

research



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ORIGINAL RESEARCH Test negative design study

FAST TRACK

Effectiveness of fourth mRNA vaccine dose against omicron in long term care residents in Canada

Grewal R, Kitchen SA, Nguyen L, et al

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Study question What is the marginal effectiveness of a fourth versus third dose and vaccine effectiveness of mRNA covid-19 vaccines against omicron related outcomes among residents of long term care facilities in Ontario, Canada?

Methods The study sample comprised 61 344 long term care residents aged ≥ 60 who were tested for covid-19 from 30 December 2021 to 27 April 2022. Marginal effectiveness (four v three doses) and vaccine effectiveness (two, three, or four doses v none) of mRNA vaccines were estimated against omicron related infection (any, symptomatic) and severe outcomes (hospital admission, death) using multivariable logistic regression adjusting for personal characteristics, comorbidities, week of test, and previous covid-19 more than 90 days previously.

Study answer and limitations 13 654 residents who tested positive for omicron and 205 862 test negative controls were included. The marginal effectiveness of a fourth dose (95% of vaccine recipients received mRNA-1273 as fourth dose) ≥ 7 days after vaccination versus a third dose ≥ 84 days previously was 19% (95% confidence interval 12% to 26%) against infection, 31% (20% to 41%) against symptomatic infection, and 40% (24% to 52%) against severe outcomes. Vaccine effectiveness in vaccine recipients (compared with unvaccinated) increased with each additional dose, and for a fourth dose was 49% (43% to 54%) against infection, 69% (61% to 76%) against symptomatic infection, and 86% (81% to 90%) against severe outcomes. It was not possible to assess the duration of protection from fourth doses.

What this study adds These findings suggest that, compared with a third dose of mRNA covid-19 vaccine, a fourth dose improved protection against omicron related infection, symptomatic infection, and severe outcomes among long term care residents.

Funding, competing interests, and data sharing
See full paper on [bmj.com](https://www.bmj.com) for details.

Marginal effectiveness of fourth mRNA vaccine dose against omicron outcomes among long term care residents compared with residents who received a third dose

Outcome	No of SARS-CoV-2 negative controls	No of omicron positive cases	Marginal effectiveness, v third dose <84 days ago (% (95% CI))	Marginal effectiveness, v third dose ≥ 84 days ago (% (95% CI))
Infection				
0-6 days	11 035	646	5 (-8 to 16)	8 (-5 to 19)
≥ 7 days	67 798	3181	16 (9 to 23)	19 (12 to 26)
Symptomatic infection				
0-6 days	316	110	-8 (-41 to 18)	8 (-19 to 29)
≥ 7 days	2658	606	20 (3 to 33)	31 (20 to 41)
Severe outcomes				
0-6 days	316	39	-12 (-58 to 20)	4 (-32 to 31)
≥ 7 days	2658	101	29 (8 to 46)	40 (24 to 52)

CI=confidence interval.

Rapid covid-19 vaccination for health workers

ORIGINAL RESEARCH Prospective multicentre cohort study (SIREN) and mathematical model

Burden of SARS-CoV-2 infection in healthcare workers during second wave in England and impact of vaccines

Pople D, Monk EJM, Evans S, et al, on behalf of the SIREN Study Group

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MARK THOMAS

Study question What was the incidence of, risk factors for, and impact of vaccines on primary SARS-CoV-2 infection during the second wave of the pandemic in susceptible hospital healthcare workers in England?

Methods The SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) study is a multicentre prospective cohort with regular SARS-CoV-2 polymerase chain reaction (fortnightly) and antibody (monthly) testing. Vaccination status was derived from national registries and self-reported. Mixed effects logistic regression and an individual based mathematical model were conducted.

Study answer and limitations Of 18 284 susceptible participants, 2353 (12.9%) became infected between September 2020 and April 2021. Infections peaked in late December 2020 and decreased from January 2021, concurrent with the cohort's rapid vaccination coverage and a national lockdown. In multivariable analysis, factors increasing the likelihood of infection were age <25 years, large household, frequent exposure to patients with covid-19, working in an emergency

COMMENTARY Infection risk increased with every day of delay

The covid-19 pandemic led to a global scientific effort to understand and control this new disease. The most obvious result was the rapid development of several vaccines,¹² in addition to other impressive exercises in collaborative epidemiological research, such as the SIREN study (SARS-CoV-2 Immunity and Reinfection Evaluation) in the UK,³ the latest article of which has been published in *The BMJ*.⁴

SIREN's methods were simple.⁵ Most NHS workers were eligible and participants completed fortnightly questionnaires detailing possible exposures to SARS-CoV-2, any symptoms, and whether they had been vaccinated; they also had polymerase chain reaction tests every fortnight for SARS-CoV-2, and serum antibody tests every month. Overall, 12.9% of susceptible participants

It is unclear what living with covid-19 means in a healthcare setting

were infected during the second wave between September 2020 and April 2021, the study period of this latest paper by Pople and colleagues.⁴ Staff working in emergency departments or ward settings, healthcare assistants, and anyone with frequent exposure to patients had significantly increased odds of infection.

