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South African Ox1Cov-19 Vaccine VIDA-Trial

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Acknowledgements

- Volunteers who participated in the study.
- Staff at seven clinical trains and other scientific collaborators across Gauteng, KZN and Western Cape.
- Sponsor:
  - University of Oxford
- Funders:
  - South African Medical Research Council/Department of Science and Innovation
  - The Bill and Melinda Gates Foundation

Study overview of non-replicating simian adenovirus Covid-19 vaccine (ChAdOx1/nCoV19)

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- Adults age 18 to 65 years, without HIV and severe co-morbidities.
- Study design: Phase Ib/IIa randomised, double-blind placebo controlled trial.
- Two doses of ChAdOx1-nCoV19 (3.5-5.0 x 10^5 vp) or placebo (0.9%NaCl).
- Co-primary objectives in people without HIV:
  - Safety.
  - Efficacy against NAAT confirmed Covid-19 >14 days after the booster dose.
- Endpoint driven analysis: Power to show at least 60% efficacy (Lower bound 95%CI >0%).

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Demographics of overall vaccine efficacy evaluable population.

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Variable	Overall	Placebo	Vaccine
N enrolled	1749	865	884
Male n (%)	987 (56.4)	476 (55)	510 (57.7)
Median Age in years (IQR)	31 (24-40)	30 (24-40)	31 (24-40)
Race n(%)			
Black African	1192 (68.3%)	585 (67.9%)	606 (68.6%)
Mixed	281 (16.1%)	138 (16%)	143 (16.2%)
White	238 (13.6%)	123 (14.3%)	115 (13%)
Other	35 (2%)	16 (1.9%)	19 (2.2%)
Health worker	154 (8.8)	85 (9.8)	69 (7.8)
Obese (BMI:≥30 to <40)	339 (19.4%)	179 (20.7%)	160 (18.2%)
Hypertension	54 (3.1%)	25 (2.9%)	29 (3.3%)
Respiratory system	59 (3.4%)	25 (2.9%)	34 (3.8%)
Diabetes	8 (0.3%)	4 (0.2%)	4 (0.4%4)
Median days between doses; (IQR)	28 (28-32)	28 (28-32)	28 (28-32)

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Covid-19 severity scoring system used in the study.

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Screening symptoms to investigate for Covid-19

Respiratory	Non-Respiratory
New onset cough	Fever or feverishness
New onset rapid breathing	Myalgia (or muscle ache)
New onset shortness of breath/difficulty breathing)	Chills
Sore throat	Loss/disturbance of taste
Loss of smell (or smell disturbance)	Headache
Nasal congestion	Diarrhea
Runny nose	Tiredness/fatigue/weakness)
	Nausea or vomiting
	Loss of appetite

Mainly mild and some moderate Covid-19 cases occurred among study participants.

COVID-19 Severity	Endpoint Definitions
Mild	Any one of: • Fever (defined by subjective or objective measure, regardless of use of anti-pyre medications) • New onset cough • ≥ 2 COVID-19 respiratory/non-respiratory symptoms in (Supplementary Table S1 **AND** • Does not meet criteria for moderate or severe
Moderate	≥ 1 of: • Fever (≥ 37.8°C) + any 2 COVID-19 symptoms in Supplementary Table S1 for ≥ 3 (need not be contiguous days) • High fever (≥ 38.4°C) for ≥ 3 days (need not be contiguous days) • Any evidence of significant LRTI: – Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (beyond baseline) – Tachypnea: 20 to 29 breaths per minute at rest – SpO_2: < 94% on room air – Abnormal chest x-ray/CT consistent with pneumonia or LRTI – Adventitious sounds on lung auscultation
Severe	≥ 1 of: • Tachypnea: ≥ 30 breaths per minute at rest • SpO_2: < 92% on room air or PAO_2/FiO_2 < 300 • High flow oxygen therapy, CPAP, or NIV (eg, CPAP/BiPAP) • Mechanical ventilation or ECMO • One or more major organ system failure[a] (eg, cardiac/circulatory, pulmonary, rei hepatic to be defined by diagnostic testing/clinical syndrome/interventions)

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Temporal association of Covid-19 trajectory, receipt of injection and circulation of different SARS-CoV-2 variants in South Africa.

