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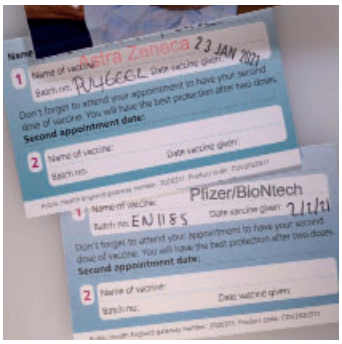

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ORIGINAL RESEARCH OpenSAFELY cohort study **FAST TRACK**

Waning effectiveness of BNT162b2 and ChAdOx1 covid-19 vaccines over six months since second dose

Horne EMF, Hulme WJ, Keogh RH, et al

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Study question What is the rate at which covid-19 vaccine effectiveness wanes over six months after the second dose?

Methods This cohort study used linked primary care, hospital, and covid-19 records within the OpenSAFELY-TPP database. People who had received two doses of BNT162b2 (Pfizer-BioNTech) or ChAdOx1 (Oxford-AstraZeneca) were compared with unvaccinated people during six consecutive comparison periods each of four weeks' duration, starting two weeks after second vaccination. The outcomes were adjusted hazard ratios for covid-19 related hospital admission, covid-19 related death, positive SARS-CoV-2 test result, and non-covid-19 related death. Waning vaccine effectiveness was quantified as ratios of adjusted hazard ratios per four week period, separately for subgroups aged ≥65, 18-64 and clinically vulnerable, 40-64, and 18-39 years.

Study answer and limitations 1 951 866 and 3 219 349 eligible adults received two doses of BNT162b2 and ChAdOx1, respectively, and 2 422 980 remained unvaccinated. Waning of vaccine effectiveness was estimated to be similar across outcomes and vaccine brands. In the ≥65 years subgroup, ratios of adjusted hazard ratios for covid-19 hospital admission, covid-19 related death, and positive SARS-CoV-2 test result ranged from 1.19 (95% confidence interval 1.14 to 1.24) to 1.34 (1.09 to 1.64) per four weeks. Despite waning, rates of covid-19 related hospital admission and death were substantially lower among vaccinated than unvaccinated adults up to 26 weeks after the second dose (estimated vaccine effectiveness ≥75%). These results may be biased by uncontrolled confounding and incomplete information on patients who left their practice without deregistering.

What this study adds The rate at which estimated vaccine effectiveness waned was consistent for covid-19 related hospital admission, covid-19 related death, and positive SARS-CoV-2 test result, and similar across subgroups defined by age and clinical vulnerability.

Funding, competing interests, and data sharing
This work was supported by the Longitudinal Health and Wellbeing COVID-19 National Core Study, Asthma UK, National Institute for Health and Care Research, and Wellcome Trust.
The Phoenix Partnership provided technical expertise and infrastructure pro bono in the context of a national emergency.
See bmj.com for competing interests.
Analytical code and codelists are available at github.com/opensafely/covid-ve-change-over-time.

Covid-19: Is omicron less lethal than delta?

ORIGINAL RESEARCH Retrospective cohort study

Risk of covid-19 related deaths for SARS-CoV-2 omicron (B.1.1.529) compared with delta (B.1.617.2)

Ward IL, Bermingham C, Ayoubkhani D et al

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Study question What is the risk of covid-19 death after infection with omicron BA.1 compared with delta (B.1.617.2) in England?

Methods The study population consisted of 1 035 149 people aged 18-100 years who tested positive for SARS-CoV-2 under the NHS Test and Trace programme (tests taken in the community, pillar 2) and had an infection identified as omicron BA.1 or delta compatible. The main outcome measure was covid-19 death as identified from death certification records. Cause specific Cox proportional hazard regression models (censoring non-covid-19 deaths) were adjusted for sex, age, vaccination status, previous infection, calendar time, ethnicity, index of multiple deprivation ranking, household deprivation, university degree, keyworker status, country of birth, main language, region, disability, and comorbidities. Interactions between variant and sex, age, vaccination status, and comorbidities were also investigated.

