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Covid-19: is omicron less lethal than delta?

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

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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 infection.[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 linked retrospective cohort study by Ward and colleagues (doi:10.1136/bmj-2022-070695) 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]

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.

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.

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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