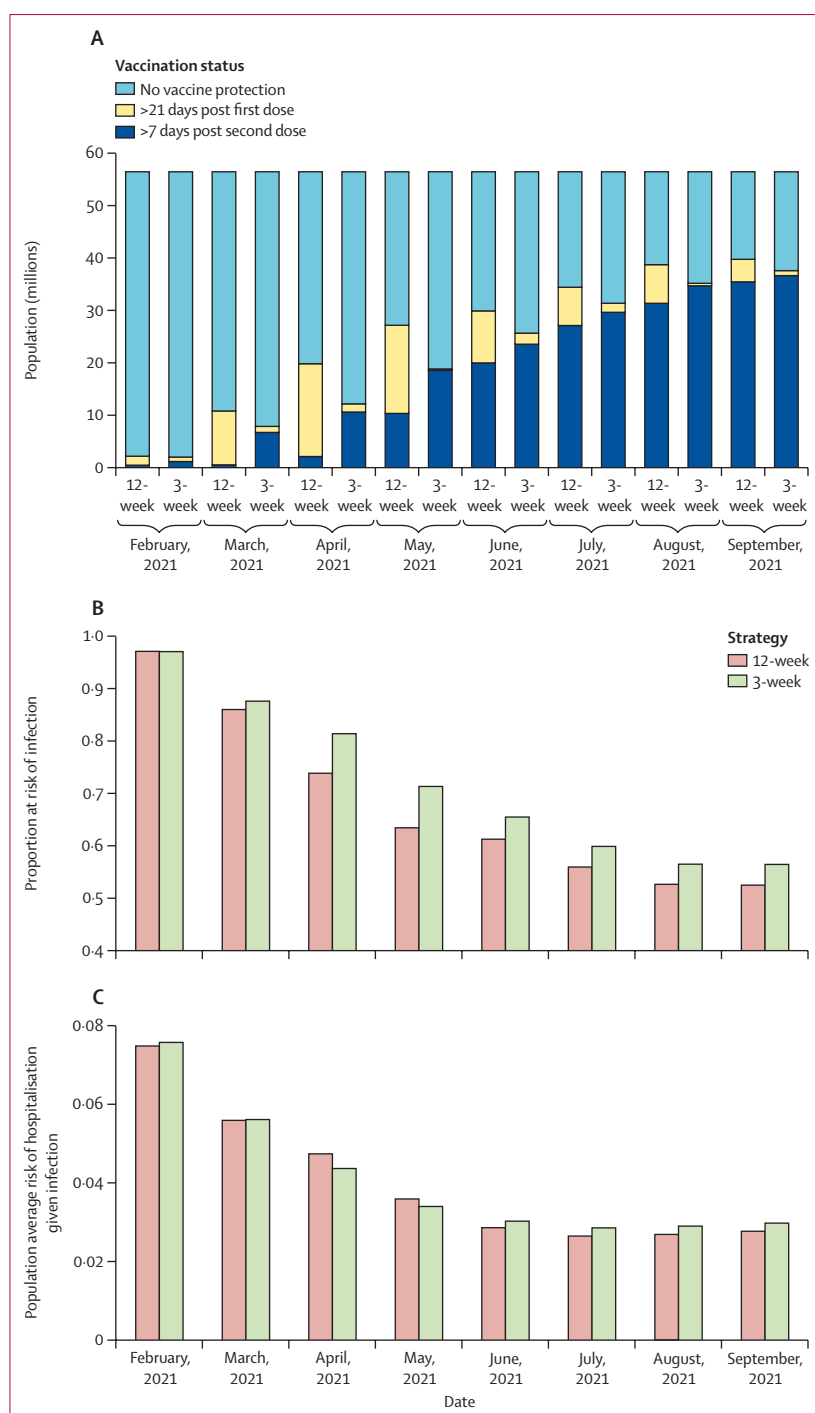


Figure 4: Vaccine-induced protection against COVID-19

(A) Vaccination status within the population for each month for the 12-week strategy (model fit) and 3-week strategy (counterfactual). (B) Proportion of the population without vaccine protection against infection with SARS-CoV-2 alpha or delta variants. Value as presented is the mean protection across all vaccine strata, all age groups, and all regions, weighted by population. (C) Mean (as above) population risk of hospitalisation given infection. These estimates account for vaccine-induced protection but not for naturally acquired protection from previous infections.

