UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

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Co-Director African Leadership in Vaccinology Expertise (ALIVE)

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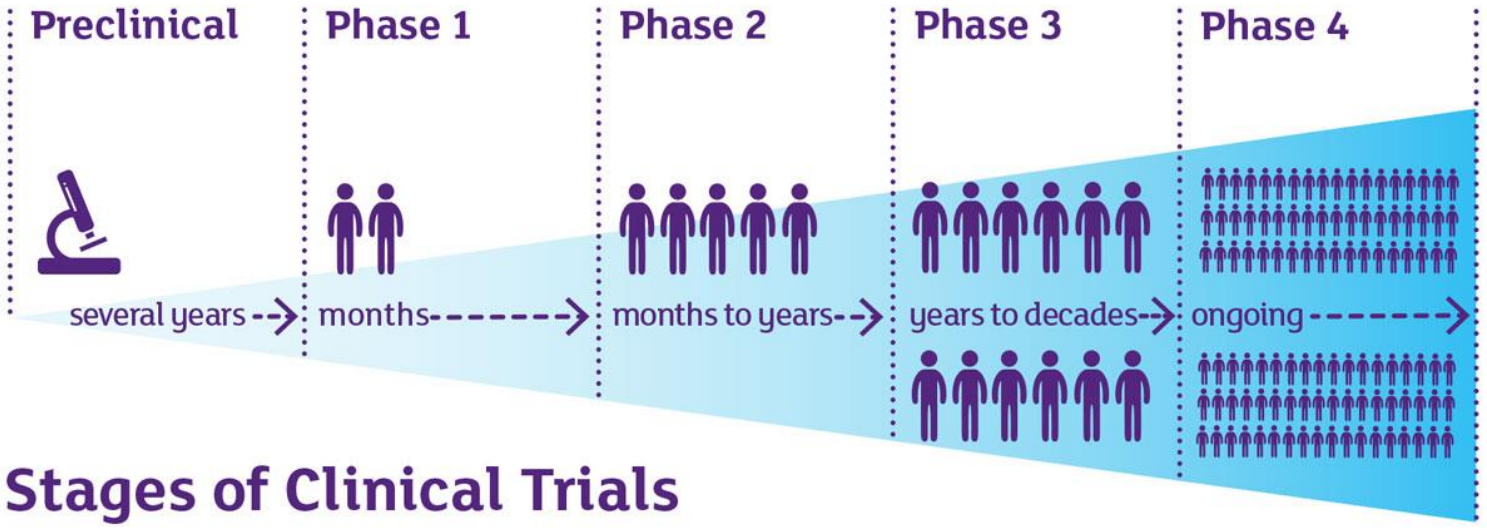
VACCINES & INFECTIOUS DISEASES ANALYTICS

Why do clinical trials?

- Increase and improve medical knowledge and improve disease prevention and patient care
- Systematic investigations
- Structured, specific protocols
- Collects data/ information on a topic



Clinical trials

- ❑ Contain an intervention (vaccine, medicine), unlike observational studies
- ❑ determines safety, immunogenicity, efficacy of a drug/ vaccine
- ❑ Establish best dosing regime, strengths

The Vaccine Testing Process

The development cycle of a vaccine, from lab to clinic.

What approvals are needed?

