SARS-CoV-2 Viral Vector Vaccines

A Review of Pertinent Drug Information for SARS-CoV-2

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SARS-CoV-2 Viral Vector Candidates

Candidate Name/Type	Sponsor	Clinical Trial Phase	Dosing	Clinical Trials
AZD1222 (Covishield)	AstraZeneca + University of Oxford	Phase 3	1-2 doses (d0, d28)	PACTR202005681895696 (Phase 1) PACTR202006922165132 (Phase 1/2) NCT04686773 (Phase 2) NCT04400838 (Phase 2/3) ISRCTN89951424 (Phase 3)
Ad26.COV2.S	Johnson & Johnson	Phase 3	1-2 doses (d0 or d0, d56)	NCT04509947 (Phase 1) NCT04436276 (Phase 1/2) EUCTR2020-002584-63-DE (Phase 2) NCT04505722 (Phase 3)
Gam-COVID-Vac Adeno-based (rAd26-S+rAd5-S)	Gamaleya Research Institute; Health Ministry of the Russian Federation	Phase 3	2 doses (d0, d21)	NCT04436471 (Phase 1/2) NCT04530396 (Phase 3)
Recombinant novel coronavirus vaccine (Ad5-nCoV)	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase 3	1 dose (d0)	ChiCTR2000030906 (Phase 1) ChiCTR2000031781 (Phase 2) NCT04526990 (Phase 3)

**All Information updated Feb 6, 2020

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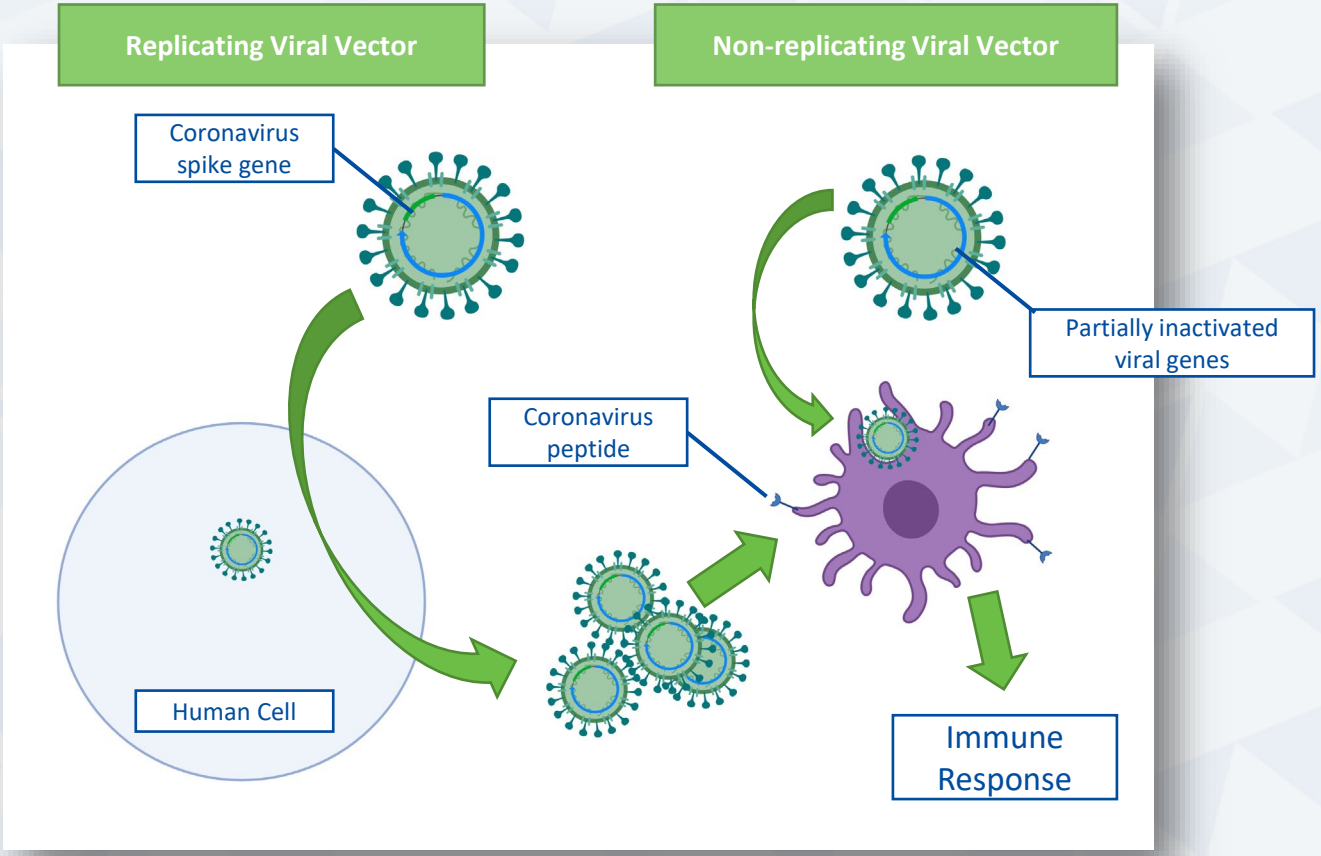
EUA: Emergency Use Authorization

World Health Organization. Draft landscape of COVID-19 candidate vaccines. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. Accessed Dec. 15, 2020

Mechanism of Action | Viral Vectors

- Typical viral vectors include adenoviruses and poxviruses
  - **Replicating**: measles virus, vesicular stomatitis virus
  - **Non-replicating**: adeno-associated virus, alphavirus, and herpes virus
- Adenovirus vectors specifically target mucosal inductive sites and infects dividing and non-dividing dendritic cells
  - Do not integrate
  - Physically and genetically stable

This platform represents a large group of vaccines currently in development



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Callaway E. Nature. 2020. 580:576-577
Krammer F. Nature. 2020. 586:516-27
Robert-Guroff M. Curr Op in Biotech. 2007. 18:546-556

Created with Biorender.com

Mechanism of Action | Prime-Boost

- Prime-boost vaccine strategy enhances cellular and humoral immunity → important for protection against viral pathogens
- Heterologous prime-boost more immunogenic than homologous prime-boost strategy

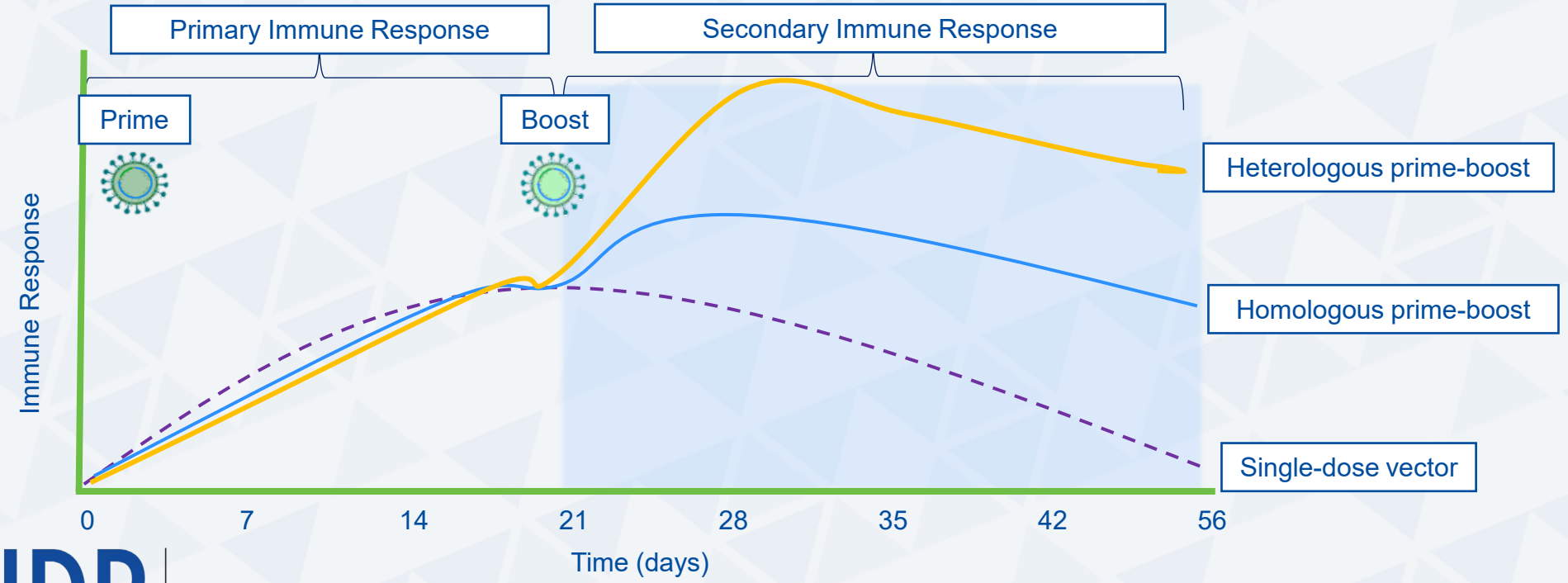

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Figure adapted from Sputnik V. Advantages of prime-boost immunization. https://sputnikvaccine.com/about-vaccine. Accessed Feb 3, 2021

