Breakthrough Covid-19 infections during periods of circulating Beta, Delta and Omicron variants of concern, among health care workers in the Sisonke Ad26.COV2.S vaccine trial, South Africa

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Abstract

Background: We report breakthrough infections (BTIs) during periods of circulating Beta, Delta and Omicron variants of concern, among health care workers (HCW) participating in the Sisonke phase 3B Ad26.COV2.S vaccine trial (ClinicalTrials.gov number, NCT04838795). Data were gathered between 17 February and 15 December 2021. Duration of each period in this study was 89 days for Beta, 180 days or Delta and 30 days for Omicron.

Results: A total of 40 538 BTIs were observed, with 609 during Beta, 22 279 during Delta and 17 650 during Omicron. By 15 December, daily infections during Omicron were three times that seen during the peak observed during Delta. However, unlike the Delta period, with Omicron there was a clear and early de-coupling of hospitalisation from cases as a percentage of the Delta peak curves. Omicron significantly infected a greater proportion of HCW in the 18-30 year age-group, compared with the 55+ age group. There were 1 914 BTI-related hospitalisations - 77, 1 429 and 408 in the Beta (89 days), Delta (180 days) and Omicron (30 days) periods, respectively. During Omicron, 91% hospitalized HCWs required general ward care, 6% high care and 3% intensive care, compared with 89% general ward care, 4% high care and 7% intensive care, during Delta and 78% general care, 7% high care and 16% intensive care during Beta ($p<0.001$). During Beta and Beta 43% of hospitalized HCW needed supplementary oxygen and 7-8% needed ventilation, compared with 16% and 0.2% respectively during the Omicron period ($p<0.001$). Median length of hospitalization was significantly lower with Omicron compared with Beta and Delta (3 days compared with 5-6 days, $p<0.001$).

Conclusions: We illustrate more BTIs but reassuringly less severe Covid-19 with Omicron. Re-infections and Omicron-driven primary infections were likely driven by high population SARS-CoV-2 seroprevalence, waning vaccine effectiveness over time, increased Omicron infectivity, Omicron immune evasion or a combination of these and need further investigation. Follow-up of this cohort will continue and reports will be updated, as time and infections accrue.

Introduction:

South Africa reported a new SARS-CoV-2 variant in November 2021.[1-3] This variant, named Omicron, declared a variant of concern (VOC) on 26 November 2021[4], spread exponentially, replacing Delta, and driving rapid increases in Covid-19 cases.[5,6] In vitro experiments demonstrate that Omicron escapes antibody neutralization in previously infected or vaccinated.[7,8] Epidemiological data suggest reduced vaccine effectiveness[9] and higher re-infection rates compared with Beta and Delta VOC.[10] There is sparsity of data on the severity of Omicron-driven break-through infections (BTI), defined as positive SARS-CoV-2 polymerase chain reaction or antigen tests 28 days or more post vaccination. We describe BTIs during periods of circulating Beta, Delta and Omicron variants of concern, among health care workers (HCW) participating in the Sisonke phase 3B Ad26.COV2.S vaccine trial (ClinicalTrials.gov number, NCT04838795).[11] The Sisonke trial was conducted in up to 350 vaccination centres, across all nine provinces of South Africa. Study procedures included an electronic consent process, on-site check for vaccination eligibility, and post-vaccination safety monitoring. Using the national Electronic Vaccination Data System (EVDS), HCW self-reported demographic characteristics and comorbidities and vaccinators recorded vaccination details. The trial administered a single dose Ad26.COV2.S vaccine to 477 234 HCWs between 17 February and 17 May 2021; 230 488 HCW voluntarily received a second Ad26.COV2.S dose between 9 November and 16 December 2021. We evaluate BTI frequency and severity between the 3 March and 15 December 2021, using proxy dates for the three VOC periods: Beta (17 February (Sisonke study start)-17 May 2021 (89 days)), Delta (18 May-14 November 2021 (180 days)) and Omicron (15 November-15th December 2021 (30 days)).