before their second dose was effective, reflected in a small proportion of older individuals in this category (>21 days post first dose; figure 5) being hospitalised during that period. Conversely, under the 3-week strategy, there were almost no hospitalisations among individuals with partial protection from a single vaccine dose. However, this short-term benefit of the 3-week strategy was rapidly lost, with many more hospitalisations occurring in the summer of 2021 under the 3-week than the 12-week strategy (figure 5).

These trends were observed regardless of age group. Across both strategies, the individuals at highest risk of severe disease (those aged ≥ 80 years) were vaccinated first. The 3-week strategy, however, gave higher protection most quickly for those at highest risk. Thus, by the peak of the delta variant wave, vaccine-induced protection in these individuals who received their last vaccine dose at least 6 months ago would have decreased, making them susceptible again to severe outcomes (appendix 1 p 56). For example, by Sept 13, 2021, we estimated that 2.8 million individuals aged 75 years and older had received their vaccine more than 24 weeks ago under the 12-week strategy, compared with 3.3 million under the 3-week strategy. Prioritising fully vaccinating the population at highest risk as quickly as possible under the 3-week strategy would have reduced the short-term morbidity and mortality in the older age groups but increased the total long-term burden because of waning vaccine-induced protection and higher levels of virus circulating in younger age groups who drive transmission.

Across all sensitivity analyses, including a scenario assuming no waning of vaccine-induced protection, we found that the 3-week strategy led to a greater number of hospitalisations and deaths than the 12-week strategy within the study period (appendix 1 pp 57–64, 68–69). In addition, in two exploratory analyses that looked beyond the end of the study period, we showed that the benefits of the 12-week strategy persisted beyond Sept 13, 2021, at least up to the start of February, 2022 (appendix 1 pp 65–67).

Discussion

Our study explored the effect of the strategy of delaying the interval between COVID-19 vaccine doses to 12 weeks in England between Dec 8, 2020, and Sept 13, 2021, comparing the observed number of hospitalisations and deaths to a counterfactual scenario in which the vaccine dose interval remained 3 weeks, as in clinical trials. We estimated in our baseline scenario that delaying the interval between the first and second COVID-19 doses from 3 to 12 weeks averted a median 58 000 hospitalisations in England by Sept 13, 2021, and averted between 39 000 and 211 000 total hospitalisations across all sensitivity analyses.

The 12-week strategy led to more partially protected individuals which temporarily led to more hospitalisations

