Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia

Logunov, et al.

ISPE-BC Journal Club

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Vaccine Characteristics

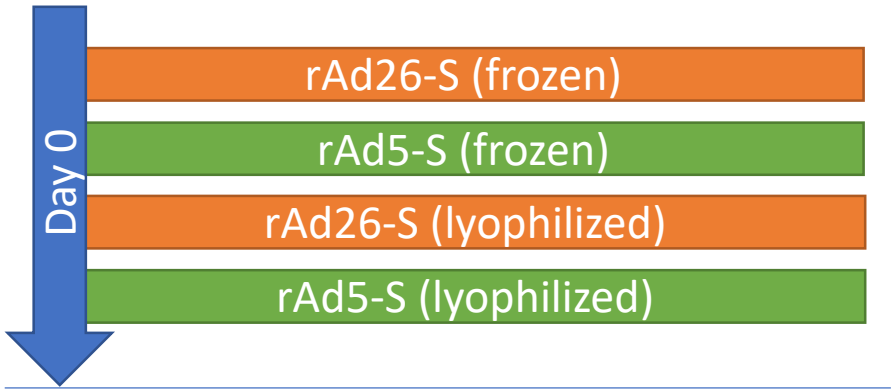
- Recombinant adenovirus vector expressing the SARS-CoV-2 spike glycoproteins
- Two different adenovirus vectors given in separate doses
  - rAd26-S
  - rAd5-S
- Two different formulations / vaccine preparations
  - Frozen (easier to produce, more suitable for widespread vaccination)
  - Lyophilized (difficult to produce, more stable, suitable for remote areas)
- Tested as 2-dose, prime-booster series
  - rAd26-S as prime dose on day 0
  - rAd5-S as booster dose on day 21

Trial Objective

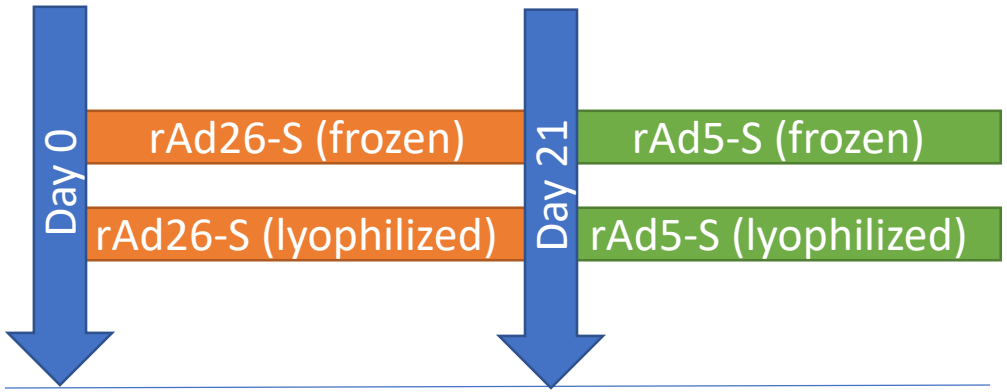
- To assess safety and immunogenicity of both vaccine formulations and to compare the humoral immune response with that recorded in people who have recovered from COVID-19

Trial Approach

- Phase 1/2 trial
  - Phase 1 tested a single dose of each vector by formulation
  - Phase 2 tested a prime-booster series including both vectors by formulation



Phase 1



Phase 2

Setting and Sites

- June 18 – August 3, 2020

Burdenko Hospital, Russia

- Frozen formulation
- Military hospital
  - Civilian and non-conscripted military personnel volunteers

Sechenov University, Russia

- Lyophilized formulation
- Civilian volunteers

Eligibility Criteria

- Aged 18 – 60 years
- BMI 18.5 – 30.0
- Negative COVID-19 PCR and antibody tests for SARS-CoV-2
- No known exposure to or history of COVID-19
- No infectious disease at vaccination or for the 14 days before
- No other vaccinations in the 30 days before vaccination

Procedure

- No randomization or selection
  - All who signed consent at each site were included in the arm of that site
- No unvaccinated control group

- Parallel, identical designs for both formulations
- Intramuscular injection into deltoid muscle
  - Phase 1, either rAd26-S or rAd5-S
  - Phase 2, first rAD26-S then rAd5-S

- Volunteers hospitalized for 28 days

Safety Outcomes

- Safety events were observed daily for 28 days (both phases) and on day 42 (phase 2)
  - Injection-site reactions
  - Systemic reactogenicity
  - Medication use to alleviate symptoms

