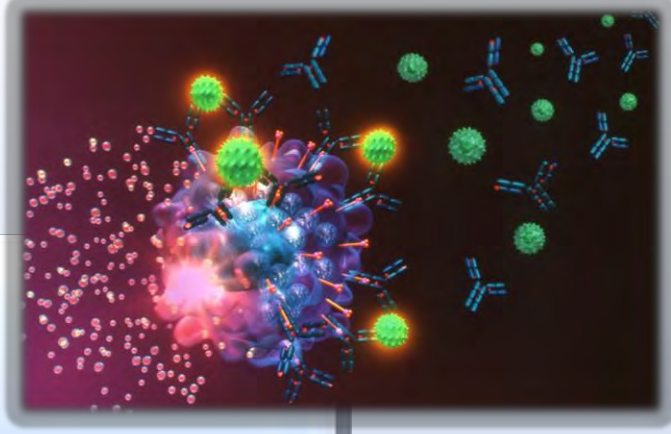


SARS-CoV-2 Vaccine

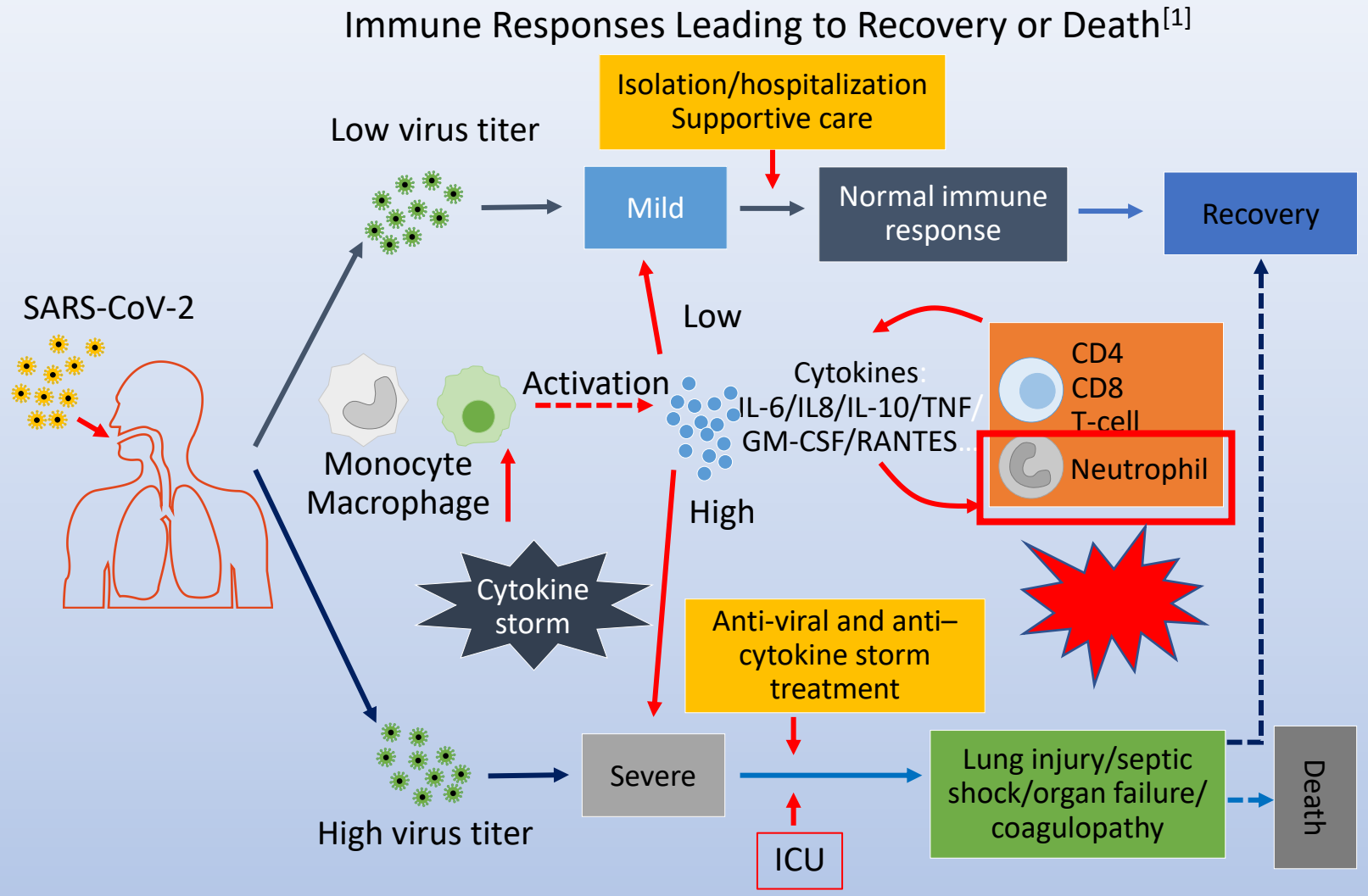
RPEA Southcentral Chapter
March 9,2021

Jeffrey G Demain, MD, FAAAAI, FACAAI, FAAP

Founder, Allergy Asthma & Immunology Center of Alaska

Clinical Professor, Dept Pediatrics, University of Washington

Immune Response to SARS-CoV-2



Adequate immune responses

- Timely innate/adaptive responses
- Quick type 1 IFN response
- Activation of efficient antiviral response (clearance by macrophages)
- Activation of Th1 cells and B-cells for production of neutralizing antibodies