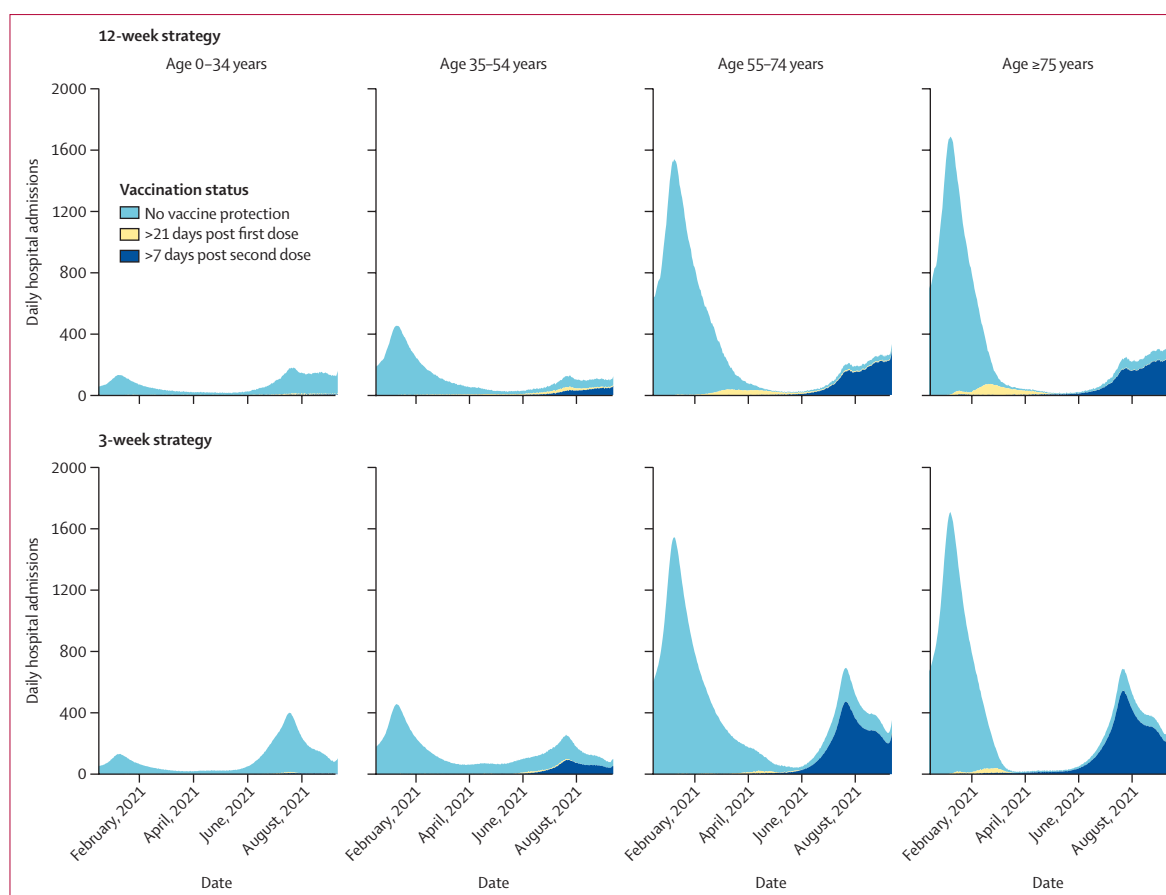


Figure 5: Modelled daily COVID-19 hospital admissions over time by age group for the 12-week and 3-week strategies
Colours show the status of vaccine-induced protection of hospitalised individuals.

and deaths in older individuals in spring 2021 (figure 5; appendix 1 p 70). However, the strategy provided partial (single-dose) protection to more age groups, including younger groups that might sustain transmission,³⁰ which indirectly protected those at high risk. Conversely, prioritising fully vaccinating the people at highest risk with two doses under the 3-week strategy led to a large proportion of the population at highest risk having a lower level of vaccine-induced immunity during the delta variant wave in summer 2021 due to waning immunity, which resulted in higher peak hospitalisations. The magnitude of the effect of the 12-week strategy might also be sensitive to the timing of the delta variant wave. Had the delta variant emerged 3 months later, the 12-week strategy would probably have still been more beneficial than the 3-week strategy, but to a smaller relative extent within the short-to-medium-term COVID-19 epidemic dynamics considered here.

Retrospective assessments of the effects of different vaccination strategies in other countries are not yet available. However, our findings are consistent with previous prospective simulation studies which also found that prioritising partial protection of a larger proportion of the population by increasing the dosing

interval could reduce hospitalisations and deaths.^{13–17} Barmounakis and colleagues³¹ found that the optimal strategy was to prioritise fully vaccinating the oldest individuals before switching to a delayed-second-dose strategy for those younger than 75 years. This is not far from the strategy that England pursued, with around 25% of people aged 80 years or older being vaccinated with a first dose before the JCVI changed their guidance. This combined strategy essentially targets a combination of susceptibility to severe disease in the highest risk groups and infectivity in the younger age groups.

Mathematical models are valuable tools to quantitatively evaluate vaccination programmes, improve their design, and monitor new vaccine initiatives.^{19,32} By using a Bayesian evidence-synthesis approach, we integrated multiple data sources to capture the epidemic in England accurately. By explicitly accounting for the introduction of variants of concern, vaccine endpoints, and the waning of immunity, we robustly explored the effects of alternative vaccination strategies and a wide range of sensitivity analyses.