Lu S. Curr Opin Immunol 2009; 21: 346–51
Logunov. Lancet. 2020;396:887-97
Kardani. Vaccine 2015. 34(4):413-423
Dolzhikova. Acta Naturae 2017. 9:4-11

AZD1222 Preclinical and Phase I/II

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AZD1222 Vaccine

Trial Design

COV001 (UK)

- Single-blind phase 1/2 clinical trial
- Originally planned as single-dose → only 88 patients still single-dose

COV002 (UK)

- Single-blind phase 2/3 study
- LD/SD and SD/SD groups
- Older adults only received SD/SD

Unintentional LD/SD regimen

COV003 (Brazil)

- Single-blind phase 3 study
- SD/SD up to 12 weeks apart (target 4 weeks)

COV005 (South Africa)

- Double-blind phase 1/2 study
- SD/SD with doses 4 weeks apart

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LD: Low dose (2.2 x10^{10} viral particles)
SD: Standard dose (5x10^{10} viral particles)

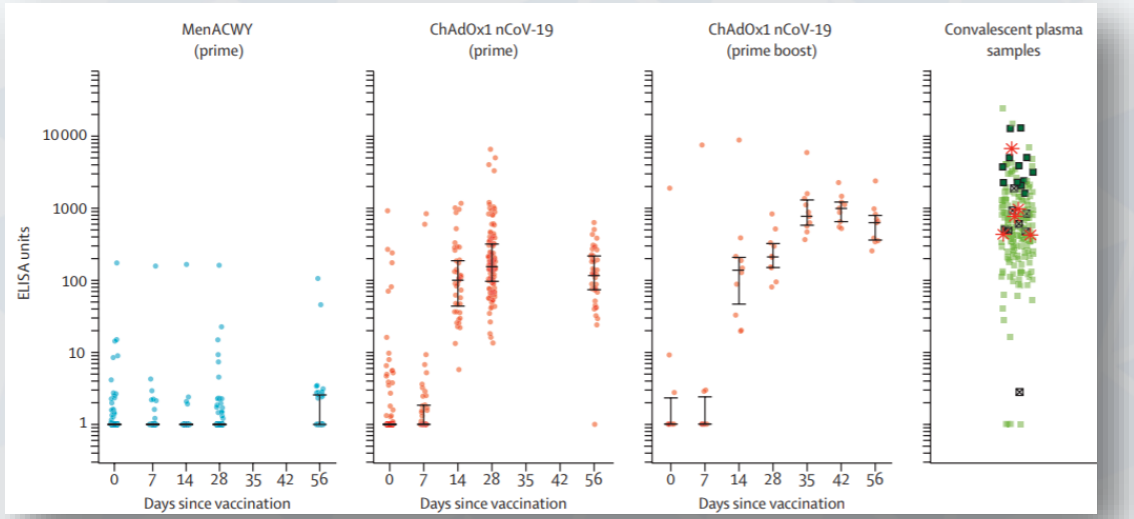
Folegatti. Lancet. 2020;396:467.
Ramasamy MN, et al. Lancet. 2020. doi: 10.1016/ S0140-6736(20)32466-1
Voysey M, et al. Lancet. 2020. doi:10.1016/S0140-6736(20)32623-4

AZD1222 VAccine

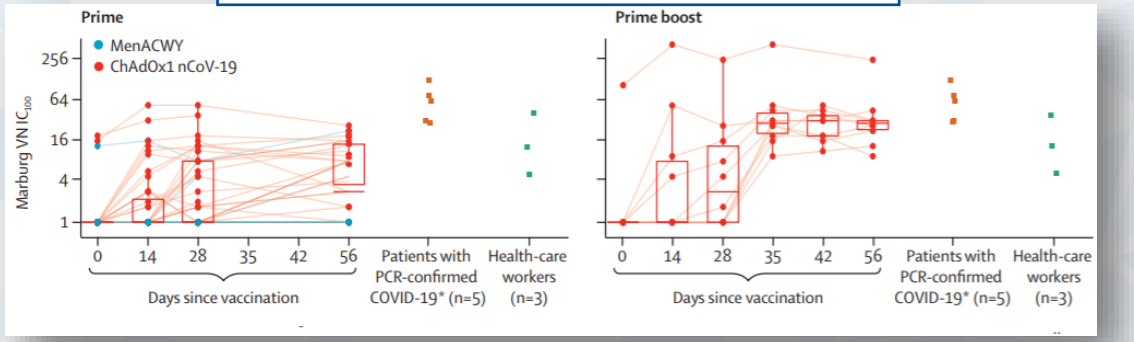
Safety and Immunogenicity

- Key Immunogenicity Findings
  - Antibodies against spike protein peaked at day 28 and persisted until day 56 in 1 dose
  - Neutralizing antibodies in all patients following booster
    - Small number of patients received booster → amendments to add booster to study protocol
  - Some patients had high levels of neutralizing antibodies at baseline

SARS-CoV-2 IgG response compared to convalescent plasma samples



SARS-CoV-2 neutralization assays



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Folegatti. Lancet. 2020;396:467.

AZD1222 Phase III

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AZD1222 Vaccine

Voysey et al.

Study Design

- Phase 3 interim pooled analysis of 4 ongoing RCTs
- 1:1 randomization to AZD1222 vs MenACWY or saline

Treatment Groups

- AZD1222 (LD/SD or SD/SD)
  - 2 doses
  - ~28 days apart
- MenACWY or saline
  - 2 doses
  - ~28 days apart

LD: Low dose (2.2 x10^{10} viral particles)
SD: Standard dose (5x10^{10} viral particles)

Outcomes

- **Primary**: efficacy of vaccine against symptomatic, lab-confirmed COVID-19
- **Secondary**: severe COVID-19, hospital/ICU admissions
- **Safety**: local/systemic reactogenicity, all ADEs

*Excluded: pregnant and breastfeeding women, severe or uncontrolled disease

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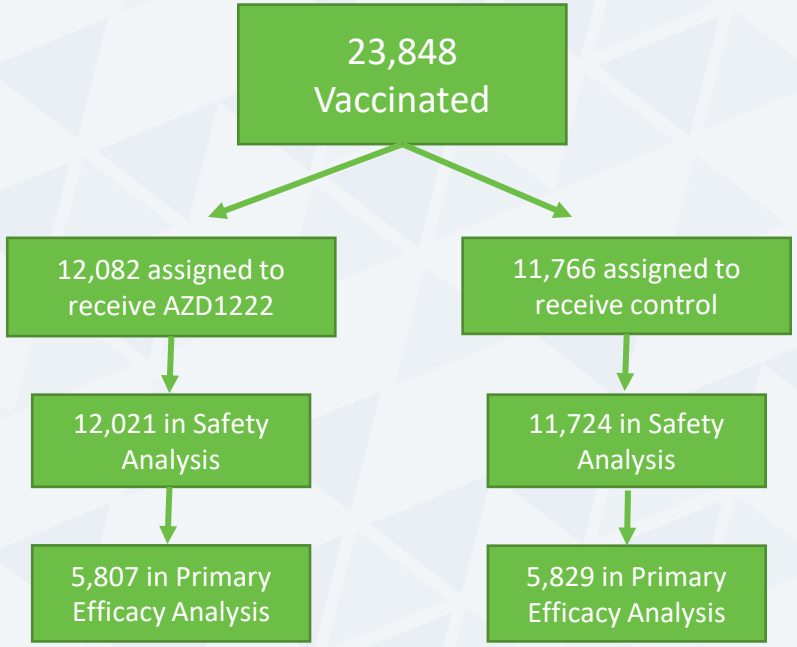
MenACWY: Meningococcal group A, C, W, and Y

Voysey M, et al. Lancet. 2020. doi:10.1016/S0140-6736(20)32623-4

AZD1222 Vaccine

Voysey et al.