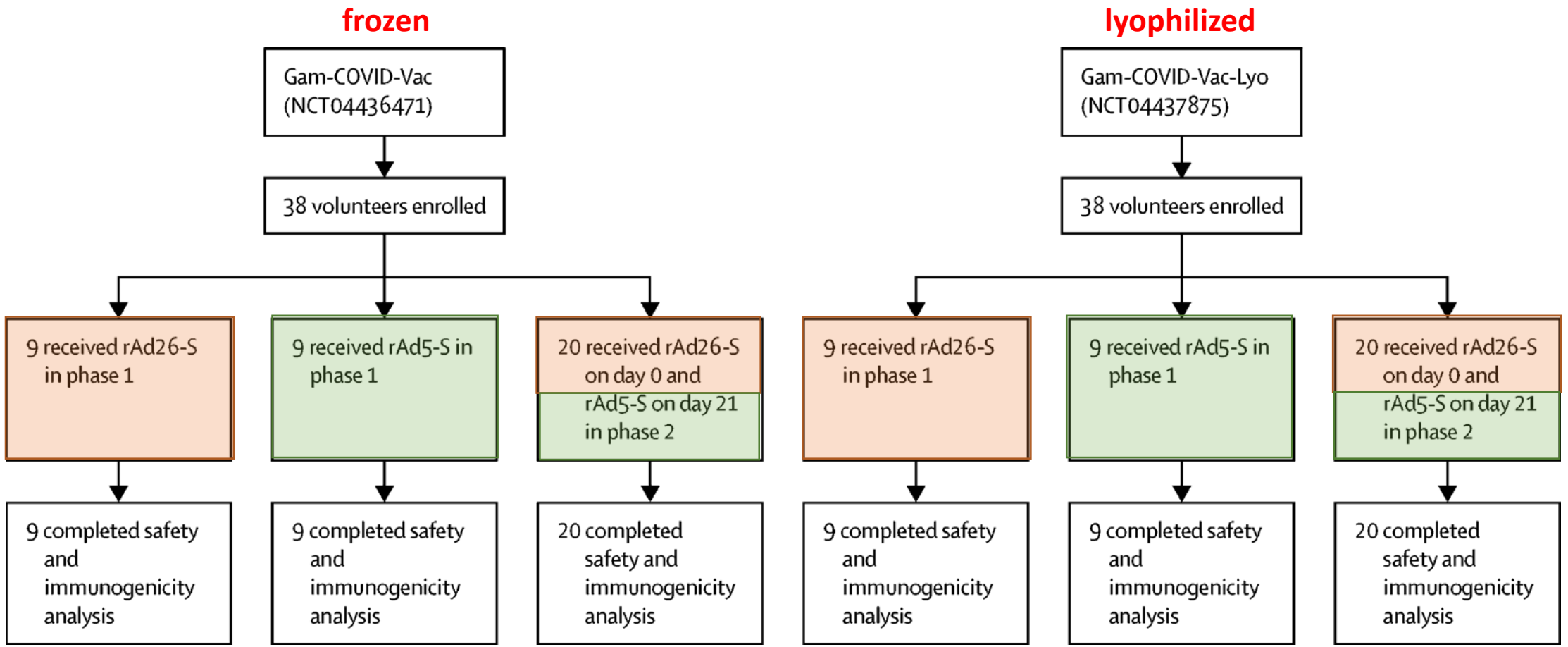
Immunogenicity Outcomes

- Primary
  - Change from baseline in antigen-specific antibody levels
- Secondary
  - Virus neutralizing antibody titers
  - Antigen-specific cellular immunity
- No unvaccinated comparison arm
- Convalescent plasma from recovered COVID-19 patients used as comparison
  - people who had a laboratory-confirmed COVID-19 diagnosis
  - recovered for at least 2 weeks, and tested negative by PCR twice

Assessment Timing

	Phase 1	Phase 2
Clinical and laboratory assessment	• Day 0 • Day 2 • Day 14	• Day 0 • Day 14 • Day 28 • Day 42
Immune status assessment	• Day 0 • Day 28	• Day 0 • Day 28 • Day 42
Neutralizing antibody titers	• Day 0 • Day 14 • Day 28	• Day 0 • Day 14 • Day 28 • Day 42
Cell-mediated immune response	• Day 0 • Day 14 • Day 28	• Day 0 • Day 14 • Day 28
Safety assessment	• Day 0 – 28	• Day 0 – 28 • Day 42

Participants



Participant Characteristics

	Gam-COVID-Vac frozen			Gam-COVID-Vac-Lyo lyophilized		
	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)
Sex						
Male	9 (100%)	9 (100%)	14 (70%)	5 (56%)	2 (22%)	14 (70%)
Female	0	0	6 (30%)	4 (44%)	7 (78%)	6 (30%)
Height, m	1·8 (0·1)	1·8 (0·1)	1·7 (0·1)	1·7 (0·1)	1·7 (0·1)	1·8 (0·1)
Bodyweight, kg	80·6 (6·0)	83·4 (13·8)	74·6 (12·5)	72·1 (13·1)	65·8 (9·4)	72·0 (12·6)
Age, years	27·8 (5·1)	25·3 (6·1)	26·4 (4·4)	31·4 (8·2)	27·0 (7·7)	26·7 (5·8)
Ethnicity						
White	9 (100%)	9 (100%)	20 (100%)	8 (89%)	9 (100%)	19 (95%)
Asian	0	0	0	1 (11%)	0	1 (5%)
SARS-CoV-2 IgM and IgG negative	9 (100%)	9 (100%)	20 (100%)	9 (100%)	9 (100%)	20 (100%)