Our study has limitations. First, there is substantial uncertainty in vaccine effectiveness by dosing interval.

UK studies are limited because of the early switch in strategy.²⁹ Studies in countries where a 3-week interval was maintained suggest that vaccine effectiveness is slightly lower compared with a 12-week interval,^{33–36} a hypothesis that we explored in a sensitivity analysis with findings similar to those of our main analysis. Second, we assumed a simple model of waning immunity with only two stages. However, sensitivity analyses varying assumptions about waning vaccine-induced protection produced results consistent with our main analysis. Third, we did not directly account for waning of vaccine-induced immunity after the first dose. Studies have estimated that protection starts to wane from 4–5 weeks after the first dose in some age groups, but with large uncertainty.^{22,37,38} According to our sensitivity analyses, such waning after the first dose did not alter our results. Fourth, although we capture temporal changes in population contact rates, we assumed that, under the 3-week strategy, mixing patterns (ie, β transmissibility values) remained identical to those estimated under the 12-week strategy.³⁹ It is possible that, under a 3-week strategy, the final step of the roadmap (in which non-pharmaceutical interventions in the UK were lifted in a controlled stepwise manner) would have been delayed further as the projected hospitalisations would have been much higher (figure 3B); behaviours might also have been different under that strategy. Therefore, our counterfactual analysis can only represent a scenario assuming only the vaccination interval changed. Fifth, we assumed the same vaccination rate for all analyses as reported in the NHS data. With more doses administered per day, the 12-week delay might not have been optimal.¹⁷ Sixth, we did not consider the potentially reduced risk of emergence of a variant of concern in the 3-week compared with the 12-week strategy. However, with SARS-CoV-2 circulating globally, and most variants of concern rapidly spreading worldwide, a change in the risk of emergence in England alone is unlikely to have affected the broader patterns of emergence and therefore the circulation of variants.

Finally, although we have quantified the relative success of the 12-week versus the 3-week strategy in terms of COVID-19 hospitalisations and deaths, and SARS-CoV-2 infections in the first 9 months of the vaccination programme, we have only considered longer-term SARS-CoV-2 dynamics in two simple exploratory analyses (appendix 1 pp 65–67), which did not account for either booster and further vaccine doses or novel variants. Our work, therefore, does not fully explore the potential effect of the delayed-second-dose strategy on future epidemic waves. We also did not consider the long-term burden of disease, such as post-COVID-19 condition (also known as long COVID), although this is likely to be proportional to the infection burden. Furthermore, we did not account for geographical or socioeconomic factors that can affect SARS-CoV-2 transmission rates and outcomes, and did not conduct

analyses by sex or ethnicity, which would require granular individual-level data not considered in this study. Therefore, our results should be interpreted as the population-level average effects at the NHS regional level, and not at higher resolution.

Our study shows that early and continuous assessment of real-world vaccine effectiveness is crucial, especially in emergency situations. There can be benefit in carefully considering and adapting guidelines in light of new emerging evidence and the population in question. Our results could also help to quantitatively inform lessons-learned exercises, such as the UK Government's ongoing COVID-19 inquiry.

Our findings might also be useful for other countries considering different vaccination intervals for future booster campaigns or in preparation for future waves of COVID-19. However, it is difficult to extrapolate findings from England to other settings because of differences in demography, behaviours, implementation of non-pharmaceutical interventions, availability of vaccines, and variants of concern in circulation. Additional retrospective studies from multiple countries with differing non-pharmaceutical interventions and variants will help to build a body of evidence regarding optimal vaccination strategies. However, across all sensitivity analyses explored, we estimated that, in England, the switch to a delayed vaccine interval was beneficial in the short to medium term. Importantly, this beneficial effect is observed across all age groups, including those at highest risk, who had higher indirect protection under the 12-week strategy.