1367 received LD/SD

	COV002 (UK; LD/SD; N=2741)		COV002 (UK; SD/SD; N=4807)		COV003 (Brazil; all SD/SD; N=4088)	
	ChAdOx1 nCoV-19 (n=1367)	MenACWY (n=1374)	ChAdOx1 nCoV-19 (n=2377)	MenACWY (n=2430)	ChAdOx1 nCoV-19 (n=2063)	MenACWY plus saline (n=2025)
Age, years						
18–55	1367 (100·0%)	1374 (100·0%)	1879 (79·0%)	1922 (79·1%)	1843 (89·3%)	1833 (90·5%)
56–69	0	0	285 (12·0%)	293 (12·1%)	209 (10·1%)	187 (9·2%)
≥70	0	0	213 (9·0%)	215 (8·8%)	11 (0·5%)	5 (0·2%)
Sex						
Female	886 (64·8%)	927 (67·5%)	1378 (58·0%)	1437 (59·1%)	1261 (61·1%)	1156 (57·1%)
Male	481 (35·2%)	447 (32·5%)	999 (42·0%)	993 (40·9%)	802 (38·9%)	869 (42·9%)
BMI, kg/m²	25·2 (22·8–28·7)	25·3 (22·7–28·8)	25·4 (22·9–28·7)	25·5 (22·9–29·1)	25·6 (22·8–29·1)	25·6 (23·1–29·0)
Ethnicity						
White	1257 (92·0%)	1278 (93·0%)	2153 (90·6%)	2214 (91·1%)	1357 (65·8%)	1366 (67·5%)
Black	6 (0·4%)	2 (0·1%)	17 (0·7%)	14 (0·6%)	230 (11·1%)	210 (10·4%)
Asian	76 (5·6%)	59 (4·3%)	137 (5·8%)	138 (5·7%)	54 (2·6%)	53 (2·6%)
Mixed	19 (1·4%)	22 (1·6%)	48 (2·0%)	42 (1·7%)	410 (19·9%)	386 (19·1%)
Other	9 (0·7%)	13 (0·9%)	22 (0·9%)	22 (0·9%)	12 (0·6%)	10 (0·5%)
Health and social care setting workers	1236 (90·4%)	1253 (91·2%)	1441 (60·6%)	1513 (62·3%)	1833 (88·9%)	1775 (87·7%)
Comorbidities						
Cardiovascular disease	104 (7·6%)	92 (6·7%)	264 (11·1%)	266 (10·9%)	271 (13·1%)	244 (12·0%)
Respiratory disease	158 (11·6%)	176 (12·8%)	285 (12·0%)	316 (13·0%)	215 (10·4%)	210 (10·4%)
Diabetes	18 (1·3%)	15 (1·1%)	58 (2·4%)	60 (2·5%)	59 (2·9%)	60 (3·0%)

Primary efficacy analysis only included participants in COV002 and COV003

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Voysey M, et al. Lancet. 2020. doi:10.1016/S0140-6736(20)32623-4

AZD1222 Vaccine

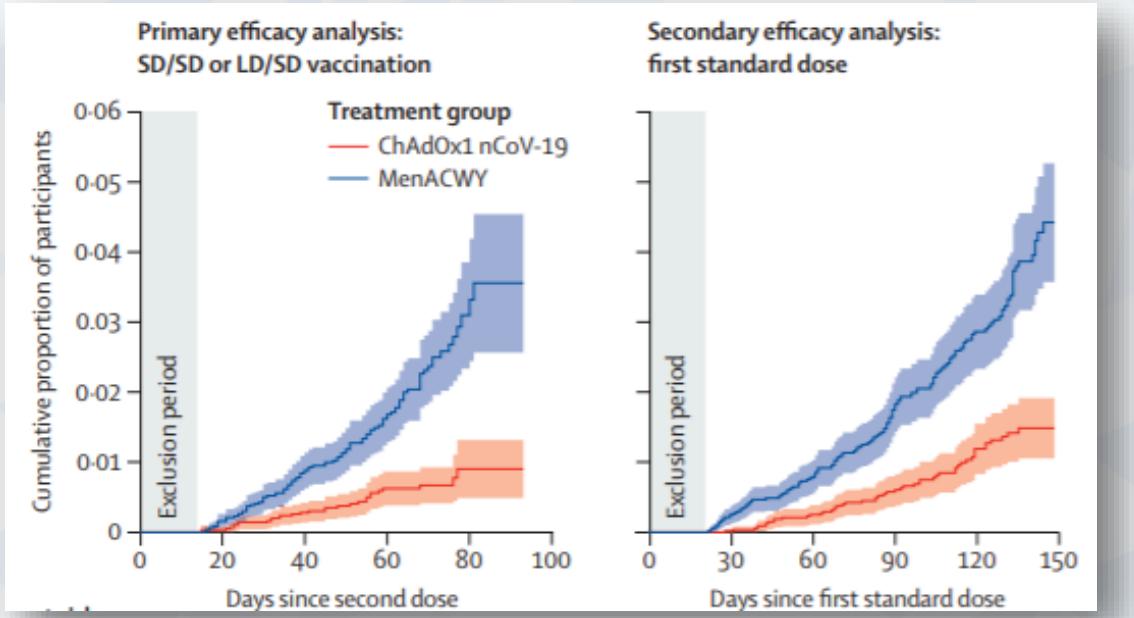
Voysey et al.

Primary and Secondary Endpoints

	AZD1222	Placebo	Efficacy (%)
Symptomatic COVID-19	30 (N=5,807)	101 (N=5,829)	70.4% (95.8% CI, 54.8 to 80.6)
Any NAAT-positive Swab	68 (N=5,807)	153 (N=5,829)	55.7 (95% CI, 41.1 to 66.7)
Asymptomatic or symptoms unknown	29 (N=3,288)	40 (N=3350)	27.3% (95%CI -17.2 to 54.9)

- Progression to Severe COVID-19:
  - 0 in AZD1222
  - 1 in placebo > 21 days after 1st dose and ≤ 14 days after 2nd
  - 1 in placebo > 14 days after 2nd dose

Kaplan-Meier cumulative incidence of primary symptomatic COVID-19 in LD/SD and SD/SD



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VE: Vaccine Efficacy

Voysey M, et al. Lancet. 2020. doi:10.1016/S0140-6736(20)32623-4

AZD1222 Vaccine Phase III Updates

- Added data from interim analysis originally published Dec. 2020
- Includes 332 symptomatic cases of COVID-19 and an analysis population of 17,177
- In-depth analysis of single-dose regimen and effects of dosing interval on vaccine efficacy

Symptomatic COVID-19 Cases > 21 days after a single SD dose	AZD1222	Control	Vaccine Efficacy (95% CI)
22 to 30 days	7/9257	30/9257	77% (47 to 90)
31 to 60 days	6/7147	27/7110	73% (33 to 89)
61 to 90 days	4/2883	19/2974	78% (36 to 93)
90 to 120 days	4/1368	6/1404	32% (-142 to 81)
22 to 90 days	17	71	76% (59 to 86)
Any PCR (+) 22 to 90 days	28	84	67% (49 to 78)

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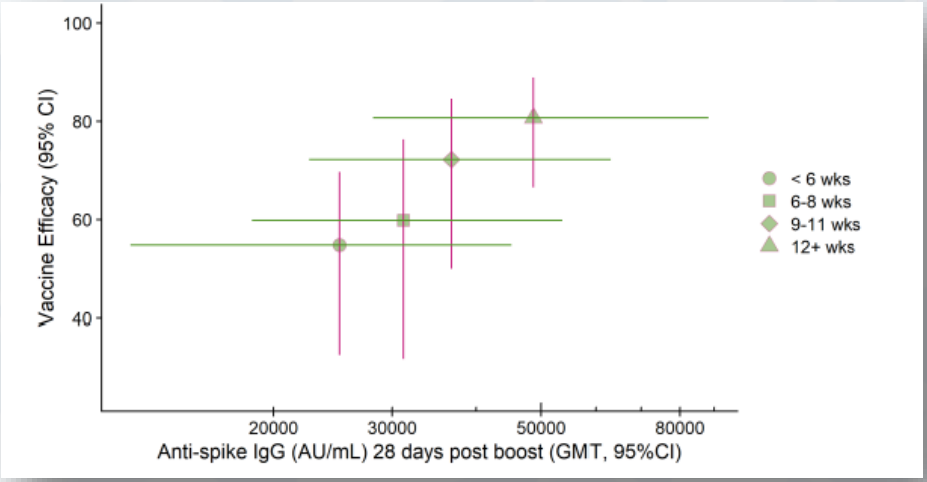
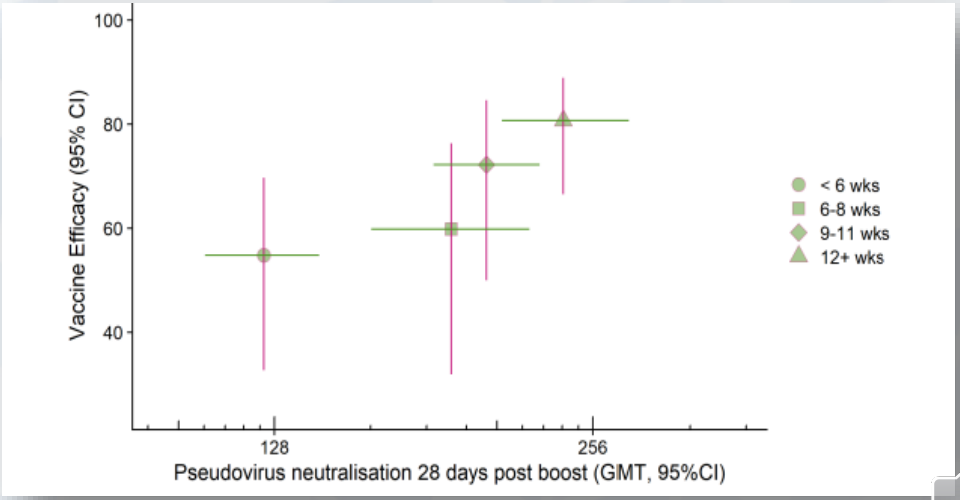
Voysey. Lancet. 2021;397:881-91. doi: 10.1016/S0140-6736(21)00432-3