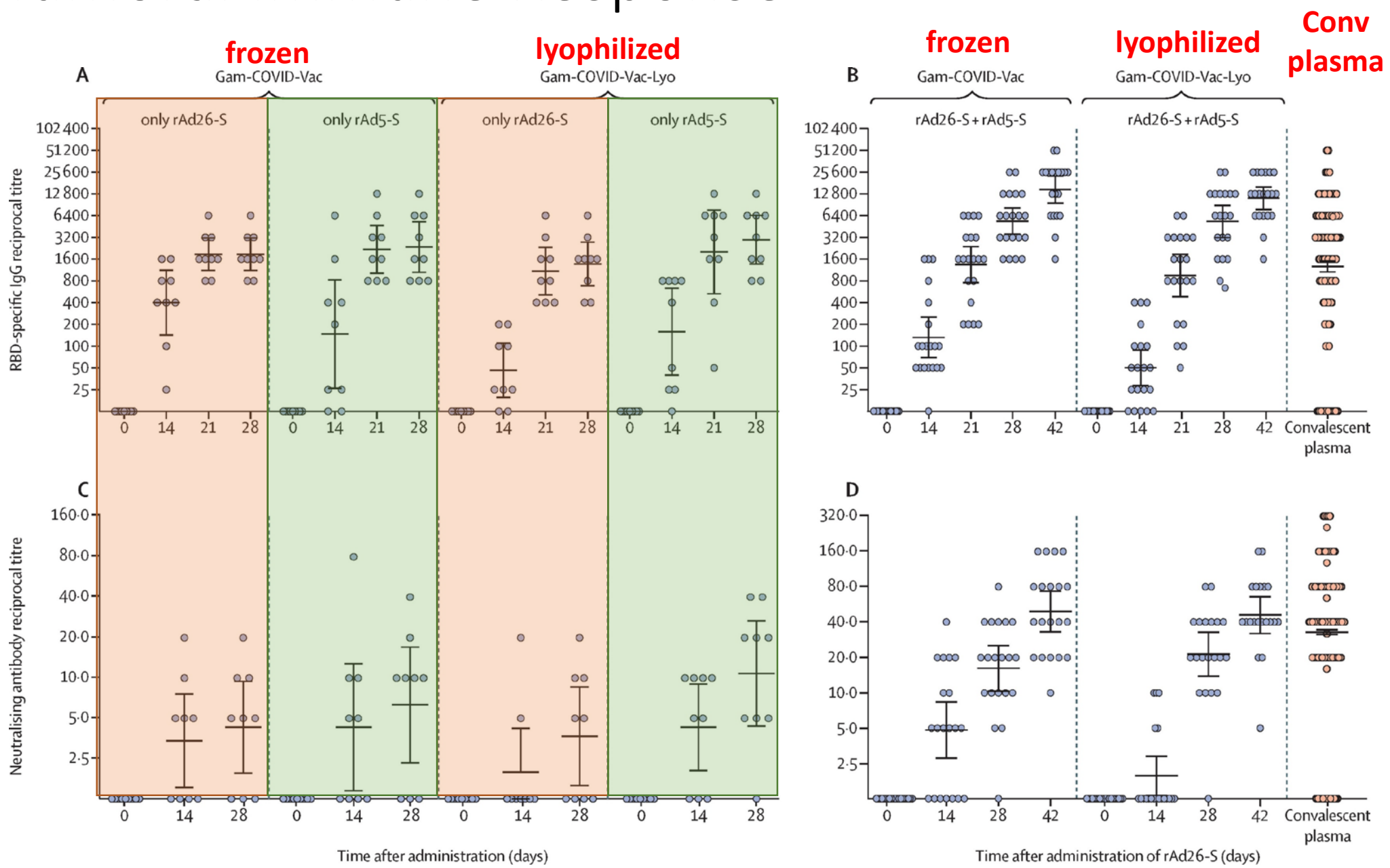
Data are n (%) or mean (SD). Gam-COVID-Vac=frozen vaccine formulation. Gam-COVID-Vac-Lyo=lyophilised vaccine formulation. rAd26-S=recombinant adenovirus type 26 carrying the gene for SARS-CoV-2 full-length glycoprotein S. rAd5-S=recombinant adenovirus type 5 carrying the gene for SARS-CoV-2 full-length glycoprotein S. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Table 1: **Baseline characteristics**