Inadequate immune responses

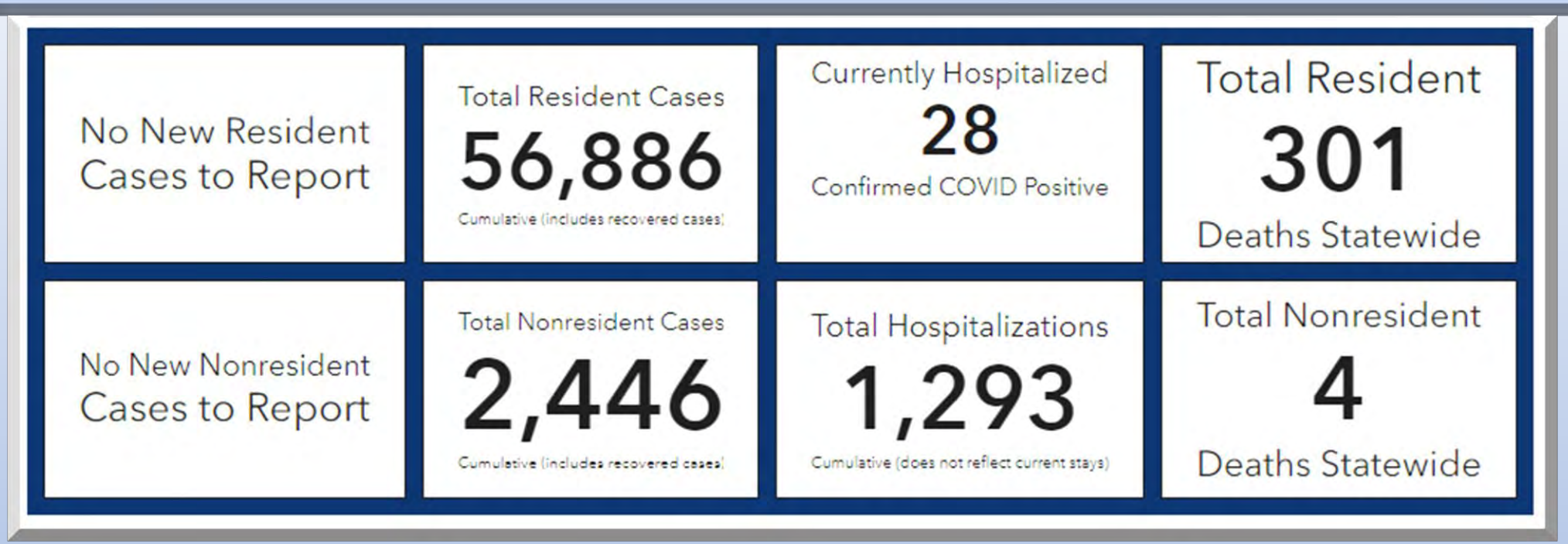
- Delayed/limited type 1 IFN
- Endothelial cell death
- Epithelial/endothelial leakage
- Overactivation/exhaustion T-cells and NK cells
- Activation of neutrophils
- Accumulation of activated macrophages → cytokine storm

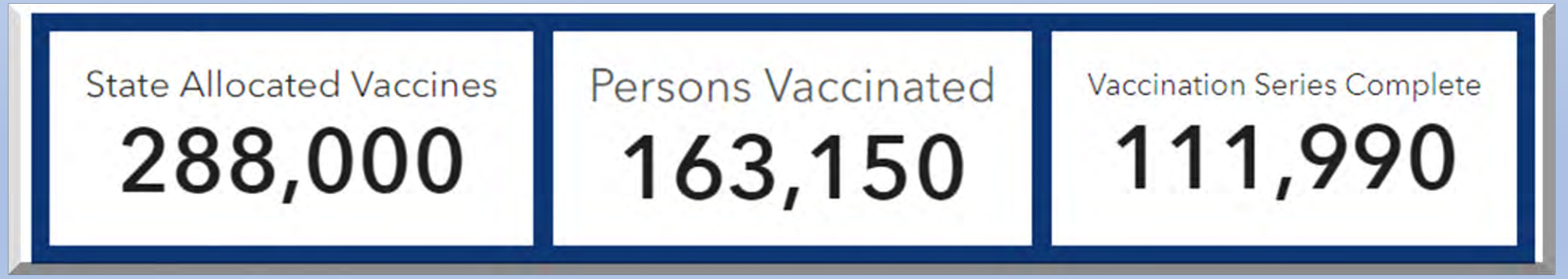
1. Wang. et al. J Leukoc Biol. 2020;108:17. 2. Sokolowska,et al. Allergy. 2020;75(10:2445-76. 3. Meizlish,et al. *Blood Adv* (2021) 5 (5): 1164–1177.

United States: as of March 5, 2021

- As of March 5th, 2021, there have been roughly
  - 28.9 million cases COVID
  - 522,000 deaths from COVID
  - 1.8% fatality rate
- Over 50 million COVID vaccines have been administered

