Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Vaccine efficacy against severe COVID-19 in relation to delta variant (B.1.617.2) and time since second dose in patients in Scotland (REACT-SCOT): a case-control study

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Summary

Background Reports have suggested that the efficacy of vaccines against COVID-19 might have fallen since the delta (B.1.617.2) SARS-CoV-2 variant replaced the alpha (B.1.1.7) variant as the predominant variant. We aimed to investigate, for the two main classes of vaccine, whether efficacy against severe COVID-19 has decreased since delta became the predominant variant and whether the efficacy of two doses of vaccine against severe COVID-19 wanes with time since second dose.

Methods In the REACT-SCOT case-control study, vaccine efficacy was estimated using a matched case-control design that includes all diagnosed cases of COVID-19 in Scotland up to Sept 8, 2021. For every incident case of COVID-19 in the Scottish population, ten controls matched for age rounded to the nearest year, sex, and primary care practice, and alive on the day of presentation of the case that they were matched to were selected using the Community Health Index database. To minimise ascertainment bias we prespecified the primary outcome measure to assess vaccine efficacy as severe COVID-19, defined as diagnosed patients with entry to critical care within 21 days of first positive test, death within 28 days of first positive test, or any death for which COVID-19 was coded as underlying cause. Although the data extracted for this study included cases presenting up to Sept 22, 2021, the analyses reported here are restricted to cases and controls presenting from Dec 1, 2020, to Sept 8, 2021, ensuring follow-up for at least 14 days after presentation date to allow classification of hospitalisation and (for most cases) severity based on entry to critical care or fatal outcome.

Findings During the study period, a total of 5645 severe cases of COVID-19 were recorded; these were matched to 50 096 controls. Of the severe cases, 4495 (80%) were not vaccinated, and of the controls, 36 879 (74%) were not vaccinated. Of the severe cases of COVID-19 who had been vaccinated, 389 had received an mRNA vaccine and 759 had received the ChAdOx1 vaccine. The efficacy of vaccination against severe COVID-19 decreased in May, 2021, coinciding with the replacement of the alpha SARS-CoV-2 variant by the delta variant in Scotland, but this decrease was reversed over the following month. In the most recent time window centred on July 29, 2021, the efficacy of two doses was 91% (95% CI 87–94) for the ChAdOx1 vaccine and 92% (88–95) for mRNA (Pfizer or Moderna) vaccines. The efficacy of the ChAdOx1 vaccine against severe COVID-19 declined with time since second dose to 69% (95% CI 52–80) at 20 weeks from second dose. The efficacy of mRNA vaccines declined in the first ten weeks from second dose but more slowly thereafter to 93% (88–96) at 20 weeks from second dose.

Interpretation Our results are reassuring with respect to concerns that vaccine efficacy against severe COVID-19 might have fallen since the delta variant became predominant, or that efficacy of mRNA vaccines wanes within the first 5–6 months after second dose. However, the efficacy of the ChAdOx1 vaccine against severe COVID-19 wanes substantially by 20 weeks from second dose. Efficacy of mRNA vaccines after 20 weeks and against newer variants remains to be established. Our findings support the case for additional protective measures for those at risk of severe disease, including, but not limited to, booster doses, at times when transmission rates are high or expected to rise.

Funding None.

Introduction

Reports have suggested that the efficacy of vaccines against COVID-19 might have fallen since the delta (B.1.617.2) variant became predominant.[1–6] Other studies have raised concerns that efficacy might wane with time since the second vaccine dose.[3,7,8] These concerns have led US and UK advisory bodies[9,10] to recommend booster doses for the general population.

