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Director: South African Medical Research Council Vaccines and Infectious Diseases Analytical Research Unit (VIDA).

National Research Foundation Research Chair in Vaccine Preventable Diseases.

Co-Director African Leadership in Vaccinology Expertise (ALIVE)

Overview

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- Covid-19 and natural induced immunity
- Covid-19 and vaccine horizon
- Covid-19 vaccine efficacy

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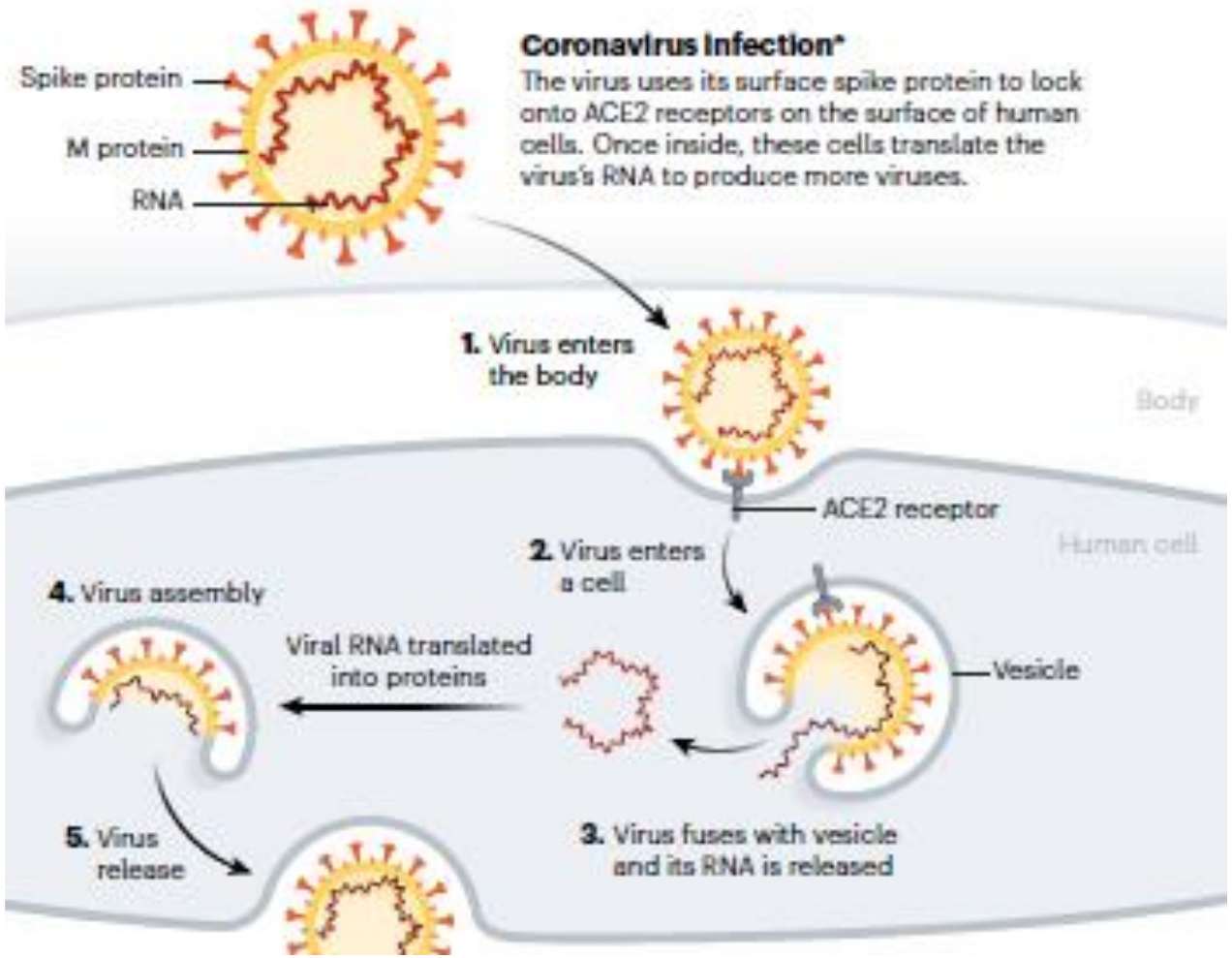
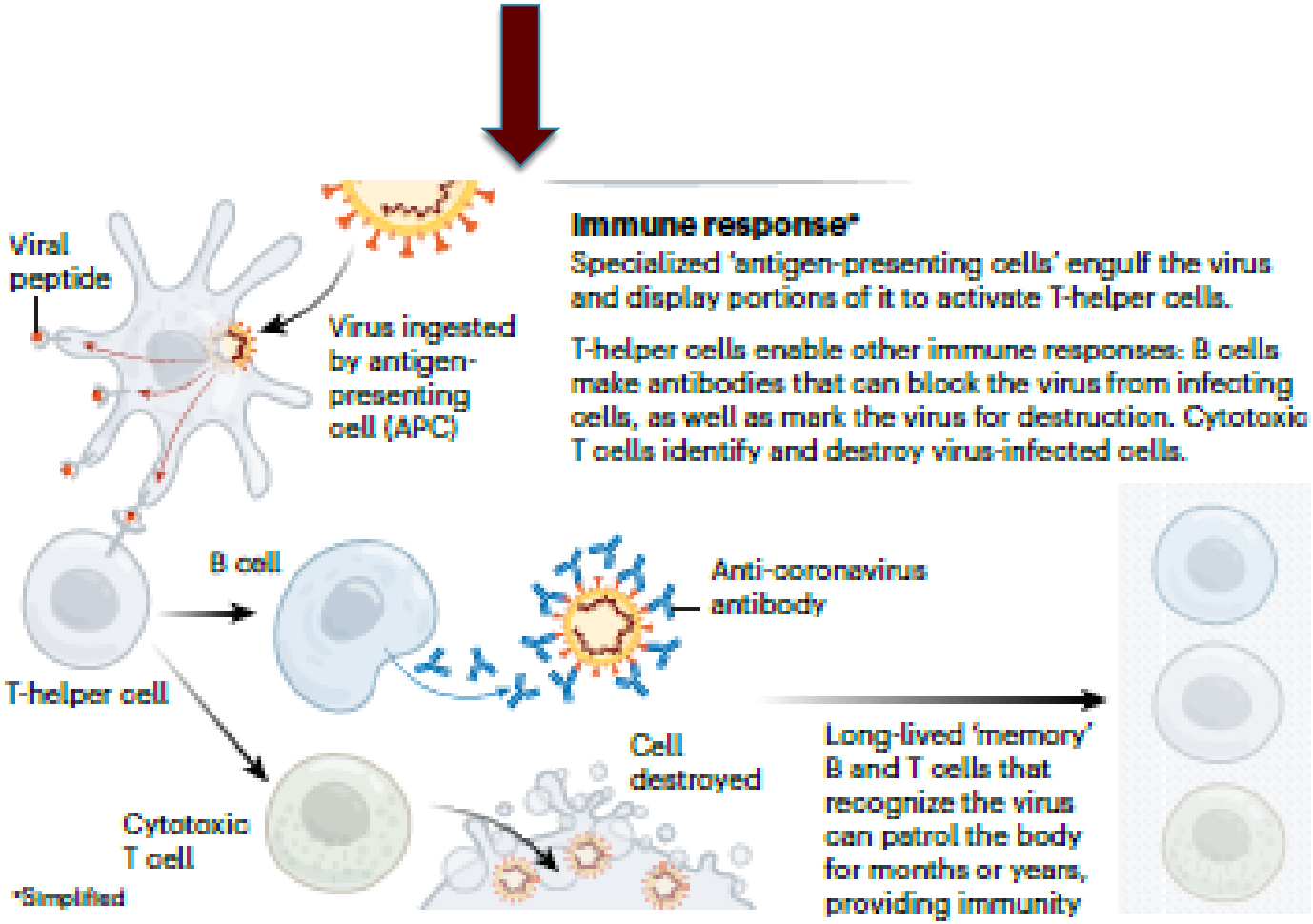
Natural immune responses to SARS-CoV-2 infection -I.