Study answer and limitations The risk of covid-19 death was 66% lower (95% confidence interval 54% to 75%) for omicron BA.1 compared with delta after adjusting for a wide range of potential confounders. The reduction in the risk of covid-19 death for omicron compared with delta was more pronounced in people aged 18-59 years (number of deaths: delta=46, omicron=11; hazard ratio 0.14, 95% confidence interval 0.07 to 0.27) than in those aged ≥70 years (number of deaths: delta=113, omicron=135; hazard ratio 0.44, 95% confidence interval 0.32 to 0.61, P<0.0001). No evidence of a difference in risk was found between variant and number of comorbidities. A limitation of this study is the small sample size compared with other research because NHS pillar 1 data (tests taken in hospital) could not be accessed.

What this study adds The risk of covid-19 death was reduced after infection with the omicron BA.1 variant compared with the delta variant.

Funding, competing interests, and data sharing No funding received. See full paper on bmj.com for competing interests. No additional data available.

COMMENTARY Death certification data support an intrinsically lower case fatality rate for omicron

Soon after the omicron SARS-CoV-2 variant of concern was first reported to the World Health Organization on 24 November 2021, preliminary observational studies in South Africa suggested this highly transmissible variant was associated with lower hospital admission and mortality rates in people with covid-19.[1] However, given omicron's increased propensity to cause reinfections and vaccine breakthrough,[2 3] it was unclear if this effect was due to previous immunity in the population or an inherent property of the genetically divergent variant.

Subsequent analyses further supported a lower risk of severe outcomes in infections with omicron compared with delta, although these data were limited to all cause deaths within 28 days of diagnosis.[4] Additionally, many public health measures previously enacted to curb SARS-CoV-2 transmission were being relaxed in early 2022, potentially resulting in more infections in relatively low risk populations. These limitations complicated efforts to assess the true risk of severe disease and mortality associated with omicron infection.

The retrospective cohort study by Ward and colleagues in this issue takes a further step towards addressing this question. The study reported new evidence that mortality rates were lower for infections with the omicron BA.1 subvariant than for the delta variant of concern, even after controlling for patient demographics, previous infection, and vaccination status.

The study team used the United Kingdom's Office for National Statistics Public Health Data Asset to access census data, mortality records, vaccination dates, and other standardised measures for over one million UK adults who tested positive for SARS-CoV-2 in December 2021 when omicron and delta were circulating. Quantitative polymerase chain reaction test results were mined for spike gene target failure, with specimens failing to amplify the S gene classified as BA.1 compatible. Although less reliable than whole genome sequencing, this technique can distinguish delta from BA.1 by detecting the deletion at positions 69 and 70 of the spike gene characteristic of BA.1 (present in almost 95% of BA.1 lineage sequences *v* 0.2% of delta).[5] Death certification records definitively identified over 350 covid-19 related deaths in the cohort. Ultimately, the risk of covid-19 related death was found to be 66% lower in people infected with omicron than in those with delta, similar to the 69% lower risk reported by Nyberg and colleagues.[4]

Combining death certification records with molecular surveillance is the main advantage of this study

Conclusive evidence

This study provides the most conclusive evidence to date that infection with the omicron subvariant BA.1 was inherently less deadly than delta when controlling for a number of key covariates. Combining death certification records with molecular surveillance is the main advantage of this study, which avoids previous biases in covid-19 death designations. Accounting for a broad array of standardised covariates, including sociodemographic variables, pre-existing health conditions, and previous immunity, is another strength.

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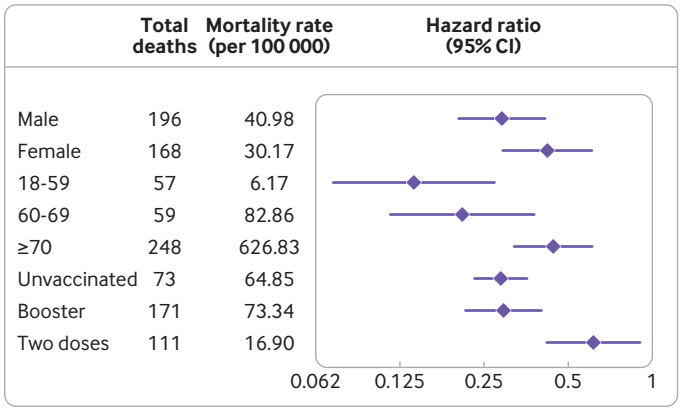