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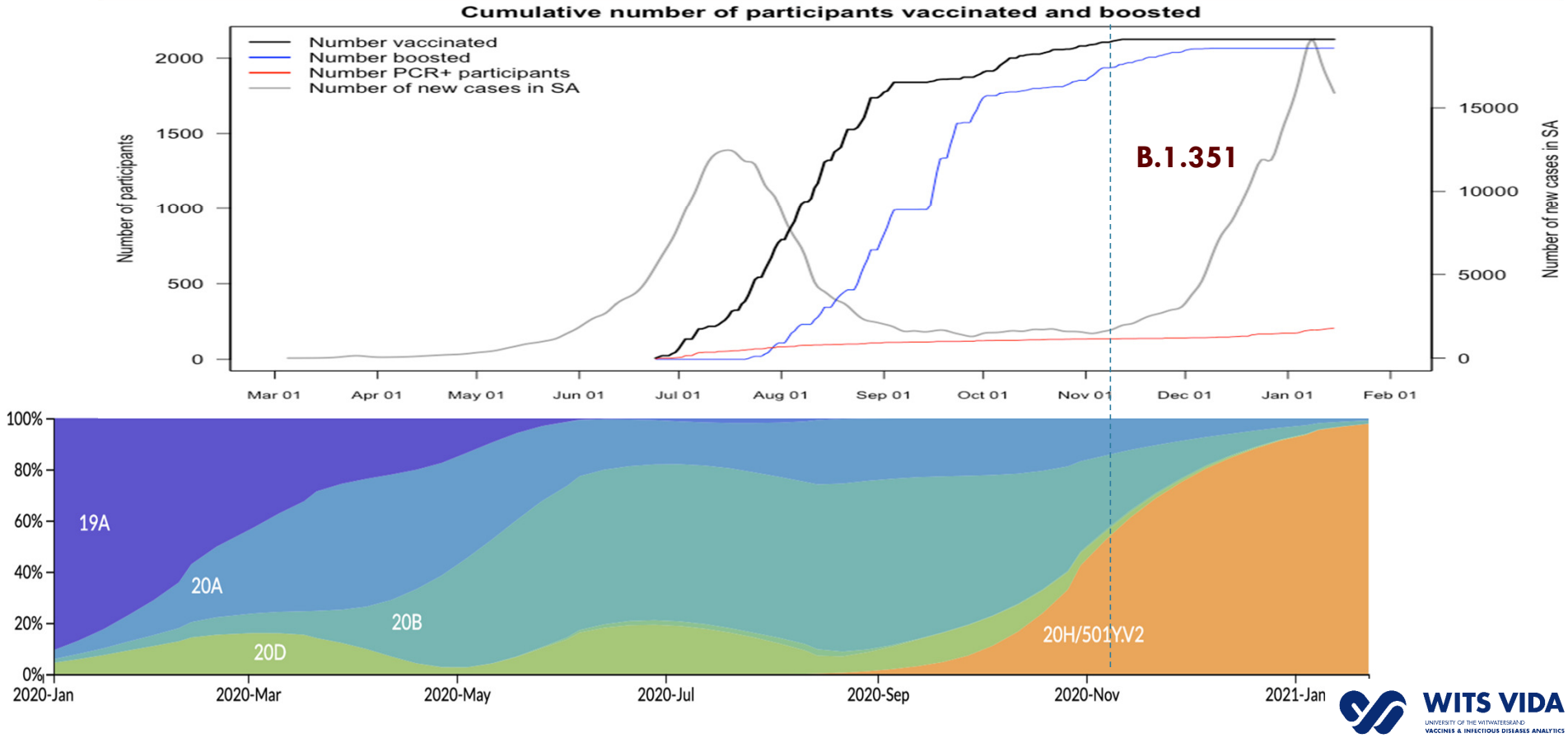

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ChAdOx1 nCoV-19 induces similar neutralizing antibody responses in South Africa, UK and Brazil.

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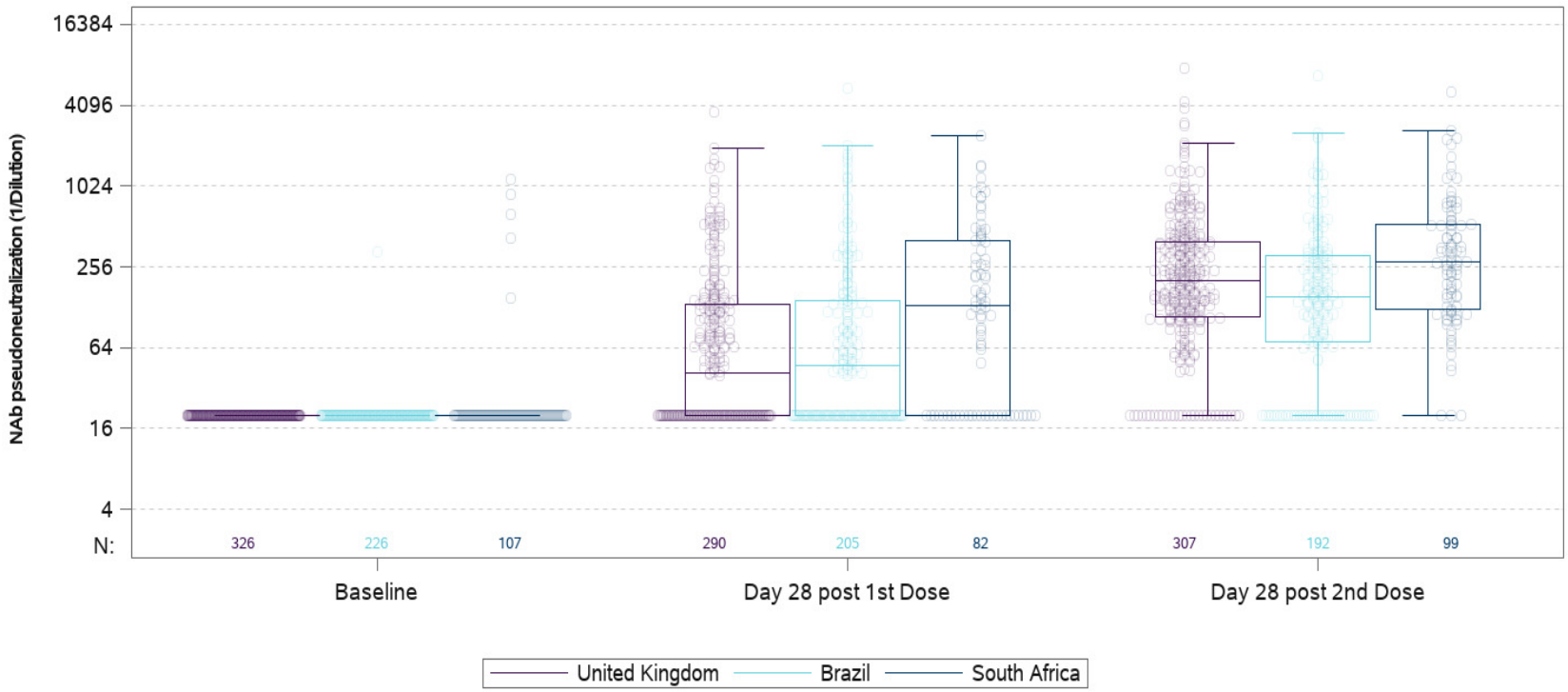
Pseudo-neutralization assay measuring neutralizing antibody to prototype virus.