- Ethics
- Regulatory

SAHPRA South African Health Products Regulatory Authority

FDA

AMA African Medicines Agency

- Registration on trials register:
  - Clinicaltrials.gov
  - PACTR

NIH U.S. National Library of Medicine ClinicalTrials.gov

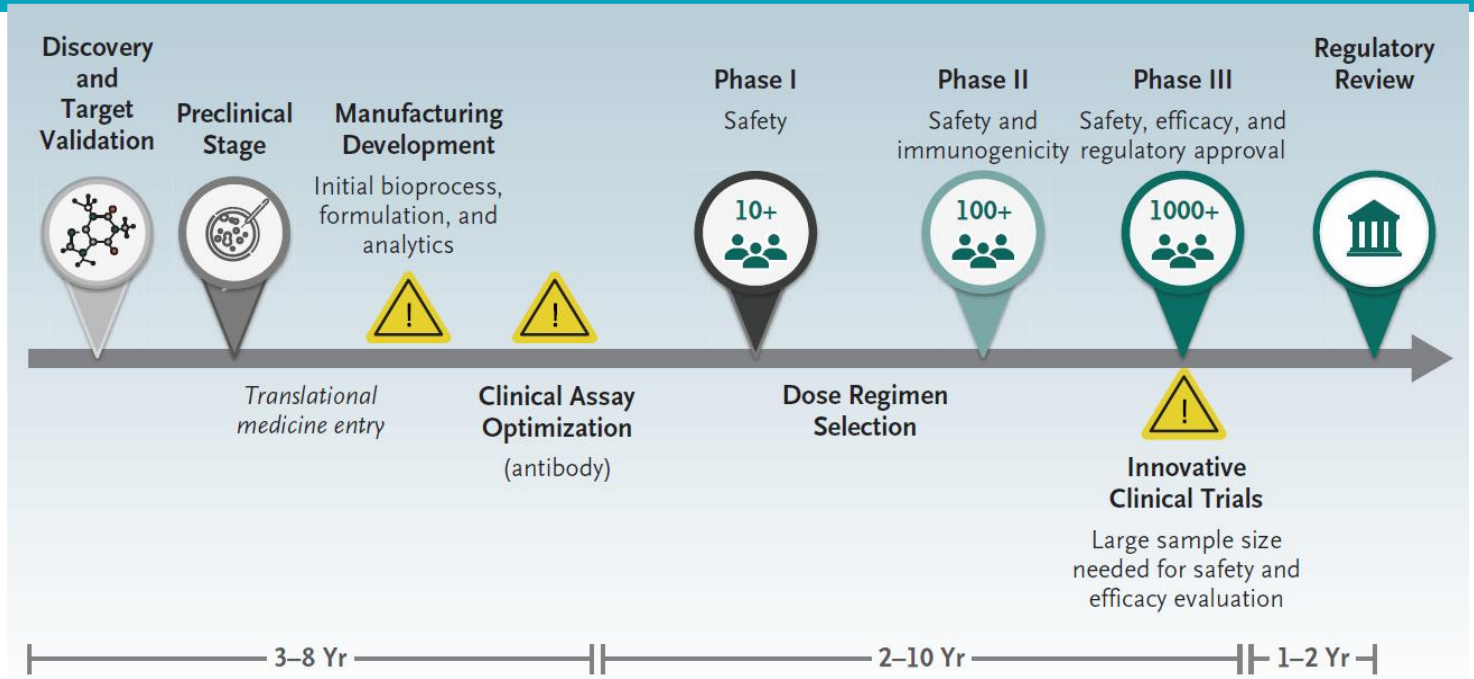
PACTR Pan African Clinical Trials Registry

- National DOH
- Local / district DOH
- Institutional – hospital/ university

Idea, protocol development, funding → Application → Application review → IRB, regulatory approvals → Trial set up, training → Enrolment, data collection → Results

The Vaccine Testing Process

The development cycle of a vaccine, from lab to clinic.



PRECLINICAL TESTING: **Animals** such as mice or monkeys to see if it produces an immune response.

PHASE I SAFETY TRIALS: **Small number of people** to test safety and dosage as well as to confirm that it stimulates the immune system.

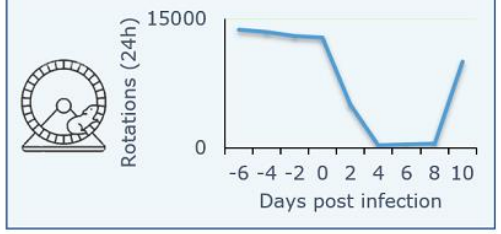
PHASE II EXPANDED TRIALS: **Hundreds of people** split into groups, such as children and the elderly, to see if the vaccine acts differently in them. These trials further test the vaccine's safety and ability to stimulate the immune system.

PHASE III EFFICACY TRIALS: **Thousands of people** compared volunteers who receive vaccine or placebo, determine if vaccine protects against the coronavirus and is safe.

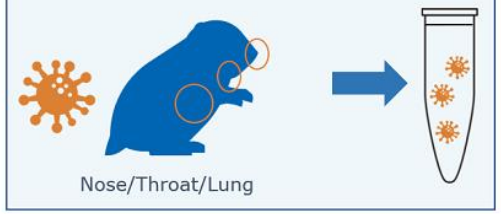
Pre-clinical: Developing suitable animal models

COVID-19 model in Syrian hamsters

Activity wheel

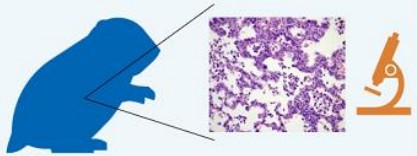


Virus quantification



Relative body weight

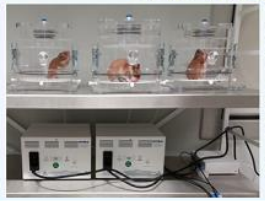
Pathology



Macroscopic & histological analysis of organs (lung & nose)

Plethysmograph (lung function parameters)

Under Development



Breathing frequency and respiratory volume of hamsters can be determined within 30 minutes. Hamsters are awake and moving in the plethysmograph.

