Title:

Breakthrough infections with SARS-CoV-2 Omicron variant despite booster dose of mRNA vaccine

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Abstract

Based on its genetic profile and preliminary *in vitro* and epidemiological data, the recently emerged SARS-CoV-2 Omicron variant is predicted to evade immune responses to some extent. We report a cluster of Omicron variant infections in individuals who had received full primary vaccination series and booster doses with mRNA vaccines. All patients experienced symptomatic COVID-19 but clinical manifestations were mild to moderate. Their SARS-CoV-2 viral RNA loads and anti-spike antibody levels were determined. This series proves that even three doses of mRNA vaccines may not be sufficient to prevent infection and symptomatic disease with the Omicron variant.

Keywords

SARS-CoV-2; Omicron variant; B.1.1.529; vaccine breakthrough infection; booster vaccination; COVID-19; mRNA vaccine

Contributors' statement:

Constanze Kuhlmann (CK) and Carla Konstanze Mayer (CM) (joint 1st authors) and Wolfgang Preiser (WP) (senior author) conceptualised and designed the study, obtained ethics approval and informed consent from the participants and organised logistics. CK and CM acquired clinical data and samples and analysed clinical data. WP and Megan Shaw (MS) oversaw and obtained funding for the laboratory investigations which were conducted by Tongai Maponga (TM), Mathilda Claassen (MC), Andrew Sutherland (AS) and Tasnim Suliman (TS). All authors verified data and analysed results. CK, CM and WP drafted and wrote the manuscript which was reviewed by all authors.

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The most recent SARS-CoV-2 variant of concern to emerge has been named Omicron (WHO 2021). Its immune evasion potential was predicted by genomic data and has been preliminarily confirmed by observation of increasing incidence of re-infections (Pulliam et al., 2021). This has triggered calls to intensify vaccination programmes including provision of vaccine booster doses (Dolgin, 2021).

We now report a group of German visitors who received three doses of SARS-CoV-2 vaccines, including at least two of a messenger ribonucleic acid (mRNA) vaccine, yet experienced breakthrough infections with the Omicron variant in late November / early December 2021 while in Cape Town, South Africa.

The reported group consisted of seven Caucasians (5 females, 2 males) with an average age of 27.7 (range 25-39) years with no relevant medical history. Four individuals were participating in clinical electives at different local hospitals while the others were in South Africa for vacation. On arrival during the first half of November all cases provided a negative SARS-CoV-2 PCR test and a record of complete vaccination including booster, or third, doses (Table 1) that were administered in accordance with European recommendations using homologous (n = 5) and heterologous (n = 2) vaccination courses (European Medicines Agency, 2021).

Six cases were fully vaccinated with BNT162b2 (Comirnaty; BioNTech, Mainz, Germany). Five of these received a third (booster) dose of BNT162b2 in October or early November 2021 and one received a full dose (0.5 mL, 100 mcg) of mRNA-1273 (Spikevax; Moderna, Cambridge, MA, USA) at the beginning of October. The seventh subject received an initial dose of ChAdOx1-S (Vaxzevria; AstraZeneca, Cambridge, U.K.), followed by a dose of BNT162b2 for completion of primary immunization, and a booster dose of the same vaccine. None of them had a reported history of a SARS-CoV-2 infection.

During a marked increase in incidence of SARS-CoV-2 infections in the Western Cape province (Western Cape Department of Health, 2021), these individuals observed onset of mild respiratory symptoms from 30 November to 2 December 2021. SARS-CoV-2 infections were diagnosed by ISO 15189-accredited diagnostic laboratories using molecular assays approved by the national regulator over the following days.

The investigation was approved by the Health Research Ethics Committee of Stellenbosch University (REFERENCE NUMBER TO BE INSERTED ONCE AVAILABLE) and all participants provided informed consent. We obtained clinical samples as early as logistically possible, between 2 to 4 days after onset of symptoms. Nasopharyngeal swab samples, obtained as dry swabs and stored at +4°C, were eluted in 1.5 millilitre (mL) of phosphate-buffered saline and RNA extracted using the NucliSens easyMAG system (bioMérieux SA, Marcy l'Etoile, France). Viral genome sequences were determined by Oxford Nanopore Technologies (Oxford, U.K.) sequencing on the GridION using the ARTIC V3 primers set (Engelbrecht et al., 2021) and SARS-CoV-2 RNA loads by quantitative real-time PCR using the E-gene target only (Corman et al., 2020). The *in vitro* transcribed RNA generated with the TranscriptAid T7 High Yield Transcription kit (Thermo Scientific, MA, U.S.A.) of a cloned E-gene (courtesy of J. Bhiman, NICD) was used as quantification standard. Blood samples were tested by the Quant II IgG anti-Spike 2-CoV-SARS (Abbott, Illinois, U.S.A.) to determine SARS-CoV-2 anti-spike IgG levels (Grupel et al., 2021).