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Covid-19 cases from >14 days after the 1st dose until 31st October 2020 (proxy for non-B.1.351 variant).

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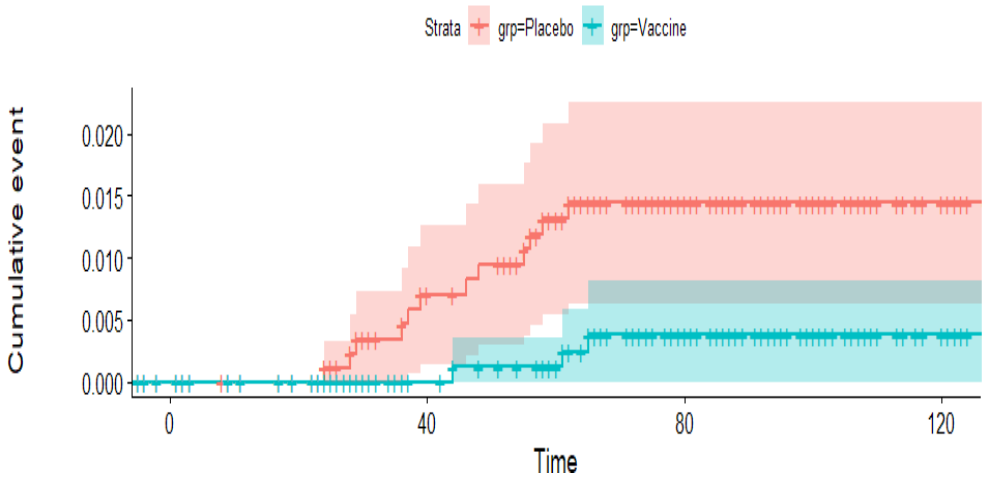

75% risk reduction in mild-moderate Covid-19 occurring at least 14 days after single dose of ChAdOx1/nCoV19 prior to evolution of B.1.351 variant In South Africa.

Baseline serology	Total cases	Placebo n/N (%)	Incidence Risk*	Vaccine n/N (%)	Incidence Risk	Vaccine Efficacy (95%CI)
>14 days post-prime and <=2020-10-31						
Overall	15	12/938 (1.3%)	31.1	3/944 (0.3%)	7.6	75.4% (8.9 to 95.5)
Negative	9	7/776 (0.9%)	21.7	2/804 (0.2%)	5.9	72.8% (-42.8 to 97.2)

*Per 1,000 person years

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SARS-CoV-2 spike mutations are occurring in humans and animals.