Methods

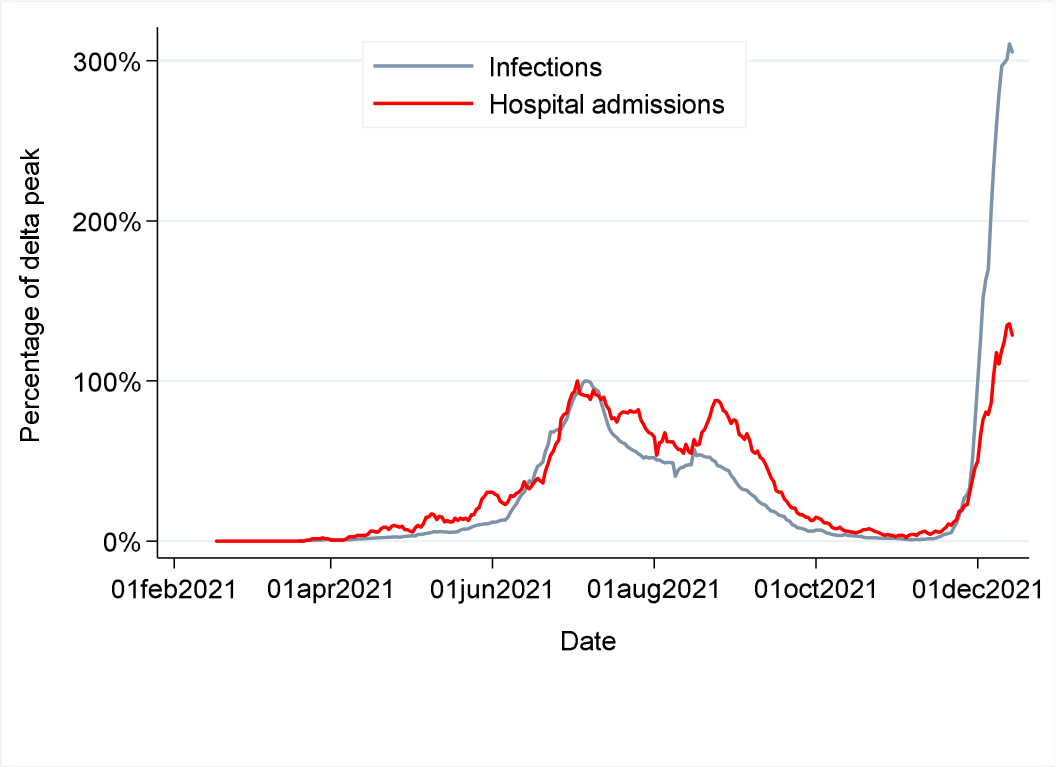
BTIs were monitored using active and passive surveillance. Linkage of Sisonke trial data with the Covid-19 Notifiable Medical Conditions Sentinel Surveillance (NMCSS) master list, DATCOV (COVID-19 related hospitalizations) list and National Population Register held by the South African Medical Research Council identified participants with Covid-19 infections/re-infections, Covid-19-related hospitalisations and deaths. Additionally, Sisonke trial participants received text messages post-vaccination encouraging them to report BTIs telephonically or via a

web-link. The protocol safety team contacted all hospitalised participants to confirm severity and ascertain outcome. HCWs with re-infections were included in all relevant study periods.

Results:

A total of 40 538 BTIs were observed, with 609 during Beta, 22 279 during Delta and 17 650 during Omicron. By 15 December, daily infections during Omicron were three times that seen during the peak observed during Delta (Supplementary Figure 1). However, unlike the Delta period, with Omicron there was a clear and early de-coupling of hospitalisation from cases as a percentage of the Delta peak curves (Figure 1).