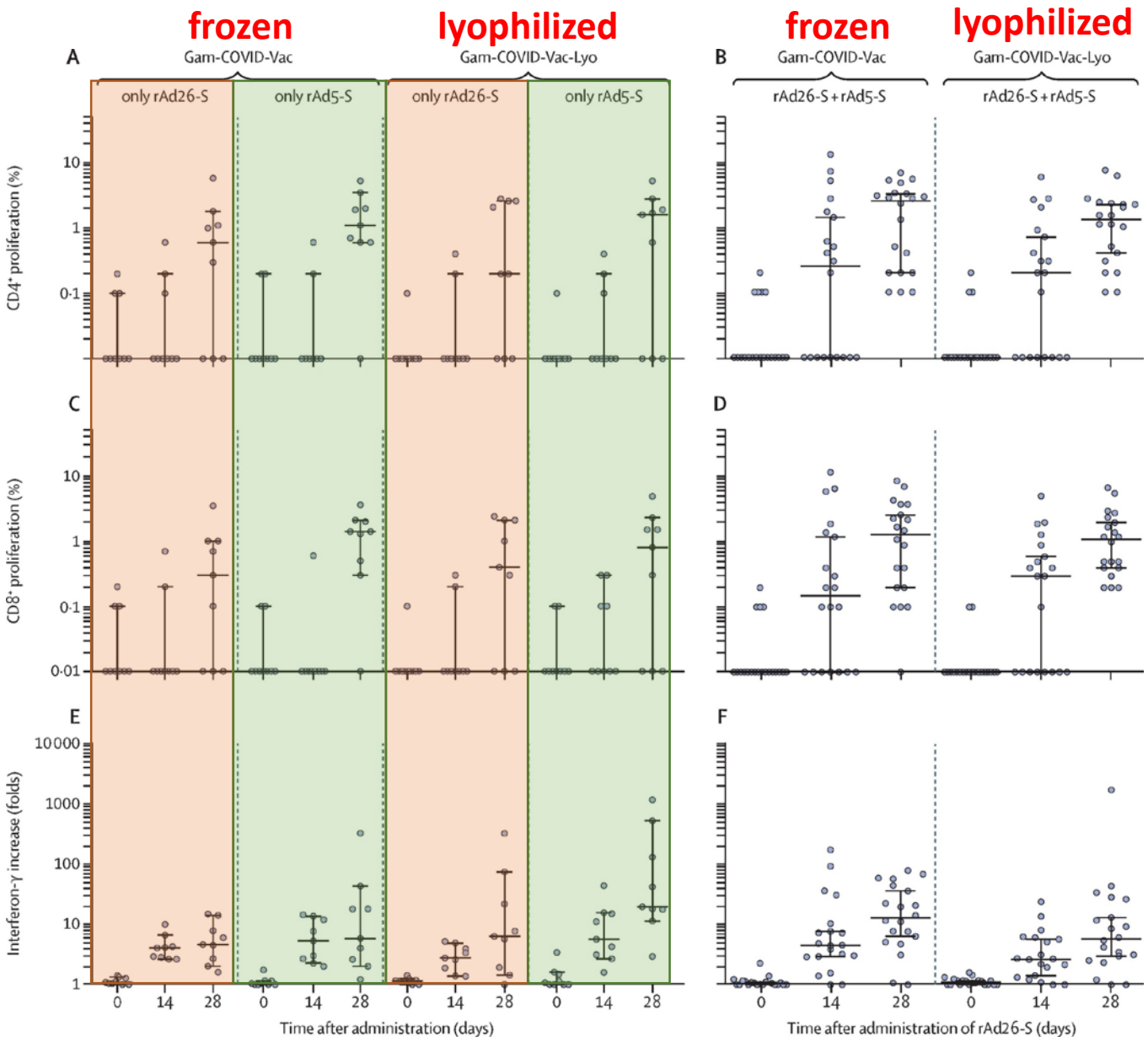
Safety Results

- Most common systemic and local reactions (combined formulations and phases):
  - Pain at injection site (58%)
  - Hyperthermia (50%)
  - Headache (42%)
  - Asthenia (28%)
  - Muscle and joint pain (24%)
- Most systemic and local reactions were mild
  - Full results given in article
- Most laboratory value changes were mild and transient

Humoral Immune Response



Cell-medicated Immune Response



Results, summary

- 100% seroconversion for antigen-specific IgG and neutralizing antibody by day 42
  - No cross-reactivity between rAd26-S and rAd5-S
- Cell-mediated immune response in 100% of volunteers by day 42 in phase 2
  - Antigen-specific T-helper (CD4+) and T-killer (CD8+)
  - Interferon-γ