Callaway E; Nature, April 2020: 580

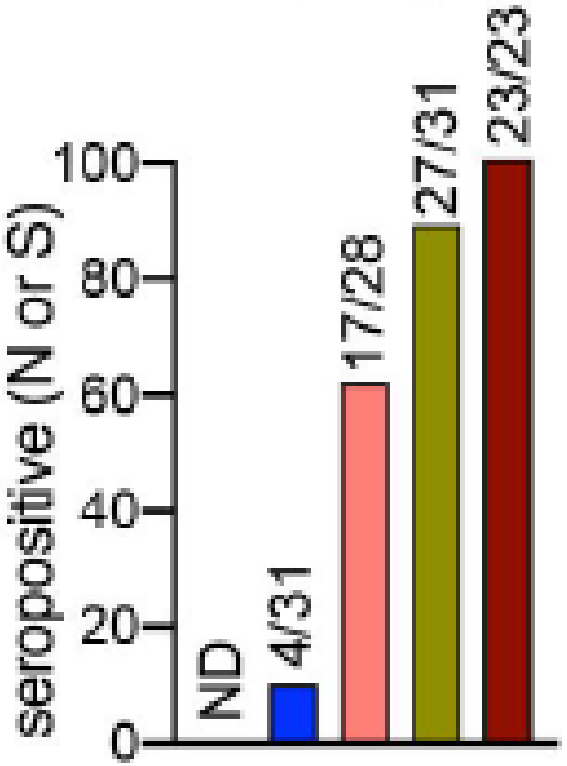
Natural immune responses to SARS-CoV-2 infection -II



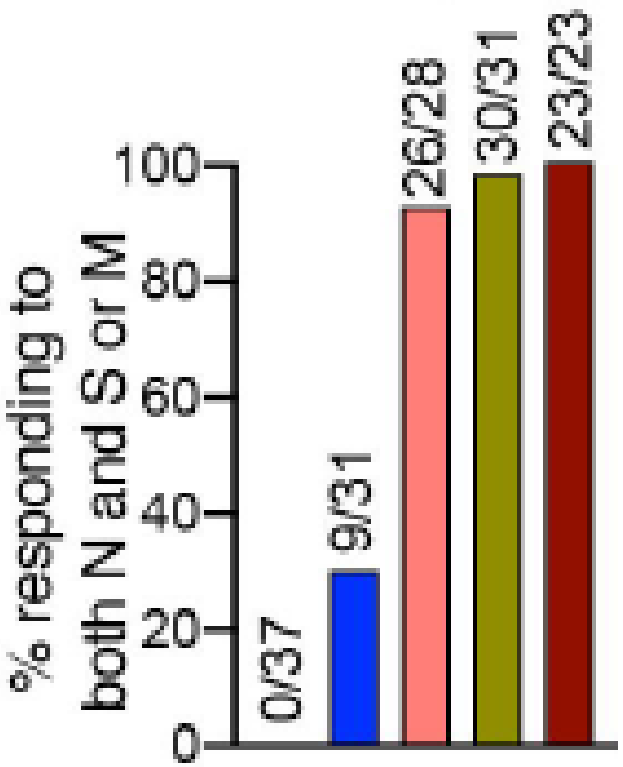
Callaway E; Nature, April 2020: 580

Proliferative capabilities of SARS-CoV-2 specific T-cells in convalescent COVID-19.

Antibody responses



T cell responses against internal (N) and Surface Antigens (M and/or S)



- 2020 blood donor,
- Exp=exposed;
- MC=asymptomatic or mild illness
- SC- severe illness

Sekine, T bioRxiv preprint doi: https://doi.org/10.1101/2020.06.29.174888.

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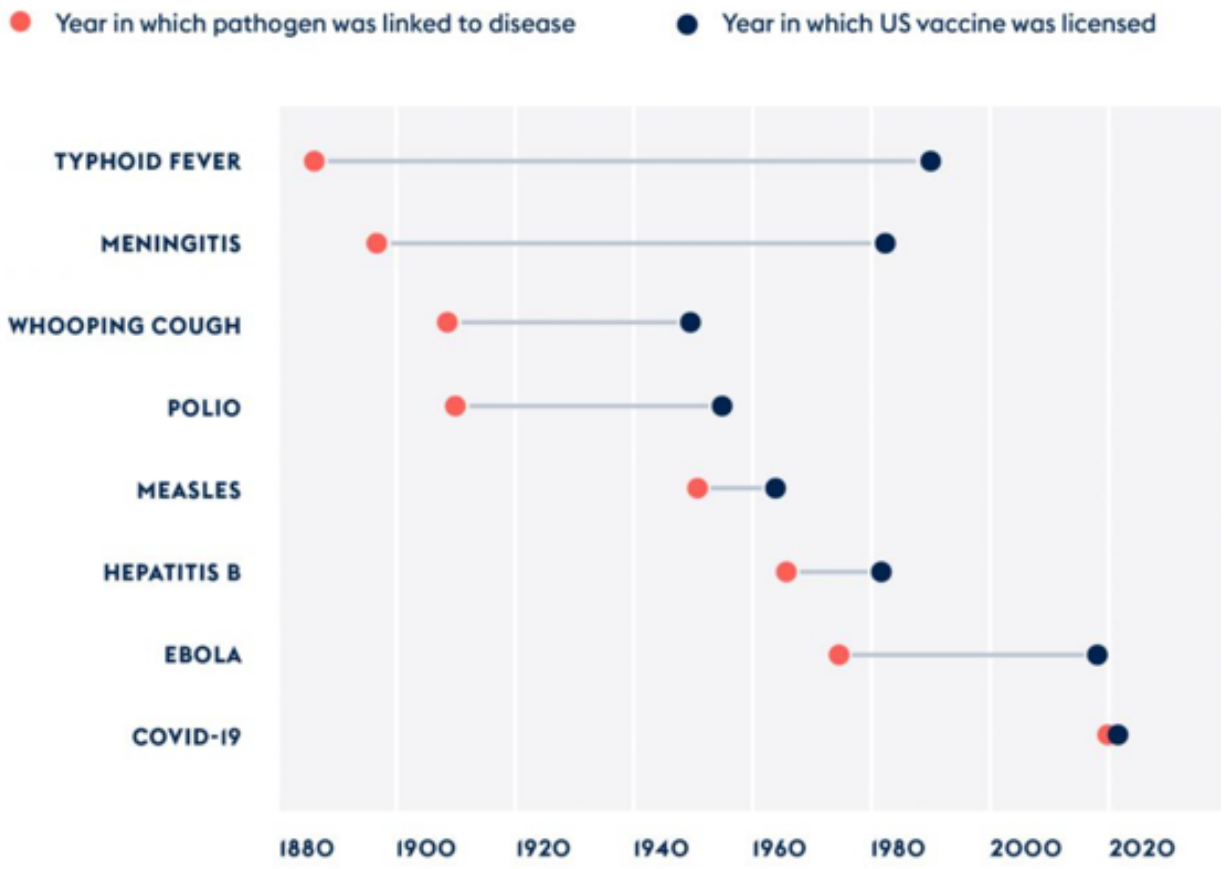
Timeline from pathogen discovery as cause of disease and vaccine introduced in USA



Data source: Our World in Data

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Next generation Covid-19 vaccines

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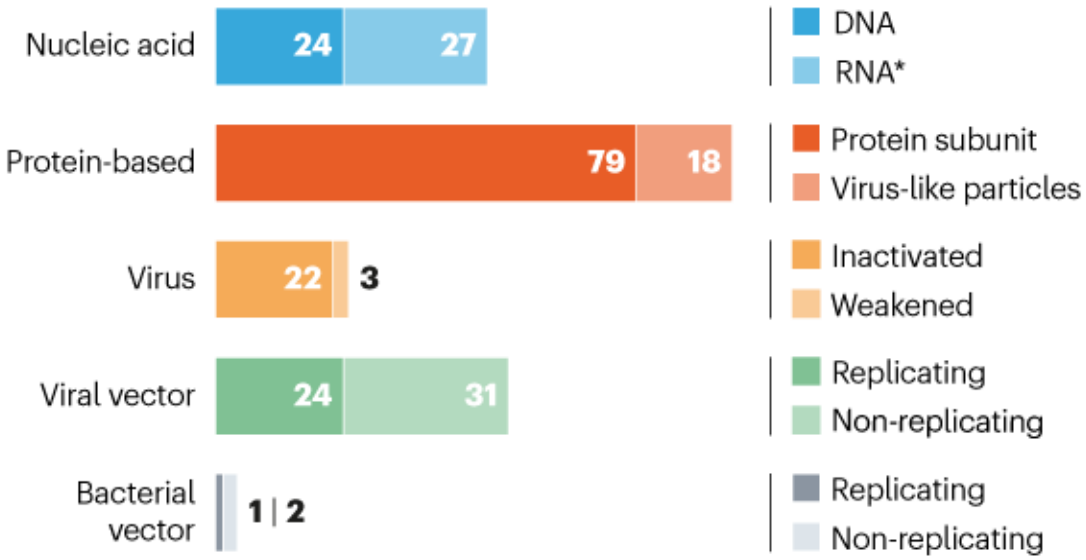
About 230 COVID-19 vaccines are in development whose trial enrolment could be affected by the authorization of first-generation shots. About 60 of them are already being tested in humans.