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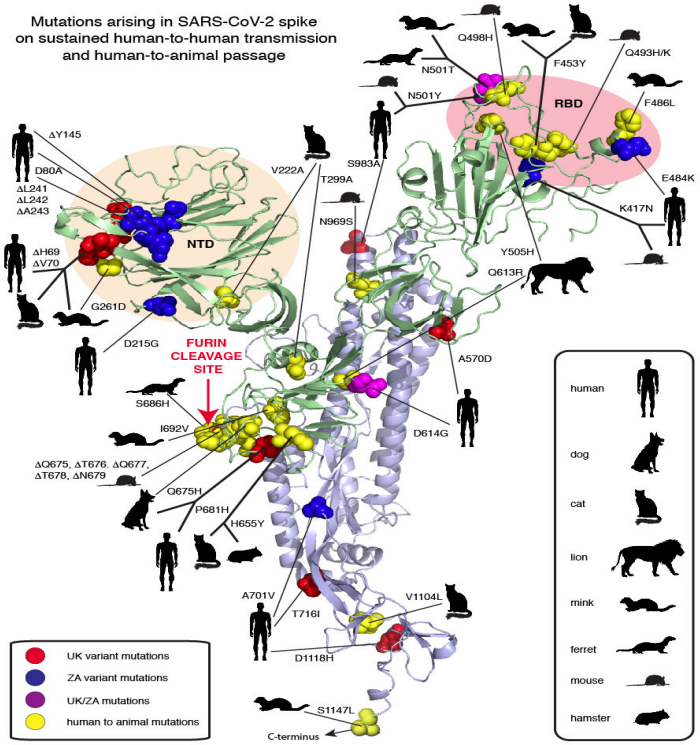
Mutations in SAR-CoV2 have been constantly occurring as would be expected for a RNA virus..



….but the emerging variants in the UK, South Africa and Brazil have multiple mutations and are of concern

- Epidemiology
- Impact on natural immunity and reinfection risk
- Impact on vaccines
- Impact on monoclonal antibody therapies
- Diagnostics
- Plans for Vx roll out

Robert Garry - virological.org

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501Y.V2 & B.1.1.7: overlapping but distinct SPIKE mutations

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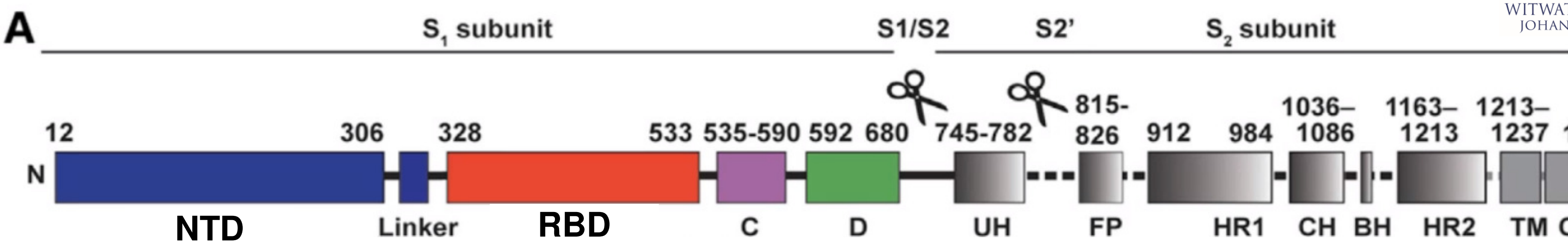

501Y.V2 (SA) L18F D80A D215G K417N E484K **N501Y** **D614G** A701V

B1.1.7 (UK) 69-70del Y144del **N501Y** A570D **D614G** P681H T716L S982A D1118H

P.1 (Brazil) L18F P26S D138Y T20N R190S K417N E484K N501Y D614G H655Y T1027I

Mutations in the RBD and NTD are of particular concern for ACE2 interactions and neutralizing antibodies:

- **N501Y** is in all three lineages. It **enhances binding affinity to ACE2 and may increase infectivity**. This is a site of recognition of some NAbs, can arise in immunocompromised individuals and is observed in mouse adapted strains-enabling efficient replication.
- **E484K** also enhances ACE2 binding and is a **key recognition site of class II NAbs** (eg Ly-COV555). Seen in mouse adapted strains and can appear under immunological selection in humans. It is associated with resistance to neutralization by polyclonal sera.
- **K417N** is a **site of recognition of class I NAb** with VH3-53. It makes direct contact with ACE2. Seen in mouse adapted strains where it is associated with increased pathogenicity.
- **69-70del** has arisen in mink mutants and in patients treated with convalescent plasma (Gupta et al)
- Neutralizing Abs directed against the **NTD domain target** a single supersite (Cerutti et al and McCallum et al)

Tegally et al medRxiv Dec 21, 2020, Nelson et al.