Hazard ratio for covid-19 death for omicron BA.1 infection versus delta infection by sex, age, and vaccination status. To investigate the interaction between variant type and sex, the model was fully adjusted (model 4, adjusted for age, sex, vaccination status, previous infection, calendar time, socioeconomic factors, and comorbidities) with an interaction term for variant and sex. For the interaction between variant and age, the fully adjusted model also included a variable for age group (18-59, 60-69, or ≥70). For the interaction between variant and vaccination status, additional interaction terms were included between variant and vaccination categories and adjusted for an interaction between variant and age

Similar to previous reports, risk of covid-19 death with omicron decreased in unvaccinated and vaccinated populations. Although the reduction was more pronounced in unvaccinated and boosted populations relative to the double vaccinated, this is likely skewed by the very low mortality rate among vaccinated people and the fact that booster shots were prioritised for at risk populations during the study period.

Limitations

The study also has some limitations that curtail its generalisability. Despite the strengths of the Public Health Data Asset, data collection is limited to adults in the UK and might not reflect observations in other countries or in children. A reliance on hospital system data likewise could skew cohort characteristics due to possible biases in the population captured by these data. Finally, as previously noted, the use of spike gene target failure as a proxy for variant identification carries some risk of misclassification.

While consensus is forming that omicron infections are associated with lower mortality rates (including preliminary data on BA.4 and BA.5), several considerations remain. Firstly, it is still unclear why the risk of death is lower. Is this due to omicron's increased capacity to avoid immune recall[6 7] leading to lower immune activation, altered viral tropism,[8 9] changes in anatomical localisation,[10] improvements in clinical care, or a combination of these and other factors? Understanding the causes is critical for assessing risks as variants continue to emerge.

Secondly, a broader discussion on optimal strategies for communicating risk and implementing appropriate public health responses is necessary. Early reports suggesting lower mortality in people with omicron infections[11] were widely broadcast with limited emphasis on the underlying uncertainty. While these early observations are ultimately being corroborated, effective communication will be essential for individual risk assessments and broader public health responses as the pandemic continues to evolve.

Finally, it is essential to continue to develop, optimise, and deploy systems that integrate molecular surveillance, demographic, epidemiological, and clinical datasets to enable timely research. Investment in this infrastructure will be critical for the continued response to covid-19 and for future pandemic preparedness.

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Role of human papillomavirus (HPV) vaccination on HPV infection and recurrence of HPV related disease after local surgical treatment

Kechagias KS, Kalliala I, Bowden SJ, et al

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Find this at doi: 10.1136/bmj-2022-070135

Study question Does human papillomavirus (HPV) vaccination reduce the risk of HPV infection and recurrent diseases related to HPV infection in individuals undergoing local surgical treatment for cervical disease or other diseases related to HPV infection?

Methods A systematic review and meta-analysis was conducted of studies reporting on the risk of HPV infection rates and recurrence of disease related to HPV infection after local surgical treatment of preinvasive genital disease in individuals who were vaccinated. The primary outcome was the risk of recurrence of cervical intraepithelial neoplasia grade 2 or higher (CIN2+) after local surgical treatment. Secondary outcomes were risk of HPV infection or other lesions related to HPV infection. Pooled risk ratios and 95% confidence intervals were calculated with a random effects meta-analysis model.

Study answer and limitations 22 studies met the inclusion criteria of the review; 18 of these studies were included in the meta-analyses (12 observational studies, two randomised controlled trials, and four post hoc analyses of randomised controlled trials). The risk of recurrence of CIN2+ was reduced in individuals who were vaccinated compared with those who were not vaccinated (11 studies, 19 909 participants; risk ratio 0.43, 95% confidence interval 0.30 to 0.60; I^2=58%, τ^2=0.14). The effect estimate was even stronger when the risk of recurrence of CIN2+ was assessed for diseases related to HPV subtypes HPV16 or HPV18 (six studies, 1879 participants; 0.26, 0.16 to 0.43; I^2=0%, τ^2=0). Confidence in the meta-analysis, assessed by GRADE (Grading of Recommendations Assessment, Development, and Evaluation), ranged from very low to moderate, probably because of publication bias as well as risk of bias and inconsistency in the included studies.