Virus vaccines contain either inactivated or weakened forms of the coronavirus. Viral- and bacterial-vector vaccines contain genetically modified versions of viruses (such as adenoviruses) or bacteria (such as *Salmonella*) that can produce coronavirus proteins while replicating or not. Nucleic acid vaccines contain either DNA or RNA instructions that, when injected, produce coronavirus proteins. Protein-based vaccines contain proteins from coronaviruses that are injected directly.

*Pfizer and BioNTech's RNA vaccine, a first-generation vaccine, is included in these numbers because the firm is currently recruiting for a trial in China.

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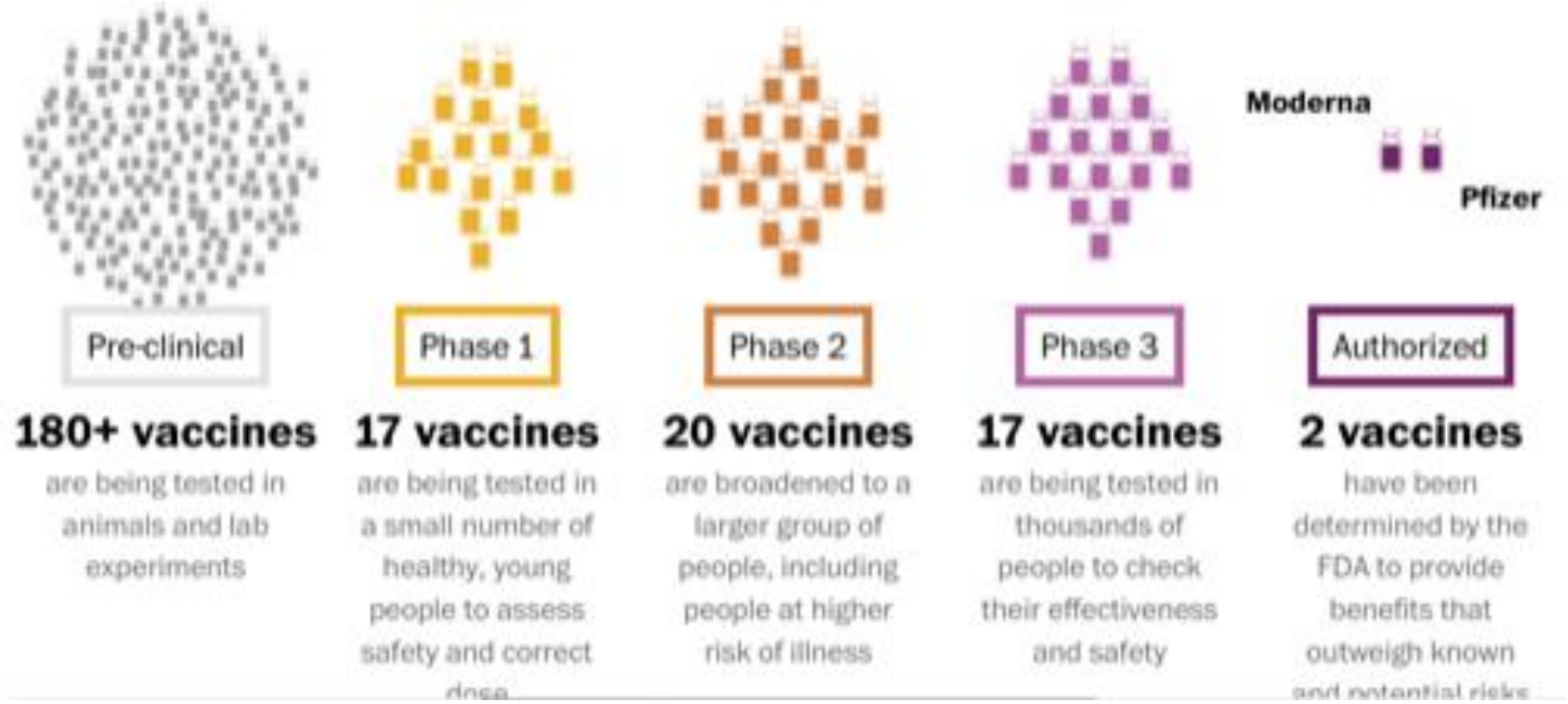
Pipeline of Covid19 vaccine development



5 vaccines
AZ1222
Sputnik V
Sinopharm
(Jansen&Jansen)
(Novavax)

Other authorised Covid-19 vaccines:

Source: Washington Post

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Overview

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- Covid-19 and natural induced immunity
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Vaccine efficacy similar or higher against severe than mild-moderate Covid-19.

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Company	Platform	Doses	Non-clinical results	Number of people who got vaccine	Protection from hospitalizations /death	Protection from severe disease (may not be hospital)	Efficacy against milder disease
moderna	mRNA-1273 mRNA in lipid nanoparticle	2	Neutralizing Abs; Strong Th1 response; protection from challenge	~15,000	100%	100% (30 cases in placebo arm; 0 in vaccine)	94.1%
Pfizer	BNT162b2 mRNA in lipid nanoparticle	2	Neutralizing Abs; Strong Th1 and Th2 response; protection from challenge	~18,600	100%	100% (9 cases in placebo arm; 0 in vaccine)	95%
AstraZeneca	AZD 1222 Non-replicating Chimp Adenovirus-DNA	2	Neutralizing Abs; Strong Th1 and Th2 response; protection from challenge	~5800	100%	100% (10 in placebo; 0 in vaccine)	90% half-full-dose; 70% overall
Johnson-Johnson	JNJ-78436725 Non-replicating human adenovirus/DNA	1	Neutralizing Abs; Strong Th1 and Th2 response; protection from challenge	~22,000	100%	85% (across South Africa, U.S., Latin America	72% US; 66% Latin America; 57% S. Africa
NOVAVAX	NVX-CoV2373 Spike protein/RBD + Matrix M adjuvant	2	Neutralizing Abs; protection from challenge	~9700	100%		89.3% UK; 60% S. Africa
Sputnik V	Ad26 and Ad5 adenovirus/DNA	2	Neutralizing Abs; Strong Th1 and Th2	~11360	100%	100% (20 cases placebo; 0 in	91.4%

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Study overview of non-replicating simian adenovirus Covid-19 vaccine (AstraZeneca Vaccine/ChAdOx1/nCoV19) in South Africa

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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^{10} 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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ChAdOx1 nCoV-19 induces similar neutralizing antibody responses in South Africa, UK and Brazil.