Added value

An earlier paper from SIREN⁶ described the protective effect of covid-19 vaccination in healthcare workers, with 85% protection after two doses during a relatively short follow-up until 5 February 2021. Pople and colleagues build on that earlier work, with a more detailed analysis of the rapid deployment of the UK vaccination programme in the NHS, which officially began on 8 December 2020.⁴ The authors

included SIREN participants in England who were susceptible to covid-19 at the start of the second wave, and tracked their progress (principally vaccination, exposures, and infection) until 30 April 2021; by then the second wave had subsided, and nearly all participants were vaccinated. The paper presents a mathematical epidemiological model, simulating a scenario in which nobody was vaccinated—enabling a theoretical estimate of the number of infections that were prevented by the vaccine rollout among healthcare workers.

The results confirm previous findings on occupational risk.⁷ They also confirmed the protective effective of vaccination, but in addition showed that each day's delay in vaccination measurably increased the risk, multiplying a participant's adjusted odds of infection by 1.02.

Although 90% of SIREN participants received the Pfizer-BioNTech vaccine, the findings are likely to apply equally to the

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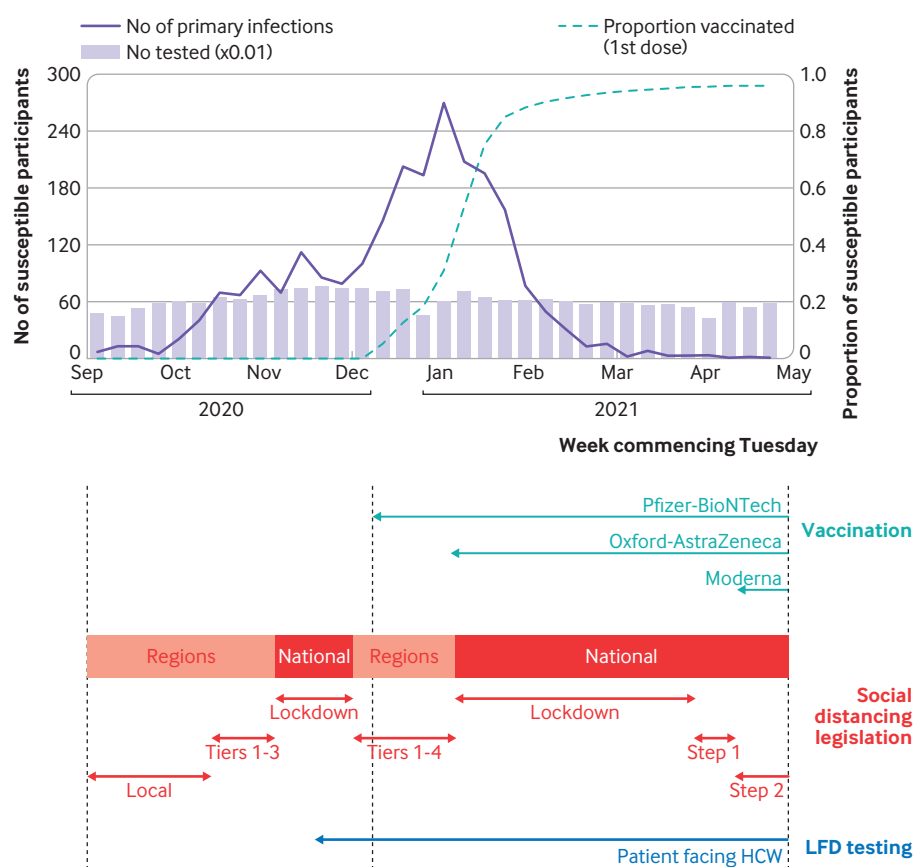
department or inpatient ward, and being a healthcare assistant. Increased time to first vaccination was strongly associated with infection ($P < 0.001$): risk increased by 1.02 for each additional day unvaccinated. Mathematical model simulations indicated that an additional 9.9% of all patient facing hospital healthcare workers would have been infected in the second wave, were it not for vaccines. The study was not designed to explore organisational variation: future research should include local infection prevention and control policy and organisational infrastructure.

What this study adds A high proportion of susceptible healthcare workers were infected during the second wave in England. Without the rapid vaccine rollout from December 2020, the burden could have been much higher. The findings also highlight occupational risk factors that persisted in healthcare workers despite vaccine rollout.

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No competing interests declared. Metadata for this analysis will be available on reasonable request.

Study registration ISRCTN Registry ISRCTN11041050.