All patients were placed in domestic isolation and used a daily symptom diary to document the course of disease. All individuals had symptoms compatible with COVID-19. Initial symptoms were sore throat (85.7 %), fatigue (71.4 %), headaches (57.14 %), dry cough (42.9%), chest pressure, sinus pressure, rhinitis and nausea (all reported by 28.6 %) (Table 2). Night sweats were seen in one patient within the first three days after symptom onset. As the infection progressed, all individuals developed a dry cough, 85.7 % had sinus pressure, and 71.4 % had rhinitis. Anosmia and dysgeusia were observed only temporarily (on day 3) in one patient. Fever was reported by 14.3 % of patients. At the end of the

observation period (day 7), dry cough (100 %), rhinitis (71.4 %), sore throat (57.1 %) and shortness of breath (42.9 %) were the predominant symptoms, with a general reduction of symptom severity. Overall, all cases described their symptoms as mild or moderate and none required hospitalisation during the observation period (Figure 1). Blood oxygenation levels remained in the normal range without exception.

Five of the cases were confirmed to be due to infection with the SARS-CoV-2 Omicron variant (PANGO lineage B.1.1.529, Nextstrain clade 21K); in two cases sequencing failed but they are inferred to be Omicron, too, based on their very close epidemiological links to the others.

Viral loads ranged from 1.41 x 10E4 to 1.65 x 10E8 (mean 4.16 x 10E7) viral RNA copies per mL of swab eluate, with highest averages (mean 6.69 x 10E7) on day 4 after symptom onset.

Anti-spike antibody levels ranged from 15,011.2 to > 40,000 with a mean of approximately 23,000 arbitrary units / millilitre (AU/mL) of serum (Table 3). These values are very similar to those reported by Grupel et al (2021) for four weeks following the second vaccine dose.

This case series is the first to report, and characterise, breakthrough infections with the Omicron variant in individuals fully vaccinated and having received a vaccine booster dose. We include those with heterologous booster doses in line with what is becoming global practice.

Booster doses were administered between 5 and 10 months after the second vaccine doses, and breakthrough infections occurred one to two months thereafter.

All individuals experiencing breakthrough infections had high levels of viral spike protein binding antibodies. This is expected after receipt of booster vaccine doses (Demonbreun et al., 2021), even in the absence of prior SARS-CoV-2 infection.

Viral RNA loads in Omicron variant infections have not yet been reported. It is thus 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 6.76 x 10^5 copies per swab was found in samples taken up to day 5 post-onset of symptoms (Wölfel et al., 2020), with a maximum of 7.11 x 10^8 copies per swab. In this group of individuals, an average of 4.16 x 10^7 was observed and the highest viral load detected was 1.65 x 10^8 copies per mlL of eluted swab on day 4 after onset of symptoms. This might indicate higher viral loads in samples from patients infected with the Omicron variant but should be regarded as preliminary.

During the first week after onset of symptoms a mild clinical course was observed. This suggests that full vaccination followed by a booster dose still provides good protection against severe COVID-19. However, the observation period is short and does not exclude subsequent deterioration or long-term sequelae of COVID-19.

This case series proves that, as predicted, the Omicron variant is able to evade immunity induced by mRNA vaccines *in vivo*. South Africa has yet to introduce 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. Hitherto unpublished *in vitro* data suggest lower titres of neutralising antibodies against the Omicron variant, compared to other SARS-CoV-2 lineages, following BNT162b2 vaccination but increased titres after a third dose (Cele et al., 2021; Wilhelm et al., 2021; Pfizer, 2021), supporting calls for booster doses while the Omicron variant may be spreading globally. Our report, however, shows that this is insufficient to prevent symptomatic infection and emphasises the need to maintain additional non-pharmaceutical interventions.