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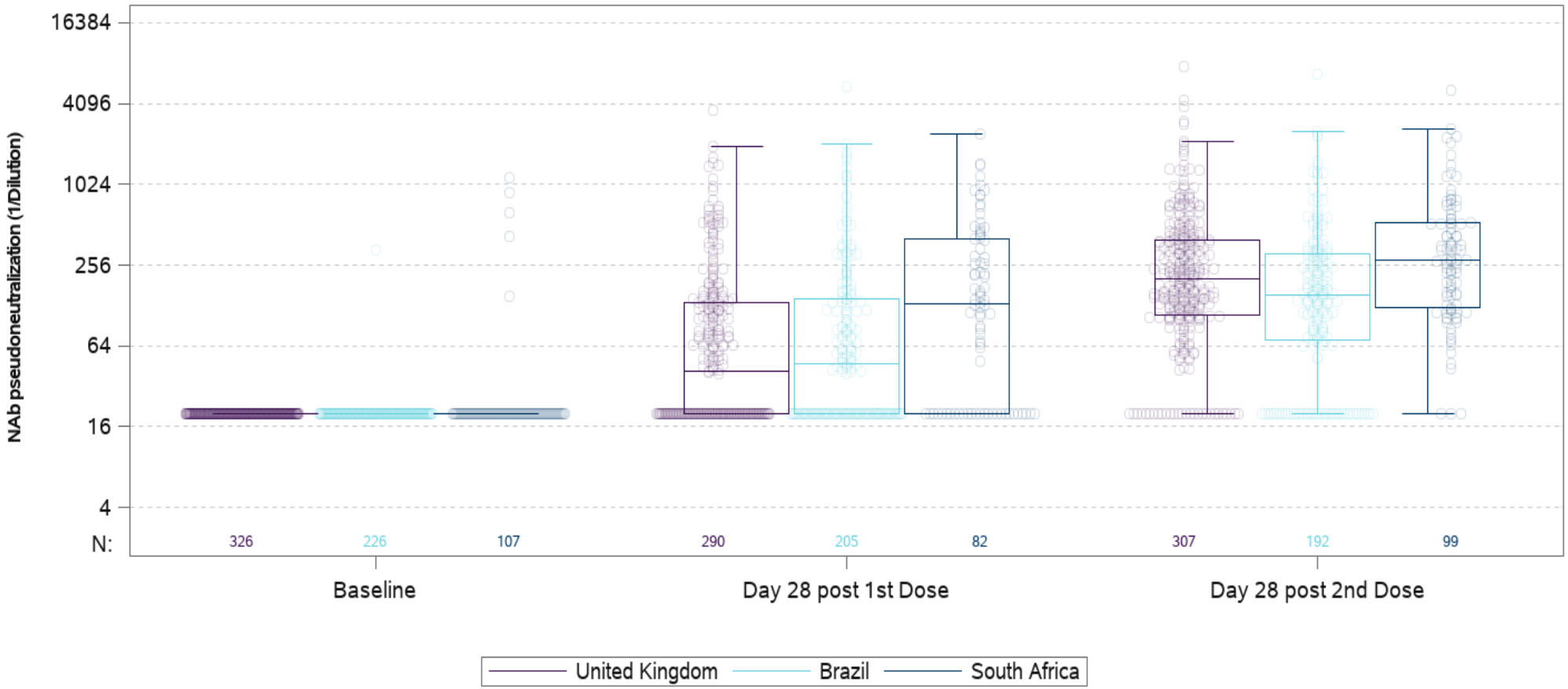
Pseudo-neutralization assay measuring neutralizing antibody to prototype virus.



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

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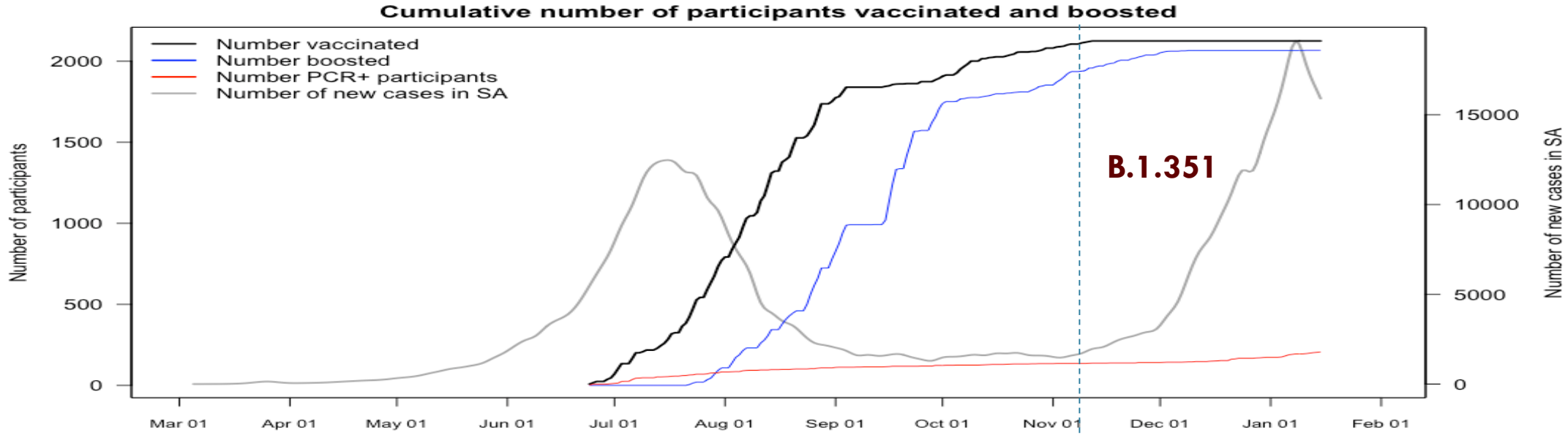

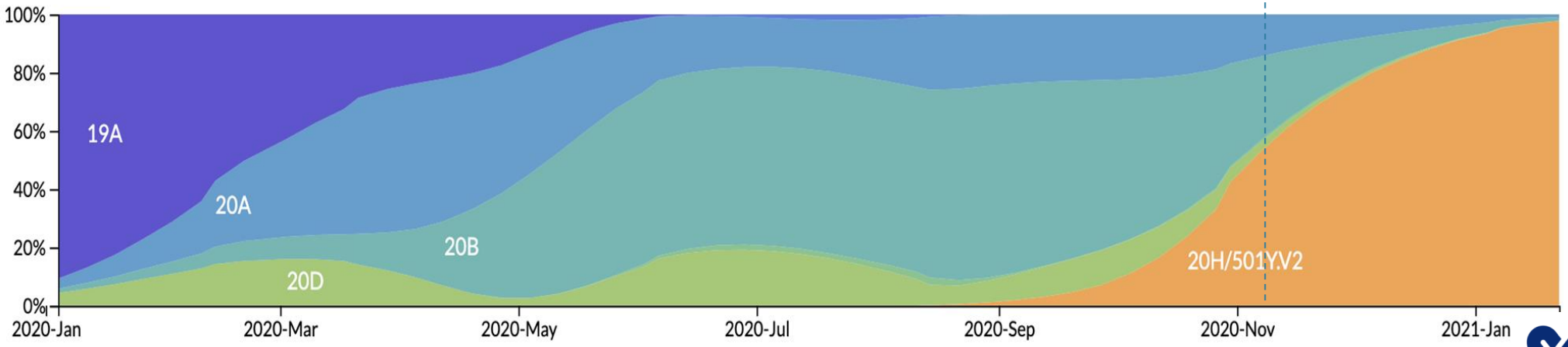

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Covid-19 cases from >14 days after the 1st dose until 31st October 2020 (proxy for non-B.1.351 variant).

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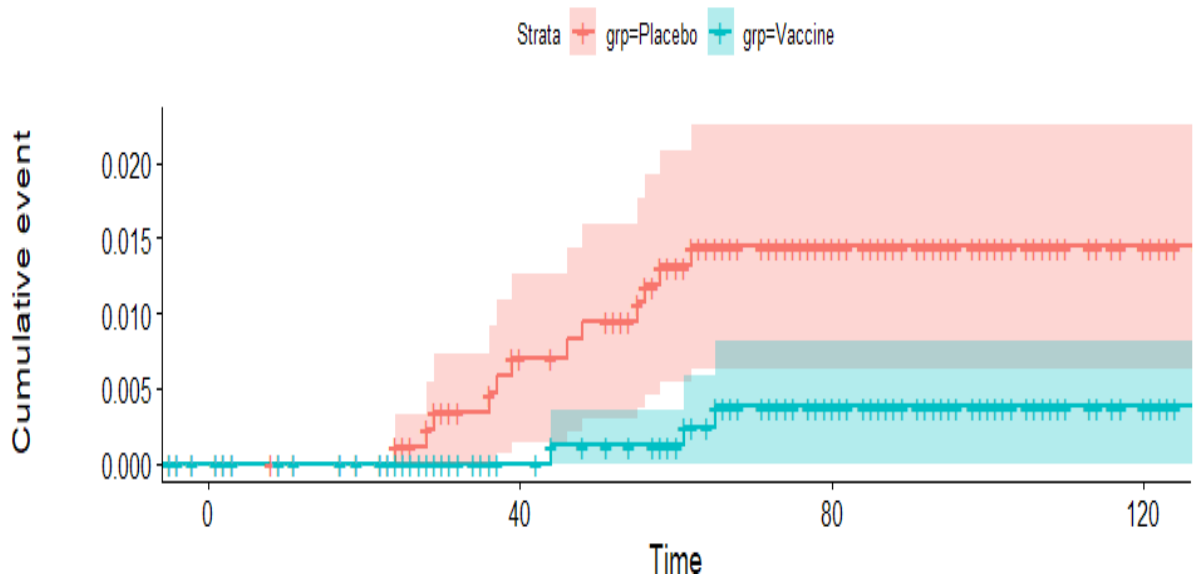

75% risk reduction in mild-moderate Covid-19 occurring at least 14 days after single dose of ChAdOx1/nCoV19 prior to evolution of B.1.351 variant In South Africa.