AZD1222 Vaccine Phase III Updates

	AZD1222	Control	Vaccine Efficacy (95% CI)
All LD/SD Recipients	10/1396 (0.7%)	51/1402 (3.6%)	80.7% (62.1 to 90.2)
All SD/SD Recipients	74/7201 (1%)	197/7178 (2.7%)	63.1% (51.8 to 71.7)
All SD/SD By Interval			
<6 weeks interval	35/3900 (0.9%)	76/3875 (2.0%)	54.9% (32.7 to 69.7)
6-8 weeks interval	20/1103 (1.8%)	44/1018 (4.3%)	59.7% (31.7 to 76.2)
9-11 weeks interval	11/905 (1.2%)	52/1593 (3.3%)	72.3% (50.0 to 84.6)
≥ 12 weeks interval	8/1293 (0.6%)	76/2093 (3.6%)	80.7% (66.5 to 88.9)





Voysey. Lancet. 2021;397:881-91. doi: 10.1016/S0140-6736(21)00432-3

AZD1222 Vaccine

Voysey et al.

- Local and systemic reactogenicity lower and less intense in older adults, lower doses, and after second dose
- Serious Adverse events occurred in 168 patients
  - 79 received AZD1222
  - 89 received MenACWY or saline control
- 3 events considered possibly related to treatment or control
  - Hemolytic anemia in control group 10 days after MenACWY
  - Transverse myelitis 14 days following AZD1222
  - Fever >40^{o}C → patient still masked and received 2nd dose without a reaction
- 2 additional cases of transverse myelitis led to study pause but deemed unrelated to vaccine

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Voysey M, et al. Lancet. 2020. doi:10.1016/S0140-6736(20)32623-4

AZD1222 Vaccine

Voysey et al.

2-dose regimen of AZD1222 is safe and effective against COVID-19

70.4% Vaccine efficacy in primary outcome group

The Good

- Serious adverse events low and consistent between groups
  - Less intense reactogenic reactions after 2nd dose
- Rapid delivery of results
- Geographically diverse and patients at high risk of disease
- Limited data on asymptomatic disease
- **Inexpensive and easily stored**

The Gap

- **Unsure of optimal dosing regimen at this point**
  - **Currently approved in UK for SD/SD regimen with 2nd dose to be given 4-12 weeks after 1st dose**
- Long-term safety outcomes
- Duration of efficacy
- Lacks data in pregnancy, immunocompromised and patients <18 years old
- Limited data in AIDS/HIV and younger patients (data to come)

The Bad

Large confidence intervals

Smaller patient population

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UK: United Kingdom

AZD1222 Regulatory Information for UK

	AZD1222 (AstraZeneca)
Dose	• $5x10^{10}$ viral particles (0.5 mL) IM
Schedule	• 2 doses • Given between 4 and 12 weeks after 1st dose
EUA Age Req.	• ≥ 18 years old
Undiluted/Unpunctured Storage Requirements	• 2°C to 8°C (6-month expiration) • DO NOT FREEZE
BUD Once Punctured	• 2°C to 25°C for up to 6 hours • Do not refreeze
Doses/Vial	• 5 mL, 10-dose vial (in packs of 10 vials) • 4 mL, 8-dose vial (in packs of 10 vials)
Preservative	• No preservatives
Interchangeable	• Not interchangeable with other vaccines

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Information for UK healthcare professionals on COVID-19 Vaccine AstraZeneca. Available online at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950250/Information_for_UK_healthcare_professionals_on_COVID-19_Vaccine_AstraZeneca.pdf

Ad26.COV2.S Preclinical and Phase I/II

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Ad26.COV2.S Vaccine

Safety and Immunogenicity

- Randomized, double-blind placebo-controlled phase 1/2a study in adults ≥18 to ≤55 and aged ≥65 years
- Safety, reactogenicity, and immunogenicity evaluation
  - 2 different dose levels as either a single dose or 2-dose regimen
- Randomized 1:1:1:1:1 ratio to one of 5 groups

Cohort 1 (≥18 to ≤55 years)

- D1: 5×10^{10} vp, D57: 5×10^{10} vp
- **D1: 5×10^{10} vp, D57: placebo**
- D1: 1×10^{11} vp, D57: 1×10^{11} vp
- **D1: 1×10^{11} vp, D57: placebo**
- D1: placebo, D57: placebo

Cohort 2 (≥18 to ≤55 years)

- **D1: 5×10^{10} vp, D57: placebo**
- D1: 5×10^{10} vp, D57: 5×10^{10} vp

Cohort 3 (≥65 years)

- D1: 5×10^{10} vp, D57: 5×10^{10} vp
- **D1: 5×10^{10} vp, D57: placebo**
- D1: 1×10^{11} vp, D57: 1×10^{11} vp
- **D1: 1×10^{11} vp, D57: placebo**
- D1: placebo, D57: placebo

Bolded regimens are single dose arms

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Vp: viral particles

Sadoff. N Engl J Med. 2021. doi: 10.1056/NEJMoa2034201

Ad26.COV2.S Vaccine

Safety and Immunogenicity

- Safety data up to Oct. 30, 2020 for cohorts 1 & 3 included
  - Data after cohort 1a second dose and cohort 3 first dose
- **Key Exclusion:** immunocompromised, pregnant, breastfeeding, comorbidities that are increased risk of severe COVID-19 (specifically for cohort 3)

Characteristic	Low-dose	High-dose	Placebo	Total
Cohort 1				
No of participants	162	158	82	402
Sex – no (%) Male Female	 78 (48) 84 (52)	 72 (46) 85 (54)	 40 (49) 42 (51)	 190 (47) 211 (52)
Mean Age (yr)	36.1	34.8	35.4	35.4
SARS-CoV-2 seropositive – no (%)	3 (2)	2 (1)	2 (2)	7 (2)
Cohort 3				
Sex – no (%) Male Female	 84 (52) 77 (48)	 79 (49) 82 (51)	 38 (47) 43 (53)	 201 (50) 202 (50)
Mean Age (yr)	69.6	70.0	69.9	69.8
SARS-CoV-2 seropositive – no (%)	1 (1)	2 (1)	1 (1)	4 (1)

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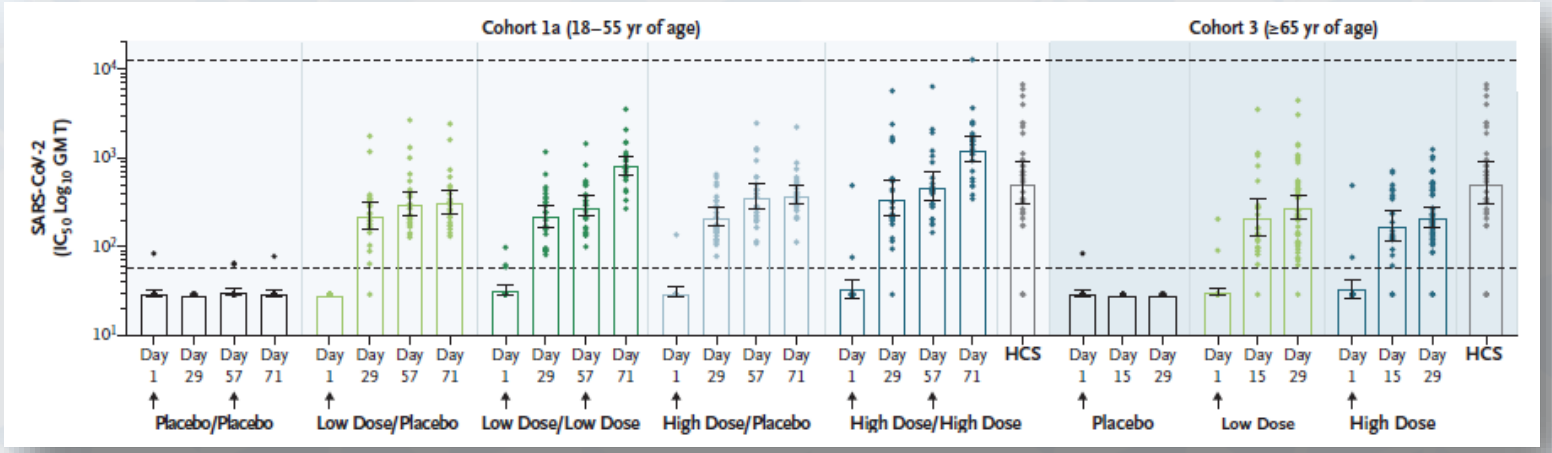
Sadoff. N Engl J Med. 2021. doi: 10.1056/NEJMoa2034201