Figure 1: Daily cases and admissions expressed as a proportion of delta peak



Omicron significantly infected a greater proportion of HCW in the 18-30 year age-group - 15% during Delta versus 21% during Omicron, and fewer in the 55+ age group (20% during Delta versus 13% during Omicron, $p<0.001$), Table 1.

Table 1: Description of breakthrough infections amongst vaccinated HCW for the Beta, Delta and Omicron periods, respectively

	Beta Period* 89 days		Delta Period* 180 days		Omicron Period* 30 days			Total	
	N	%	N	%	N	%	p-value	N	%
Sex							<0.001		
female	453	74.4	16977	76.2	13769	78		31199	77
male	156	25.6	5302	23.8	3881	22		9339	23
Total	609		22279		17650			40538	
Age							<0.001		
18-30	95	15.6	3304	14.8	3623	20.5		7022	17.3
31-54	367	60.3	14576	65.4	11764	66.7		26707	65.9
55+	147	24.1	4399	19.7	2262	12.8		6808	16.8
Total	609		22279		17649			40537	
Province							<0.001		
Eastern Cape	13	2.1	1852	8.3	1573	8.9		3438	8.5
Free State	164	26.9	1200	5.4	1159	6.6		2523	6.2
Gauteng	151	24.8	7831	35.1	8110	45.9		16092	39.7
KwaZulu-Natal	29	4.8	2420	10.9	2271	12.9		4720	11.6
Limpopo	12	2	1472	6.6	929	5.3		2413	6
Mpumalanga	50	8.2	882	4	610	3.5		1542	3.8
North West	57	9.4	1031	4.6	727	4.1		1815	4.5
Northern Cape	59	9.7	440	2	174	1		673	1.7
Western Cape	74	12.2	5151	23.1	2097	11.9		7322	18.1
Total	609		22279		17650			40538	

* Proxy dates for the Beta, Delta and Omicron periods, respectively were 17 February (Sisonke study start)-17 May 2021 (89 days), 18 May-14 November 2021 (180 days) and 15 November-15th December 2021 (30 days)

There were 1 914 BTI-related hospitalisations - 77, 1 429 and 408 in the Beta, Delta and Omicron periods, respectively (Table 2). The proportion of BTI-related hospitalisations in the 31-54 year age group significantly increased from 51% during Beta to 60% during Delta and 67% during the Omicron periods, with a concomitant reduction in the 55+ age group (46% during Beta, to 33% during Delta and 19% during Omicron ($p<0.001$; Table 2)). Compared with the Beta and Delta periods, the prevalence of hypertension and diabetes in hospitalized HCW was significantly lower during Omicron, (Table 2); 47% hypertension and 25% diabetes during Beta, respectively, versus 35% and 23% during Delta and 23% and 10% respectively during Omicron, $p<0.001$.

During Omicron, 91% hospitalized HCWs required general ward care, 6% high care and 3% intensive care. This was significantly different from 89% general ward care, 4% high care and 7% intensive care, during Delta and 78% general care, 7% high care and 16% intensive care during Beta ($p<0.001$).

During Beta and Beta 43% of hospitalized HCW needed supplementary oxygen and 7-8% needed ventilation, compared with 16% and 0.2% respectively during the Omicron period ($p<0.001$).

Amongst HCWs discharged from hospital with available data (n=1 780 of 1914), the median length of hospitalisation was 6 days (IQR 4-11; n=77) for Beta, 5 days (IQR 3-9; n=1416) for Delta and 3 days (IQR 1-5; n=287) days for Omicron, with significant differences between Omicron and Delta, $p<0.0001$.

Of the 17 650 infections during the Omicron period, 28 (2%) were previously infected during the Beta period and 786 (5%) during the Delta period, possibly signifying some cross-protection from Beta VOC infections. There were no significant differences in baseline characteristics (age, sex, comorbidities) between re-infected HCW who were initially infected during the Beta versus Delta periods.