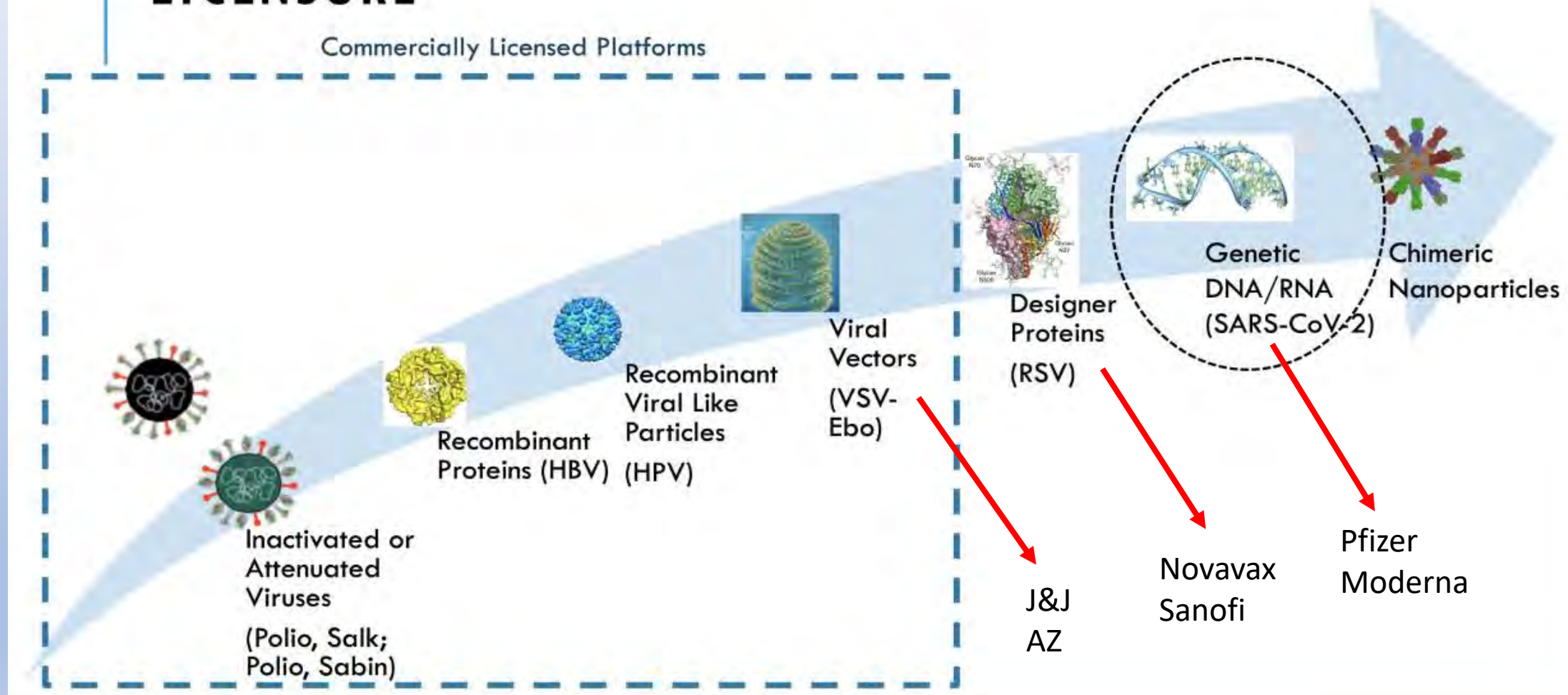
Alaska: as of March 5, 2021





1,731,628 Test conducted	20% Genotyped

EVOLUTION OF VACCINE DEVELOPMENT AND LICENSURE

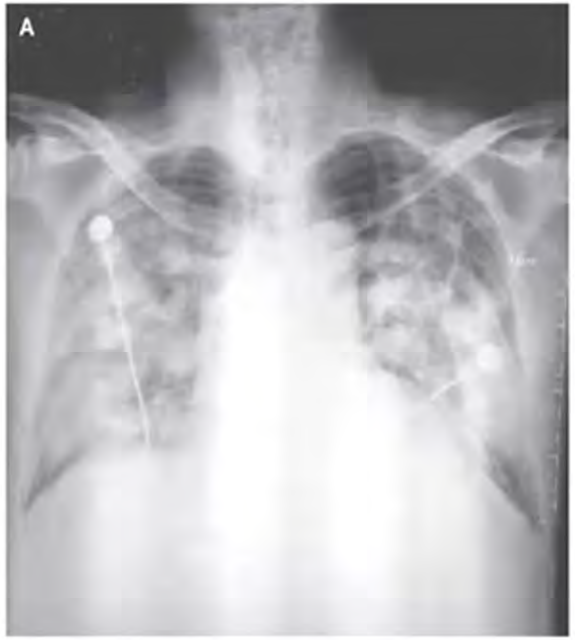


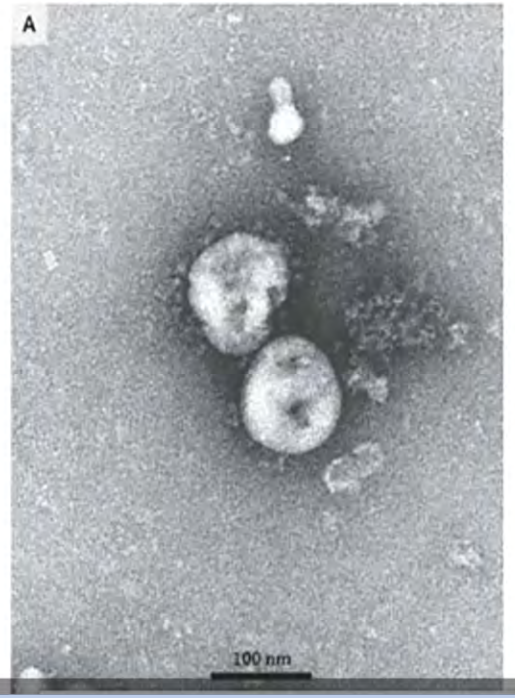
The NEW ENGLAND JOURNAL of MEDICINE

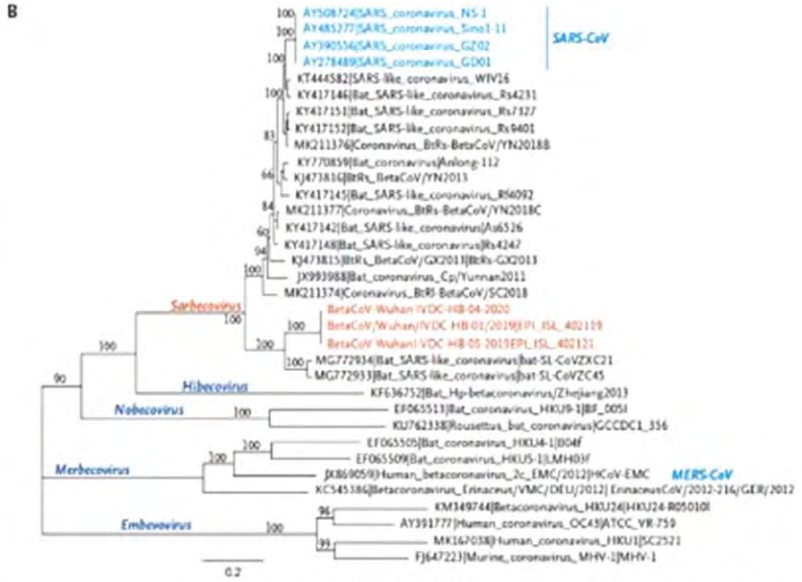
BRIEF REPORT

A Novel Coronavirus from Patients with Pneumonia in China, 2019

NEJM Jan 24, 2021