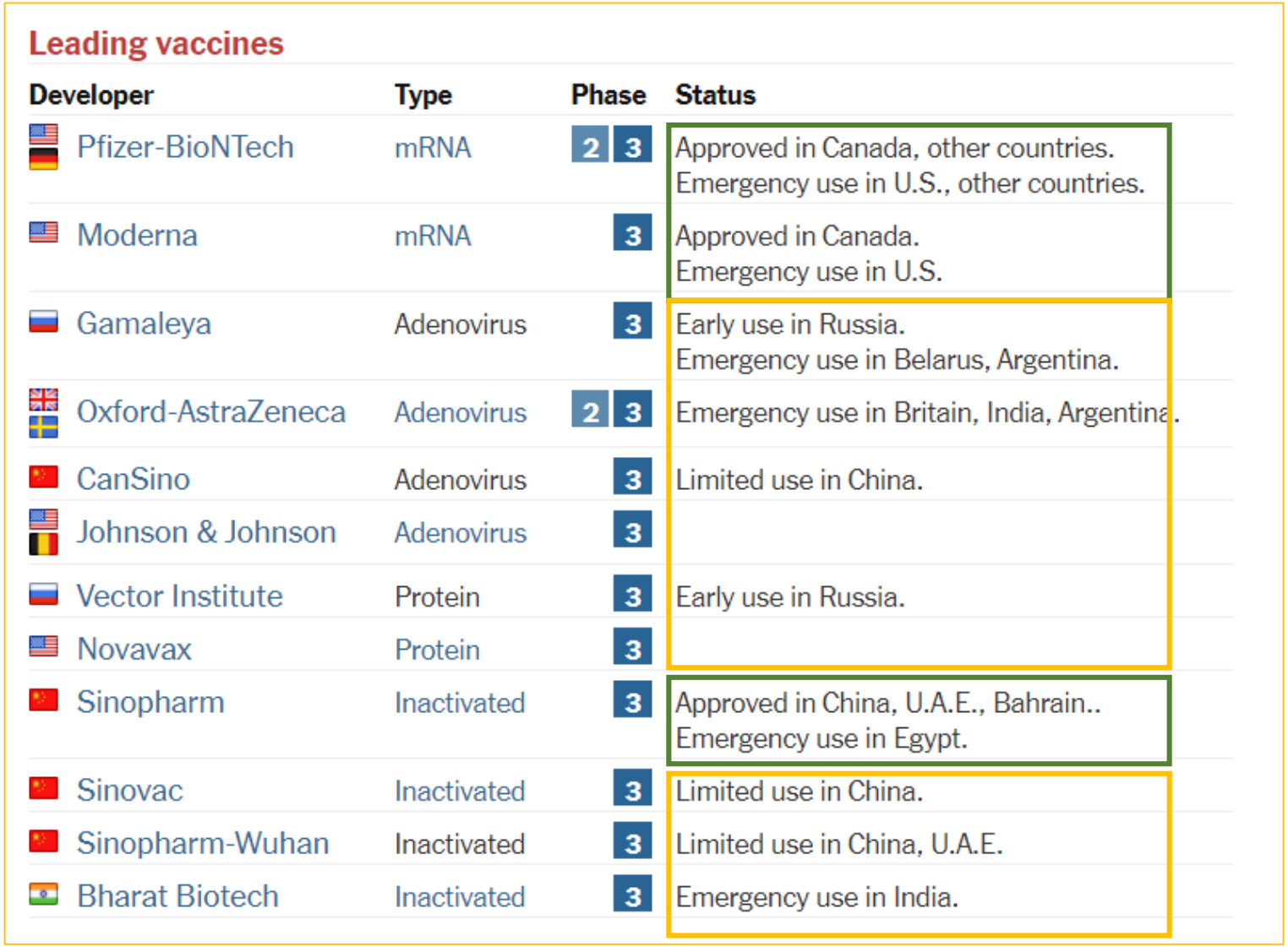
Points Raised in Editorials

Editorial Point	Author's Response
Planned 180-day follow-up not reported	Will be published when available (not yet published)
Potential confusion about the timing between the phase 1 and phase 2	Phase 2 began concurrently phase 1. 2nd dose of phase 2 given after interim analysis of phase 1 1st dose.
Potentially suspect repeated patterns (see next slide)	Small numbers and discrete titration steps resulted in some repetition, especially if there's a plateau of a response. Not all the boxed values are identical.
Individual-level data not available to track individual immunogenicity trajectories	Data available upon request

Potentially Suspect Patterns?

Non-systematic update on COVID-19 vaccines

Licensed/emergency authorized COVID-19 vaccines



Leading vaccines

Developer	Type	Phase	Status
Pfizer-BioNTech	mRNA	2 3	Approved in Canada, other countries. Emergency use in U.S., other countries.
Moderna	mRNA	3	Approved in Canada. Emergency use in U.S.
Gamaleya	Adenovirus	3	Early use in Russia. Emergency use in Belarus, Argentina.
Oxford-AstraZeneca	Adenovirus	2 3	Emergency use in Britain, India, Argentina.
CanSino	Adenovirus	3	Limited use in China.
Johnson & Johnson	Adenovirus	3	
Vector Institute	Protein	3	Early use in Russia.
Novavax	Protein	3	
Sinopharm	Inactivated	3	Approved in China, U.A.E., Bahrain.. Emergency use in Egypt.
Sinovac	Inactivated	3	Limited use in China.
Sinopharm-Wuhan	Inactivated	3	Limited use in China, U.A.E.
Bharat Biotech	Inactivated	3	Emergency use in India.

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

World Health Organization

R&DBlueprint
Powering research to prevent epidemics

COVID-19 - Landscape of novel coronavirus candidate vaccine development worldwide

Tuesday, December 29, 2020

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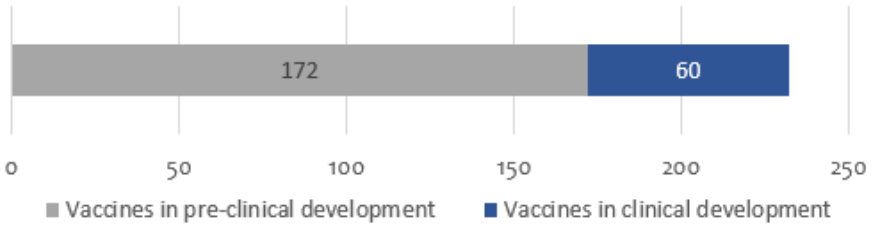
Summary Information on Vaccine Products in Clinical Development

1. - Number of vaccines in clinical development 60

2. - Number of vaccines in pre-clinical development 172

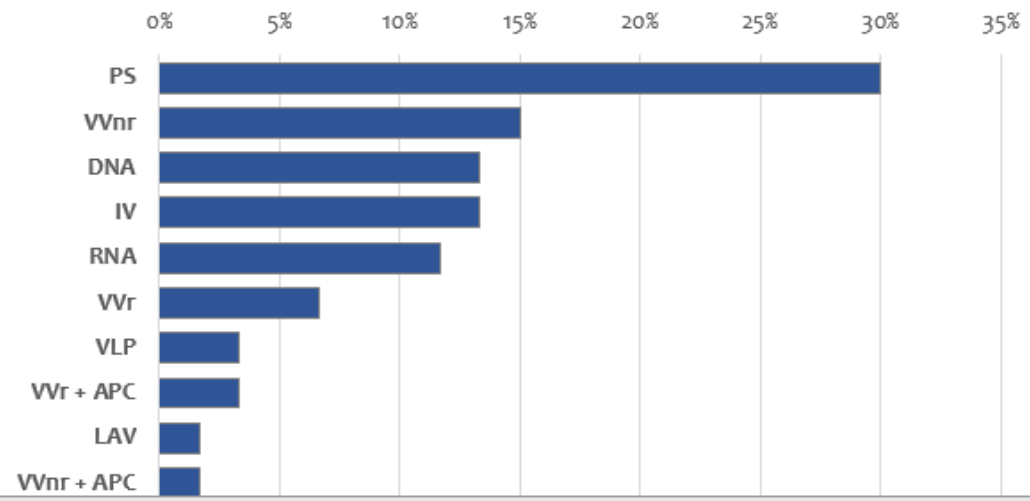


3. - Candidates in clinical phase

Filter: All

Select phase of development (default is all)