Wageningen Bioveterinary Research developed an infection model in Syrian hamsters using a Dutch SARS-CoV-2 isolate representative for the pandemic. Most important read-out parameters are activity and weight of the hamsters, morphology and histology of lungs and viral load in throat swabs, lungs and nasal tissue.
Prophylactic and/or therapeutic treatments against SARS-CoV-2 infection can be evaluated in this model.

WAGENINGEN UNIVERSITY & RESEARCH

Medical News Today

COVID-19 vaccine successfully protects macaques against virus

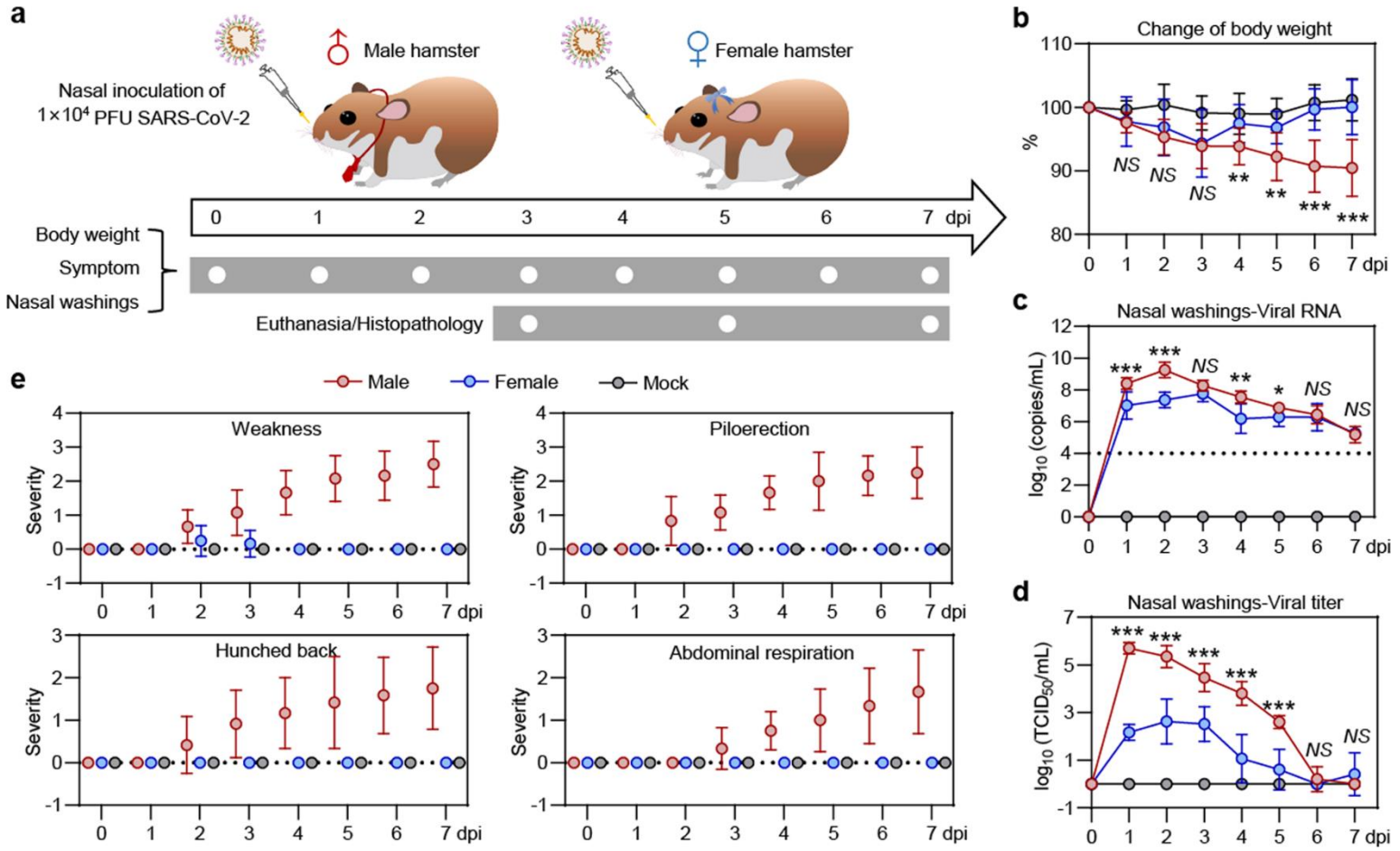
Written by Timothy Huzar on August 5, 2020 — Fact checked by Hannah Flynn, MS

A new study has found that a COVID-19 vaccine candidate is highly effective in protecting rhesus macaque monkeys from the disease.