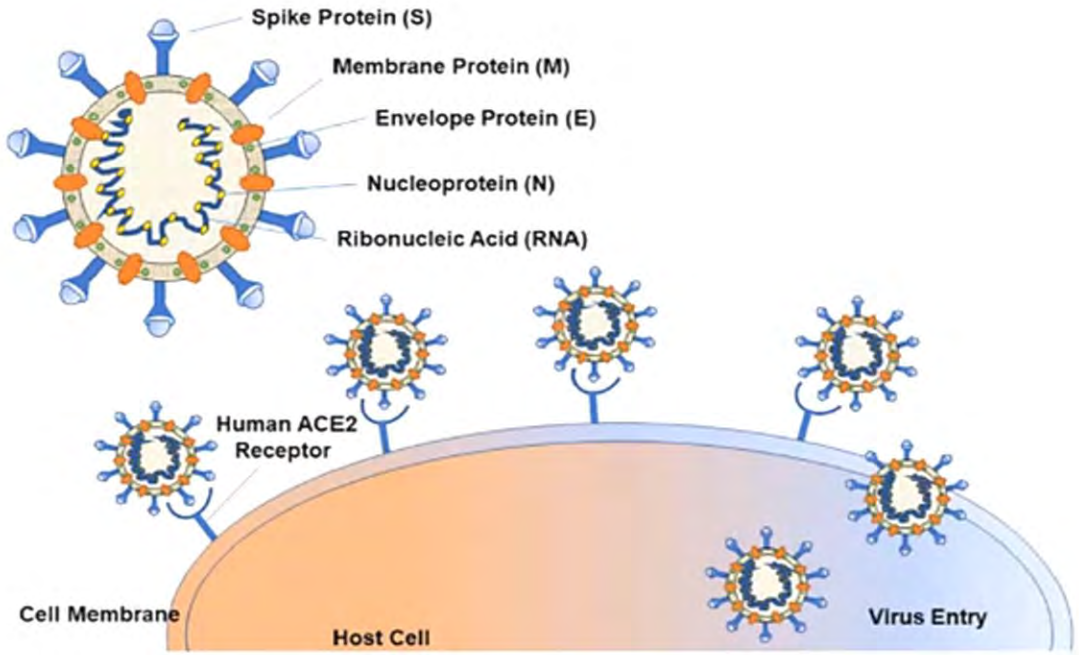






Zhu N NEJM 24Jan2020

Viral Genome



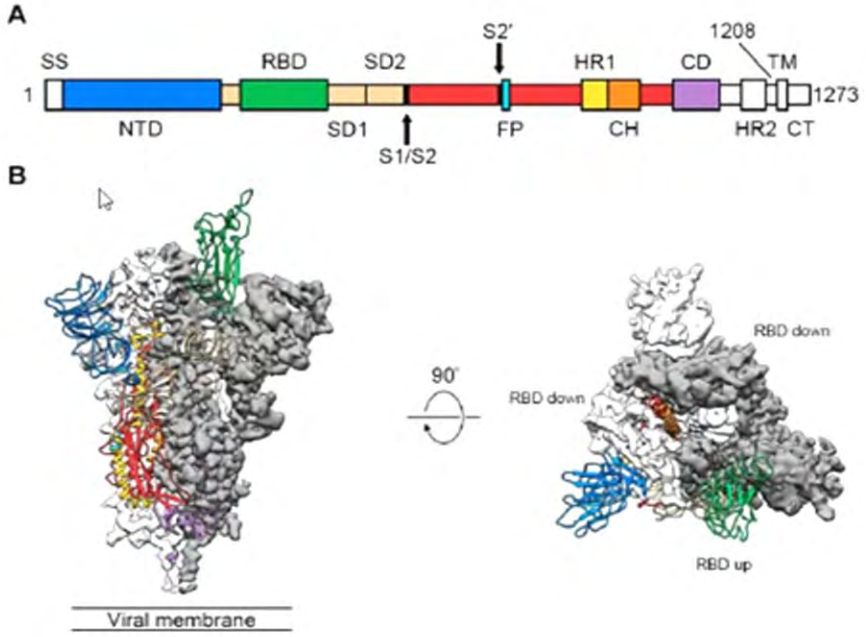


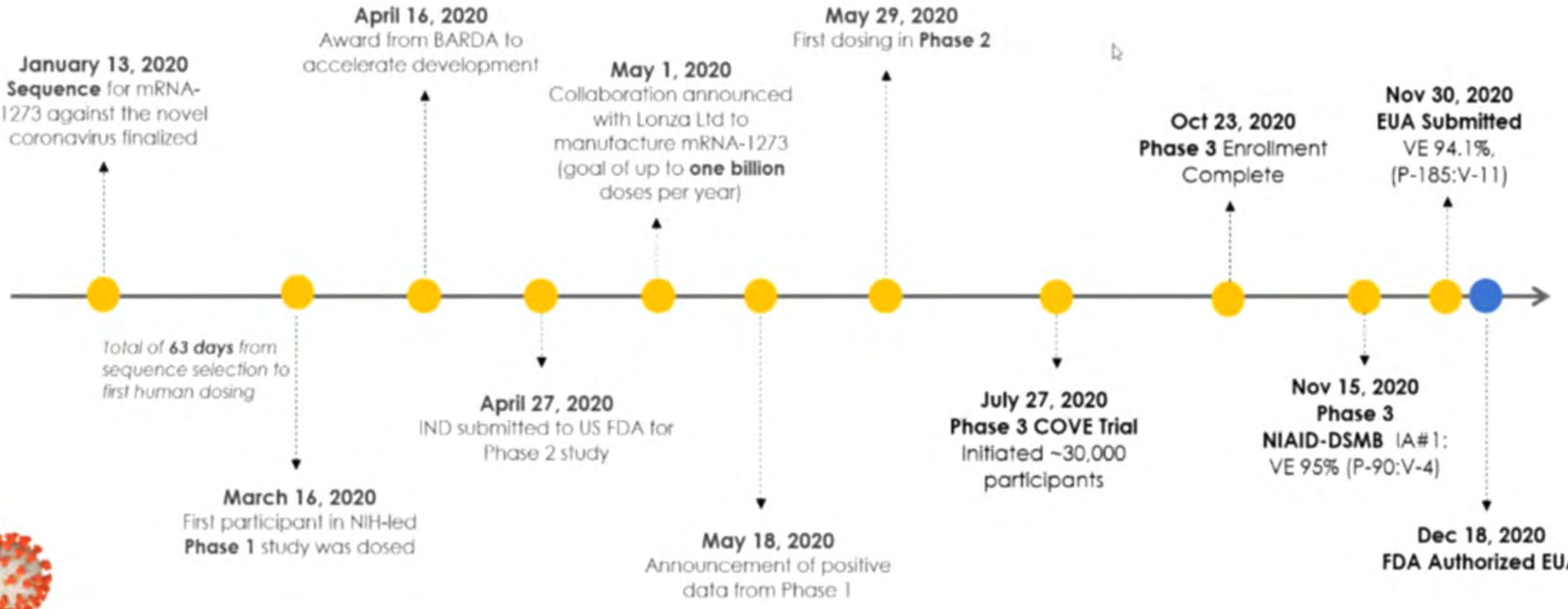
Fig. 1. Structure of 2019-nCoV S in the prefusion conformation. (A) Schematic of 2019-nCoV S primary structure.

COVID-19
Prevention Network

Within 2 weeks

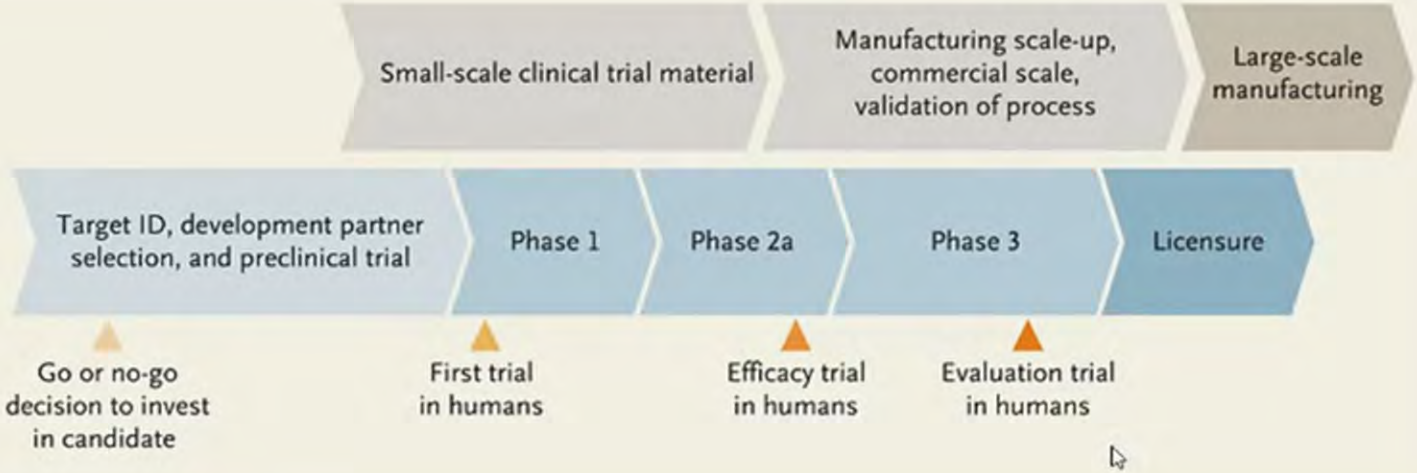
Wrapp et al. Science 19 Feb 2020
Naqvi A et al. Vaccine 13Jun2020