Table 2: Description of characteristics of hospitalized, vaccinated HCW by period

	Beta Period* 89 days		Delta Period* 180 days		Omicron Period* 30 days			Total	
	N	%	N	%	N	%	p-value	N	%
Sex							<0.001		
Female	56	72.7	1057	74	348	85.3		1461	76.3
Male	21	27.3	372	26	60	14.7		453	23.7
Total	77		1429		408			1914	
Age							<0.001		
18-30	3	3.9	95	6.6	57	14		155	8.1
31-54	39	50.6	861	60.3	275	67.4		1175	61.4
55+	35	45.5	473	33.1	76	18.6		584	30.5
Total	77		1429		408			1914	
Province							<0.001		
Eastern Cape	1	1.3	118	8.3	26	6.4		145	7.6
Free State	16	20.8	96	6.7	21	5.1		133	6.9
Gauteng	16	20.8	394	27.6	177	43.4		587	30.7
KwaZulu-Natal	5	6.5	261	18.3	88	21.6		354	18.5
Limpopo	0	0	84	5.9	29	7.1		113	5.9
Mpumalanga	2	2.6	56	3.9	17	4.2		75	3.9
North West	19	24.7	131	9.2	20	4.9		170	8.9
Northern Cape	8	10.4	39	2.7	6	1.5		53	2.8
Western Cape	10	13	250	17.5	24	5.9		284	14.8
Total	77		1429		408			1914	
Cancer									
No	76	98.7	1418	99.2	402	98.5		1896	99.1
Yes	1	1.3	11	0.8	6	1.5		18	0.9
Total	77		1429		408			1914	
TB									
No	77	100	1428	99.9	408	100		1913	99.9
Yes	0	0	1	0.1	0	0		1	0.1
Total	77		1429		408			1914	
HIV							0.074		
No	76	98.7	1347	94.3	377	92.4		1800	94
Yes	1	1.3	82	5.7	31	7.6		114	6
Total	77		1429		408			1914	
Hypertension							<0.001		
No	41	53.2	934	65.4	314	77		1289	67.3
Yes	36	46.8	495	34.6	94	23		625	32.7
Total	77		1429		408			1914	
Diabetes							<0.001		
No	57	74	1101	77	369	90.4		1527	79.8
Yes	20	26	328	23	39	9.6		387	20.2
Total	77		1429		408			1914	

Chronic Lung Disease									
No	76	98.7	1414	99	405	99.3		1895	99
Yes	1	1.3	15	1	3	0.7		19	1
Total	77		1429		408			1914	
Ward upon Admission							<0.001		
General Ward	60	77.9	1276	89.3	372	91.2		1708	89.2
High care	5	6.5	60	4.2	25	6.1		90	4.7
Intensive Care Unit	12	15.6	93	6.5	11	2.7		116	6.1
Total	77		1429		408			1914	100
Ever Ventilated							<0.001		
No	68	91.9	1272	92.9	401	99.8		1741	94.4
Yes	6	8.1	97	7.1	1	0.2		104	5.6
Total	74		1369		402			1845	
Ever Oxygenated							<0.001		
No	42	56.8	784	57.3	336	83.6		1162	63
Yes	32	43.2	585	42.7	66	16.4		683	37
Total	74		1369		402			1845	

* Proxy dates for the Beta, Delta and Omicron periods, respectively were 17 February (Sisonke study start)-17 May 2021 (89 days), 18 May-14 November 2021 (180 days) and 15 November-15th December 2021 (30 days)

Discussion

We report on the first 30-days of the Omicron period and it may be too early to measure the full effect of the Omicron VOC. However, 30 days into the Omicron period, BTI cases had far surpassed that seen during the Delta peak. We did not account for person-time in follow-up - we present proportions by period. We included all hospitalized BTIs across all study periods, including incidental diagnoses amongst asymptomatic HCWs hospitalized for other reasons e.g. surgery; thus the number and proportion of BTIs needing Covid-19-related hospitalisation is likely over-estimated. Lastly, the course of COVID-19 due to Omicron in South Africa may be tempered by high population SARS-CoV-2 seroprevalence which was as high as 68% in some populations by April 2021; thus our findings may not be generalizable to all settings or populations globally.[12]