It was fortunate that both vaccines licensed in England were highly effective, combined with a high uptake of both doses despite the longer dosing interval. In other settings where vaccine supply is limited, or where vaccines with lower effectiveness are widely used, a switch to a 12-week strategy might not be advantageous. Therefore, it is crucial to consider the likely acceptance of new vaccines or doses and the potential barriers to uptake, especially during periods of sustained high transmission when vaccine-evading variants might emerge. Models have shown that long-term COVID-19 dynamics are strongly shaped by vaccination policies with wide-ranging epidemiological and evolutionary outcomes.⁴⁰ Therefore, as further vaccine doses are rolled out, it will be important to continue evaluating vaccine effectiveness against any new variants and waning vaccine-induced protection.

Beyond the immediate priority of COVID-19, understanding the effect that changing COVID-19 vaccination guidance has had or might have on hesitancy towards other vaccines or on overall trust in public health guidance is crucial.

Contributors

NI, TR, NMF, ACG, MB, and AC conceived the study. NI and TR analysed the data, created the figures, and wrote the original draft of the manuscript. TR, LKW, RS, RGF, ESK, YE, DTK, PNP-G, MB, and AC

developed the code base. All authors contributed to interpretation, investigation, and reviewing and editing of the manuscript. WH, KAMG, NI, HW, BAD, KF, ESK, and PNP-G accessed and verified the underlying data used in the study.

Declaration of interests

AC has received payment from Pfizer for teaching of mathematical modelling of infectious diseases. KAMG has received honoraria from Wellcome Genome Campus for lectures. LKW has received consultancy payments from the Wellcome Trust. ABH has received consultancy payments from WHO for COVID-19-related work; provides advice on COVID-19 modelling to the New South Wales Ministry of Health, Australia; and was previously engaged by Pfizer to advise on modelling of RSV vaccination strategies, for which she received no financial compensation. RS and NI are currently employed by the Wellcome Trust. All other authors declare no competing interests.

Data sharing

All code, scripts, and data used to produce the results in this Article are available online at GitHub.

Acknowledgments

This work was supported jointly by the Wellcome Trust and the Foreign, Commonwealth and Development Office (formerly Department for International Development; 221350). We acknowledge joint centre funding from the UK Medical Research Council (MRC) and the Foreign, Commonwealth and Development Office (MR/R015600/1). This work was also supported by the National Institute for Health Research (NIHR) Health Protection Research Unit in Modelling Methodology, a partnership between the UK Health Security Agency (UKHSA; formerly Public Health England), Imperial College London, and the London School of Hygiene & Tropical Medicine (NIHR200908); Community Jameel; and the EDCTP2 programme, supported by the EU. LKW acknowledges support from a Wellcome Trust fellowship (grant number 218669/Z/19/Z). ABH acknowledges support from an Australian National Health and Medical Research Council investigator grant. We thank all colleagues at the UKHSA and front-line health professionals who have driven and continue to drive the daily response to the COVID-19 epidemic in England and provided the necessary data to inform this study. The use of pillar-2 PCR testing data, vaccination data, and the variant and mutation data was made possible thanks to UKHSA colleagues, and we thank Nick Gent and André Charlett for facilitation and insights into these data. The use of serological data was made possible by colleagues at UKHSA Porton Down, Colindale, and the NHS Blood Transfusion Service; we are particularly grateful to Gayatri Amirthalingam and Nick Andrews for helpful discussions around these data. We thank all the Real-time Assessment of Community Transmission (REACT) Study investigators for sharing PCR prevalence data. We also thank the entire Imperial College London COVID-19 response team for support and feedback throughout. The views expressed are those of the authors and not necessarily those of the UK Department of Health and Social Care, the NHS, the NIHR, UKHSA, UK MRC, UK Research and Innovation, or the EU.