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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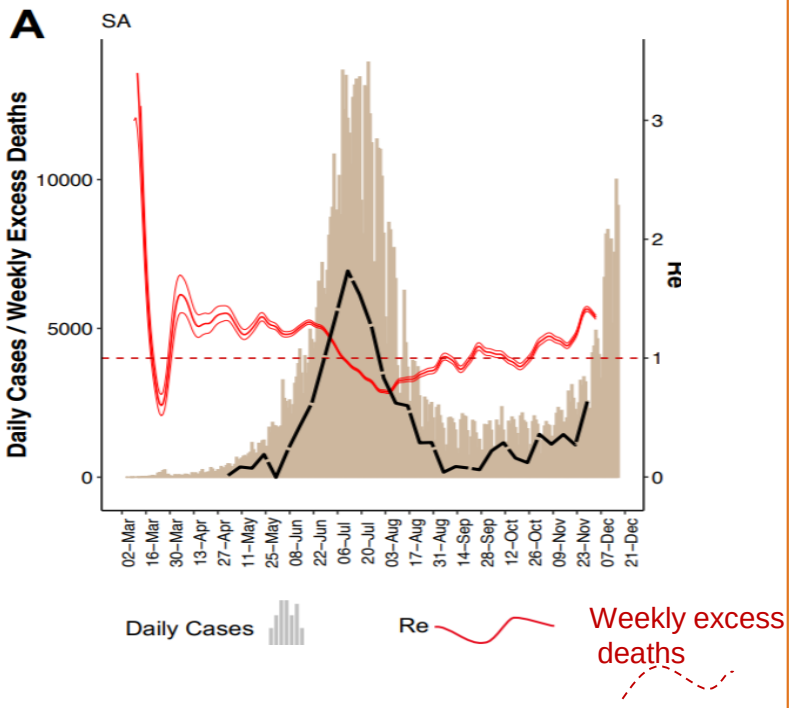
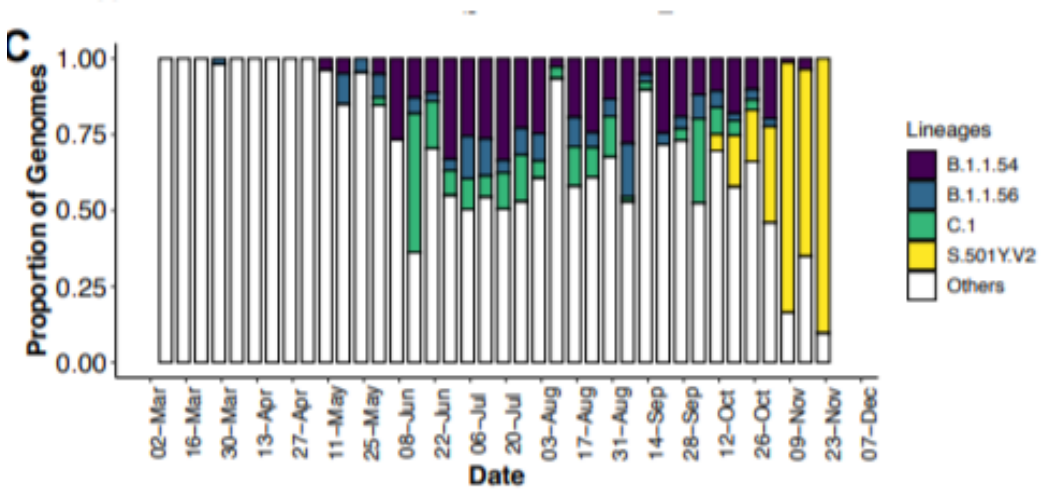
Emergence and rapid spread of **501Y.V2** lineage with multiple spike mutations in South Africa

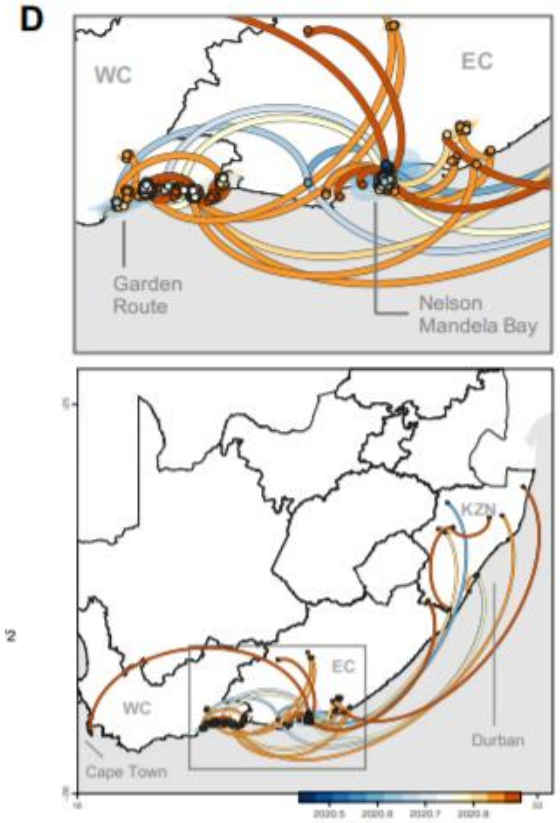
Early and rapid resurgence prompted intensified genomic surveillance in October. Positivity rates >30% in many areas and increasing Re….



…..by mid December 501Y.V2 had replaced the precedent D614G strain…..