Ad26.COV2.S Vaccine

Safety and Immunogenicity

- Key Immunogenicity Findings
  - Binding-antibody geometric mean concentration (GMC):
    - Cohort 1→ after 1st dose seroconversion 100% in all but 1 group
    - Cohort 3→ after 1st dose seroconversion was 96% by day 29
  - SARS-CoV-2 neutralizing-antibody titer (IC_{50}):
    - Cohort 1→ after 1st dose seroconversion 88-96%
    - Cohort 3→ after 1st dose seroconversion 88% in low dose and 96% in high dose groups

- Th1 predominant response to S peptides
- 2 participants had measurable Th2 response
  - Response was skewed to Th1 and therefore not concerning



Humoral Immunogenicity: wild-type virus neutralization assay

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Sadoff. N Engl J Med. 2021. doi: 10.1056/NEJMoa2034201

Ad26.COV2.S Phase III

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Ad26.COV2.S Candidate VRBPAC Briefing

Study Design

- Phase 3, randomized, double-blind, placebo-controlled
- 1:1 randomization to Ad26.COV2.S or placebo
- Target enrollment: 40,000
  - At least 30% ≥ 60 years old

Treatment Groups

- Ad26.COV2.S $5x10^{10}$ vp (0.5mL)
  - 1 dose
- Sodium chloride solution (0.5mL)
  - 1 dose

*Staged enrollment process starting with younger patients without comorbidities

Outcomes

- **Primary**: efficacy of single dose to prevent moderate/severe/critical COVID-19 at least 14 days after vaccination or at least 28 days after
- **Secondary**: COVID-19 classified as severe/critical or requiring medical intervention/death, asymptomatic COVID-19
- **Safety**: local/systemic reactogenicity, all ADEs

*Excluded: pregnant women, participants with abnormal immune function (chronic steroid use, autoimmune disease, immunodeficiency)

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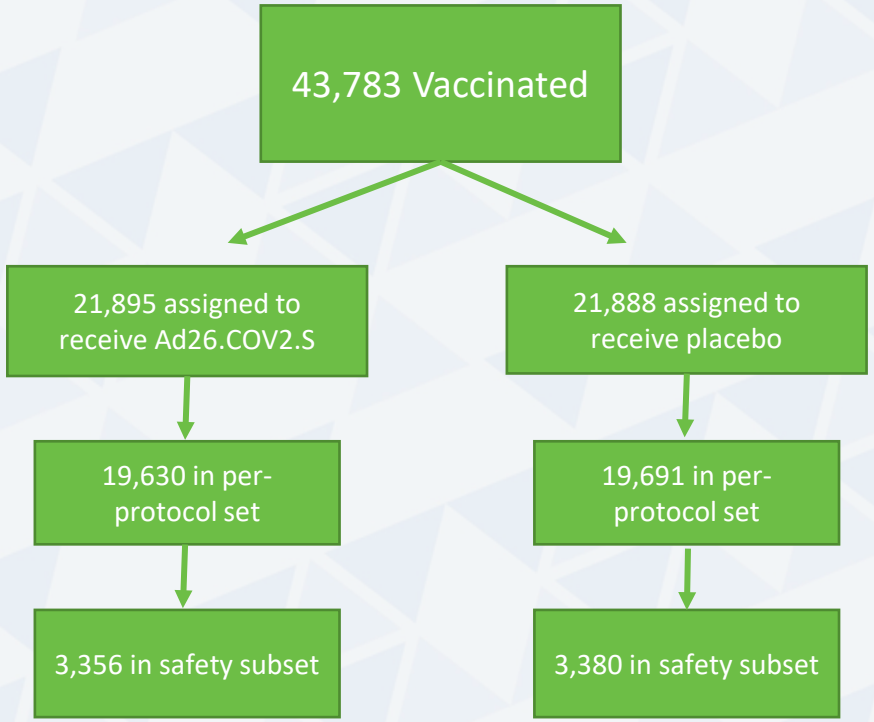
Vp: viral particles; ADEs: adverse drug events;

Sadoff. N Engl J Med. 2021. doi:10.1056/NEJMoa2101544

Ad26.COV2.S Candidate

VRBPAC Briefing



Subgroup	Ad26.COV2.S (N=21,895)	Placebo (N=21,888)
Age		
Mean (SD)	50.7 (15.1)	50.7 (15)
18-59	14,564 (66.5%)	14,547 (66.5%)
≥60	7,331 (33.5%)	4,341 (33.5%)
≥75	809 (3.7%)	732 (3.3%)
Sex		
Female	9,820 (44.9%)	9,902 (45.2%)
Race		
White	12,858 (58.7%)	12,838 (58.7%)
Black or African American	4,251 (19.4%)	4,264 (19.5%)\
American Indian or Alaskan Native	2,083 (9.5%)	2,060 (9.4%)
Asian	743 (3.4%)	687 (3.1%)
Multiple	1,204 (5.5%)	1,245 (5.7%)
Ethnicity		
Hispanic or Latino	9,874 (45.1%)	9,963 (45.5%)
SARS-CoV-2 Status		
Positive	2,151 (9.8%)	2,066 (9.4%)
Baseline Comorbidities		
One or more	8,936 (40.8%)	8,922 (40.8%)
Obesity	6,277 (28.7%)	6,215 (28.4%)
Hypertension	2,225 (10.2%)	2,296 (10.5%)
Type 2 diabetes mellitus	1,600 (7.3%)	1,594 (7.3%)
HIV	601 (2.7%)	617 (2.8%)

Full Analysis Set for Phase 3 Data

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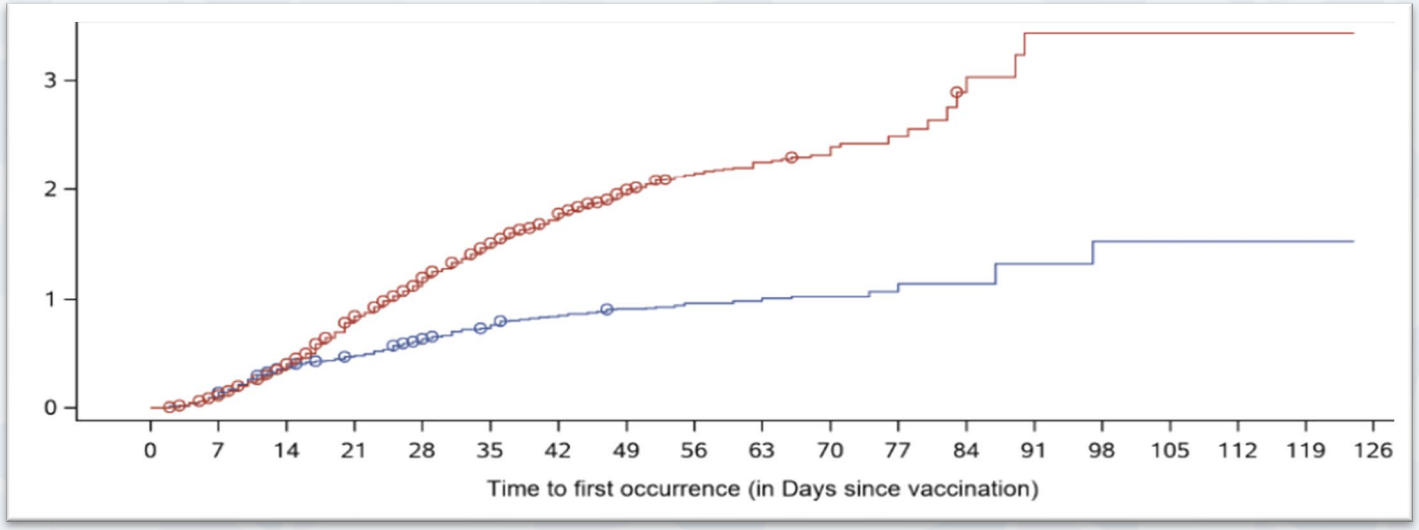
Sadoff. N Engl J Med. 2021. doi:10.1056/NEJMoa2101544