Studies of efficacy against infection are subject to ascertainment bias unless they are based on testing at predetermined regular intervals.[3] Studies of efficacy against severe COVID-19, defined as cases that are fatal or require critical care, are less susceptible to ascertainment bias and this is also the outcome most relevant to health-care capacity. We aimed to investigate, for the adenovirus-vectored (ChAdOx1 nCov-19) and mRNA (BNT162b2 and

Research in context

Evidence before this study

Several reports have suggested that the efficacy of COVID-19 vaccines has fallen since the delta variant (B.1.617.2) became the predominant variant, or that efficacy wanes with time since the second dose. The impetus for this study was the evidence of waning efficacy cited by the US Centers for Disease Control and Prevention (up to Dec 9, 2021) and the UK Joint Committee on Vaccination and Immunisation (up to Nov 14, 2021) in support of their recommendations that booster doses should be delivered to the general population. We searched reports and supporting documents issued by these agencies since the start of vaccination programmes for mention of studies that investigated waning of efficacy of COVID-19 vaccines; where no link to the original report was given, other sites including preprint servers were searched to retrieve it. We also searched PubMed, with no language restrictions, using the terms \texttt{(SARS-CoV-2 OR COVID-19) AND vaccines AND (effectiveness OR efficacy)} for studies published between April 2, 2021, and Nov 1, 2021, with no language restrictions; this search did not identify any additional studies of waning of efficacy.

Added value of this study

This study focused on severe COVID-19—cases that were fatal or required critical care—as the primary outcome measure. This outcome measure is less susceptible to ascertainment bias than is diagnosed infection, and more specific than hospitalisation. Our results show that the efficacy of both ChAdOx1 and mRNA vaccines against severe COVID-19 remain high (around 90%) in the most recent time window centred on July 29, 2021, but that efficacy of the ChAdOx1 vaccine wanes to about 70% by 20 weeks after second dose. By contrast, the efficacy of the mRNA vaccines wanes rapidly at first but stabilises at about 90% by 20 weeks from the second dose.

Implications of all the available evidence

This study and others suggest that the efficacy of mRNA vaccines against severe disease caused by the SARS-CoV-2 delta variant remains high up to at least 5–6 months after second vaccine dose. However, the efficacy of the ChAdOx1 vaccine against severe COVID-19 wanes substantially by 20 weeks from second dose. Efficacy of vaccines after 20 weeks and against newer COVID-19 variants remains to be established.

mRNA-1273) vaccines, whether efficacy against severe COVID-19 has decreased since delta became the predominant variant and whether the efficacy of two doses of vaccine against severe COVID-19 wanes with time since the second dose.

Methods

Study design and participants

The design of the REACT-SCOT case-control study has been described in detail previously.[11,12] Briefly, for every incident case of COVID-19 in the Scottish population, ten controls matched for age rounded to the nearest year, sex, and primary care practice, and alive on the day of presentation of the case that they were matched to were selected using the Community Health Index database. Individuals previously diagnosed with COVID-19 were excluded from the sampling of incident cases and matched controls. Patients diagnosed with COVID-19 were those with a positive PCR test, a hospital discharge diagnosis coded as COVID-19, or a death certificate with mention of COVID-19. All nucleic acid tests for SARS-CoV-2 in Scotland are held in the Electronic Communication of Surveillance in Scotland database. For the community testing programme (pillar 2; in the UK the PCR testing programme is undertaken through pillar 1 [tests in health care settings] and pillar 2 [testing for the wider population]), PCR cycle thresholds for each channel are reported, allowing delta and alpha (B.1.1.7) variants to be distinguished based on spike gene dropout.

Individual consent is not required for Public Health Scotland staff to process personal data to perform specific tasks in the public interest that fall within its statutory role. This study was conducted under approvals from the Public Benefit and Privacy Panel for Health and Social Care, which includes public and patient representatives. This study was done within Public Health Scotland as part of its statutory duty to monitor and investigate public health problems. Under the UK Policy Framework for Health and Social Care Research set out by the NHS Health Research Authority, this study does not fall within the definition of research and ethical review was therefore not required.

Procedures and outcomes

To minimise ascertainment bias we prespecified the primary outcome measure as severe COVID-19, defined as diagnosed patients with entry to critical care within 21 days of first positive test, death within 28 days of first positive test, or any death for which COVID-19 was coded as underlying cause.[11] We also examined, as a secondary outcome, the broader category of hospitalised or fatal COVID-19, with hospitalisation defined as admission within 14 days of first positive test. Although the REACT-SCOT study samples included all diagnosed cases together with matched controls, the analyses reported here are restricted to severe or hospitalised cases, together with their matched controls. Although the data extracted for this study included cases presenting from March 1, 2020, to Sept 22, 2021, the analyses reported here are restricted to cases and controls presenting from Dec 1, 2020, to Sept 8, 2021, ensuring follow-up for at least 14 days after presentation date to allow classification of hospitalisation and (for most cases) severity based on entry to critical care or fatal outcome.