Early studies show that a COVID-19 vaccine candidate is highly effective in rhesus macaque monkeys.

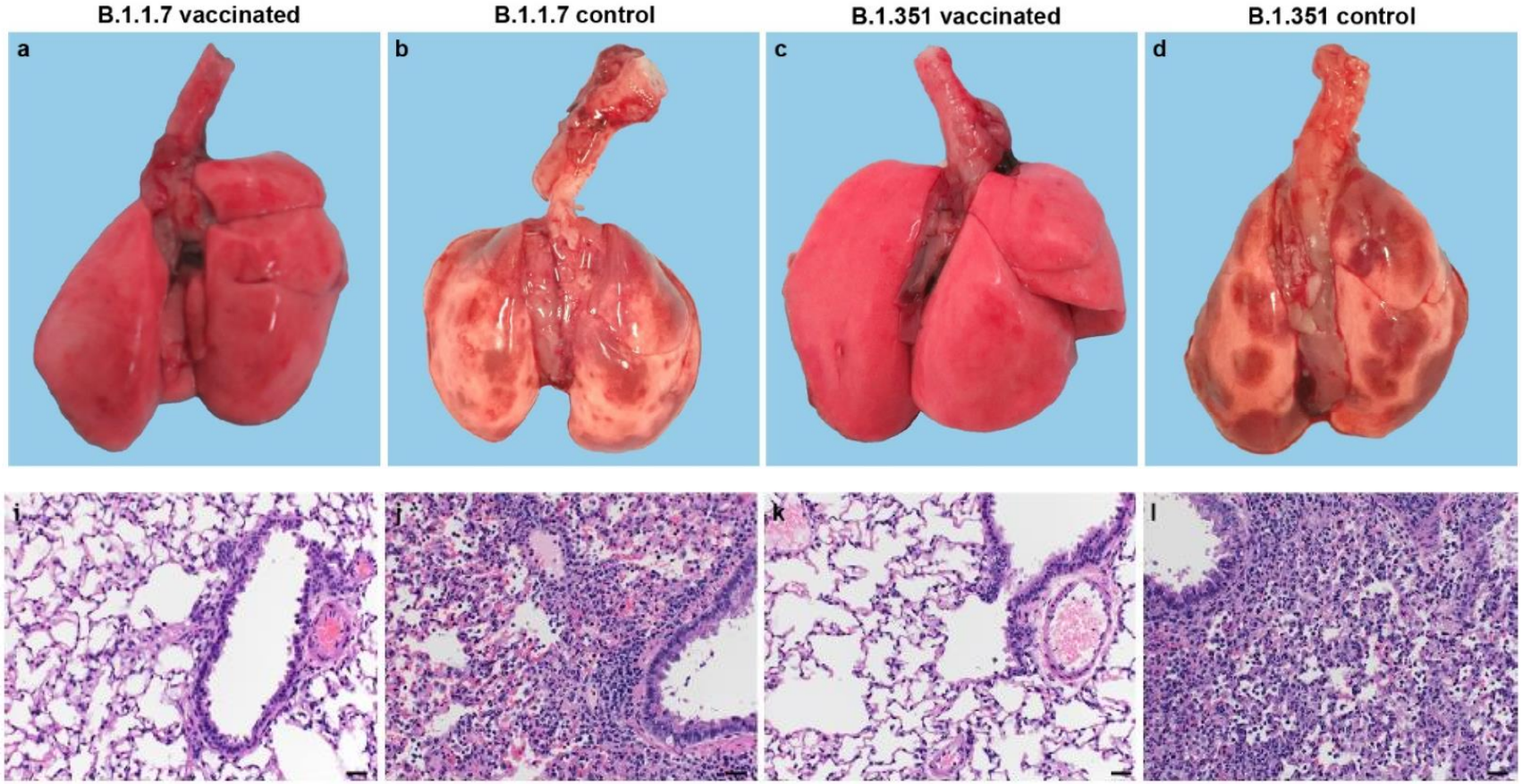
Developing a safe and effective vaccine is central to stopping the spread of SARS-CoV-2, the virus responsible for COVID-19.

Gender associates with both susceptibility to infection and pathogenesis of SARS-CoV-2 in Syrian hamster.