Ad26.COV2.S Candidate

VRBPAC Briefing

Kaplan-Meier cumulative incidence of moderate to severe/critical COVID-19- full analysis set



Primary and Secondary Endpoints: Per-Protocol Set

	Ad26.CoV2.S	Placebo	Efficacy (%)
Moderate to severe/critical COVID-19 at least 14 days after vaccination	116	348	66.9% (95% CI, 59 to 73.4)
Moderate to severe/critical COVID-19 at least 28 days after vaccination	66	193	66.1 (95% CI, 53.3 to 75.8)
Severe/Critical COVID-19 with onset at least 28 days after vaccination	5	34	85.4% (95% CI, 54.2 to 96.9)
COVID-19 requiring medical intervention with onset at least 28 days after vaccination	0	7	100% (95% CI, 31.1 to 100.0)
Asymptomatic SARS-CoV-2 Infection	10	37	74.2% (95% CI, 47.1 to 88.6)
COVID-19 related deaths	0	7	-

VE: Vaccine Efficacy

Sadoff. N Engl J Med. 2021. doi:10.1056/NEJMoa2101544

Ad26.COV2.S Candidate

VRBPAC Briefing

Vaccine Efficacy by Geographical Location and Comorbidity

	Ad26.CoV2.S	Placebo	Efficacy (%)
Moderate to severe/critical COVID-19 at least 28 days after vaccination			
18-59 years, no comorbidity	58	180	68% (95%CI, 56.8 to 76.6)
18-59 years, with comorbidity	29	79	64% (95%CI, 44.3 to 77.3)
≥60 years, no comorbidity	11	39	72.4% (95%CI, 45 to 87.3)
≥60 years, with comorbidity	15	26	42.3% (95%CI, -13.1 to 71.6)
Moderate to severe/critical COVID-19 at least 28 days after vaccination			
United States	32	112	72% (95%CI, 58.2 to 81.7)
South Africa	23	64	64% (95%CI, 41.2 to 78.7)
Latin America	58	148	61% (95%CI, 46.9 to 71.8)

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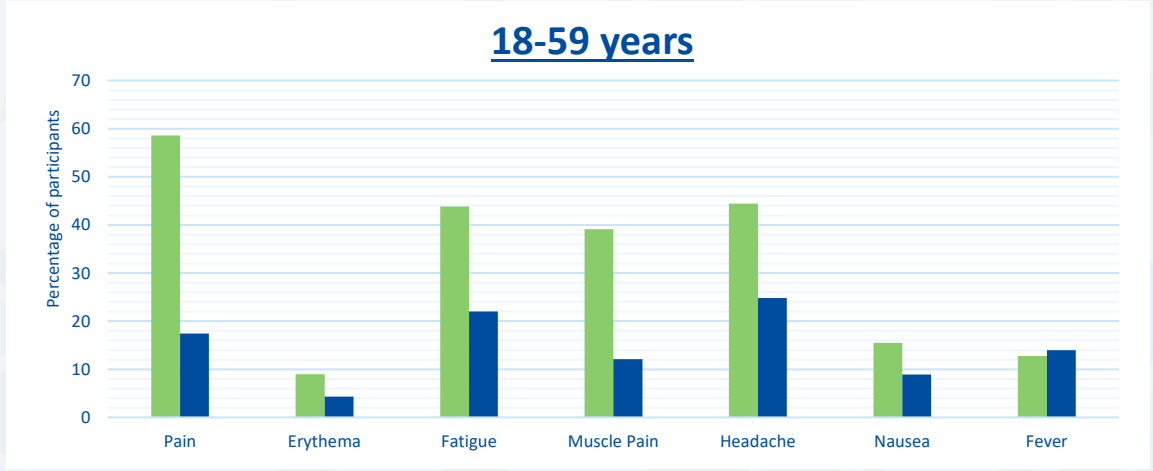
VE: Vaccine Efficacy

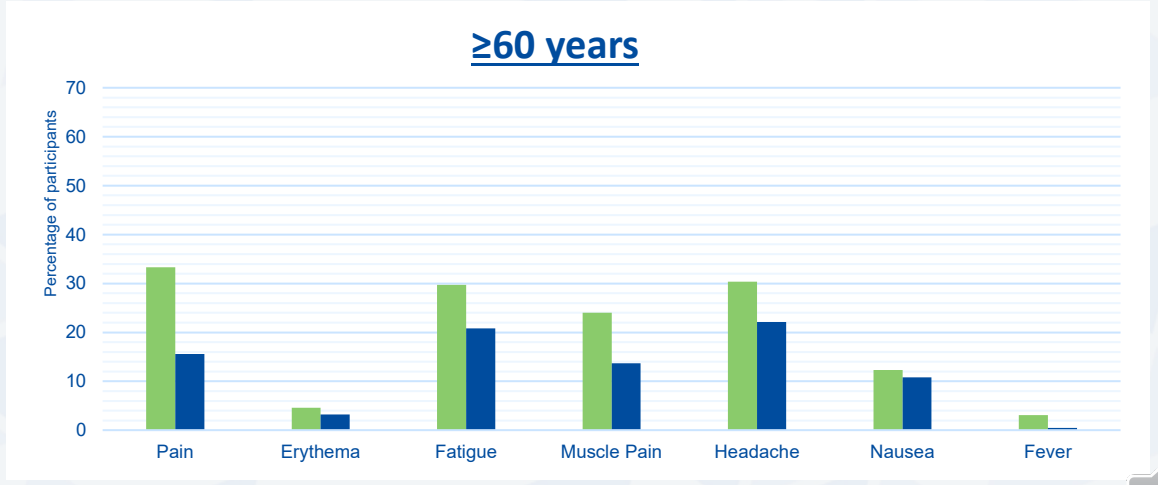
Sadoff. N Engl J Med. 2021. doi:10.1056/NEJMoa2101544

Ad26.COV2.S Candidate

VRBPAC Briefing

- Medically attended adverse events, serious adverse events and deaths were balanced between groups
- Unsolicited AEs were balanced between groups → more related to study product in vaccine group
- Solicited ARs were higher in the vaccine group compared to placebo
  - Rates of ARs were lower in participants ≥60 years
  - Local reactions time to onset within 2 days and median duration was 2 days
  - Systemic reactions time to onset was 2 days and median durations were 1-7 days





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Sadoff. N Engl J Med. 2021. doi:10.1056/NEJMoa2101544

Ad26.COV2.S Candidate Summary

1-dose regimen of Ad26.COV2.S is safe and effective against COVID-19

66.9% Vaccine efficacy in primary outcome at least 14 days after vaccination

66.1% Vaccine efficacy in primary outcome at least 28 days after vaccination

The Good

- Single dose efficacy!
- Serious adverse events low and consistent between groups
  - Less intense reactions in older participants and when compared to other vaccine platforms
- Rapid delivery of results
- Geographically diverse
- Limited data on asymptomatic disease and clinical efficacy against variants → more data to come
- **Inexpensive and easily stored**

The Gap

- Long-term safety outcomes
- Duration of efficacy
- Lacks data in pregnancy, immunocompromised, and patients <18 years old
- Limited data in AIDS/HIV
- Limited data for protection of severe disease

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The Bad

Short follow-up period, especially for certain patient populations → large confidence intervals

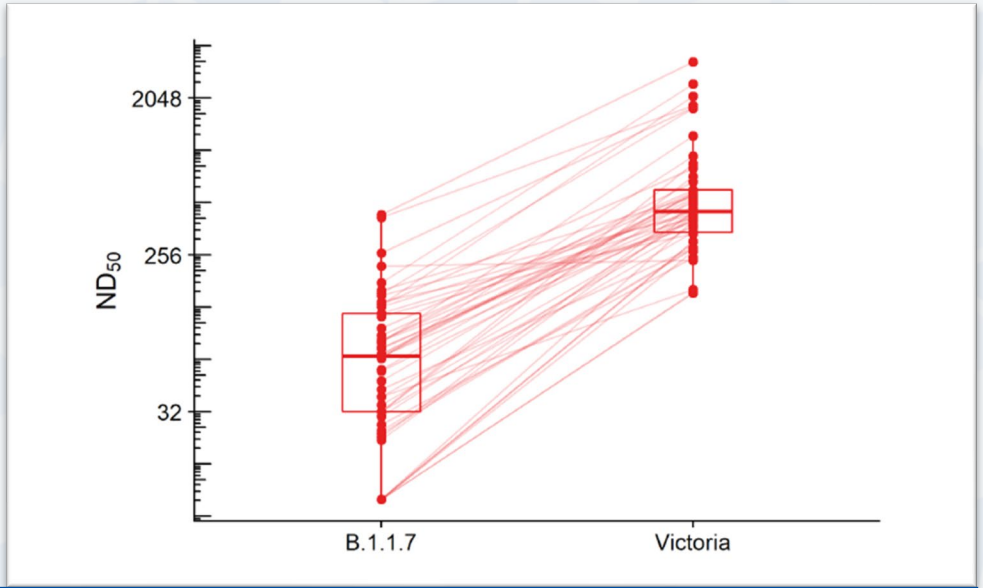
***trials currently enrolling for pregnant patients and adolescents (12-17 years old)**