The vaccination programme in Scotland began on Dec 8, 2020. By March 24, 2021, half the adult population had received a first dose, and by June 7, half the adult population had received a second dose.[13] Vaccination status was defined by the number of doses received at least 14 days before presentation date.

Statistical analysis

The incidence density sampling design of this study controlled for the matched factors of age, sex, and primary care practice and for calendar time. Rate ratios (RRs) for severe COVID-19 were estimated from conditional logistic regression models. The efficacy of vaccination was calculated as 1 minus the rate ratio. Covariates included in each model were those previously identified as strong predictors of severe disease in this population, including care home residence, clinical risk category (no risk condition, moderate risk condition, or clinically extremely vulnerable and thus eligible for shielding), number of non-cardiovascular drug classes dispensed in last 240 days, and recent hospital stay (defined as 5 to 14 days before presentation date).[11,12,14] The criteria used to assign clinical risk categories are described in the appendix (p 1).

See Online for appendix

To investigate the effect of the delta variant, we examined how efficacy varied with calendar time and, to investigate possible waning of vaccine efficacy, we examined how efficacy varied with time since last dose. To show these relationships without predefined categories, the initial analysis presents line plots of log RRs estimated within sliding 42-day time windows against calendar time and against time since last dose. These sliding time windows were used only to generate plots. For a formal comparison between time periods before and after delta became the predominant SARS-CoV-2 variant, we defined June 15, 2021, as a cutoff date for when delta became the predominant variant in Scotland, and estimated RRs before and after this date.

A key question for policy is whether the early waning of vaccine efficacy after the second dose tapers off. To investigate this, we compared the fit of two families of model: a waning to zero efficacy model, in which the effect of vaccination on the scale of log RR decays exponentially to zero, with time since second dose encoded as a term of the form,

$$exp(-t\ [log2]/h)$$

where t is the time since second dose and h is the decay half-life; and a waning to constant efficacy model, in which the effect of vaccination is the sum of two terms, a waning effect and a term for vaccination status that does not decay with time since second dose. For each of these two model families, a model was fitted for each value of the decay half-life over a sequence of values from 10 days to 500 days, and a profile likelihood CI for the half-life was obtained as the range of half-life values over which the log-likelihood of the model was within 1·92 natural log units of its maximum value.[15] Comparison between the best-fitting waning to zero model and the best-fitting waning to constant efficacy model was based on the difference in log-likelihood between these nested models.

We used R version 3.6 for all statistical analyses.

Role of the funding source

There was no funding source for this study.

Results

Between Dec 1, 2020, and Sept 8, 2021 there were 393 936 incident cases of COVID-19, of whom 5645 cases (median age 75, IQR 61–85; 3028 [54%] male) met the criteria for the primary outcome of severe COVID-19 and were matched to 500 096 controls, and 21 879 cases (median age 64, IQR 46–80; 10 660 [49%] male) met the broader outcome of hospitalised or fatal COVID-19 and were matched to 2 014 154 controls.