Key mRNA-1273 Development Timeline

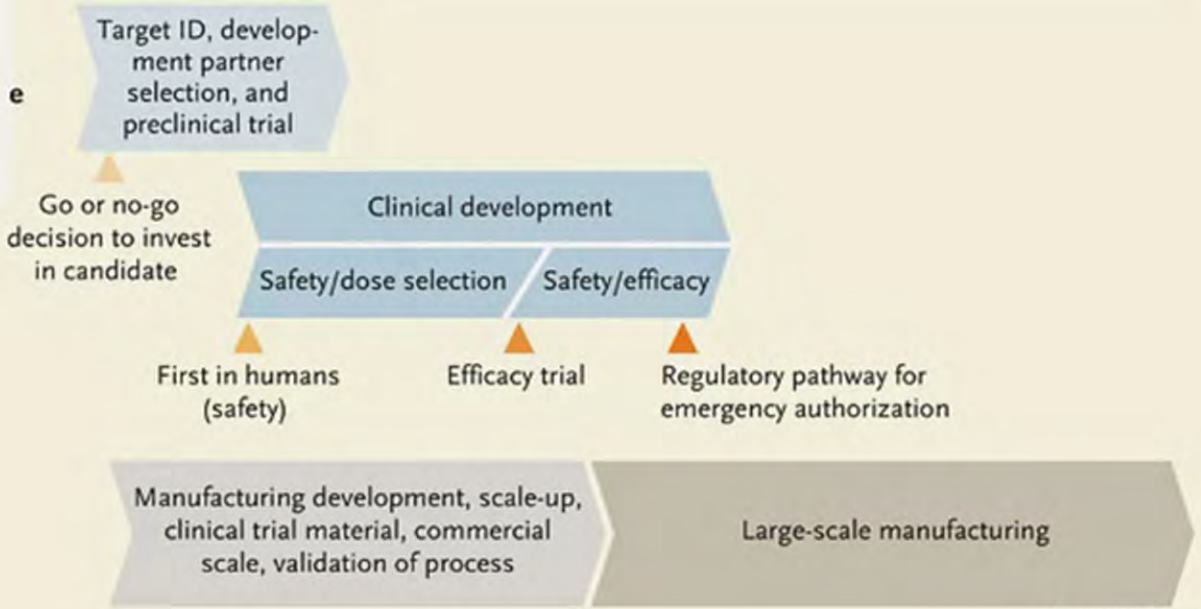


COVID-19

Traditional: Multiple Years



Pandemic: Overlapping Phases



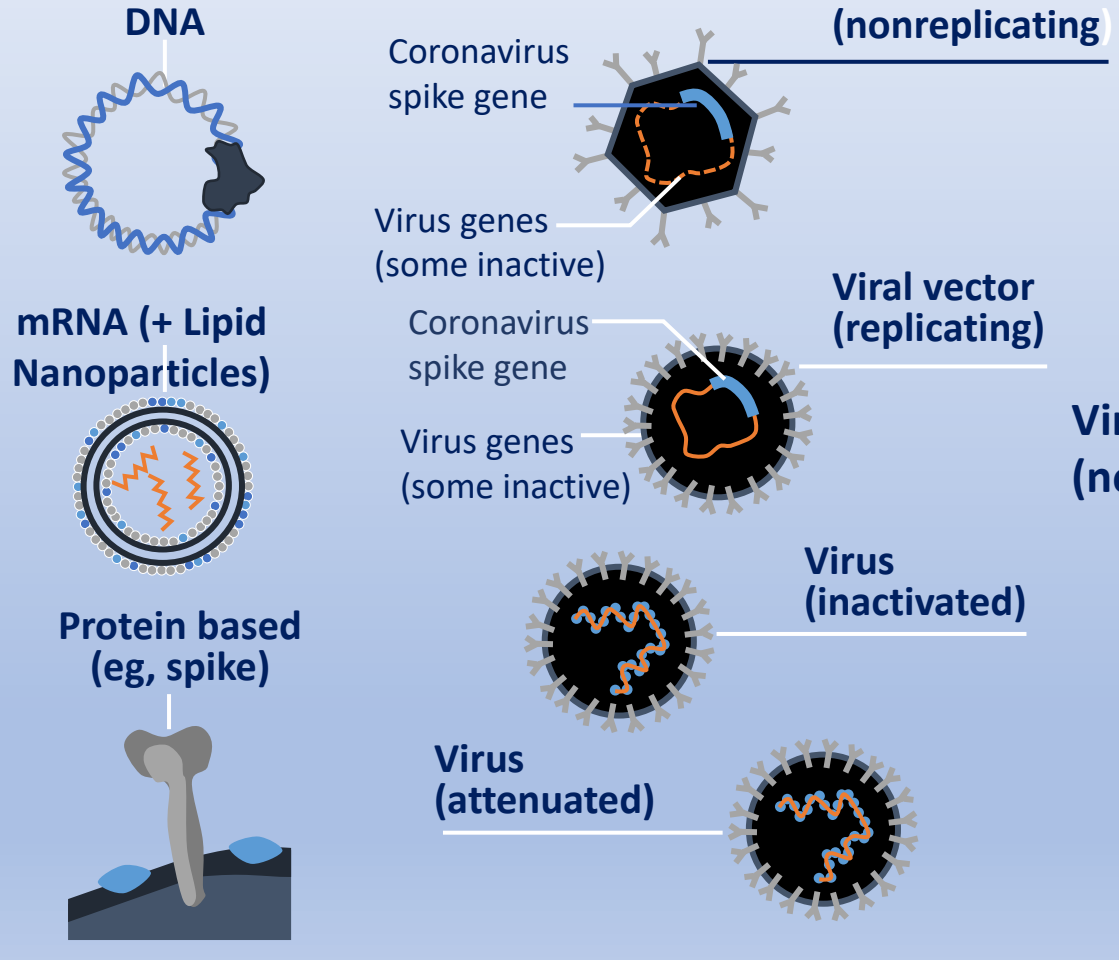
Access: Geographic spread of manufacturing and development sites and pursuit of emergency authorization before licensure