While our findings underscore the need for updated vaccines to provide better protection against symptomatic infection with the Omicron variant (Devlin and Kollewe, 2021), protection from severe disease is probably still intact in individuals who have received booster doses.

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Table 1: Basic demographic data and vaccination history of cases

ID	age/ years	sex	1st dose		2nd dose		3rd dose	
			date	vaccine	date	vaccine	date	vaccine
1	26	f	7 Feb 2021	BNT162b2	28 Feb 2021	BNT162b2	10 Nov 2021	BNT162b2
2	27	f	30 Dec 2020	BNT162b2	19 Jan 2021	BNT162b2	3 Oct 2021	mRNA-1273 (100 mcg)
3	39	m	28 Apr 2021	BNT162b2	13 May 2021	BNT162b2	8 Nov 2021	BNT162b2
6	25	f	21 Jan 2021	BNT162b2	11 Feb 2021	BNT162b2	26 Oct 2021	BNT162b2
7	25	f	26 Mar 2021	BNT162b2	7 May 2021	BNT162b2	3 Nov 2021	BNT162b2
8	25	m	30 Apr 2021	BNT162b2	11 Jun 2021	BNT162b2	3 Nov 2021	BNT162b2
14	27	f	28 Feb 2021	ChAdOx1-S	3 May 2021	BNT162b2	26 Oct 2021	BNT162b2

Legend: ID = Patient Identification No.; BNT162b2 (Comirnaty, BioNTech, Mainz, Germany); mRNA-1273 (Spikevax; Moderna, Cambridge, MA, USA); ChAdOx1-S (Vaxzevria, AstraZeneca, Oxford, UK).

Table 2: Prevalence (in %) of clinical symptoms during different time points of the observation period.

	Prevalence (%)			
Clinical symptoms	Day 1	Day 3	Day 5	Day 7
Anosmia	0	14.3	0	0
Backpain	0	14.3	14.3	0
Chest pain	0	14.3	14.3	14.3
Chest pressure	28.6	14.3	14.3	14.3
Diarrhoea	0	0	0	0
Dry cough	42.9	85.7	100	100
Dysgeusia	0	14.3	0	0
Fatigue	71.4	57.1	57.1	57.1
Fever	14.3	14.3	14.3	14.3
Headache	57.1	57.1	28.6	42.9
Myalgia	0	28.6	14.3	28.6
Nausea	28.6	0	0	0
Night sweat	14.3	14.3	0	0
Red eyes	0	0	0	0
Rhinitis	28.6	57.1	57.1	71.4
Shortness of breath	0	28.6	42.9	42.9
Sinus pressure	28.6	85.7	71.4	57.1
Skin rash	0	0	14.3	14.3
Sore throat	85.7	85.7	85.7	57.1

Legend: Day 1 = Onset of symptoms, Day 7 = End of observation

Table 3: Laboratory results of cases

ID	Interval / days	PANGO lineage	SARS-CoV-2 viral load	Anti-SARS-CoV-2 spike antibody results
1	2	B.1.1.529 inferred	3,69 x 10^4 copies / ml	15011 AU / ml
2	4	B.1.1.529	1,65 x 10^8 copies / ml	> 40000 AU / ml
3	2	B.1.1.529	1,41 x 10^4 copies / ml	23026 AU / ml
6	4	B.1.1.529	4,67 x 10^5 copies / ml	19123 AU/mL
7	4	B.1.1.529	9,65 x 10^7 copies / ml	18507 AU/mL
8	3	B.1.1.529	2,35 x 10^7 copies / ml	16752 AU/mL
14	4	B.1.1.529 inferred	5,89 x 10^6 copies / ml	No sample tested

Legend: ID = patient identifier; Interval = interval between symptom onset and sample collection; copies / ml = viral RNA copies / ml sample; AU = arbitrary unit.

SEQUENCES HAVE BEEN SUBMITTED TO GISAID AND ACCESSION NUMBERS WILL BE ADDED AS SOON AS AVAILABLE

Figure 1. Self-assessment of symptom severity in daily symptom diaries. The patients could choose to describe their symptoms as mild, moderate or severe. None of the patients reported symptoms perceived as severe during the observation period.