Yuan L *Signal Transduction and Targeted Therapy* **volume 6,** Article number: 136 (2021)

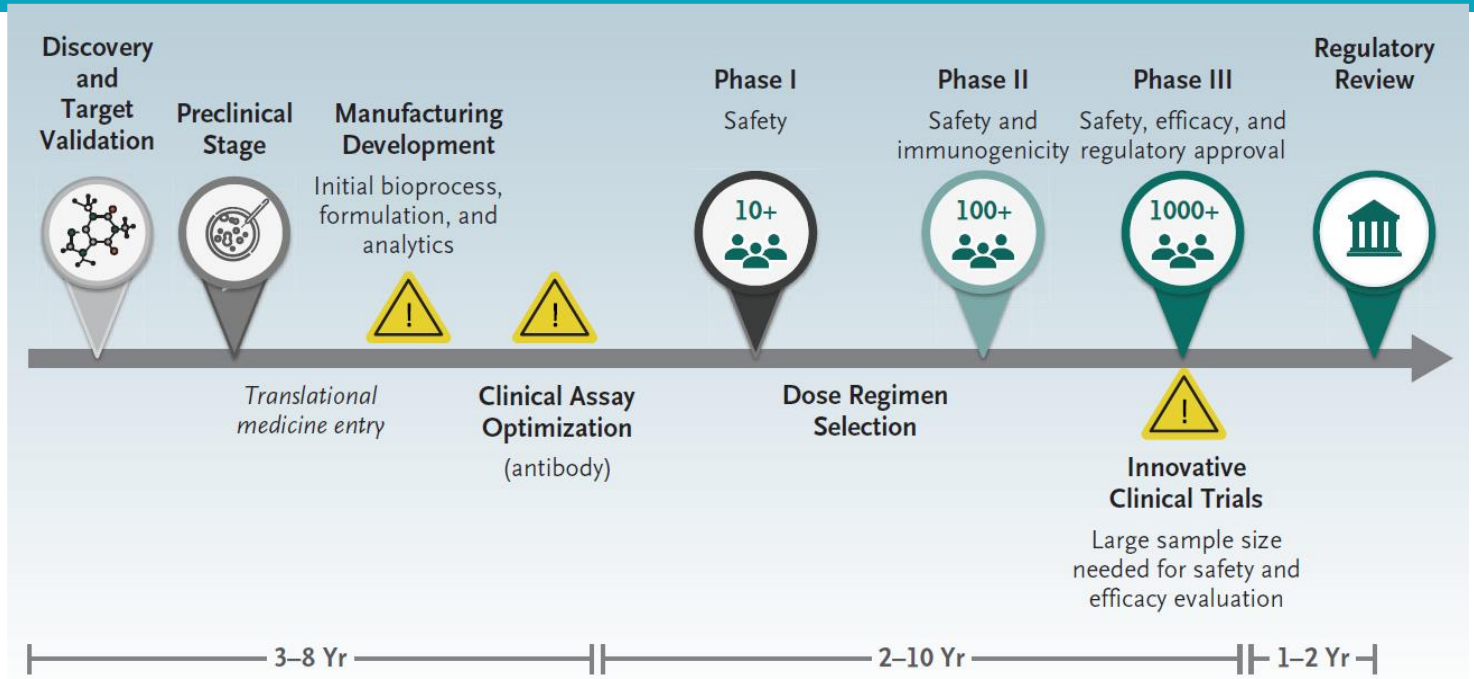
AZ Covid-19 vaccination and gross pathology of lungs following direct intranasal challenge with SARS-CoV-2 variants B.1.1.7 and B.1.351 in Syrian hamsters.



Fisher RJ et al; BioRxiv preprint doi: https://doi.org/10.1101/2021.03.11.435000

The Vaccine Testing Process

The development cycle of a vaccine, from lab to clinic.



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PHASE III EFFICACY TRIALS: **Thousands of people** compared volunteers who receive vaccine or placebo, determine if vaccine protects against the coronavirus and is safe.

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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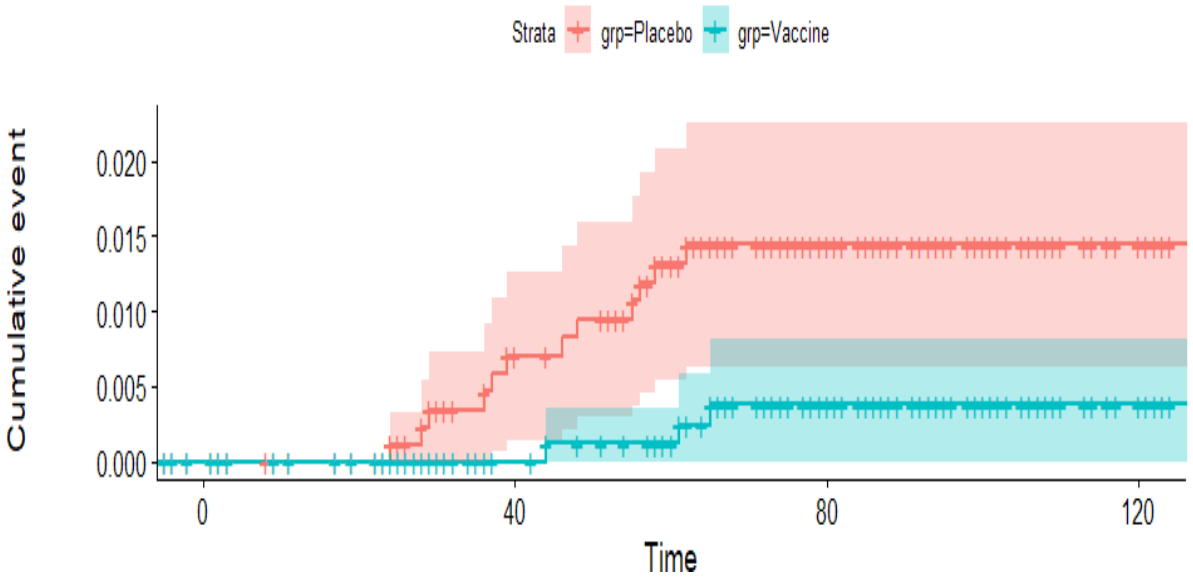