COVID-19 Prevention Network

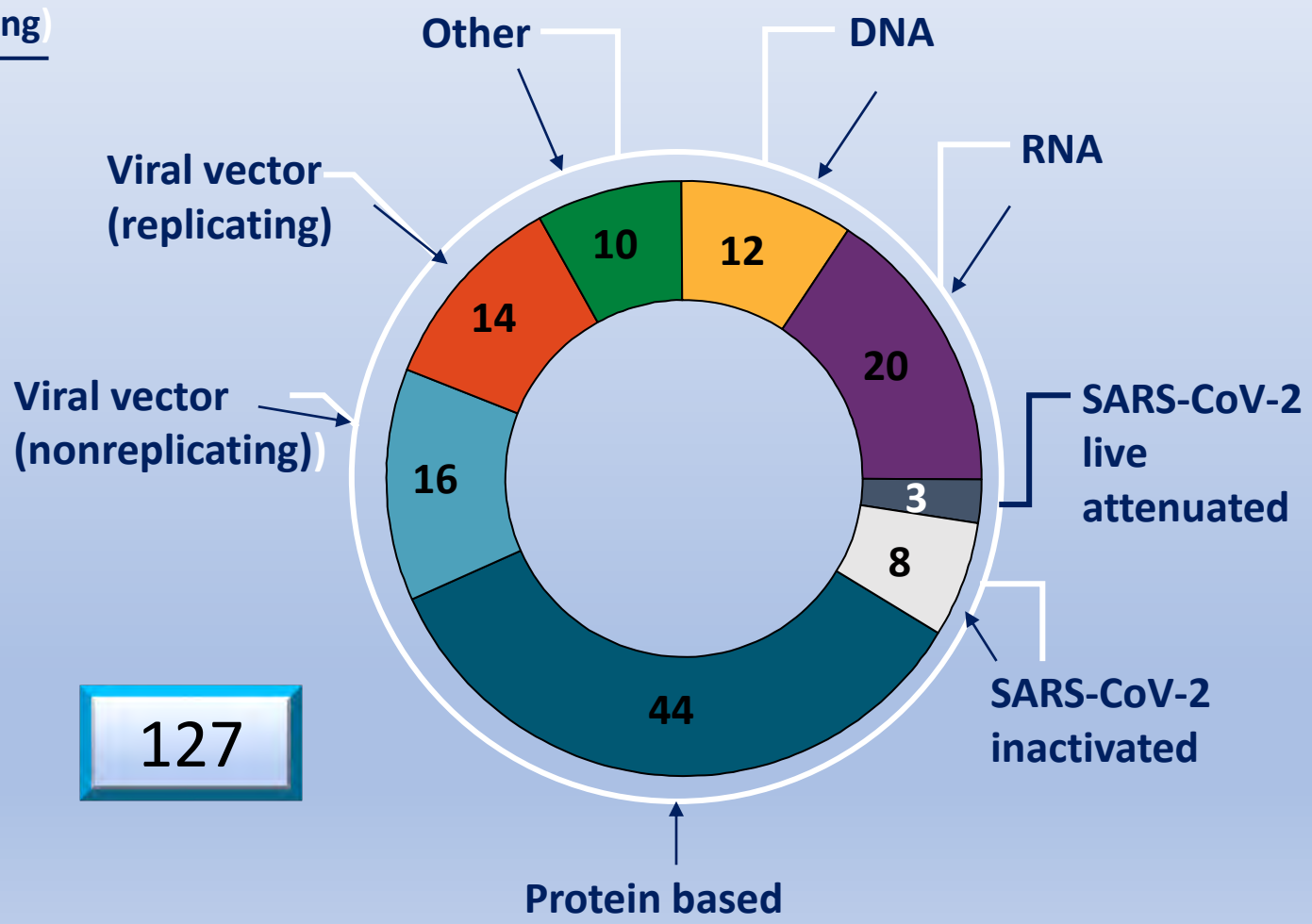
Lurie et al. *NEJM* 2020;382:1969

Vaccine Candidates in Development for SARS-Cov-2

Vaccine Platforms



Vaccine Candidates



Funk. Frontiers in Pharmacology. 2020; 11:937.

Vaccine Landscape: WHO

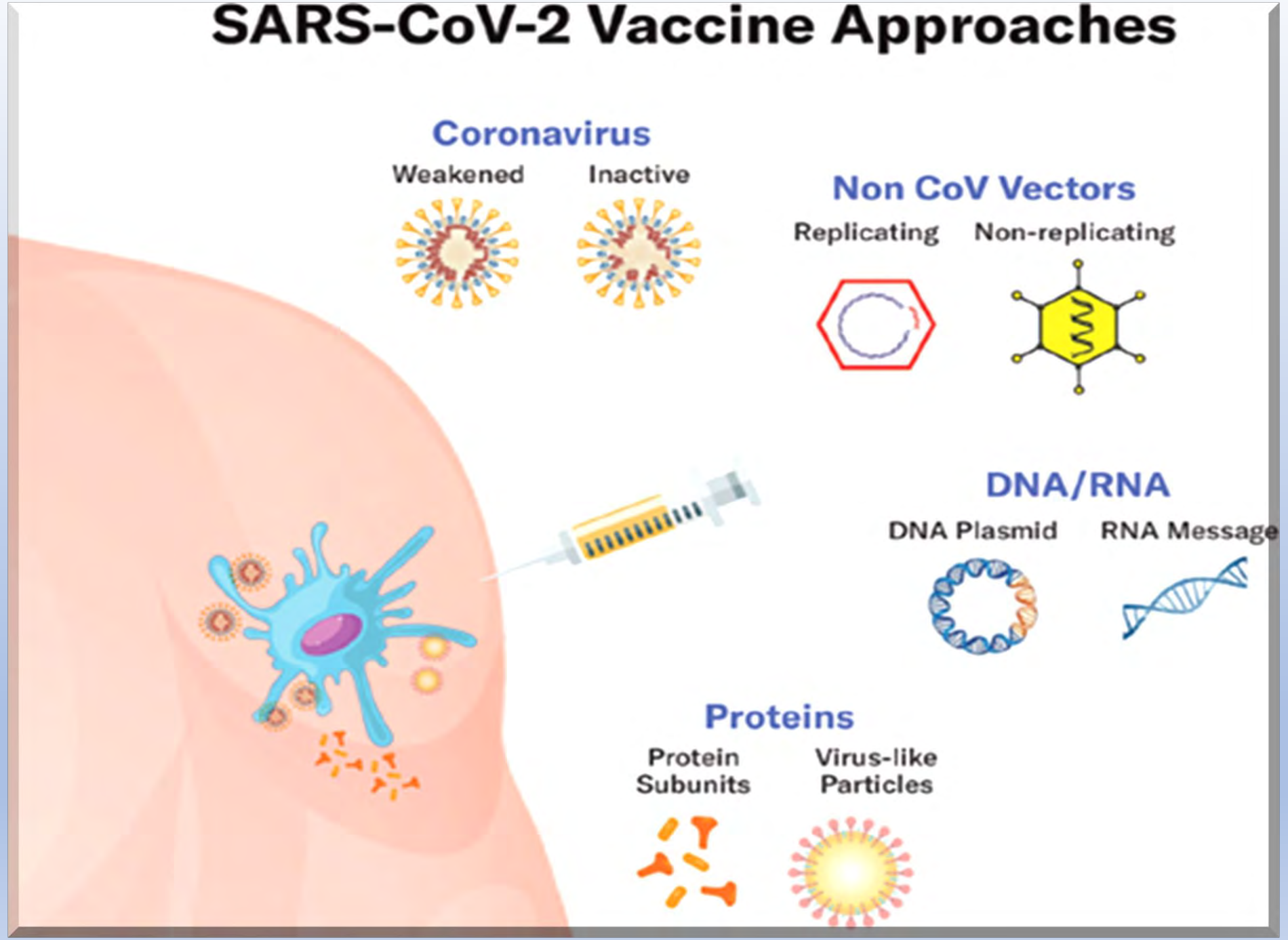
Vaccine candidates in clinical studies			
Platform		Candidate vaccines (no. + %)	
PS	Protein subunit	23	33%
VVnr	Viral Vector (non-replicating)	11	16%
DNA	DNA	10	14%
IV	Inactivated Virus	10	14%
RNA	RNA	7	10%
VVr	Viral Vector (replicating)	3	4%
VLP	Virus Like Particle	2	3%
VVr + APC	VVr + Antigen Presenting Cell	2	3%
LAV	Live Attenuated Virus	1	1%
VVnr + APC	VVnr + Antigen Presenting Cell	1	1%