UK: United Kingdom

Viral Vector Vaccines

Variant Implications

Ad26.COV2.S Clinical Variant Efficacy Data (Moderate to Severe COVID-19)	
South Africa (94.5% of sequenced variants: B.1.351)	**64% (95%CI, 41.2 to 78.7)**
AZD1222 Clinical Variant Efficacy Data (Mild to Moderate COVID-19)	
B.1.1.7	70.4% (95%CI, 43.6 to 84.5)
B.1.351	**10.4% (95%CI, -76.8 to 54.8)**



Emary et al: Live virus microneutralization antibody titers of sera against B.1.1.7 and a non-B.1.1.7 strain

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Sadoff. N Engl J Med. 2021. doi: 10.1056/NEJMoa2101544
Emary. Lancet. 2021. doi: 10.1016/S0140-6736(21)00628-0
Madhi. N Engl J Med. 2021. doi: 10.1056/NEJMoa2102214

Viral Vector Vaccines RARE Adverse Events

Vaccine	No. Reported Patients w/ CVST	Age Range	Risk Factors	Vaccine to admission	Positive Heparin PF4 ELISA
Ad26.COV2.S	12	<60 years	7/12; obesity, hypothyroidism, OC	10-25 days	11/12 (1 not completed)
AZD1222	44	21-70 years (most under 55)	NA	6-24 days	22/23 patients*

- Rare, but clinically serious adverse event observed in association with viral vector vaccines
- Observed cases of CVST appear to exceed expected background rate, specifically for women aged 20-50 years

Signs and Symptoms

Initial: headache, chills, fever, abdominal pain, nausea

Later: severe headache with neck stiffness, speech difficulty, seizure, loss of consciousness

Laboratory Findings

- Platelet levels <100,000
- PF4 HIT ELISA antibody positive
- SARS-CoV viral assay negative
- SARS-CoV-2 serology negative

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CVST: cerebral venous sinus thrombosis; OC: oral contraceptives; NA: not available

See. JAMA. 2021. doi: 10.1001/jama.2021.7517
Scully. N Engl J Med. 2021. doi: 10.1056/NEJMoa2103384
Nazy. ISTH SCC Subcommittee on Platelet Immunology. doi: 10.111/jth.15341
Shimabukuro. Thrombosis with thrombocytopenia syndrome (TTS) following Janssen COVID-19 vaccine. Presentation to Advisory Committee on Immunization Practices.

rAd26-S+rAd5-S (Sputnik V) Phase I/II

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Sputnik V Vaccine

Phase I/II Data

- **Reactogenicity and Safety**
  - Most common → pain at injection site, hyperthermia, headache, asthenia, and muscle/joint pain
  - Changes in lab values were mild and transient
  - Most events occurred after the second vaccination
  - No adverse events led to withdrawal

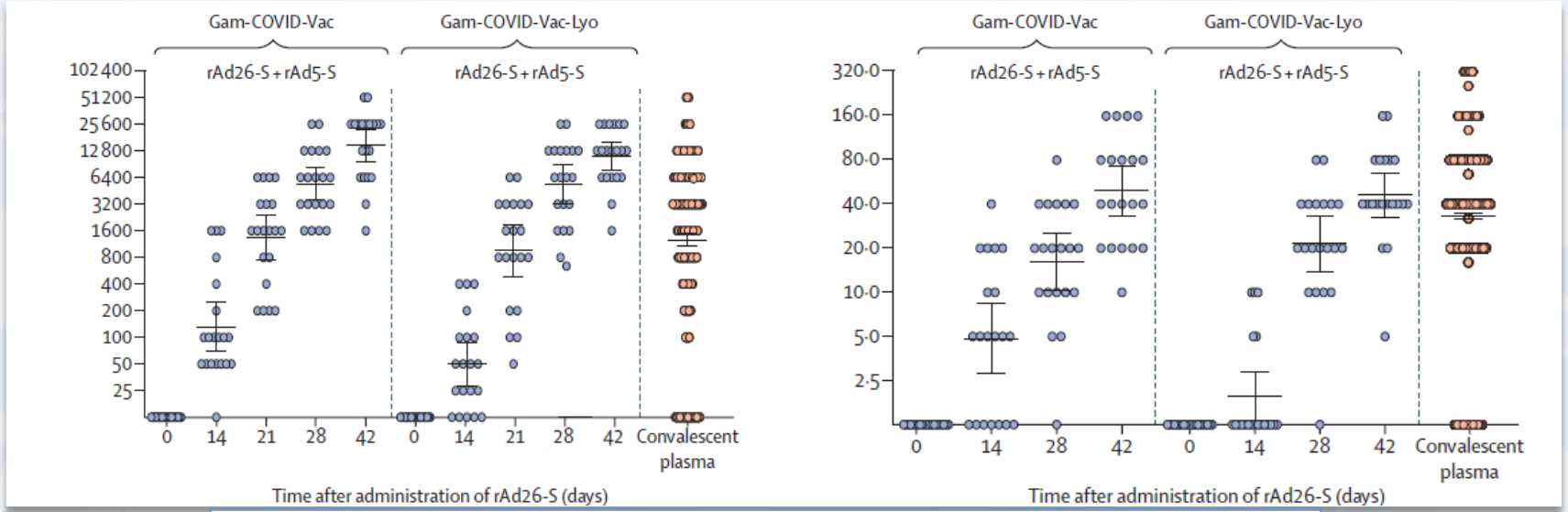
Systemic Reactions	Gam-COVID-Vac			Gam-COVID-Vac-Lyo		
	rAd26-S (n=9)	rAd5-S (n=9)	rAd26-S plus rAd5-S (n=20)	rAd26-S (n=9)	rAd5-S (n=9)	rAd26-S plus rAd5-S (n=20)
Hyperthermia	8 (89%)	3 (33%)	20 (100%)	1 (11%)	1 (11%)	7 (35%)
Headache	6 (67%)	3 (33%)	11 (55%)	3 (33%)	4 (44%)	5 (25%)
Muscle/Joint Pain	3 (33%)	2 (22%)	5 (25%)	1 (11%)	2 (22%)	6 (30%)
Asthenia	3 (33%)	3 (33%)	11 (55%)	0 (0%)	0 (0%)	4 (20%)
Change in lab values	9 (100%)	9 (100%)	20 (100%)	7 (78%)	6 (67%)	18 (90%)

Logunov. Lancet. 2020;396:887-97

Sputnik V Vaccine

Phase I/II Data

- SARS-CoV-2 RBD-specific IgGs detectable in 100% of participants by day 21 post prime dose
  - Day 28 GMTs following rAd26-S only were significantly lower than prime-boost vaccination
- Neutralizing antibody analysis → only boost regimen led to 100% production



Neutralizing antibody response to rAd26 and rAd5 vectors

Vector Immune Response:

- rAd26 and rAd5 did not increase neutralizing antibody titers to each other
- No cross-reactivity between vectors

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RBD: receptor binding domain

Logunov. Lancet. 2020;396:887-97

rAd26-S+rAd5-S (Sputnik V) Phase III

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Sputnik V Vaccine

Phase III

Study Design

- Phase III, placebo-controlled, double-blind, preliminary results
- 3:1 randomization (vaccine: placebo)
- ≥18 years old, healthy with no history of COVID-19 (negative PCR, IgM, and IgG)

Treatment Groups

- rAd26-S and rAd5-S, 10^{11} vp per dose (0.5mL)*
  - 2 doses
  - 21 days apart
- Placebo, vaccine buffer (0.5mL)
  - 2 doses
  - 21 days apart

Outcomes

- **Primary**: Efficacy of vaccine against symptomatic, lab-confirmed COVID-19 21 days after 1st dose
- **Secondary**: Prevention of severe COVID-19 disease, immunogenicity
- **Safety**: Local/systemic reactogenicity, all ADEs during specified time frames

