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Breakthrough infections with SARS-CoV-2 omicron despite mRNA vaccine booster dose

The most recent SARS-CoV-2 variant of concern to emerge has been named omicron.¹ Its immune evasion potential was predicted by genomic data and has been preliminarily confirmed by observations of an increased incidence of reinfections and breakthrough infections.² This has triggered calls to intensify vaccination programmes including provision of vaccine booster doses.³

A group of German visitors who had received three doses of SARS-CoV-2 vaccines, including at least two doses of an mRNA vaccine, experienced breakthrough infections with omicron between late November and early December, 2021, while in Cape Town, South Africa. The group consisted of five White women and two White men with an average age of 27.7 years (range 25–39) and a mean body-mass index of 22.2 kg/m² (range 17.9–29.4), with no relevant medical history. Four of the individuals were participating in clinical elective training at different hospitals in Cape Town, whereas the others were on vacation. The individuals were members of two unlinked social groups and participated in regular social life in Cape Town, in compliance with applicable COVID-19 protocols. Upon arrival during the first half of November, 2021, each individual tested negative for SARS-CoV-2 by PCR and provided records of complete vaccination, including booster or third, doses administered via intramuscular injection using homologous (n=5) and heterologous (n=2) vaccination courses (appendix p 3).⁴

Six individuals were fully vaccinated with BNT162b2 (Comirnaty, Pfizer–BioNTech, Mainz, Germany), five of whom received a third (booster) dose of BNT162b2 in October or early November, 2021.

One individual had received a full dose of CX-024414 (Spikevax, Moderna, Cambridge, MA, USA) in early October, 2021; this was not in line with the European Medicines Agency recommendations at that time, which suggested a half dose to boost healthy individuals.⁵ The seventh individual received an initial dose of ChAdOx1-S (Vaxzevria, AstraZeneca, Cambridge, UK), followed by a dose of BNT162b2 for completion of primary immunisation, and a booster dose of the same vaccine. Except for the CX-024414 booster, all vaccinations were in accordance with European recommendations.^{4,5} The early timepoints of some individuals' primary and booster vaccinations were due to their occupation in the medical field. Nobody reported a history of SARS-CoV-2 infection.

During a marked increase in incidence of SARS-CoV-2 infections in the Western Cape province, these individuals observed onset of respiratory symptoms between Nov 30 and Dec 2, 2021. SARS-CoV-2 infections were diagnosed by ISO 15189-accredited diagnostic laboratories using molecular assays approved by the national regulator.

The investigation was approved by the Health Research Ethics Committees of Stellenbosch University (C21/12/004_COVID-19) and the University of Cape Town (279/2021) and all participants provided informed consent.

We obtained swab and serum samples 2–4 days after onset of symptoms. Further details of how samples were processed are provided in the appendix (p 2). All patients were placed in domestic isolation and used a daily symptom diary to document the course of disease during the observation period of 21 days.

Illness was classified as mild (n=4) or moderate (n=3; shortness of breath) according to National Institutes of Health COVID-19 Treatment Guidelines. Two individuals were asymptomatic by the end of the observation period (day 21). Blood oxygenation levels

(SPO₂) remained in the normal range (>94%) without exception and none of the patients required hospitalisation. Prevalence of symptoms over time is provided in the appendix (p 4).

All seven individuals were infected with omicron (PANGO lineage B.1.1.529, Nextstrain clade 21K). Viral loads ranged from 4.07 to 8.22 (mean 6.38) log₁₀ viral RNA copies per mL of swab eluate. Anti-spike antibody levels ranged from 15 000 arbitrary units (AU) per mL to more than 40 000 AU/mL, with a mean of approximately 22 000 AU/mL of serum (appendix p 3).

Robust CD4 and CD8 T-cell responses to SARS-CoV-2 spike, nucleocapsid, and membrane proteins were detected in six of the participants tested after a minimum of 2 weeks after onset of symptoms (appendix p 5), at frequencies of 0.011–0.192% for CD4+ and 0.004–0.079% for CD8+ T cells.