Platform		Candidate vaccines (no. and %)	
PS	Protein subunit	18	30%
VVnr	Viral Vector (non-replicating)	9	15%
DNA	DNA	8	13%
IV	Inactivated Virus	8	13%
RNA	RNA	7	12%
VVr	Viral Vector (replicating)	4	7%
VLP	Virus Like Particle	2	3%
VVr + APC	VVr + Antigen Presenting Cell	2	3%
LAV	Live Attenuated Virus	1	2%
VVnr + APC	VVnr + Antigen Presenting Cell	1	2%
		60	



Summary | Clinical | Pre-Clinical

https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

WHO issues its first emergency use validation for a COVID-19 vaccine and emphasizes need for equitable global access

31 December 2020 | News release | Geneva | Reading time: 3 min (695 words)

The World Health Organization (WHO) today listed the Comirnaty COVID-19 mRNA vaccine for emergency use, making the Pfizer/BioNTech vaccine the first to receive emergency validation from WHO since the outbreak began a year ago.

The WHO's Emergency Use Listing (EUL) opens the door for countries to expedite their own regulatory approval processes to import and administer the vaccine. It also enables UNICEF and the Pan-American Health Organization to procure the vaccine for distribution to countries in need.

https://www.who.int/news/item/31-12-2020-who-issues-its-first-emergency-use-validation-for-a-covid-19-vaccine-and-emphasizes-need-for-equitable-global-access

Sputnik V development and testing timeline

- 17 June: Began recruitment in 2 hospitals
- 3 August: 42-day follow-up completed
- 11 August: Provisional approval of frozen vaccine
- 26 August: Provisional approval of lyophilized vaccine; Phase 3 trial in 40,000 participants approved
- 11 Nov: Phase 3 results at first control point (VE: 92%)
- 14 Dec: Phase 3 results at second control point (VE: 91.4%)
  - No phase 3 data are published

Sputnik V Safety

- Phase 2 began at least 5 days after start of phase, 1 for preliminary safety assessment
- Hospitalization of participants allowed for daily recording of AE in first 28 days
  - Doesn’t describe recording through day 42 for Phase 2 participants
- Used Medical Dictionary for Regulatory Activities (MedDRA) coding
  - Categorizes AE by System Organ Classes, then breaks down into specific terms

MedDRA "System Organ Classes" (SOCs)	Number of participants with AEs (%)			
	Gam-COVID-Vac		Gam-COVID-Vac-Lyo	
	rAd26-S (n=9)	rAd5-S (n=9)	rAd26-S (n=9)	rAd5-S (n=9)
SOC General disorders and administration site conditions				
Administration site induration	0	0	0	1 (11·1)
Asthenia	3 (33·3)	3 (33·3)	0	0
Decreased appetite	2 (22·2)	0	0	0
Hyperthermia	8 (88·9)	2 (22·2)	1 (11·1)	1 (11·1)
Pain (muscle and joint pain)	3 (33·3)	2 (22·2)	1 (11·1)	2 (22·2)
Pyrexia	0	1 (11·1)	0	0
Mild (Grade 1)	0	0	0	0
Moderate (Grade 2)	0	1 (11·1)	0	0
Vaccination site pain	7 (77·8)	5 (55·6)	5 (55·6)	7 (77·8)
Vaccination site pruritus	1 (11·1)	0	0	0
Vaccination site warmth	0	0	0	1 (11·1)

	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)
Systemic reactions						
Hyperthermia						
Mild (37·0–38·4°C; grade 1)	8 (89%)	2 (22%)	19 (95%)	1 (11%)	1 (11%)	6 (30%)
Moderate (38·5–38·9°C; grade 2)	0	1 (11%)	1 (5%)	0	0	1 (5%)

MedDRA "System Organ Classes" (SOCs)	Number of participants with AEs (%)					
	Gam-COVID-Vac			Gam-COVID-Vac-Lyo		
	Total number rAd26-S + rAd5-S (n=20)	After rAd26-S till 21 day (n=20)	After rAd5-S from day 21 till day 42 (n=20)	Total number rAd26-S + rAd5-S (n=20)	After rAd26-S till 21 day (n=20)	After rAd5-S from day 21 till day 42 (n=20)
SOC General disorders and administration site conditions						
Asthenia	11 (55)	6 (30)	7 (35)	4 (20)	0	4 (20)
Chills	2 (10)	0	2 (10)	0	0	0
Decreased appetite	1 (5)	2 (10)	0	0	0	0
Hyperthermia	19 (95)	18 (80)	8 (40)	7 (35)	5 (25)	2 (10)
Malaise	2 (10)	0	2 (10)	0	0	0
Pain (muscle and joint pain)	4 (20)	3 (15)	4 (20)	6 (30)	1 (5)	6 (30)
Mild (Grade 1)	4 (20)	2 (10)	4 (20)	4 (20)	0	4 (20)
Moderate (Grade 2)	1 (5)	1 (5)	0	2 (10)	1 (5)	2 (10)
Pyrexia	1 (5)	0	1 (5)	0	0	0
Mild (Grade 1)	0	0	0	0	0	0
Moderate (Grade 2)	1 (5)	0	1 (5)	0	0	0
Vaccination site edema	1 (5)	1 (5)	0	0	0	0
Vaccination site pain	8 (40)	6 (30)	4 (20)	12 (60)	8 (40)	11 (55)
Vaccination site warmth	2 (10)	0	2 (10)	0	0	0