The distributions of risk factors in patients with COVID-19 and their matched controls, for the 5645 severe cases and the 21879 cases in the broader category of hospitalised or fatal, are shown in the appendix (pp 8–9). The frequency tabulations presented in the appendix are provided for reference only—the unconditional odds ratios calculated from these tables cannot be used to estimate the RRs because of the matched design.[16,17] Vaccination status by calendar month of those sampled as age-matched controls of the hospitalised or fatal cases is shown in the appendix (p 3). Of the 62 684 hospitalised of fatal cases and their matched controls who had received a second dose of mRNA vaccine by Sept 22, 2021, only 2707 (4%) had received the Moderna mRNA-1273 product. In those who had received two doses either of the two classes of vaccine, the median time since second dose was 101 days (IQR 76–127) in severe cases of COVID-19 during the study period and 88 days (59–117) in their matched controls, and 112 days (78–139) in hospitalised or fatal cases during the study period and 96 days (60–132) days in matched controls. Data showing the emergence of the delta variant (with no spike gene dropout in the PCR test) and its predominance and replacement of the alpha variant (with spike gene dropout) in Scotland over a few weeks between May and June, 2020, is presented in the appendix (p 4). This switch was accompanied by a temporary increase in the RR for severe disease (corresponding to a decline in efficacy) associated with a single dose of vaccine, but by July, 2021, the RR had returned to the pre-delta value (figure 1A). The RRs associated with two doses of vaccine showed a similar perturbation between May and June, 2021, but the estimates of RRs for this period are imprecise because at this time few individuals had received their second dose. To compare the RR before and after the date that the delta variant became predominant, a conditional logistic regression model was fitted with the effect of two doses versus none nested within each level of an indicator variable, defined as presentation date on or after

June 15, 2021. The RR for severe disease associated with two doses of vaccine was 0·09 (95% CI 0·04–0·19) from Dec 1, 2020, to June 14, 2021, and 0·09 (0·07–0·11) from June 15, 2021, to Sept 8, 2021. The CI for the RR before June 15 is wide because few individuals had received a second done of vaccine more than 14 days before April 1, 2021 (only two severe cases and 47 controls matched to severe cases), and because there were only 131 severe cases from April to May, 2021. The RR for the broader category of hospitalised or fatal disease associated with two doses of vaccine increased (and thus efficacy was lower) after the delta variant became predominant (figure 1B). The RR for hospitalisation or fatal disease was estimated to be 0·15 (95% CI 0·12–0·20) before June 15, 2021, and 0·17 (0·15–0·18) from June 15, 2021, onwards.

The efficacy of two doses of the ChAdOx1 compared with mRNA vaccines against severe COVID-19 did not differ after May, 2021 (figure 1A), but against the broader category of hospitalised or fatal COVID-19 cases, the ChAdOx1 vaccine had lower efficacy than did the mRNA vaccines (figure 1B). In the most recent 42-day time window centred on July 29, 2021, the efficacy of two doses of vaccine against severe COVID-19 was 91% (95% CI 87–94) for the ChAdOx1 vaccine and 92% (88–95) for mRNA (Pfizer or Moderna) vaccines. Against the broader category of hospitalised or fatal COVID-19 cases, efficacy in this time window was slightly lower for the ChAdOx1 product (86% [95% CI 83–88]) than for mRNA vaccines (90% [88–92]).

The log RR for severe COVID-19 increased (and thus efficacy decreased) over the first ten weeks after the second dose for both ChAdOx1 and mRNA vaccines (figure 2A). After this period, the slope of this association flattened for mRNA vaccines but not for the ChAdOx1 vaccine. Figure 2B shows the same analysis for the broader category of hospitalised or fatal COVID-19 cases. In the 42-day time window centred on 20 weeks from the second vaccine dose, the efficacy of the ChAdOx1 vaccine against severe COVID-19 was 69% (95% CI 52–80), but the efficacy of mRNA vaccines was 93% (88–96). For efficacy against hospitalised or fatal COVID-19 cases at 20 weeks from second vaccine dose, the corresponding estimates were 58% (50–64) and 89% (86–91).

The association between efficacy against hospitalisation to time since second vaccine dose by clinical risk category is shown in the appendix (p 5). Differences between the ChAdOx1 vaccine and the mRNA vaccines in pattern of waning are evident in each risk category; thus, these differences cannot be explained by the different risk profiles of those who received mRNA vaccines and those who received ChAdOx1 vaccines.