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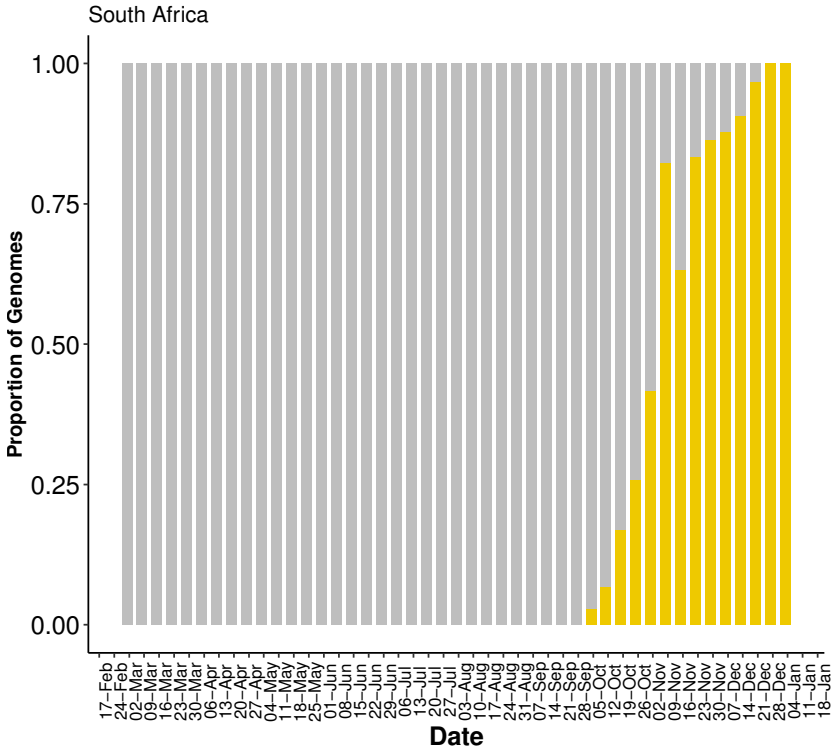
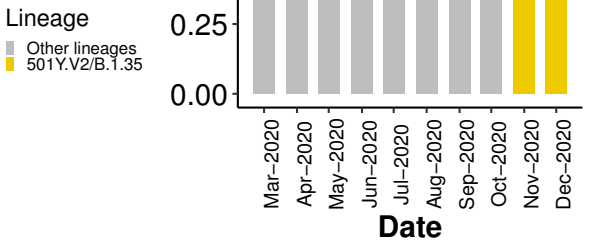
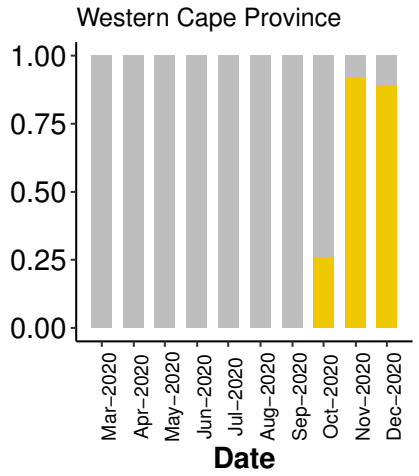
Evolution of B.1.351 variant in South Africa and study site settings.







B.1.351 variant only identified
In Cape Metro week 23rd Nov

Source: GISAID + NICD report (DOMINANCE OF THE SARS-COV-2 501Y.V2 LINEAGE IN GAUTENG - 28 Jan 2021)

Sequencing alignment of 42 primary endpoint cases among vaccine and placebo recipients

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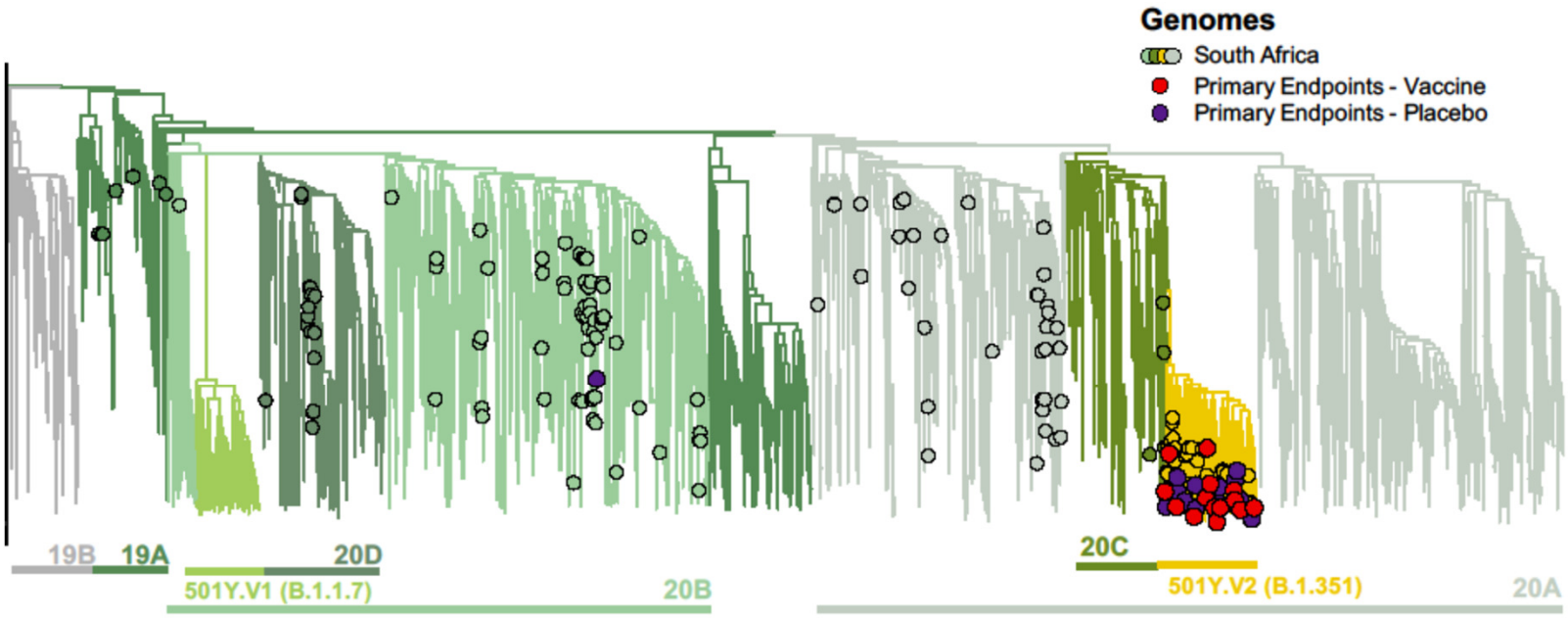