References

- Medicines and Healthcare products Regulatory Agency. Regulatory approval of Pfizer/BioNTech vaccine for COVID-19. Dec 2, 2020. <https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19> (accessed March 23, 2021).
- Medicines and Healthcare products Regulatory Agency. Regulatory approval of COVID-19 vaccine AstraZeneca. Dec 30, 2020. <https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca> (accessed March 23, 2021).
- Department of Health & Social Care. Optimising the COVID-19 vaccination programme for maximum short-term impact. Jan 26, 2021. <https://www.gov.uk/government/publications/prioritising-the-first-covid-19-vaccine-dose-jcvi-statement/optimising-the-covid-19-vaccination-programme-for-maximum-short-term-impact> (accessed March 23, 2021).
- Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on COVID-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ* 2021; 373: n1088.
- Tauzin A, Gong SY, Beaudoin-Bussi res G, et al. Strong humoral immune responses against SARS-CoV-2 spike after BNT162b2 mRNA vaccination with a 16-week interval between doses. *Cell Host Microbe* 2022; 30: 97–109.e5.
- Robertson JFR, Sewell HF, Stewart M. Delayed second dose of the BNT162b2 vaccine: innovation or misguided conjecture? *Lancet* 2021; 397: 879–80.
- Humphreys IR, Godkin AJ. The potential risks of delaying the second vaccine dose during the SARS-CoV-2 pandemic. *QJM* 2021; 114: 163–65.
- Government of Canada. Archived 5: NACI rapid response: extended dose intervals for COVID-19 vaccines to optimize early vaccine rollout and population protection in Canada. March 3, 2021. <https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/rapid-response-extended-dose-intervals-covid-19-vaccines-early-rollout-population-protection.html> (accessed June 1, 2021).
- Danish Health Authority. How you will get vaccinated. <https://www.sst.dk/en/English/Corona-eng/Vaccination-against-COVID-19/How-you-will-get-vaccinated> (accessed June 1, 2021).
- Norwegian Institute of Public Health. Vaccination scenarios: 12.03.2021—conservative and optimistic. March 12, 2021. https://www.fhi.no/contentassets/71e97765e43c41ee8f059efbd4016ca8/vedlegg/2021.03.12_vaksinasjonskalender_fhi_nettside_en.pdf (accessed Feb 4, 2022).
- Ministry of Health and Family Welfare Government of India. FAQs on COVID-19 vaccines and vaccination program. https://www.mohfw.gov.in/covid_vaccination/vaccination/faqs.html#how-will-we-be-vaccinated (accessed Feb 4, 2022).
- National Institute for Communicable Diseases. What you need to know about the COVID-19 vaccine. <https://www.nicd.ac.za/what-you-need-to-know-about-the-covid-19-vaccine/> (accessed Feb 4, 2022).
- Moghadas SM, Vilches TN, Zhang K, et al. Evaluation of COVID-19 vaccination strategies with a delayed second dose. *PLoS Biol* 2021; 19: e3001211.
- Hill EM, Keeling MJ. Comparison between one and two dose SARS-CoV-2 vaccine prioritization for a fixed number of vaccine doses. *J R Soc Interface* 2021; 18: 20210214.
- Kim D, Lee YJ. Vaccination strategies and transmission of COVID-19: evidence across advanced countries. *J Health Econ* 2022; 82: 102589.
- Silva PJS, Sagastiz bal C, Nonato LG, Struchiner CJ, Pereira T. Optimized delay of the second COVID-19 vaccine dose reduces ICU admissions. *Proc Natl Acad Sci USA* 2021; 118: e2104640118.
- Romero-Brufau S, Chopra A, Ryu AJ, et al. Public health impact of delaying second dose of BNT162b2 or mRNA-1273 covid-19 vaccine: simulation agent based modeling study. *BMJ* 2021; 373: n1087.
- Imperial College London. The REACT-1 programme. <https://www.imperial.ac.uk/medicine/research-and-impact/groups/react-study/studies/the-react-1-programme/> (accessed Nov 20, 2022).
- Sonabend R, Whittles LK, Imai N, et al. Non-pharmaceutical interventions, vaccination, and the SARS-CoV-2 delta variant in England: a mathematical modelling study. *Lancet* 2021; 398: 1825–35.
- Knock ES, Whittles LK, Lees JA, et al. Key epidemiological drivers and impact of interventions in the 2020 SARS-CoV-2 epidemic in England. *Sci Transl Med* 2021; 13: eabg4262.
- Ades AE, Sutton AJ. Multiparameter evidence synthesis in epidemiology and medical decision-making: current approaches. *J R Statist Soc A* 2006; 169: 5–35.
- Andrews N, Stowe J, Kirsebom F, et al. COVID-19 vaccine effectiveness against the omicron (B.1.1.529) variant. *N Engl J Med* 2022; 386: 1532–46.
- Ismail SA, Garcia Vilaplana T, Elgohari S, et al. Effectiveness of BNT162b2 mRNA and ChAdOx1 adenovirus vector COVID-19 vaccines on risk of hospitalisation among older adults in England: an observational study using surveillance data. May 10, 2021. <https://khub.net/documents/135939561/430986542/Effectiveness-of-BNT162b2-mRNA-and-ChAdOx1-adenovirus-vector-COVID-19-vaccines-on-risk-of-hospitalisation-among-older-adults-in-England.pdf/9e18c525-dde6-5ee4-1537-91427798686b> (accessed Sept 15, 2021; preprint).
- Andrews N, Tessier E, Stowe J, et al. Duration of protection against mild and severe disease by COVID-19 vaccines. *N Engl J Med* 2022; 386: 340–50.