Modelling of the association between efficacy and time since second vaccine dose was based on comparison of waning to zero efficacy and waning to constant efficacy models. Results are shown in the appendix (p 7). Decay curves corresponding to the best-fitting waning to constant efficacy model for each outcome are shown in the appendix (p 6). For severe COVID-19 cases, there was no clear evidence (difference in log-likelihood <2) favouring waning to constant efficacy over waning to zero. For the broader category of hospitalised or fatal COVID-19 cases, there was strong evidence favouring waning to constant efficacy over waning to zero. For mRNA vaccines, the model best supported by the data was one in which efficacy was the sum of a rapidly waning effect with a half-life of 16 days (95% CI 4–101) days and a time-invariant vaccine efficacy of 93%. For the ChAdOx1 vaccine the model with waning to constant efficacy was supported, but with a much longer decay half-life (95% CI 216 to infinity) such that the decay curve for the log RR up to 30 weeks is barely distinguishable from a straight line.

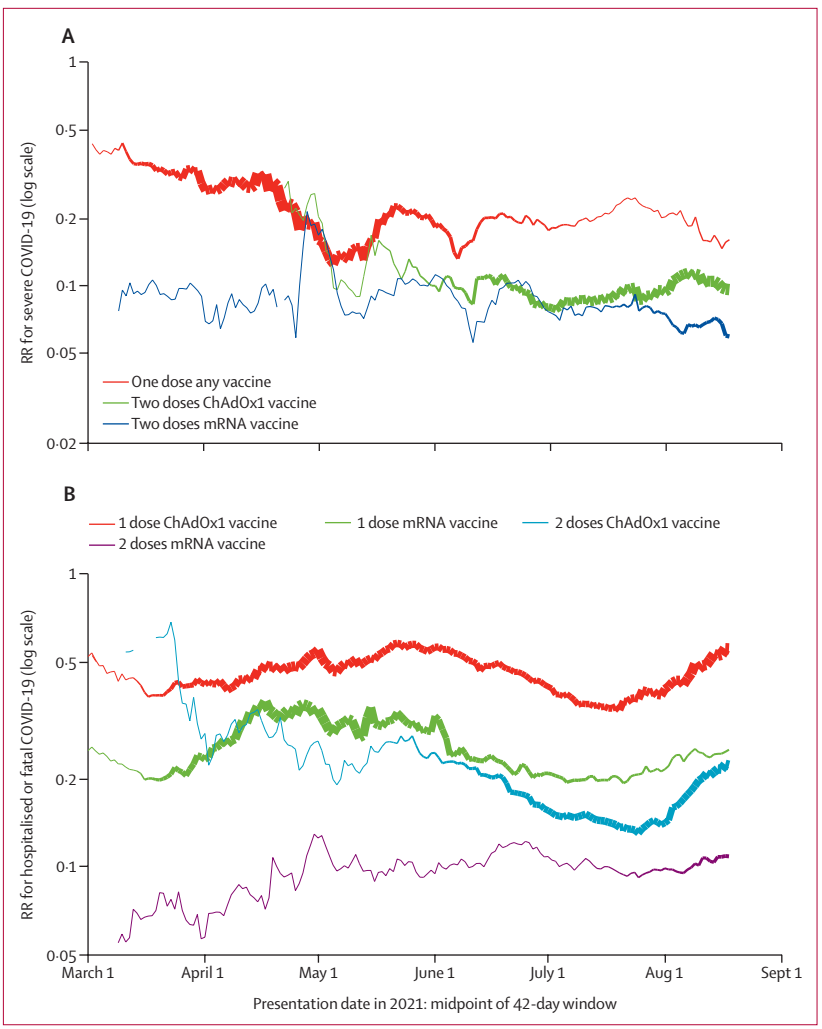

Figure 1: **Association between vaccine efficacy and calendar time**
(A) Severe COVID-19 (single-dose categories for ChAdOx1 and mRNA vaccines have been combined as the numbers of events in those with one dose of mRNA vaccine were small). (B) Hospitalised or fatal COVID-19 cases. RRs in conditional logistic regression model, adjusted for covariates. The efficacy of vaccination was calculated as 1 minus the RR. For each effect, line thickness is proportional to precision (inverse variance) of estimate, scaled to the same maximum thickness for each effect. RR=rate ratio.