39 (95%) of 41 sequenced endpoint cases due to B.1.351 variant

Sequencing done at VIDA (Vicky Baillie) and KRISP (Tulio de Oliveria laboratory)

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Antibody activity induced by the ChAdOx1-nCoV19 has very low activity against the B.1351 variant circulating in South Africa.

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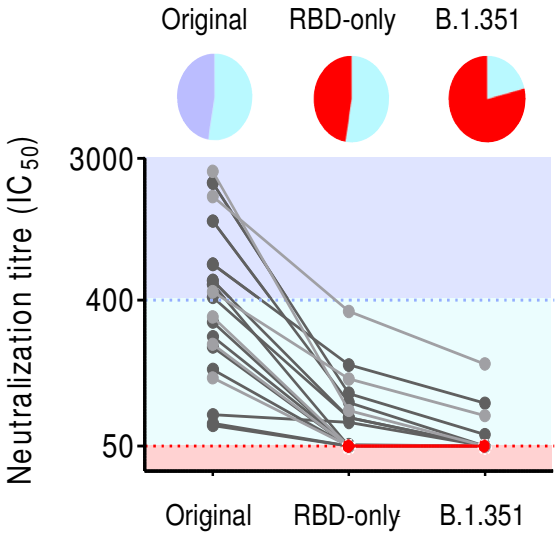
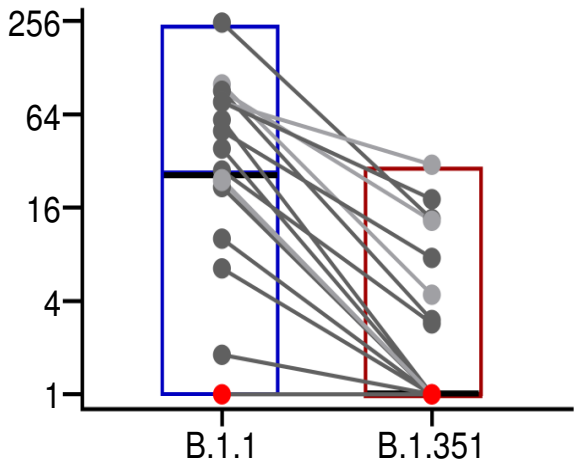
Dilutional titers <50 50-500 >400

Pseudo-neutralization assay



Live virus neutralization assay



Experiments done at laboratories of Wits/NICD (Penny Moore) and Alex Sigel (AHRI)

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ChAdOx1-nCoV19 not efficacious in protecting against mild to moderate Covid-19 due to the B.1351 variant.

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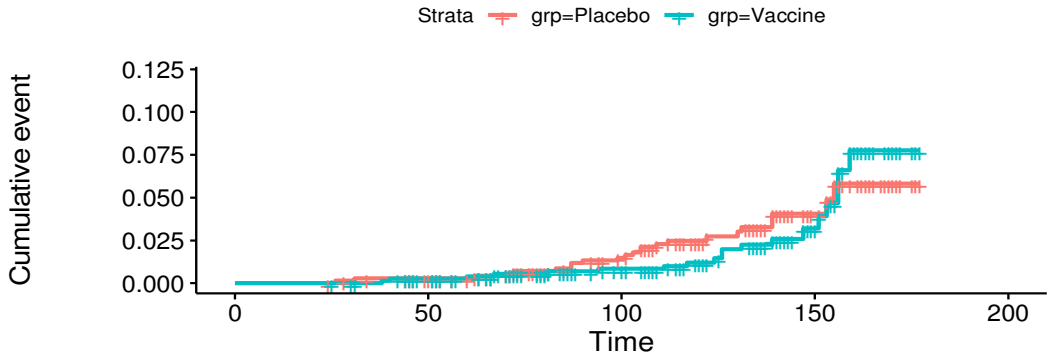

No significant risk reduction in mild-moderate Covid-19 from B.1351 variant occurring at least 14 days after 2nd dose of ChAdOx1/nCoV19.