What this study adds Although this systematic review and meta-analysis suggests that prophylactic HPV vaccination at the time of local treatment for CIN might reduce the risk of high grade preinvasive cervical recurrence, the evidence was inconclusive. Large, appropriately powered randomised controlled trials are required to establish the effectiveness of HPV vaccination at the time of surgical treatment of cervical preinvasive disease based on failure rates and costs in different settings.

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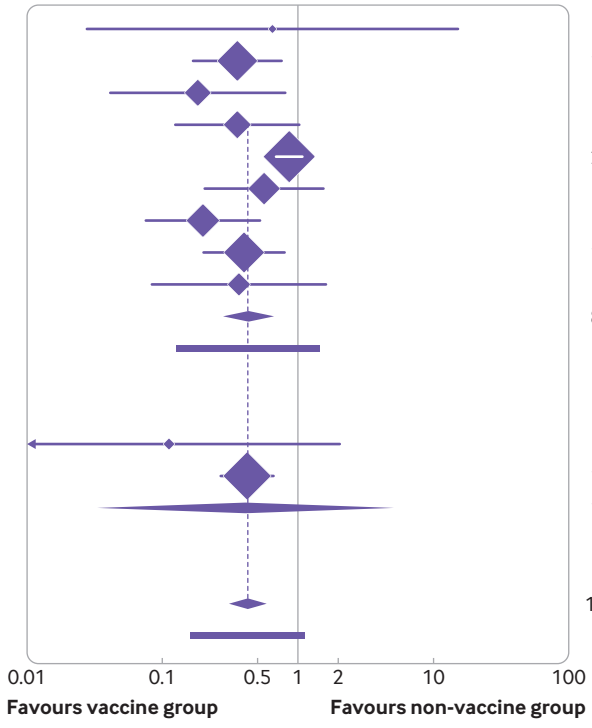
Systematic review registration PROSPERO CRD42021237350.

Study	Event V	Total V	Event C	Total C	Weight (%)	Risk ratio (95% CI)
CIN2+ recurrence rates irrespective of HPV type						
Design = observational						
Grzes 2011	0	25	1	50	1.2	0.65 (0.03 to 15.50)
Kang 2013	9	360	27	377	11.7	0.35 (0.17 to 0.75)
Ghelardi 2018	2	172	11	172	4.7	0.18 (0.04 to 0.81)
Ortega-Quinonero 2018	5	103	22	139	7.9	0.36 (0.13 to 1.03)
Sand 2019	82	2074	777	15 054	21.2	0.86 (0.67 to 1.10)
Vinnytska 2019	7	76	6	37	8.3	0.57 (0.21 to 1.57)
Del Pino 2020	5	153	12	112	8.8	0.20 (0.08 to 0.53)
Petrillo 2020	6	182	14	103	12.7	0.40 (0.20 to 0.80)
Bogani 2021	2	100	11	200	4.8	0.36 (0.08 to 1.61)
Random effects model					81.2	0.43 (0.29 to 0.64)
Prediction interval						(0.14 to 1.27)
Heterogeneity: τ^2=0.1811; P=0.01; I^2=60%						
Design = randomised controlled trial						
Pieralli 2018	0	89	4	89	1.5	0.11 (0.01 to 2.03)
Karimi-Zachri 2020	23	138	41	104	17.4	0.42 (0.27 to 0.66)
Random effects model					18.8	0.41 (0.03 to 5.13)
Prediction interval: not applicable						
Heterogeneity: τ^2=0; P=0.37; I^2=0%						
Random effects model					100.0	0.43 (0.30 to 0.60)
Prediction interval						(0.16 to 1.12)
Heterogeneity: τ^2=0.1472; P<0.01; I^2=58%						
Test for subgroup differences: χ^2=0.03, df=1, P=0.87						



Forest plots assessing risk of recurrence of cervical intraepithelial neoplasia grade 2 or higher (CIN2+) between human papillomavirus (HPV) vaccinated (V) and non-vaccinated control (C) groups after local conservative treatment for cervical intraepithelial neoplasia, irrespective of HPV type (randomised controlled trials and observational studies)