These were the first documented breakthrough infections with the omicron variant in fully vaccinated individuals after receipt of booster vaccine doses. Some of these individuals had received heterologous vaccine doses, in line with emerging global practice. Booster doses were administered 21–37 weeks after the second vaccine doses, and breakthrough infections occurred 22–59 days thereafter. At the onset of their breakthrough infections, all individuals had high levels of viral spike protein binding antibodies, similar to levels reported 4 weeks following second vaccine doses⁶ and as expected after receipt of booster vaccine doses.⁷

Viral RNA loads in omicron variant infections have yet to be reported. It remains unknown whether the viral loads observed in our group are different from those in unvaccinated, or differently vaccinated, individuals. During wild-type SARS-CoV-2 infection, an average viral RNA load of 5.83 log₁₀ viral RNA copies per swab was found in samples taken up to day after onset of symptoms,⁸ with a maximum of 8.85 log₁₀ viral RNA copies per swab.



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For SARS-CoV-2 infections in the Western Cape province see <https://coronavirus.westerncape.gov.za/covid-19-dashboard>

See Online for appendix

For National Institutes of Health COVID-19 Treatment Guidelines see <https://www.covid19treatmentguidelines.nih.gov>

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In this group of individuals, an average of $6.38 \log_{10}$ viral RNA copies per mL of eluted swab was detected, with the highest viral load ($8.22 \log_{10}$) detected on day 4 after onset of symptoms. This suggests that the individuals were infectious, in keeping with the occurrence of infection clusters sparing none of the members of the two groups.

Specific T-cell responses were detected in all participants tested at least 2 weeks after symptom onset, in the range reported after vaccination,⁹ with additional T-cell responses to the viral nucleocapsid and membrane proteins.

The mild to moderate course of illness suggests that full vaccination followed by a booster dose still provides good protection against severe disease caused by omicron. However, we cannot exclude long-term sequelae of COVID-19. Furthermore, our findings are limited to a low number of individuals in relatively young and otherwise healthy individuals (n=7). This case series adds further evidence that, as predicted, omicron is able to evade immunity induced by mRNA vaccines in vivo. South Africa only recently introduced booster vaccinations for individuals immunised with two doses of BNT162b2, so the presence of this group from Germany presented a unique opportunity to study omicron breakthrough infections in individuals with mRNA vaccine boosters.

In-vitro data suggest lower titres of neutralising antibodies against omicron compared with other SARS-CoV-2 lineages following BNT162b2 vaccination but increased titres after a third dose,^{10–12} supporting calls for booster doses while the omicron variant appears to be spreading globally. Our study, however, demonstrates insufficient prevention of symptomatic infection in otherwise healthy individuals who had received three doses of COVID-19 mRNA vaccines.

These findings support the need for updated vaccines to provide better protection against symptomatic infection with omicron¹³ and emphasise

that non-pharmaceutical measures should be maintained. Encouragingly, early data from South Africa suggest maintained if reduced effectiveness of the BNT162b2 vaccine against hospital admission.¹⁴

CK and CKM contributed equally. We declare no competing interests.

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Stigma, vaccination, and moral accountability

Günter Kampf[†] argues that use of the term pandemic of the unvaccinated by officials in Germany is both overly simplistic and dangerous. The danger he says arises from “engender[ing] negative experiences by stigmatising parts of the population...I call on high-level officials and scientists to stop the inappropriate stigmatisation of unvaccinated people, who include our patients, colleagues, and other fellow citizens”.¹ I leave it to epidemiologists to comment on whether the description that Kampf condemns is simplistic. I disagree that it is dangerous.

Stigma involves an unwarranted or unfounded negative attribution to a group of people. It is not the same as holding a group morally accountable and responsible for