For the GitHub repository related to this study see <https://github.com/mrc-ide/sarscov2-vaccine-delay>

- 25 Bernal JL, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against the B.1.617.2 (delta) variant. *N Engl J Med* 2021; **385**: 585–94.
- 26 Sheikh A, McMenamin J, Taylor B, Robertson C. SARS-CoV-2 delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet* 2021; **397**: 2461–62.
- 27 Kojima N, Shrestha NK, Klausner JD. A systematic review of the protective effect of prior SARS-CoV-2 infection on repeat infection. *Eval Health Prof* 2021; **44**: 327–32.
- 28 UK Cabinet Office. COVID-19 response—spring 2021 (summary). Feb 22, 2021. <https://www.gov.uk/government/publications/covid-19-response-spring-2021/covid-19-response-spring-2021-summary> (accessed Feb 2, 2023).
- 29 Amirthalingam G, Bernal JL, Andrews NJ, et al. Serological responses and vaccine effectiveness for extended COVID-19 vaccine schedules in England. *Nat Commun* 2021; **12**: 7217.
- 30 Monod M, Blenkinsop A, Xi X, et al. Age groups that sustain resurging COVID-19 epidemics in the United States. *Science* 2021; **371**: eabe8372.
- 31 Barmounakis P, Demiris N, Kontoyiannis I, Pavlakis GN, Sypsa V. Evaluating the effects of second-dose vaccine-delay policies in European countries: a simulation study based on data from Greece. *PLoS One* 2022; **17**: e0263977.
- 32 Moore S, Hill EM, Tildesley MJ, Dyson L, Keeling MJ. Vaccination and non-pharmaceutical interventions for COVID-19: a mathematical modelling study. *Lancet Infect Dis* 2021; **21**: 793–802.
- 33 Martínez-Baz I, Trobajo-Sanmartín C, Miqueleiz A, et al. Product-specific COVID-19 vaccine effectiveness against secondary infection in close contacts, Navarre, Spain, April to August 2021. *Euro Surveill* 2021; **26**: 2100894.
- 34 Lauring AS, Tenforde MW, Chappell JD, et al. Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. *BMJ* 2022; **376**: e069761.
- 35 Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *Lancet* 2021; **398**: 1407–16.
- 36 Puranik A, Lenehan PJ, Silvert E, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of alpha and delta variant prevalence. *medRxiv* 2021; published online Aug 21. <https://doi.org/10.1101/2021.08.06.21261707> (preprint, version 3).
- 37 Vasileiou E, Simpson CR, Shi T, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *Lancet* 2021; **397**: 1646–57.
- 38 Pérez-Alós L, Armenteros JJA, Madsen JR, et al. Modeling of waning immunity after SARS-CoV-2 vaccination and influencing factors. *Nat Commun* 2022; **13**: 1614.
- 39 Atchison C, Bowman LR, Vrinten C, et al. Early perceptions and behavioural responses during the COVID-19 pandemic: a cross-sectional survey of UK adults. *BMJ Open* 2021; **11**: e043577.
- 40 Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. *Science* 2020; **368**: 860–68.