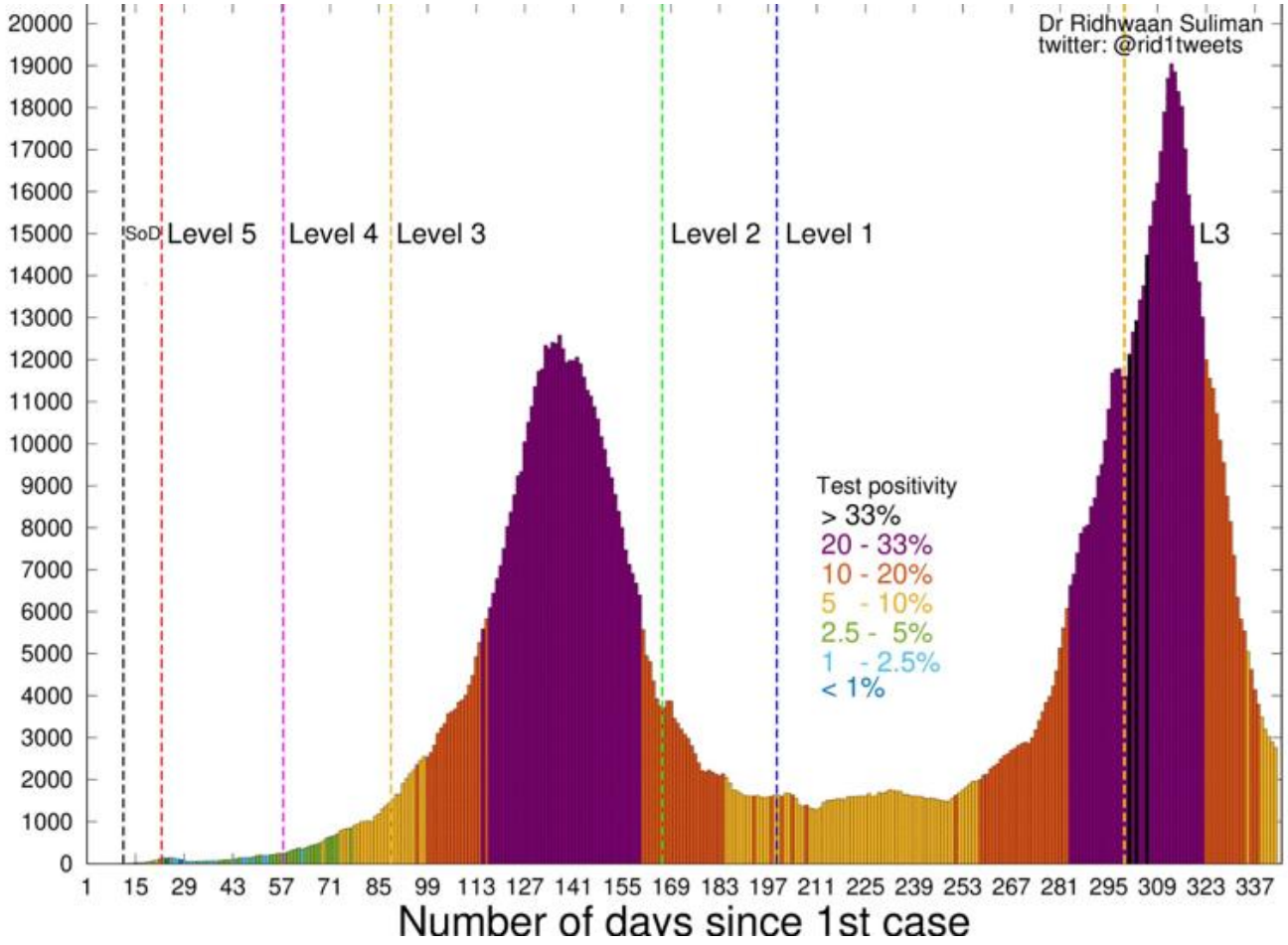


…..and spread from the Eastern Cape



Tegally et al medRxiv Dec 21, 2020

Seven-day moving average of Covid-19 cases and positivity rate in South Africa



Variants of concern arise and spread globally

Colors indicate reports of imported cases (pink) or of local transmission (darker purple) as of 15 Feb, 2021

B.1.1.7 report

Daily global report for lineage B.1.1.7

B.1.351 report

Daily global report for lineage B.1.351

P.1 report

Daily global report for lineage P.1

https://cov-lineages.org/global_report.html

Novavax study: Attack rate in placebo groups by serostatus

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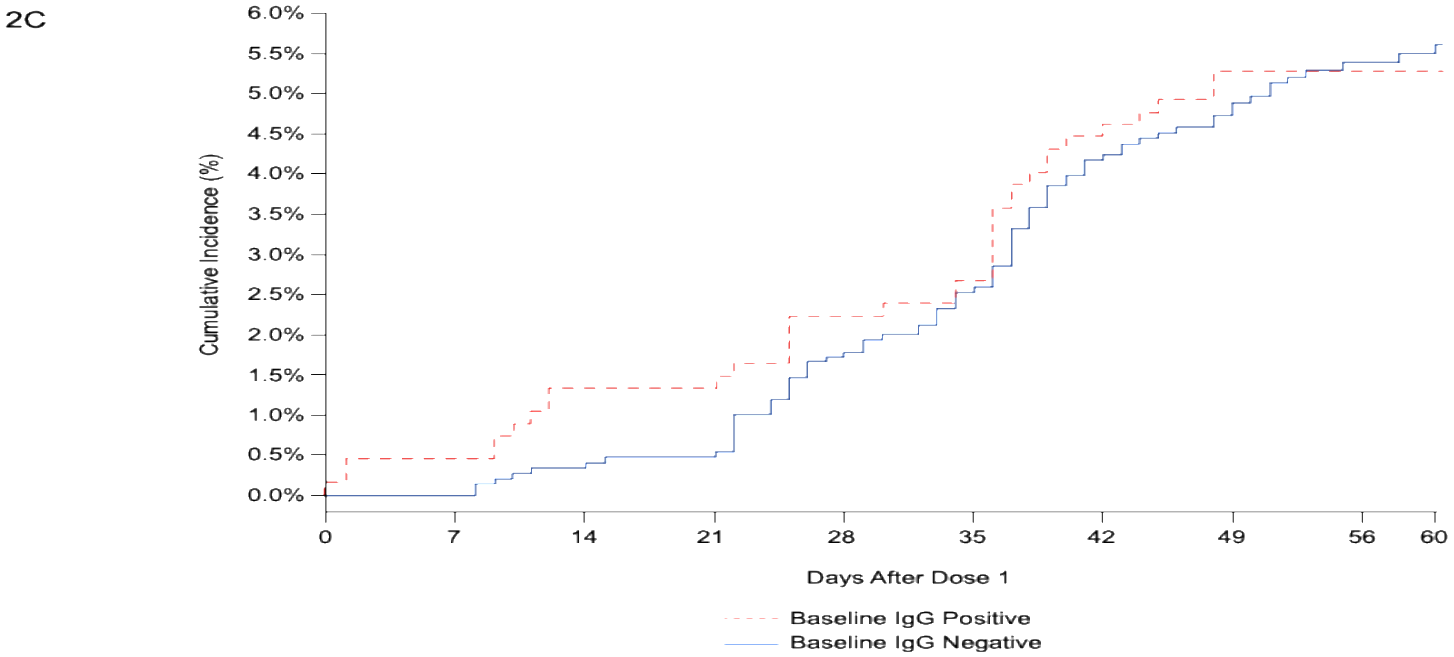
- Seronegative (No past infection): 80/1516 5.3% (4.3; 6.6)
- Seropositive (Past infection) : 35/674 5.2% (3.6; 7.2)



Past infection by "original" variants of SARS-CoV-2 do NOT protect against mild and moderate Covid-19 from B.1.351 variant.

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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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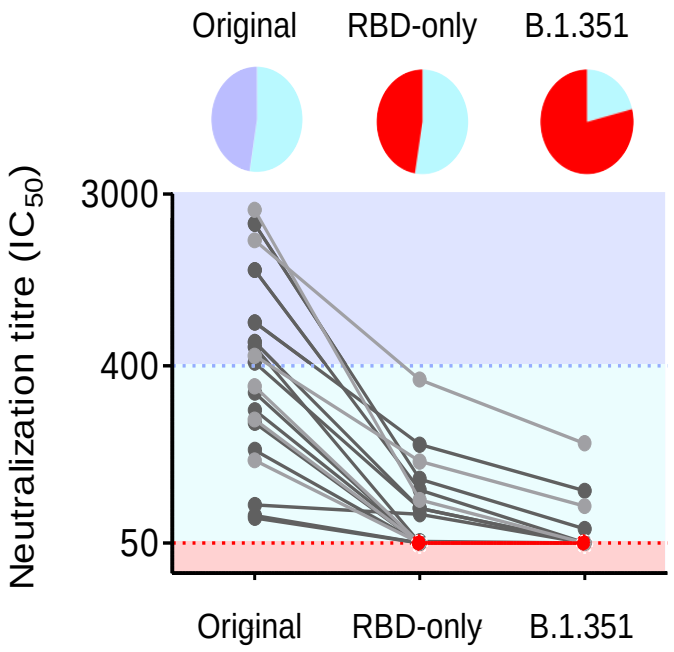
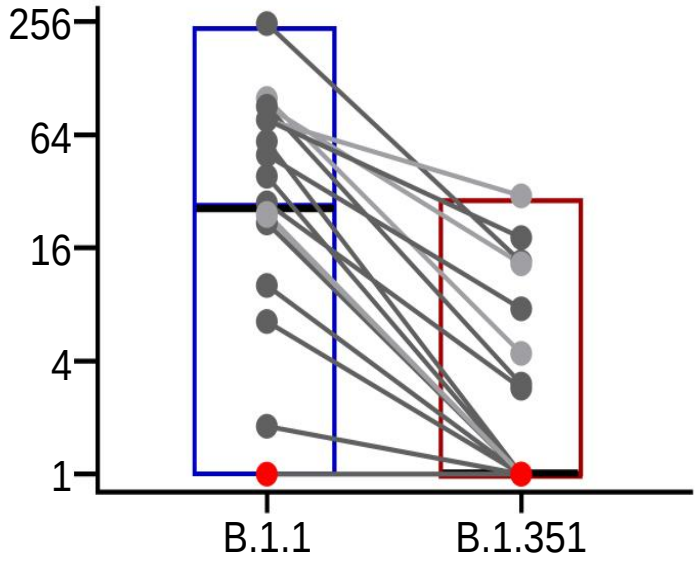
Dilutional titers <50 50-500 >400