Despite these limitations, our large dataset provides an early snapshot of the effect of Omicron in a low-middle income, high SARS-CoV-2 seroprevalence setting. We illustrate more BTIs but reassuringly less severe Covid-19 with Omicron. Re-infections and Omicron-driven primary infections were likely driven by high population SARS-CoV-2 seroprevalence, waning vaccine effectiveness over time, increased Omicron infectivity, Omicron immune evasion or a

combination of these and need further investigation. Follow-up of this cohort will continue and reports will be updated, as time and infections accrue.

References

1. Chotiner I. How South African Researchers Identified the Omicron Variant of COVID. The New Yorker. 2021 30 November 2021. Available from https://www.newyorker.com/news/q-and-a/how-south-african-researchers-identified-the-omicron-variant-of-covid. Accessed 17 December 2021.
2. Callaway E. Heavily mutated Omicron variant puts scientists on alert. Nature Magazine. 2021. Available from https://www.scientificamerican.com/article/heavily-mutated-omicron-variant-puts-scientists-on-alert/. Accessed 17 December 2021.
3. National Institute for Communicable Diseases. New COVID-19 variant detected in South Africa. 2021. Available from https://www.nicd.ac.za/new-covid-19-variant-detected-in-south-africa/. Accesses 18 December 2021.
4. World Health Organization. Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern. Available from https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern. Accesed 17 December 2021.
5. Grabowski F, Kochańczyk M, Lipniacki T. Omicron strain spreads with the doubling time of 3.2—3.6 days in South Africa province of Gauteng that achieved herd immunity to Delta variant. *MedRxiv* 2021: doi: https://doi.org/10.1101/2021.12.08.21267494.
6. de Oliveira T, Venter M, Bhiman J, Scheepers C, Preiser W. Here's what Omicron can tell us about how COVID-19 variants are discovered. World Economic Forum, 2021. Available from https://www.weforum.org/agenda/2021/11/coronavirus-variant-discovery-omicron-health/. Accessed 17 December 2021.
7. Callaway E. Omicron likely to weaken COVID vaccine protection. Nature. 2021. Available from https://www.nature.com/articles/d41586-021-03672-3. Accessed 17 December 2021.
8. Wilhelm A, Widera M, Grikscheit K, et al. Reduced Neutralization of SARS-CoV-2 Omicron Variant by Vaccine Sera and Monoclonal Antibodies. 2021; **MedRxiv**: doi: https://www.medrxiv.org/content/10.1101/2021.12.07.21267432v4.
9. Discovery Health. Discovery Health, South Africa's largest private health insurance administrator, releases at-scale, real-world analysis of Omicron outbreak based on 211 000 COVID-19 test results in South Africa, including collaboration with the South African Medical Research Council. Johannesburg; 2021. Available from https://www.discovery.co.za/corporate/news-room. Accessed 17 December 2021.
10. Pulliam J, van Schalkwyk C, Govender N, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa. *medRxiv* 2021: doi: https://doi.org/10.1101/2021.11.11.21266068.
11. Bekker L, Garrett N, AE G, et al. Effectiveness of Ad26.COV2.S vaccine in health care workers in South Africa. *the Lancet* 2021: in press.
12. Kleynhans J, Tempia S, Wolter N, et al. SARS-CoV-2 Seroprevalence in a Rural and Urban Household Cohort during First and Second Waves of Infections, South Africa, July 2020–March 2021. . *Emerg Infect Dis* 2021; **27**(12): 3020-9. https://doi.org/10.201/eid2712.211465.