60

WHO website 22Feb2020

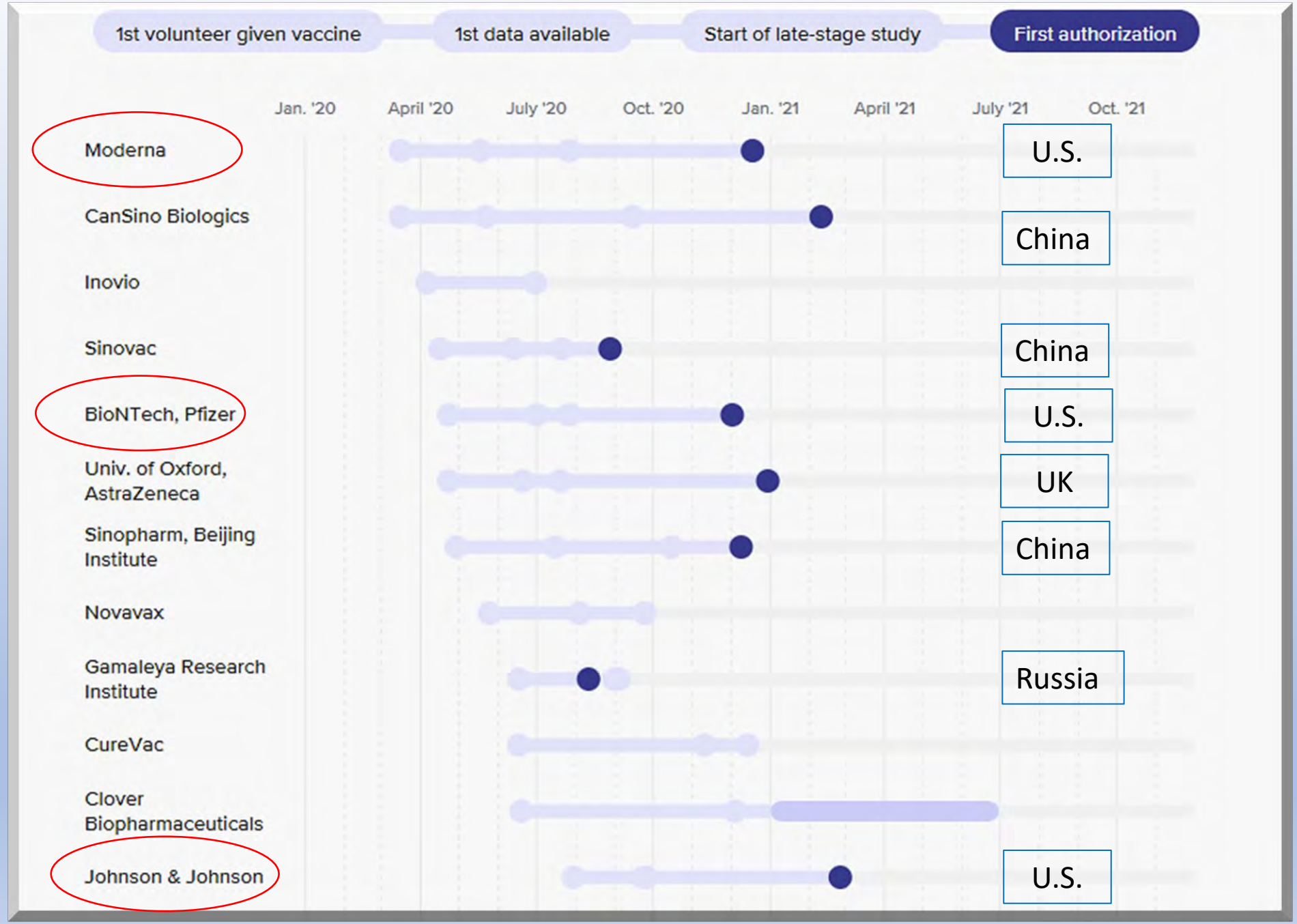
COVID-19 Prevention Network

SARS-CoV-2 Vaccine Approaches

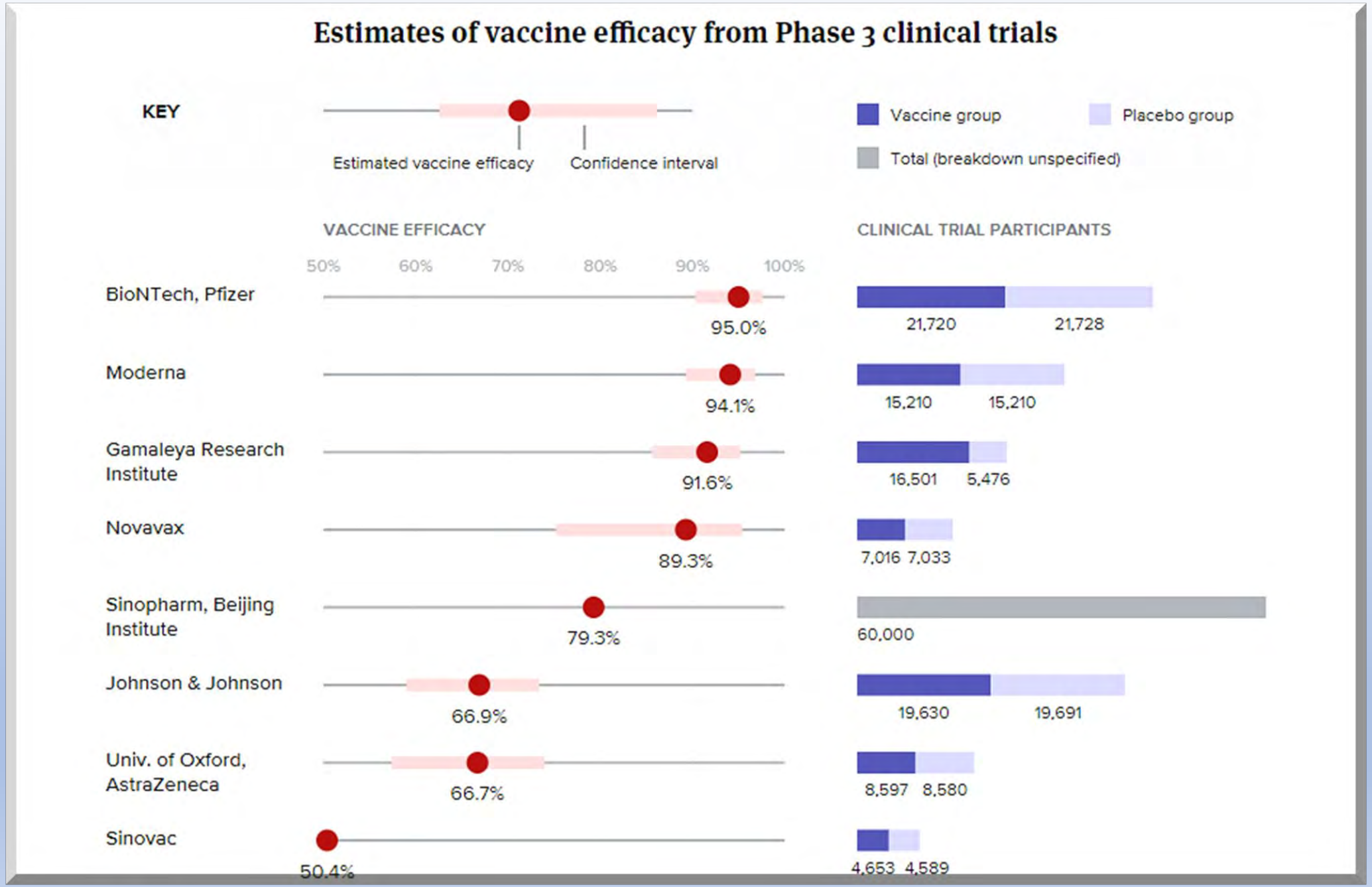


Overview of Operation Warp Speed COVID-19 Vaccine Candidates

Company	Platform	Product	Vaccination dose/schedule	Phase 3 Start
moderna	 mRNA	mRNA: encodes 2P-stabilized Spike, TM, FI	2 doses at 100 µg (0, 28 days)	27July2020
BIONTECH Pfizer	 mRNA	mRNA: encodes stabilized SARS-CoV-2 Spike	2 doses at 30µg (0, 21 days)	27July2020
OXFORD AstraZeneca	 Ad Vector	Replication incompetent ChAdOx1 wild type Spike; ΔF; TM	2 doses at 5 × 10^{10} vp, (0, 28 days)	28Aug2020
janssen	 Ad Vector	Replication Incompetent Ad26; stabilized Spike; ΔF; TM	1 dose at 5 × 10^{10} vp	23Sept2020
NOVAVAX	 Recombinant protein Adjuvanted	Baculovirus Expressed trimeric Stabilized Spike, ΔF; TM; trimerization domain; Matrix M	2 doses at 5 µg with Matrix M (0, 21 days)	27Dec2020
gsk SANOFI	 Recombinant protein Adjuvanted	Baculovirus Expressed trimeric Stabilized Spike, ΔF; TM; trimerization domain; AS03	5/15 µg +AS03 (0, 21 days)	2Q2021