Weekly incidence of SARS-CoV-2 primary infections, and weekly cumulative vaccination coverage, in SIREN participants susceptible to primary infection in England, with calendar of England-wide covid-19 interventions during second wave (1 September 2020 to 30 April 2021). HCW=healthcare workers; LFD=lateral flow device

Oxford-AstraZeneca vaccine, the other principal vaccine used in the UK: both appear to have similar efficacy (as shown in another study in *The BMJ*, doi:10.1136/bmj-2021-068946).⁸ What is more novel in the study by Pople and colleagues is the detailed modelling of this protection: the authors conclude that infection rates in patient facing healthcare workers would have been 69% higher without vaccination.⁴ This proportion would have greatly worsened the considerable staff shortages that were seen in the NHS and other health services at the time.⁹

Pople and colleagues' paper is important for several reasons. It shows the value of a rapid vaccine deployment, prioritising healthcare workers, even during a surge in hospital (as well as community) infections that might feel overwhelming at the time. Weeks or even days made a substantial difference to infection rates, and therefore staff absences and patient safety. The

authors also emphasise that any such vaccine deployment needs to be equitable across different occupational and ethnic groups of healthcare workers.

The study's findings remind us that some categories of staff remain at higher risk of occupational covid-19 (and presumably other respiratory infections), despite using personal protective equipment as advised at the time—raising the question of whether vaccines and immunity are a good enough defence, or whether more stringent measures such as better personal protective equipment and ventilation are still required in high risk healthcare settings.¹⁰

Certainly, things are very different now compared to early 2021; SARS-CoV-2 infection remains common despite vaccination, but causes much less harm (morbidity and mortality).^{11,12} The NHS now faces a dilemma—it is unclear what living with covid-19¹³ means in a healthcare setting, and whether we should now tolerate

spread of a much milder infection in our hospitals. Further surveillance and research will help inform this debate, but ethical and political considerations are also likely to play a part.

The SIREN study also reminds us that other less well scrutinised respiratory viruses such as influenza virus, adenovirus, and other seasonal coronaviruses are likely to spread in the same fashion among staff in healthcare settings every winter—something we have always known but chose to ignore.¹⁴ To suggest that the scope of SIREN could be extended to include other respiratory viruses is tempting, but a switch to anonymised or delayed testing would be needed unless clear protocols are developed for managing the many positive results and multiple viral infections likely to be detected.

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Comparative effectiveness of ChAdOx1 versus BNT162b2 covid-19 vaccines in health and social care workers in England

Hulme WJ, Williamson EJ, Green ACA, et al

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Study question What is the effectiveness of a first dose of the ChAdOx1 vaccine or BNT162b2 vaccine, administered as part of the national covid-19 vaccine roll-out, in health and social care workers in England?

Methods The OpenSAFELY-TPP database was used to study health and social care workers vaccinated between 4 January and 28 February 2021, with risk adjusted pooled logistic regression models with time varying vaccination effects. Recipients were followed for 20 weeks after vaccination. Primary outcomes were recorded SARS-CoV-2 infection, covid-19 related attendance at an emergency department, and unplanned covid-19 related hospital admission.

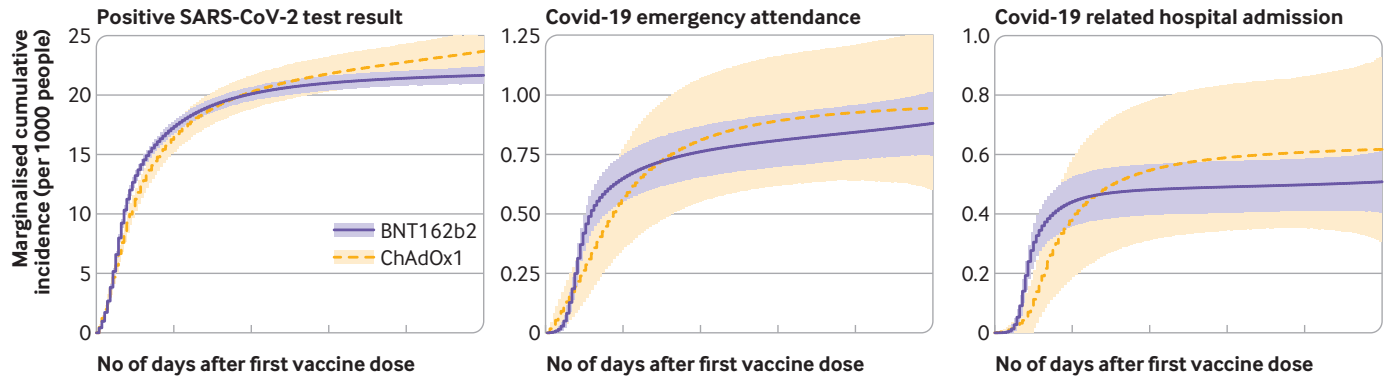
Study answer and limitations Similar outcomes were observed in health and social care workers receiving either the BNT162b2 or the ChAdOx1 vaccine during 20 weeks of follow-up in the era of the SARS-CoV-2 alpha variant. Differences in protection against severe outcomes could not be precisely measured in this relatively healthy population owing to so few events.



LIAM MCBURNEY/PALAWAY

What this study adds Health and social care workers in England had similar protection against covid-19 outcomes when vaccinated with either BNT162b2 or ChAdOx1.

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Comparative effectiveness of covid-19 vaccine ChAdOx1 and BNT162b2 for each outcome

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