Baseline N-protein IgG	Total number of cases	Placebo n/N (%)	Vaccine n/N (%)	Vaccine efficacy (95%CI)
Primary endpoints: All severity COVID-19 clinical >14 days post-boost				
Negative	42	23/717 (3.2%)	19/750 (2.5%)	21.9% (-49.9 to 59.8)
Secondary endpoint: All severity COVID-19 clinical disease due to B1.351 variant >14 days post-boost				
Negative	39	20/714 (2.3%)	19/748 (2.5%)	10.4% (-78.8 to 54.8)

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Novavax study: Attack rate in placebo groups by serostatus

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- Seronegative (No past infection): 58/1494 3.9% (3.0; 5.0)
- Seropositive (Past infection) : 26/674 3.9% (2.5; 5.6)

Past infection by "original" variants of SARS-CoV-2 do NOT protect against mild and moderate Covid-19 from B.1351 variant.

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Novavax sub-unit protein vaccine protects against mild-moderate illness from the B.1.351 variant in South Africa.

Severity	NVX-CoV2373 (n=2,206)	Placebo (n=2,200)
Vaccine Efficacy (HIV negative)	**60.1 %** (95% CI: 19.9, 80.1)	
Vaccine Efficacy (overall)	**49.4%** (95% CI: 6.1, 72.8)	

Primary Endpoint: PCR-confirmed mild, moderate, or severe COVID-19 illness occurring ≥7 days after second dose in baseline seronegative participants

- **Sequencing data available for 27/44 cases**
- **25/27 (93%) of cases attributable to SA 501Y.V2 escape variant**

Vaccine efficacy unknown in people living with HIV, as is the case for ALL Covid-19 cases.

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Could the AZ ChAdOx1-nCoV19 still protect against severe Covid-19 in high risk groups??

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ChAdOx1-nCoV19 (AZD1222) induced T-lymphocyte immunity.

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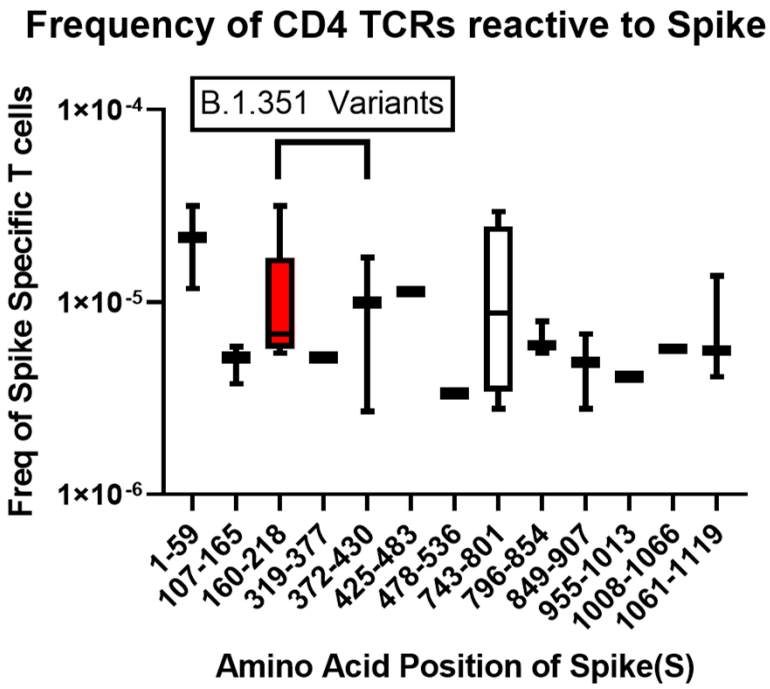

- **87 spike specific antigens identified by T-cell receptor variable beta chain sequencing (24 for CD4 T cells and 63 for CD8 T cells).**
- **Based on the location of changes in the B.1.351 strain, 76 out of the 87 antigens not impacted by B.1.315 site mutations.**
- **B.1.351 mutation sites (an AA change) are not the dominant Spike-specific T cell responses in AZD1222 vaccinees.**
- **T cell response that recognizes B.1.351 is likely to be present in AZD1222 recipients**