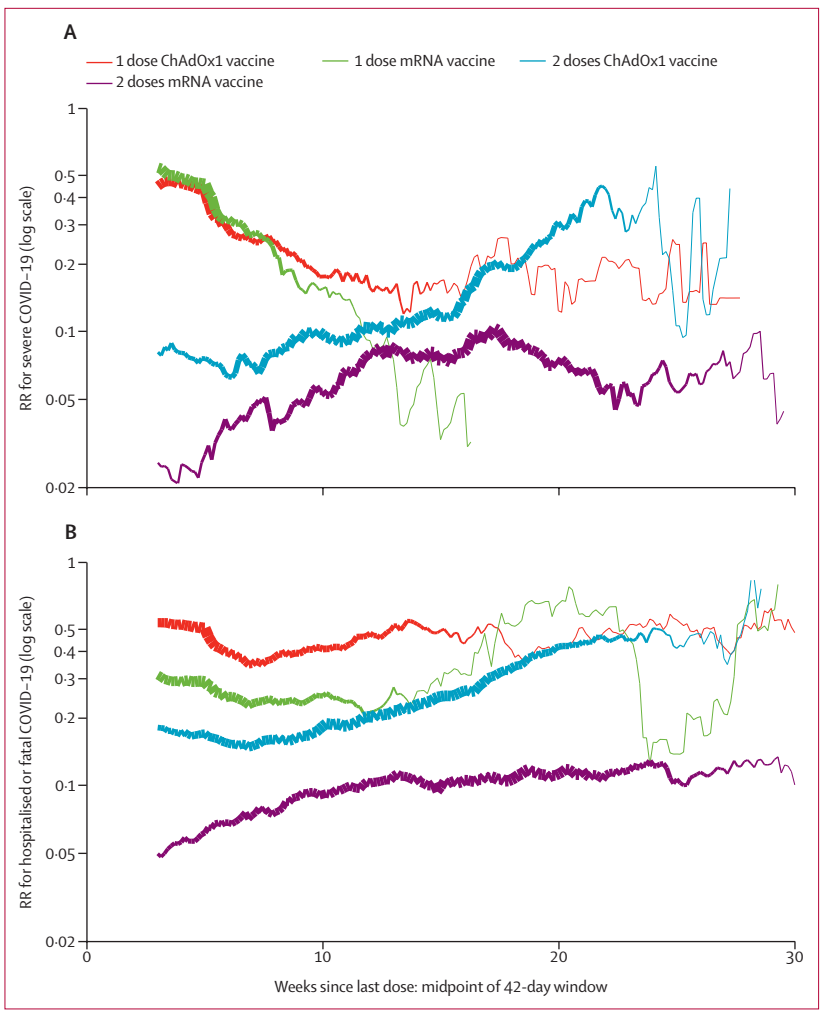

Figure 2: **Association between vaccine efficacy and time since last vaccine dose**
(A) Severe COVID-19. RRs in conditional logistic regression model, adjusted for covariates. (B) Hospitalised or fatal COVID-19 cases. RRs in the 42-day time window centred on 20 weeks from the most recent vaccine dose are presented. The efficacy of vaccination is 1 minus the RR. For each effect, line thickness is proportional to precision (inverse variance) of estimate, scaled to the same maximum thickness for each effect. RR=rate ratio.

Discussion

In this analysis of the REACT-SCOT study, the efficacy of two vaccine doses against severe COVID-19 in the most recent time window centred on July 29, 2021, was around 92% and differed only slightly between ChAdOx1 and mRNA vaccines. Efficacy against the broader category of hospitalised or fatal COVID-19 cases was lower for the ChAdOx1 vaccine than for mRNA vaccines (86% *vs* 90%). The replacement of the alpha variant of SARS-CoV-2 by the delta variant in May, 2021, was accompanied by a temporary reduction in vaccine efficacy against severe disease—a possible explanation for this is that the early spread of the new variant was associated with higher infecting doses, as suggested by the lower PCR cycle threshold values recorded in surveillance data for England.[18]