$$\text{Vaccine efficacy} = \frac{\text{AR unvaccinated} - \text{AR vaccinated}}{\text{AR unvaccinated}} \times 100$$

$$= 1 - \text{RR vaccinated / unvaccinated} \times 100$$

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

Madhi SA et al .In press

WITS VIDA UNIVERSITY OF THE WITWATERSRAND VACCINES & INFECTIOUS DISEASES ANALYTICS

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

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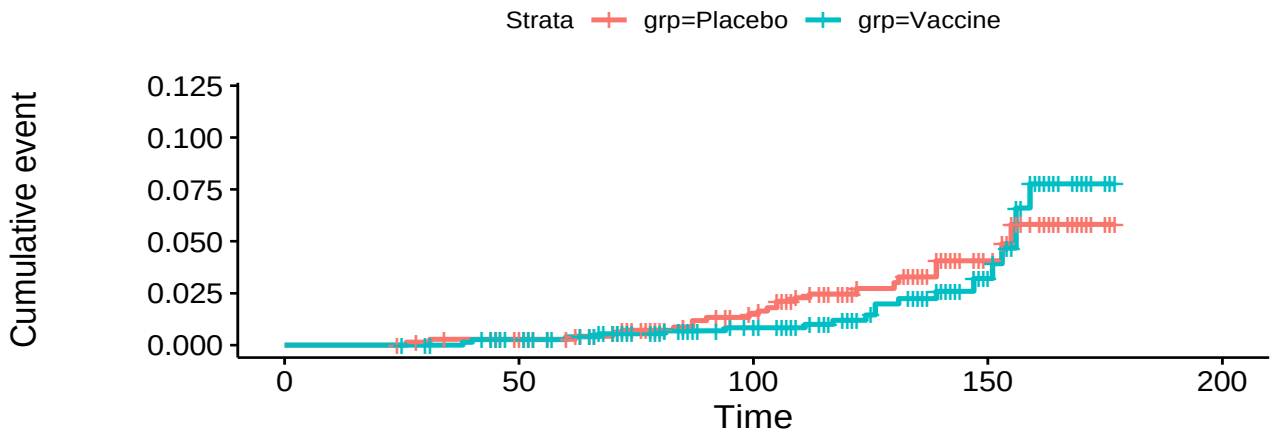

No significant risk reduction in mild-moderate Covid-19 from B.1.351 variant occurring at least 14 days after 2nd dose of ChAdOx1/nCoV19.

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)

Madhi SA et al .In press

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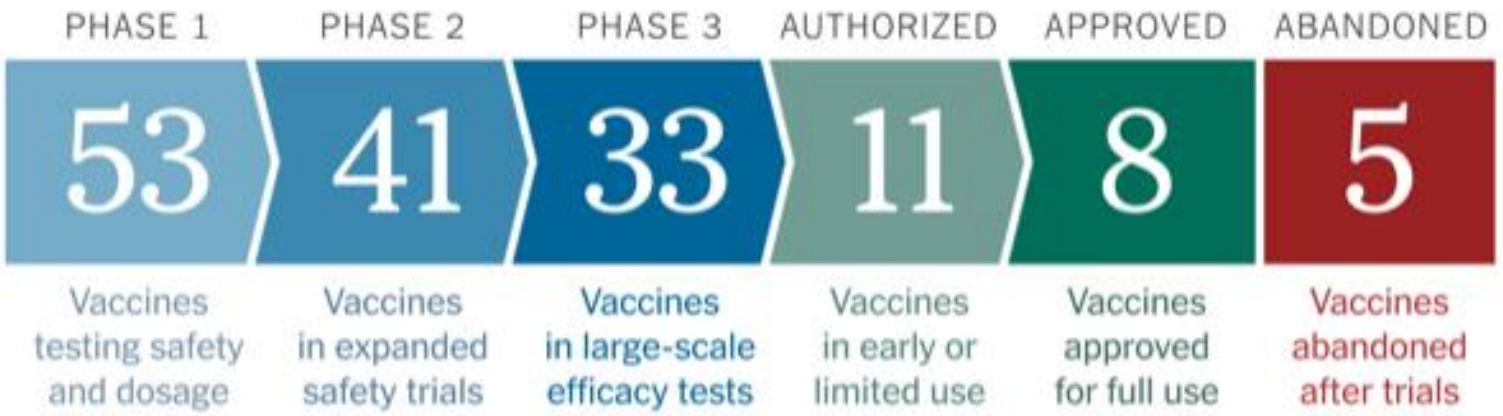
Covid-19 development and pipeline.