Pseudo-neutralization assay



Live virus neutralization assay



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

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

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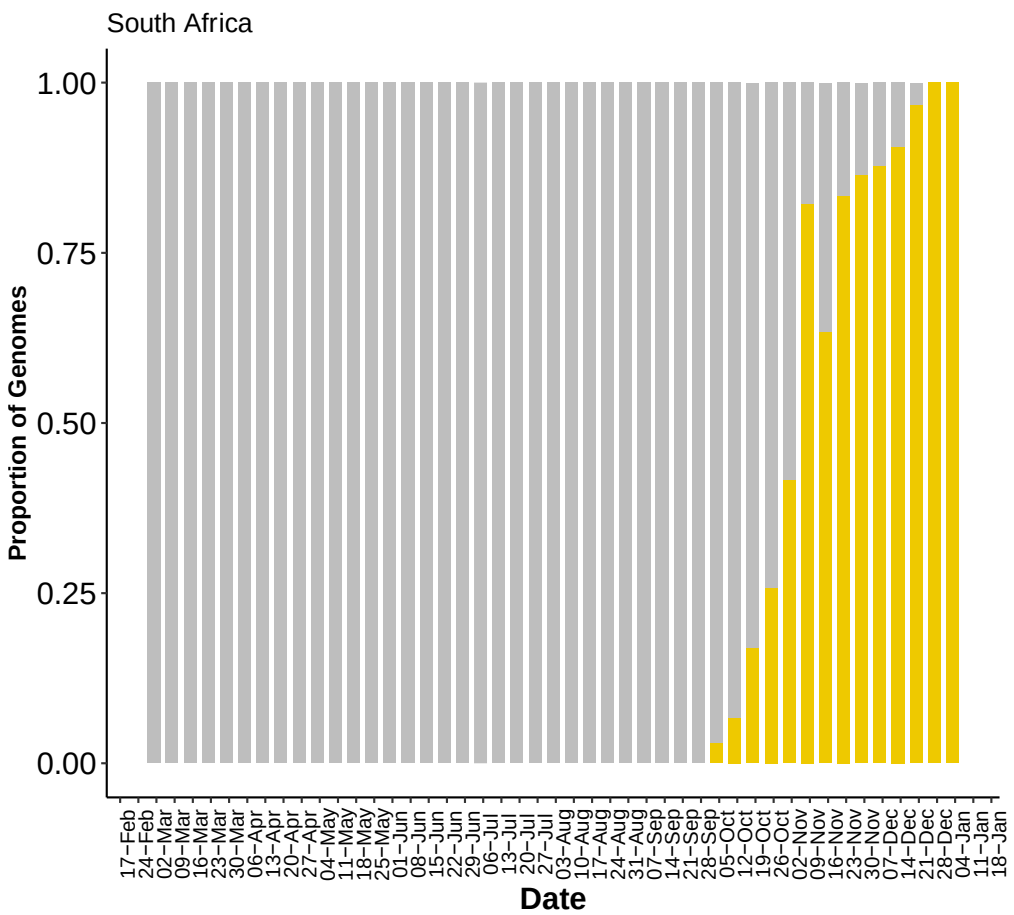

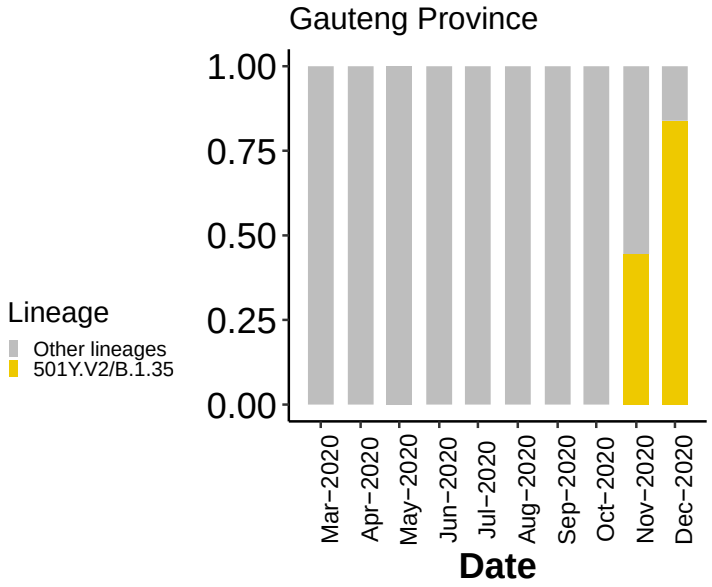

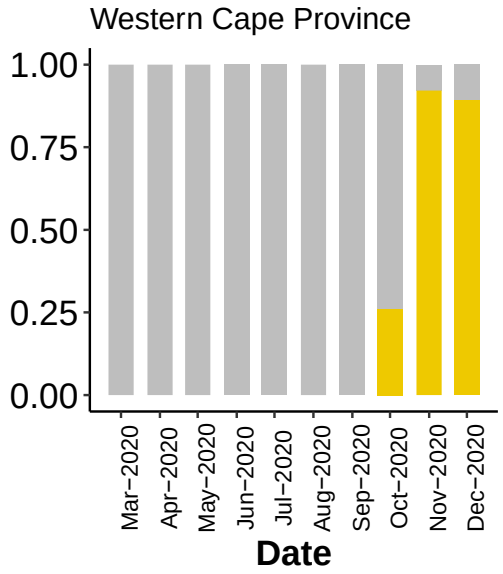

B.1.351 variant only identified
In Cape Metro week 23rd Nov

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

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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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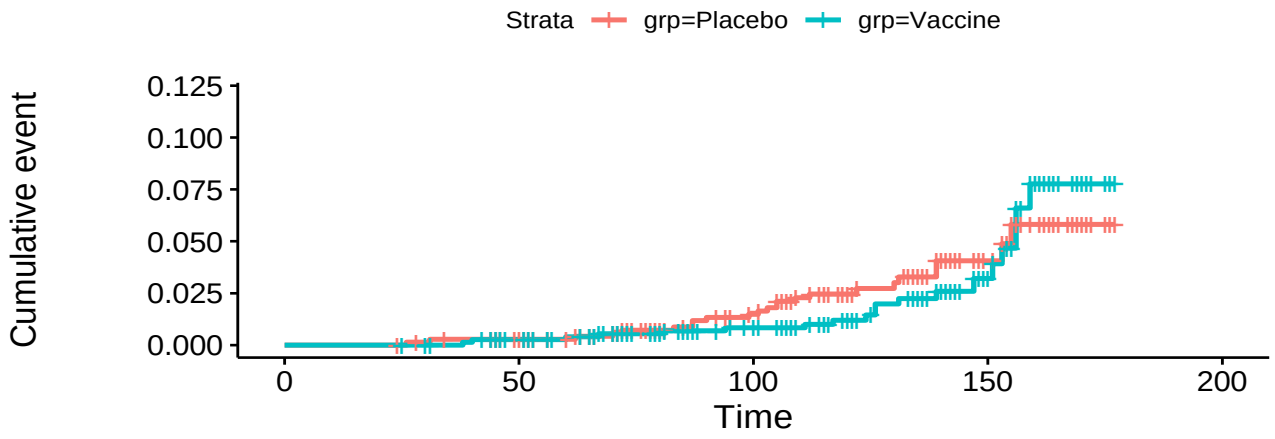

No significant risk reduction in mild-moderate Covid-19 from B.1351 variant occurring at least 14 days after 2nd dose of ChAdOx1/nCoV19.

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

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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.

