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Omicron: fewer adverse outcomes come with new dangers

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With wave after wave of SARS-CoV-2 variants, COVID-19 patients filled the worlds' hospitals and morgues because not everybody had access to vaccines or were willing to be vaccinated.[1,2] Omicron (B.1.1.529) is no different. Although most scientists were expecting an increase in cases during late 2021, it was surprising that vaccinated and previously infected people were contracting the novel omicron variant so easily and how fast it was transmitting,[3] which raised several questions. Would existing vaccines still prevent SARS-CoV-2 infection?[4] Was omicron more transmissible than previous variants?[5] What were the consequences of omicron's wide and rapid spread infecting millions of people, including a high number of breakthrough cases? Would it have worse or better outcomes than the worst SARS-CoV-2 variant on record, the delta variant (B.1.617.2)? In *The Lancet*, Tommy Nyberg and colleagues report their findings about omicron for individuals who are vaccinated, previously infected, or unvaccinated.[6] This outstanding study included an unparalleled 37% of SARS-CoV-2 cases in England. A longitudinal cohort was analysed when the delta variant was still ongoing and omicron outcompeted delta to become the dominant variant.

Initial omicron studies included fewer cases than included by Nyberg and colleagues[6] because analysis occurred earlier in the outbreak, such as in South Africa,[7] Denmark,[8] Norway,[9] or Scotland,[10] or were restricted to smaller regions and hospitals. Nyberg and colleagues have conducted the first large scale severity study based on 1 516 702 individuals with COVID-19, of whom 1 067 859 were infected with the omicron variant, using a mix of epidemiological and genetic molecular data.[9] This study reports both encouraging and discouraging findings related to decreased severity of disease (*vs* delta) and partial vaccine escape, respectively.

Nyberg and colleagues found that the risk of hospitalisation and death due to omicron is substantially lower than for delta. Except for children younger than 10 years, individuals with a documented previous SARS-CoV-2 infection had lower hospitalisations and deaths than for delta, even unvaccinated individuals. However, individuals who had received an mRNA vaccination faired far better than unvaccinated or previously infected individuals. Patients who had been boosted with an mRNA vaccine had 70% fewer adverse outcomes than unvaccinated individuals. This cohort was 53·2% female, all age groups were well represented, and 83·3% participants were White and 5·3% were Black. Comparing omicron with delta, the hazard ratios (HRs) were 0·56 (95% CI 0·54–0·58) for a hospital visit, 0·41 (0·39–0·43) for hospital admission, and 0·31 (0·26–0·37) for death. Past infection gave protection for omicron and delta variants against death in both vaccinated (HR 0·47 [0·32–0·68]) and unvaccinated (HR 0·18 [0·06–0·57]) individuals. Notably, for vaccinated individuals, past infection offered no additional protection (HR 0·96 [0·88–1·04]).

Coronaviruses in general have significant waning immunity requiring boosters, even with previous infections.[11] Similarly, immunised individuals or those with previous documented SARS-CoV-2 infections had little protection against contracting the omicron variant, raising the question of whether it is time to develop a novel vaccine more effective against the SARS-CoV-2 infections. Nevertheless, Nyberg and colleagues show that the individual risk of omicron versus delta for severe outcomes (such as hospitalisations and death) is significantly less. This study also highlights that, although vaccines cannot prevent infections or reinfections with the omicron variant, mRNA vaccine boosters still offer a high level of protection against hospitalisations and deaths.

Although this study is timely and an important contribution to the SARS-CoV-2 literature, there are also some limitations. Despite decreased individual risks for hospitalisation and death (omicron *vs* delta), Nyberg and colleagues did not emphasise the considerable threat to public health. Given that omicron is more transmissible than the delta variant, there were record levels of cases globally that led to record numbers of hospitalisations in some countries, such as the USA.[12] For every new infection, there is the risk of SARS-CoV-2 evolving yet again due to novel mutations, either within the omicron lineages (such as further evolution of the BA.1 and BA.2 omicron subvariants) or from new independent lineages (as has happened with every variant of concern thus far). However, as this study shows, omicron has led to a new pandemic scenario where a substantial proportion of the population in countries with high incidence rates has acquired immunity either through vaccination, infection,

or both. In this environment, spikes in hospitalisations are rarer due to a combination of pre-existing immunity and selection of less pathogenic SARS-CoV-2 variants, such as omicron. Yet, we cannot dismiss the fact that highly pathogenic or transmissible variants might develop. In low-income and middle-income countries where fewer people are vaccinated, SARS-CoV-2 will diversify more rapidly.

The global community must keep pushing for equity in access to COVID-19 vaccines and treatments in countries with low immunisation rates. Preventing the spread of SARS-CoV-2 will obstruct the virus from adapting whilst more directed data-driven prevention measures are implemented in highly immunised countries. With advancing SARS-CoV-2 knowledge—especially from large studies like that of Nyberg and colleagues—together with new and developing vaccines, treatments, and therapeutics, we might be on the precipice of more targeted, preventive measures that allow us to avoid blanket, highly restrictive policies that have harmful costs to the economy, society, and public health.

We declare no competing interests.

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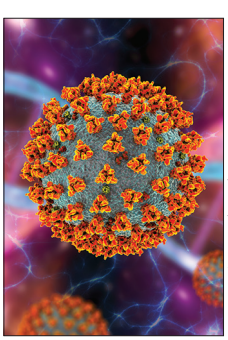
DNA vaccines join the fight against COVID-19

As of March, 2022, just over 1 year has passed since the authorisation of first-generation vaccines against COVID-19. Since then, almost 10 billion doses of COVID-19 vaccines have been administered globally.[1] Although the delivery of this number of vaccines is a remarkable achievement, there is still a disparity in vaccine equity, access, and affordability between high-income and low-income countries. According to the Global Dashboard for Vaccine Equity (established by the UN Development Programme, WHO, and the University of Oxford), as of Jan 18, 2022, approximately 67·6% of people in high-income countries have had at least one dose, compared with only approximately 11·36% of people in low-income countries.[2] This inequity has major negative implications for global pandemic control; thus, there is an imperative to develop more affordable, scalable, and easily distributable vaccines.

In the current landscape of mRNA, viral vector, and inactivated COVID-19 vaccines, one modality that has been largely under-represented is DNA vaccines. In *The Lancet*, Akash Khobragade and colleagues[3] report an interim analysis of a phase 3, randomised, double-blind, placebo-controlled study of a DNA vaccine, ZyCoV-D, against COVID-19. The vaccine contains a 2 mg dose of a DNA plasmid (pVAX-1) expressing the Wuhan Hu-1 spike antigen of SARS-CoV-2 and an IgE signal peptide, which is delivered intradermally using a needle-free injection system. Participants received three doses of vaccine or placebo at 28-day intervals. The primary outcome of this study was the number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