The efficacy of mRNA vaccines against severe or hospitalised COVID cases declined during the first ten weeks after the second dose, but stabilised thereafter at about 90%. The efficacy of the ChAdOx1 vaccine against hospitalised or fatal COVID-19 continued to decline to about 60% at 20 weeks. Although the logarithmic scale is the natural scale on which to model effects on rates, we emphasise that changes on this scale do not equate to changes in absolute risk; thus, a two-times increase in the RR can represent a decline of efficacy from 97·5% to 95%, or a decline from 80% to 60%. It is natural to model waning as an exponential decay of the log RR (a linear effect would imply that efficacy eventually becomes negative). Although a model in which efficacy against hospitalisation is the sum (on a scale of log RR) of a rapidly waning effect and a time-invariant effect is supported by these data, the underlying mechanism of this unclear, as the rate of decline of neutralising antibodies induced by mRNA vaccines[19] appears too slow to explain the rapid decline of efficacy in the first 2 months since second vaccine dose.

The strengths of this study are the focus on severe COVID-19 as an outcome measure for which ascertainment is complete and ascertainment bias should be minimal, the elimination of confounding by calendar time in the matched case-control design, and the ability to control for confounding by comorbidities and recent inpatient stay through linkage to electronic health records. Confounding by unmeasured health-seeking behaviour is likely to occur where unvaccinated people are a small and possibly extreme minority, but even towards the end of the study period more than 20% of control cases remained unvaccinated. The clear difference in waning between the two vaccine types cannot easily be explained by confounding by differences in health-seeking behaviour between unvaccinated and vaccinated individuals. The incidence density case-control design excludes those who have previously tested positive for COVID-19; a study of reinfections will be reported elsewhere. Our estimates for the waning of mRNA vaccine efficacy are based almost entirely on the Pfizer vaccine; only relatively recently has the Moderna vaccine been used in Scotland. For the secondary outcome of hospitalised or fatal COVID-19 cases, the numbers of events are larger but we cannot easily distinguish admissions caused by COVID-19 from admissions for other conditions where a positive COVID-19 test is an incidental finding on admission. Where hospitalisations with COVID-19 are misclassified as hospitalisations caused by COVID-19, efficacy of a vaccine against hospitalisation caused by COVID-19 might be underestimated if its efficacy against test-positive infection is lower than its efficacy against disease.

For investigating the possible effect of the delta variant of SARS-CoV-2 on vaccine efficacy, a limitation is that we do not have direct measurements of variant type except for those cases ascertained through pillar 2 testing. However, in Scotland the alpha variant of SARS-CoV-2 was almost completely replaced by delta over a few weeks in May to June, 2021,[20] and the effect of this switch is

visible in the time window plots as a temporary perturbation of efficacy. As few people had received their second vaccine dose before April, 2021, and from April to May, 2021, the number of severe cases of COVID-19 was low, estimates of efficacy of two doses against severe COVID-19 are based mainly on cases occurring after May, 2021. Although the effects of calendar time and time since second dose are confounded with other factors not considered in this analysis—including seasonality, the build-up of natural immunity, and the changing morbidity profile of cases—the objective of this study was to establish whether efficacy is waning in the population as a whole and thus to lay an evidence base for policy.

Several studies have suggested that vaccine efficacy against COVID-19 infection might have fallen since delta became the predominant variant, or that efficacy wanes with increasing time since second dose. For efficacy against infection, the most reliable evidence is from the UK Office for National Statistics COVID-19 Infection Survey, based on regular monthly PCR testing. A study based on this survey reported that efficacy against infection had fallen from 79% to 67% for the ChAdOx1 vaccine since delta became the predominant variant of SARS-CoV-2, but remained around 80% for the Pfizer vaccine.[3] Three other studies from the UK[2,20,21] using test-negative controls have estimated the efficacy against symptomatic infection to be lower for the ChAdOx1 vaccine than for the Pfizer vaccine. In Scotland, a study based on community testing (where delta and alpha variants of SARS-CoV-2 can be distinguished) estimated efficacy against mortality from the delta variant to be around 90% for both vaccines,[22] similar to our estimate for the broader outcome of all diagnosed cases of severe COVID-19.