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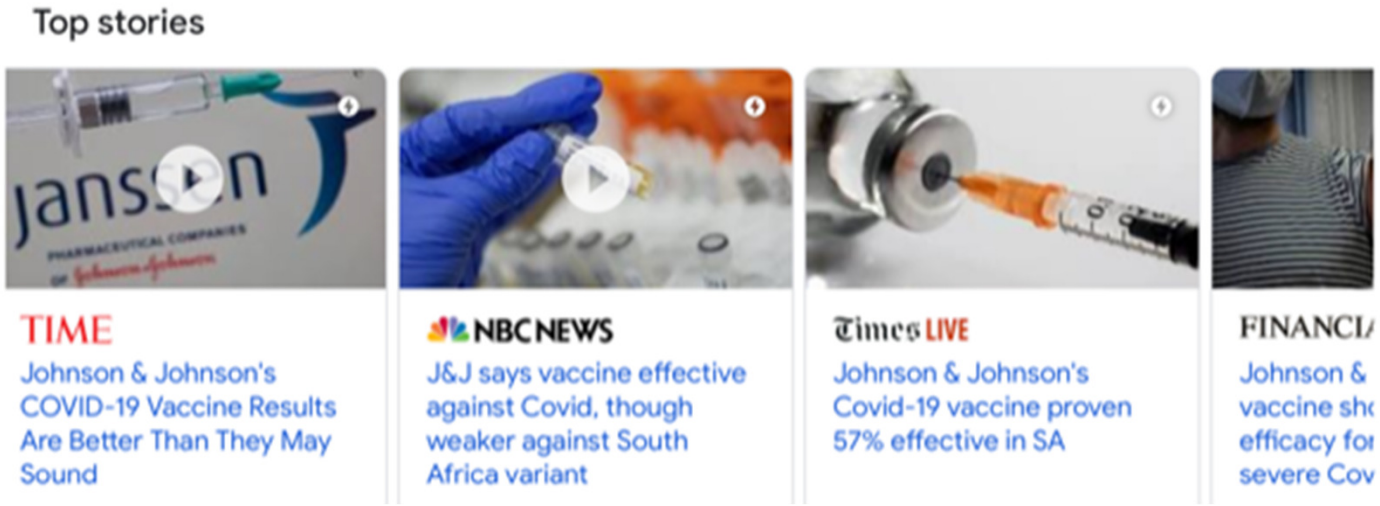
Jansen Covid-19 vaccine efficacy protects against moderate-severe Covid-19 from B.1.351 variant >14 days after a single dose in South Africa.



- 57% efficacy against moderate to severe disease
- 89% efficacy against severe disease and death

Analogous neutralising antibody induction by ChADOx1-nCoV19 and Ad26COV2S1 vaccines

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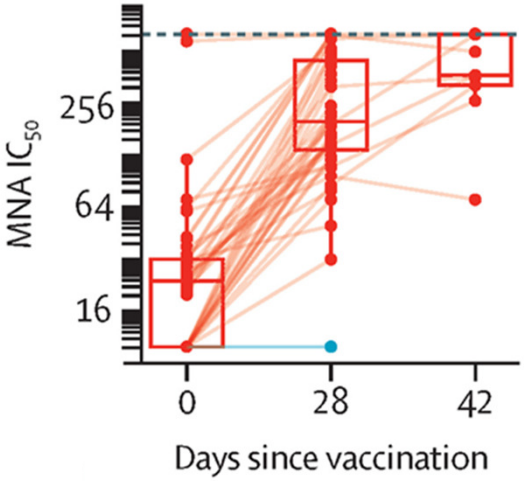
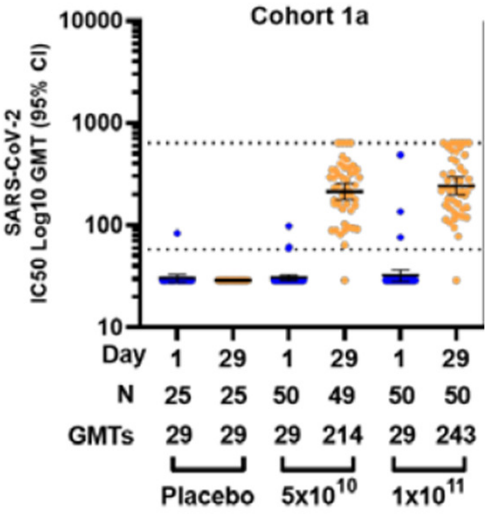
Live neutralization assays conducted with identical validated method at PHE

AstraZeneca



Similar vaccine induced neutralising antibody following a single dose of AZ and JJ Covid-19 vaccines.

Janssen



D28 Median IC_{50}=200
D56 Median IC_{50}= 372
(Cohort 1, 3 respectively)

Data reported as IC_{50} GMT
Cohort 1a (n=50) **$5x10^{10}$ GMT 214; $1x10^{11}$ GMT 243**

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Discussion

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- Vaccine efficacy of >75% at 14 days after 1st dose against non-B.1.351 variant Covid-19 (through to 31st October 2020).
- No vaccine efficacy against B.1.351 variant at 14 days after 2nd dose of injection.
- Novavax subunit protein vaccine has 60% efficacy (HIV-) against mainly B.1.351variant mild-moderate Covid-19 in South Africa.
- ChAdOx1/nCoV19 and Jansen Covid-19 vaccine (single dose) has comparable neutralising activity against "original" variants.
- Jansen Covid-19 vaccine shown to reduce severe Covid-19 from B.1.351 variant by 89% in South Africa.

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Conclusion

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- Evolution of SARS-CoV-2 variant with immune-evasion potential, similar to seasonal influenza virus, are likely to be ongoing into the future.
- Need for recalibration on how we respond to Covid-19 pandemic, and expectations of Covid-19 vaccines.
- Covid-19 vaccines remain the only sustainable option for reducing risk of sever disease and death, and warrants ongoing urgent targeted approach for high-risk individuals.
- Ongoing work on development of next generation Covid-19 vaccines, inclusive of B.1.351-like variant.

South African
Ox1Cov-19
Vaccine VIDA-Trial

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