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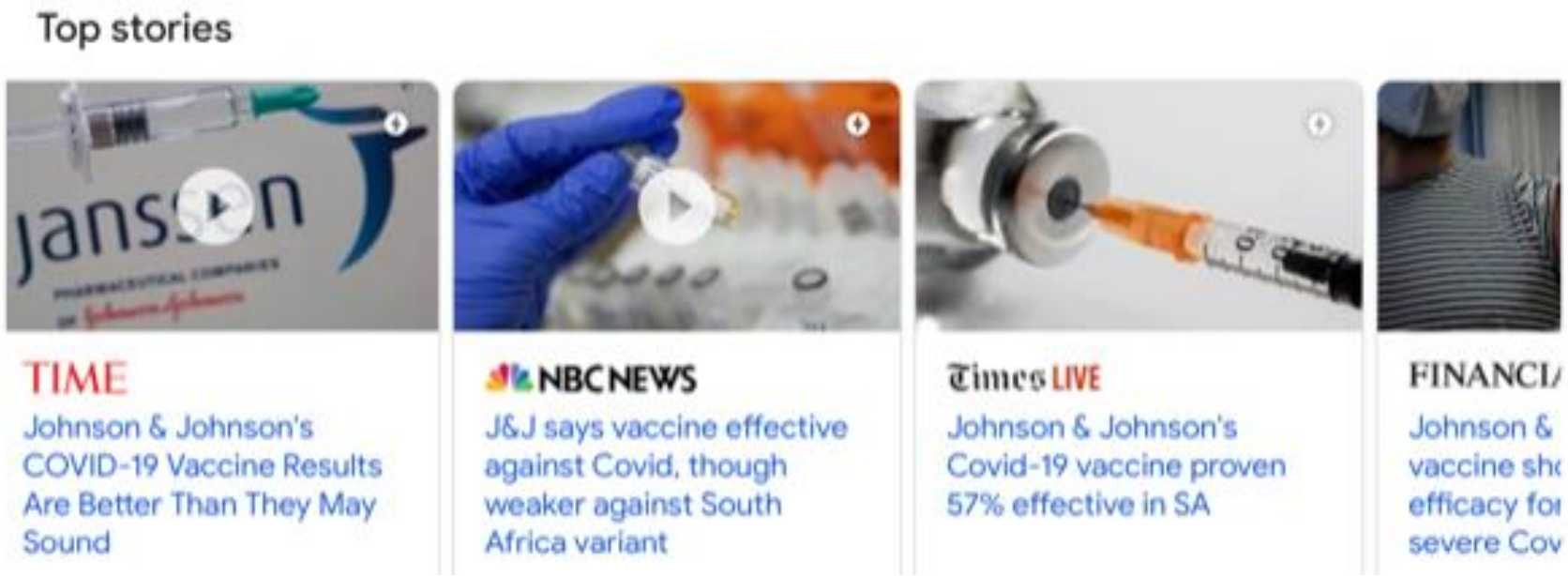

- 57% efficacy against moderate to severe disease
- 89% efficacy against severe disease and death

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Analogous neutralising antibody induction by ChADOx1-nCoV19 and Ad26COV2S1 vaccines

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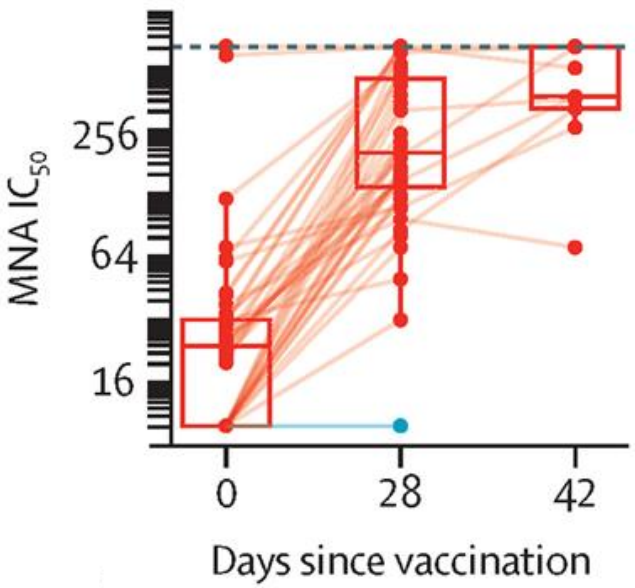
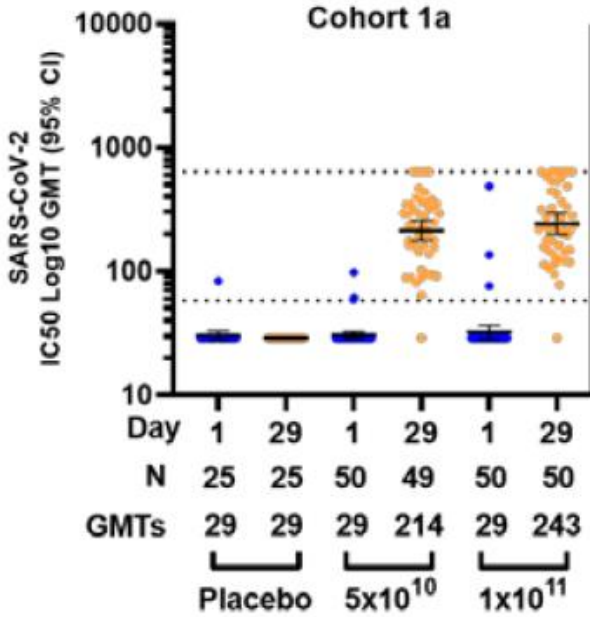
Live neutralization assays conducted with identical validated method at PHE

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; $1x\ 10^{11}$ GMT 243**

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

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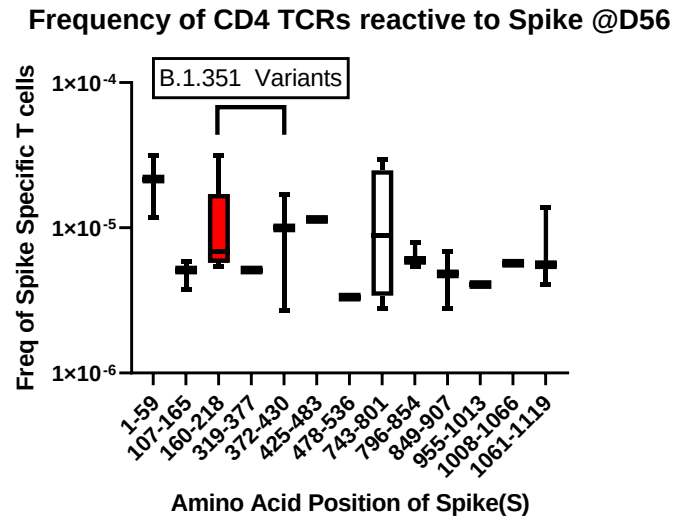

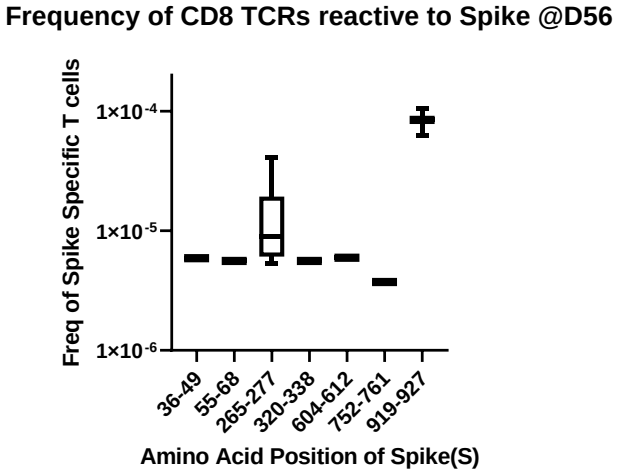

- **87 spike specific antigens identified by T-cell receptor variable beta chain sequencing (24 for CD4 T cells and 63 for CD8 T cells).**
- **Based on the location of changes in the B.1.351 strain, 76 out of the 87 antigens not impacted by B.1.351 site mutations.**
- **B.1.351 mutation sites (an AA 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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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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- Prefusion stabilised spike may impact antibody responses, although not evident between the ChAdOx1-nCoV19 and Johnson & Johnson vaccines on pseudo-neutralization assay in the same laboratory.

- T cells bind to cleaved/degraded proteins, hence, stabilisation of spike protein motif should have impact on T cell responses.

- If antibody responses are suboptimal, cellular immune responses to contribute to protection against severe Covid19 in macaques challenge models challenge. McMahan K et al. Nature, 2020

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.

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