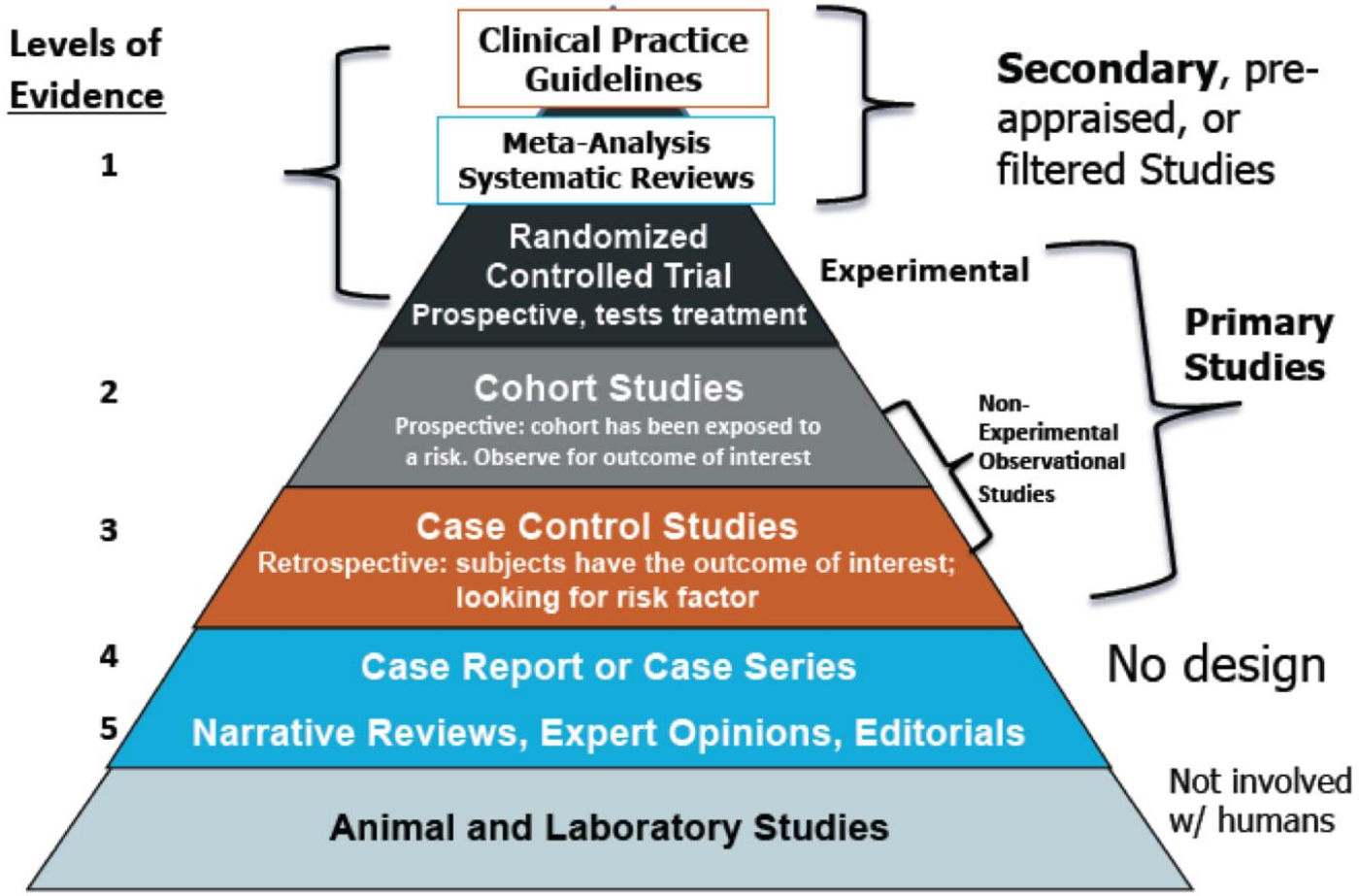
???Evaluation of future Covid-19 vaccines????