Table 1. Local reactions in persons aged 18–55 years, Pfizer–BioNTech COVID-19 vaccine and placebo

	Dose 1		Dose 2	
	Pfizer-BioNTech Vaccine N=2291	Placebo N=2298	Pfizer-BioNTech Vaccine N=2098	Placebo N=2103
Redness[a], n (%)				
Any	104 (4.5)	26 (1.1)	123 (5.9)	14 (0.7)
Mild	70 (3.1)	16 (0.7)	73 (3.5)	8 (0.4)
Moderate	28 (1.2)	6 (0.3)	40 (1.9)	6 (0.3)
Severe	6 (0.3)	4 (0.2	10 (0.5)	0 (0)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)
Swelling[a], n (%)				
Any	132 (5.8)	11 (0.5)	132 (6.3)	5 (0.2)
Mild	88 (3.8)	3 (0.1)	80 (3.8)	3 (0.1)
Moderate	39 (1.7)	5 (0.2)	45 (2.1)	2 (0.1)
Severe	5 (0.2)	3 (0.1)	7 (0.3)	0 (0)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)
Pain at the injection site[b], n (%)				
Any	1904 (83.1)	322 (14.0)	1632 (77.8)	245 (11.7)
Mild	1170 (51.1)	308 (13.4)	1039 (49.5)	225 (10.7)
Moderate	710 (31.0)	12 (0.5)	568 (27.1)	20 (1.0)
Severe	24 (1.0)	2 (0.1)	25 (1.2)	0 (0)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)

https://www.cdc.gov/vaccines/covid-19/info-by-manufacturer/pfizer/reactogenicity.html

Table 3. Systemic reactions in persons aged 18–55 years, Pfizer-BioNTech COVID-19 vaccine and placebo

	Dose 1		Dose 2	
	Pfizer-BioNTech Vaccine N=2291	Placebo N=2298	Pfizer-BioNTech Vaccine N=2098	Placebo N=2103
Fever, n (%)				
≥38.0°C	85 (3.7)	20 (0.9)	331 (15.8)	10 (0.5)
≥38.0°C to 38.4°C	64 (2.8)	10 (0.4)	194 (9.2)	5 (0.2)
>38.4°C to 38.9°C	15 (0.7)	5 (0.2)	110 (5.2)	3 (0.1)
>38.9°C to 40.0°C	6 (0.3)	3 (0.1)	26 (1.2)	2 (0.1)
>40.0°C	0 (0)	2 (0.1)	1 (0)	0 (0)
Fatigue[a], n (%)				
Any	1085 (47.4)	767 (33.4)	1247 (59.4)	479 (22.8)
Mild	597 (26.1)	467 (20.3)	442 (21.1)	248 (11.8)
Moderate	455 (19.9)	289 (12.6)	708 (33.7)	217 (10.3)
Severe	33 (1.4)	11 (0.5)	97 (4.6)	14 (0.7)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)
Headache[a], n (%)				
Any	959 (41.9)	775 (33.7)	1085 (51.7)	506 (24.1)
Mild	628 (27.4)	505 (22.0)	538 (25.6)	321)15.3)
Moderate	308 (13.4)	251 (10.9)	480 (22.9)	170 (8.1)
Severe	23 (1.0)	19 (0.8)	67 (3.2)	15 (0.7)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)

https://www.cdc.gov/vaccines/covid-19/info-by-manufacturer/pfizer/reactogenicity.html

Table 4. Systemic reactions in persons aged >55 years, Pfizer-BioNTech COVID-19 vaccine and placebo

	Dose 1		Dose 2	
	Pfizer-BioNTech Vaccine N=1802	Placebo N=1792	Pfizer-BioNTech Vaccine N=1660	Placebo N=1646
Fever				
≥38.0°C	26 (1.4)	7 (0.4)	181 (10.9)	4 (0.2)
≥38.0°C to 38.4°C	23 (1.3)	2 (0.1)	131 (7.9)	2 (0.1)
>38.4°C to 38.9°C	1 (0.1)	3 (0.2)	45 (2.7)	1 (0.1)
>38.9°C to 40.0°C	1 (0.1)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.1)	0 (0)	0 (0)	0 (0)
Fatigue[a], n (%)				
Any	615 (34.1)	405 (22.6)	839 (50.5)	277 (16.8)
Mild	373 (20.7)	252 (14.1)	351 (21.1)	161 (9.8)
Moderate	240 (13.3)	150 (8.4)	442 (26.6)	114 (6.9)
Severe	2 (0.1)	3 (0.2)	46 (2.8)	2 (0.1)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)
Headache[a], n (%)				
Any	454 (25.2)	325 (18.1)	647 (39.0)	229 (13.9)
Mild	348 (19.3)	242 (13.5)	422 (25.4)	165 (10.0)
Moderate	104 (5.8)	80 (4.5)	216 (13.0)	60 (3.6)
Severe	2 (0.1)	3 (0.2)	9 (0.5)	4 (0.2)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)

https://www.cdc.gov/vaccines/covid-19/info-by-manufacturer/pfizer/reactogenicity.html