A study from the Kaiser Permanente Health Program showed that the efficacy of two doses of the Pfizer vaccine against hospitalisation with COVID-19 remained around 90% after 6 months since second dose.[23] consistent with our findings. A study from South Carolina reported that efficacy of the Pfizer vaccine against hospitalisation and death remained around 88% after 7 months.[24] By contrast, a case-control study with data from 21 US hospitals estimated that efficacy against hospitalisation declined from 91% at 14–120 days since second dose to 77% after 120 days since second dose;[25] interpretation of this result is complicated by the use of a control sampling frame comprising test-negative hospitalised individuals. Few studies have compared the waning of efficacy of mRNA and ChAdOx1 vaccines against hospitalisation. A study from Public Health England based on data from Dec 8, 2020, to Sept 3, 2021, estimated that in those aged over 65 years, efficacy against hospitalisation of two doses of the Pfizer vaccine declined from 98% at 2–9 weeks to 91% at 20 weeks or more from second dose. For the ChAdOx1 vaccine the corresponding estimates were 92% at 2–9 weeks and 76% at 20 weeks or more from second dose. Limitations of the study from Public Health England are the restriction to cases ascertained from pillar 2 community testing (likely to have less comorbidity than cases ascertained in health-care settings) and the test-negative control design, which is not necessary where the outcome under study is hospitalisation (for which case ascertainment should be complete).

On the basis of reports that vaccine efficacy against SARS-CoV-2 had fallen since delta became the predominant variant, and that efficacy waned with time since second dose, the US Centers for Disease Control and Prevention and the US Food and Drug Adminstration recommended booster doses for all adults in the USA,[9] although the Vaccines and Related Biological Products Advisory Committee subsequently limited their recommendation to those aged over 65 years. In the UK, the Joint Committee on Vaccination and Immunisation recommended booster doses for all those aged over 50 years[10] and later updated this to lower the age threshold to 40 years.[26] Others have expressed doubts about the evidence of waning efficacy, and argued that "currently available evidence does not show the need for widespread use of booster vaccination in populations that have received an effective primary vaccination regimen."[27] A report from Public Health England suggested that declining efficacy against infection might even be beneficial in the long term by "boosting the primed immune system of vaccinees who would experience mild or asymptomatic infections."[28]

In conclusion, with respect to the delta variant, our results are more reassuring than earlier reports, in that we found that although the efficacy of a single dose of vaccine against severe COVID-19 declined when the alpha variant was replaced by the delta variant, this decline was only temporary. As for waning of efficacy with time since second dose, although the efficacy of mRNA vaccines against severe COVID-19 and hospitalisation appears to stabilise at about 90% after rapid waning in the first 10 weeks from second dose, the efficacy of the ChAdOx1 vaccine against severe disease and hospitalisation continues to wane to about 60% by 20 weeks. This finding supports the case for additional protective measures for those at risk of severe disease, including, but not limited to, booster doses at times when transmission rates are high or expected to rise. However, the basis for recommending booster doses in relatively low-risk individuals depends upon whether boosters are effective in reducing transmission in the population and upon the balance between policies that focus on reducing transmission and policies that focus on protecting the vulnerable during the transition to endemicity.

Contributors

All authors conceived the study. PMM did the formal data analysis. PMM and HMC wrote the original draft of the manuscript. All authors reviewed and edited the manuscript. PMM, DAM, CR, and HMC had access to and verified the study data. PMM, HMC, and DS had final responsibility for the decision to submit for publication. As the manuscript's guarantor, PMM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any

discrepancies from the study as originally planned and registered have been explained. This manuscript has been generated directly from the source data by a reproducible research pipeline.

Declaration of interests

HMC receives research support and honoraria and is a member of advisory panels or speaker bureaus for Sanofi Aventis, Regeneron, Novartis, Novo-Nordisk, and Eli Lilly. HMC receives or has recently received non-binding research support from ChAdOx1 and Novo-Nordisk. SJH received honoraria from Gilead. All other authors declare no competing interests.

Data sharing

To **apply for data access** please see https://www.informationgovernance.scot.nhs.uk/pbpphsc

For **source code** see https://github.com/pmckeigue/covid-scotland_public

The component datasets used here are available to researchers via application to the Public Benefits and Privacy Panel for Health and Social Care. All source code used for derivation of variables, statistical analysis, and generation of this manuscript is available online.

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