Leading vaccines

Developer	How It Works	Phase	Status
Pfizer-BioNTech	mRNA	2 3	Approved in several countries. Emergency use in U.S., E.U., other countries.
Moderna	mRNA	3	Approved in Switzerland. Emergency use in U.S., E.U., other countries.
Gamaleya	Ad26, Ad5	3	Emergency use in Russia, other countries.
Oxford-AstraZeneca	ChAdOx1	2 3	Approved in Brazil. Emergency use in U.K., E.U., other countries.
CanSino	Ad5	3	Approved in China. Emergency use in other countries.
Johnson & Johnson	Ad26	3	Emergency use in U.S., E.U., other countries.
Vector Institute	Protein	3	Early use in Russia. Approved in Turkmenistan.
Novavax	Protein	3	
Sinopharm	Inactivated	3	Approved in China, U.A.E., Bahrain. Emergency use in other countries.
Sinovac	Inactivated	3	Approved in China. Emergency use in other countries.
Sinopharm-Wuhan	Inactivated	3	Approved in China. Limited use in U.A.E.
Bharat Biotech	Inactivated	3	Emergency use in India, other countrie

https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

Ranking robustness of clinical trials.



Observational study: UK data delta variant

Table 2. Vaccine Effectiveness against the Alpha Variant or *S* Target–Negative Status and the Delta Variant or *S* Target–Positive Status, According to Dose and Vaccine Type.*

Vaccination Status	Test-Negative Status	Alpha Variant or *S* Target–Negative Status			Delta Variant or *S* Target–Positive Status		
	Controls	Cases	Case:Control Ratio	Adjusted Vaccine Effectiveness (95% CI)	Cases	Case:Control Ratio	Adjusted Vaccine Effectiveness (95% CI)
	no.	*no.*		%	*no.*		%
Unvaccinated	96,371	7313	0.076	Reference	4043	0.042	Reference
Any vaccine							
Dose 1	51,470	2226	0.043	48.7 (45.5–51.7)	1493	0.029	30.7 (25.2–35.7)
Dose 2	23,993	143	0.006	87.5 (85.1–89.5)	340	0.014	79.6 (76.7–82.1)
BNT162b2 vaccine							
Dose 1	8,641	450	0.052	47.5 (41.6–52.8)	137	0.016	35.6 (22.7–46.4)
Dose 2	15,749	49	0.003	93.7 (91.6–95.3)	122	0.008	88.0 (85.3–90.1)
ChAdOx1 nCoV-19 vaccine							
Dose 1	42,829	1776	0.041	48.7 (45.2–51.9)	1356	0.032	30.0 (24.3–35.3)
Dose 2	8,244	94	0.011	74.5 (68.4–79.4)	218	0.026	67.0 (61.3–71.8)

* The adjusted analysis of vaccine effectiveness was adjusted for period (calendar week), travel history, race or ethnic group, sex, age, index of multiple deprivation, clinically extremely vulnerable group, region, history of positive test, health or social care worker, and care home residence. CI denotes confidence interval.

Bernal JL et al. NEJM; July 21, 2021

ND case–control		
nfluenza-confirmed cases	A	B
ll others in cohort	C	D

$$\frac{A/p(A+C)}{B/p(B+D)} = \frac{A/(A+C)}{B/(B+D)} = RR$$

Requires assessment for bias and confounding that may exist in the absence of randomised participation and blinded follow-up.

COVID-19 and reduction in household transmission.

Table 1. Numbers of Household Contacts and Secondary Cases of Covid-19, According to Vaccination Status of Index Patient, and Adjusted Odds Ratios.*

Vaccination Status of Index Patient	Household Contacts	Secondary Cases	Adjusted Odds Ratio (95% CI)
	no.	*no. (%)*	
Not vaccinated before testing positive	960,765	96,898 (10.1)	Reference
Vaccinated with ChAdOx1 nCoV-19 vaccine ≥21 days before testing positive	3,424	196 (5.7)	0.52 (0.43–0.62)
Vaccinated with BNT162b2 vaccine ≥21 days before testing positive	5,939	371 (6.2)	0.54 (0.47–0.62)

* Odds ratios were adjusted for the age and sex of the index patient and their household contact, geographic region, calendar week of the index case, and an index of multiple deprivation and household type and size. CI denotes confidence interval, and Covid-19 coronavirus disease 2019.

Harris RJ et al. NEJM Aug 2021

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