*Frozen formulation of vaccine used during trial

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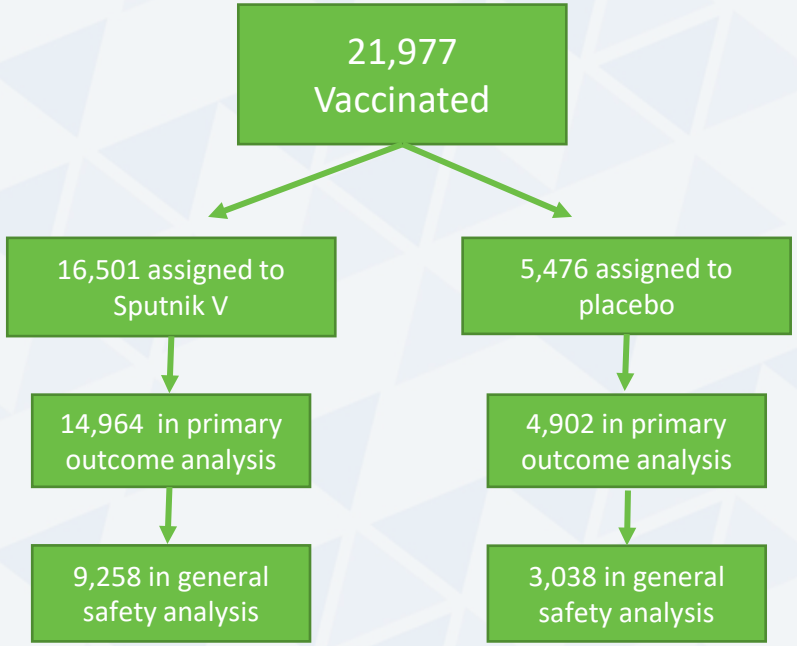
Vp: viral particles

Logunov. Lancet. 2021. doi: 10.1016/S0140-6736(21)00234-8

Sputnik V Vaccine

Phase III



Immunogenicity analyses:

- 456 in RBD-specific IgG analysis
- 100 in neutralizing antibodies analysis
- 58 in IFN. analysis

Characteristic	Sputnik V (N=14,965)	Placebo (N=4,902)
Sex, no. (%)		
Male	5,821 (38.9)	1,887 (38.5)
Female	9,143 (61.1)	3,015 (61.5)
Age group, no. (%)		
18-30 yrs	1,596 (10.7)	521 (10.6)
31-40 yrs	3,848 (25.7)	1,259 (25.7)
41-50 yrs	4,399 (29.4)	1,443 (29.4)
51-60 yrs	3,510 (23.5)	1,146 (23.4)
>60 yrs	1,611 (10.8)	533 (10.9)
Risk of infection		
High risk	65/14,567 (0.4%)	23/4,778 (0.5%)
Medium risk	3,853/14,567 (26.5%)	1,280/4,778 (26.8%)
Low risk	10,649/14,567 (73.1%)	3,475/4,778 (72.7%)
Concomitant diseases*	3,687/14,944 (24.7%)	1,235/4,892 (25.2%)

*diabetes, hypertension, ischemic heart disease, obesity

RBD: receptor binding domain

Logunov. Lancet. 2021. doi: 10.1016/S0140-6736(21)00234-8

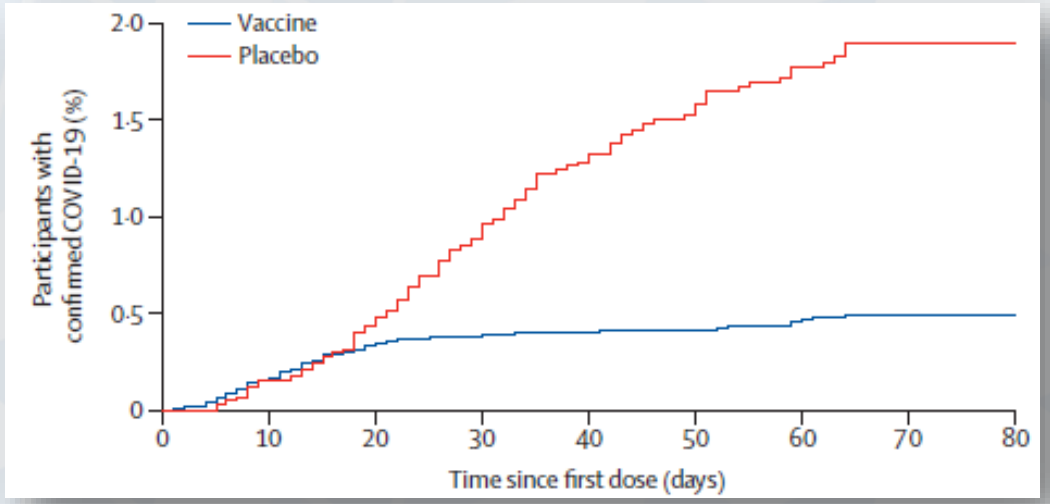
Sputnik V Vaccine

Phase III

Primary and Secondary Endpoints

	Sputnik V	Placebo	Efficacy (%)
1st COVID-19 after dose 2	13 (N=14,094)	47 (N=4,601)	91.1 (95% CI, 83.8 to 95.1)
1st COVID-19 14 days after dose 1	30 (N=14,999)	79 (N=4,950)	87.6 (95% CI, 81.1 to 91.8)
1st COVID-19 21 days after dose 1	16 (N=14,964)	62 (N=4,902)	91.6 (95% CI, 85.6 to 95.2)
Moderate or Severe COVID-19 21 days after dose 1	0 (N=14,964)	20 (N=4,902)	100 (95% CI, 94.4 to 100)

Kaplan-Meier cumulative incidence of first symptomatic, PCR-positive COVID-19 after dose 1



- Immunogenicity Findings:
  - Robust humoral response in all ages (6/342 non-responders noted)
  - 15% of placebo group had RBD-specific antibodies on day 42 → thought to be asymptomatic COVID-19
  - Induced similar virus-neutralizing response in participants >60 as younger groups

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Logunov. Lancet. 2021. doi: 10.1016/S0140-6736(21)00234-8

Sputnik V Vaccine | Phase III

- Most common adverse events were flu-like illness, injection site reactions, headache, and asthenia
  - Grade 1 or grade 2 → 0.38% were grade 3 in severity
- Serious Adverse events occurred in 68 patients (70 episodes)
  - 45 (0.3%) received Sputnik V
  - 23 (0.4%) received placebo
  - None were considered associated with vaccination
- 4 deaths occurred → 3 with Sputnik V and 1 with placebo
  - 2 in Sputnik V were associated with COVID-19, the other participant death was unrelated
  - Placebo group death was associated with hemorrhagic stroke

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Logunov. Lancet. 2021. doi: 10.1016/S0140-6736(21)00234-8

Sputnik V Vaccine

Phase III

2-dose regimen of Sputnik V is safe and effective against COVID-19

91.1% Vaccine Efficacy after dose 2

The Good

- Serious adverse events low and consistent between groups
- Rapid delivery of results
- Immunogenicity data similar between all age groups
  - Older age group with similar immunogenicity and clinical outcomes

The Gap

- Long-term safety outcomes
- Prevention of asymptomatic infection
- Duration of efficacy
- Limited data in AIDS/HIV, <18-year-olds, other higher risk COVID-19 groups
- Limited data for protection of severe disease

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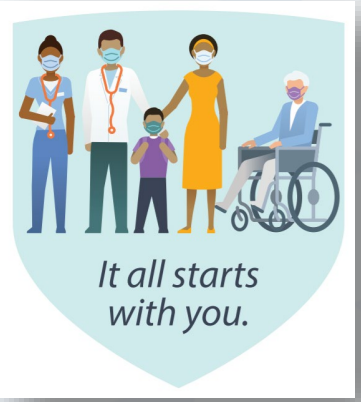
The Bad

Studies conducted in 1 geographical area

Phase III data for -18 °C storage

Primary endpoint after 1st dose

Useful Links



- CDC Website
  - https://www.cdc.gov/vaccines/covid-19/index.html
- CDC Vaccine Communication Toolkit
  - https://www.cdc.gov/vaccines/covid-19/health-systems-communication-toolkit.html
- CDC Guidance for Infection Prevention Considerations Post Vaccination
  - https://www.cdc.gov/coronavirus/2019-ncov/hcp/post-vaccine-considerations-healthcare-personnel.html
- COVID-19 Real-Time Learning Network (CDC and IDSA)
  - https://www.idsociety.org/covid-19-real-time-learning-network/

1. Get Vaccinated
2. Tell Others Why
3. Build the Confidence

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SARS-CoV-2 Viral Vector Vaccines

A Review of Pertinent Drug Information for SARS-CoV-2

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May 19, 2021

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