Table 1. Local reactions in persons aged 18–64 years, Moderna COVID-19 vaccine and placebo

	Dose 1		Dose 2	
	Moderna Vaccine N=11401	Placebo N=11404	Moderna Vaccine N=10357	Placebo N=10317
Any Local, n (%)				
Any	9960 (87.4)	2432 (21.3)	9371 (90.5)	2134 (20.7)
Grade 3	452 (4.0)	39 (0.3)	766 (7.4)	41 (0.4)
Pain[a], n (%)				
Any	9908 (86.9)	2179 (19.1)	9335 (90.1)	1942 (18.8)
Grade 3	367 (3.2)	23 (0.2)	479 (4.6)	21 (0.2)
Redness[a], n (%)				
Any	345 (3.0)	46 (0.4)	928 (9.0)	42 (0.4)
Severe	34 (0.3)	11 (<0.1)	206 (2.0)	12 (0.1)
Swelling[b], n (%)				
Any	768 (6.7)	33 (0.3)	1309 (12.6)	35 (0.3)
Grade 3	62 (0.5)	3 (<0.1)	176 (1.7)	4 (<0.1)
Axillary Swelling/Tenderness[c], n (%)				
Any	1322 (11.6)	567 (5.0)	1654 (16.0)	444 (4.3)
Grade 3	36 (0.3)	13 (0.1)	45 (0.4)	10 (<0.1)

https://www.cdc.gov/vaccines/covid-19/info-by-product/moderna/reactogenicity.html

Table 3. Systemic reactions in persons aged 18-64 years, Moderna COVID-19 vaccine and placebo

	Dose 1		Dose 2	
	Moderna Vaccine N=11405	Placebo N=11406	Moderna Vaccine N=10358	Placebo N=10320
Any systemic, n (%)				
Any	6503 (57.0)	5063 (44.4)	8484 (81.9)	3967 (38.4)
Grade 3	363 (3.2)	248 (2.2)	1801 (17.4)	215 (2.1)
Grade 4	5 (<0.1)	4 (<0.1)	10 (<0.1)	2 (<0.1)
Fever[a], n (%)				
Any	105 (0.9)	39 (0.3)	1806 (17.4)	38 (0.4)
Grade 3	10 (<0.1)	1 (<0.1)	168 (1.6)	1 (<0.1)
Grade 4	4 (<0.1)	4 (<0.1)	10 (<0.1)	1 (<0.1)
Headache[b], n (%)				
Any	4031(35.4)	3303 (29.0)	6500 (62.8)	2617 (25.4)
Grade 3	219 (1.9)	162 (1.4)	515 (5.0)	124 (1.2)
Fatigue[c], n (%)				
Any	4384 (38.5)	3282 (28.8)	7002 (67.6)	2530 (24.5)
Grade 3	120 (1.1)	83 (0.7)	1099 (10.6)	81 (0.8)
Grade 4	1 (<0.1)	0 (0)	0 (0)	0 (0)
Myalgia[c], n (%)				
Any	2698 (23.7)	1626 (14.3)	6353 (61.3)	1312 (12.7)
Grade 3	73 (0.6)	38 (0.3)	1032 (10.0)	39 (0.4)

https://www.cdc.gov/vaccines/covid-19/info-by-product/moderna/reactogenicity.html

Table 4. Systemic reactions in persons aged ≥65 years, Moderna COVID-19 vaccine and placebo

	Dose 1		Dose 2	
	Moderna Vaccine N=3761	Placebo N=3748	Moderna Vaccine N=3589	Placebo N=3549
Any systemic, n (%)				
Any	1818 (48.3)	1335 (35.6)	2580 (71.9)	1102 (31.1)
Grade 3	84 (2.2)	63 (1.7)	387 (10.8)	58 (1.6)
Grade 4	0 (0)	0 (0)	2 (<0.1)	1 (<0.1)
Fever[a], n (%)				
Any	10 (0.3)	7 (0.2)	366 (10.2)	5 (0.1)
Grade 3	1 (<0.1)	1 (<0.1)	18 (0.5)	0 (0)
Grade 4	0 (0)	2 (<0.1)	1 (<0.1)	1 (<0.1)
Headache[b], n (%)				
Any	921 (33.3)	443 (11.8)	1665 (46.4)	635 (17.9)
Grade 3	30 (0.8)	34 (0.9)	107 (3.0)	32 (0.9)
Fatigue[c], n (%)				
Any	1251 (38.5)	851 (22.7)	2094 (58.4)	695 (19.6)
Grade 3	120 (1.1)	23 (0.6)	248 (6.9)	20 (0.6)
Myalgia[c], n (%)				
Any	743 (19.8)	443 (11.8)	1683 (46.9)	385 (10.8)
Grade 3	17 (0.5)	9 (0.3)	201 (5.6)	10 (0.3)

https://www.cdc.gov/vaccines/covid-19/info-by-product/moderna/reactogenicity.html

More info needed

- Considerations for preferential recommendations?
  - Comparative vaccine safety
  - Long-term safety
  - Duration of protection
- Cross-protection against novel variants
- Effectiveness in preventing transmission
- Pregnant women and children