1st volunteer given vaccine
1st data available
Start of late-stage study
First authorization
Jan. '20
April '20
July '20
Oct. '20
Jan. '21
April '21
July '21
Oct. '21
Moderna
U.S.
CanSino Biologics
China
Inovio
Sinovac
China
BioNTech, Pfizer
U.S.
Univ. of Oxford, AstraZeneca
UK
Sinopharm, Beijing Institute
China
Novavax
Gamaleya Research Institute
Russia
CureVac
Clover Biopharmaceuticals
Johnson & Johnson
U.S.

Estimates of vaccine efficacy from Phase 3 clinical trials



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NIAID, VACCINE RESEARCH CENTER STUDIES LEADING TO MRNA-1273

2008 — Response to CoV Outbreaks

McLellan, Graham, et al

2013 — RSV FP stabilization

Vaccine

Ledgerwood, Graham, et al

2016 — Initial Collaboration

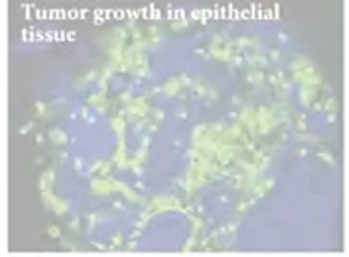
moderna

2016 — CoV FP stabilization

Kirchdoerfer, Ward, et al

2017 — PoC for CoV Spike immunization

PNAS



Pallesen, McLellan, et al

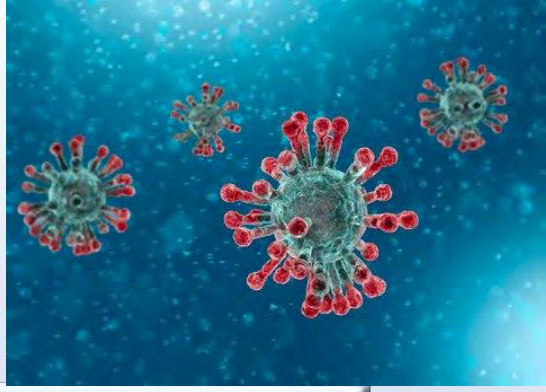
2019 — moderna

Preparedness Pilot Program

And PoC for mRNA vaccine development

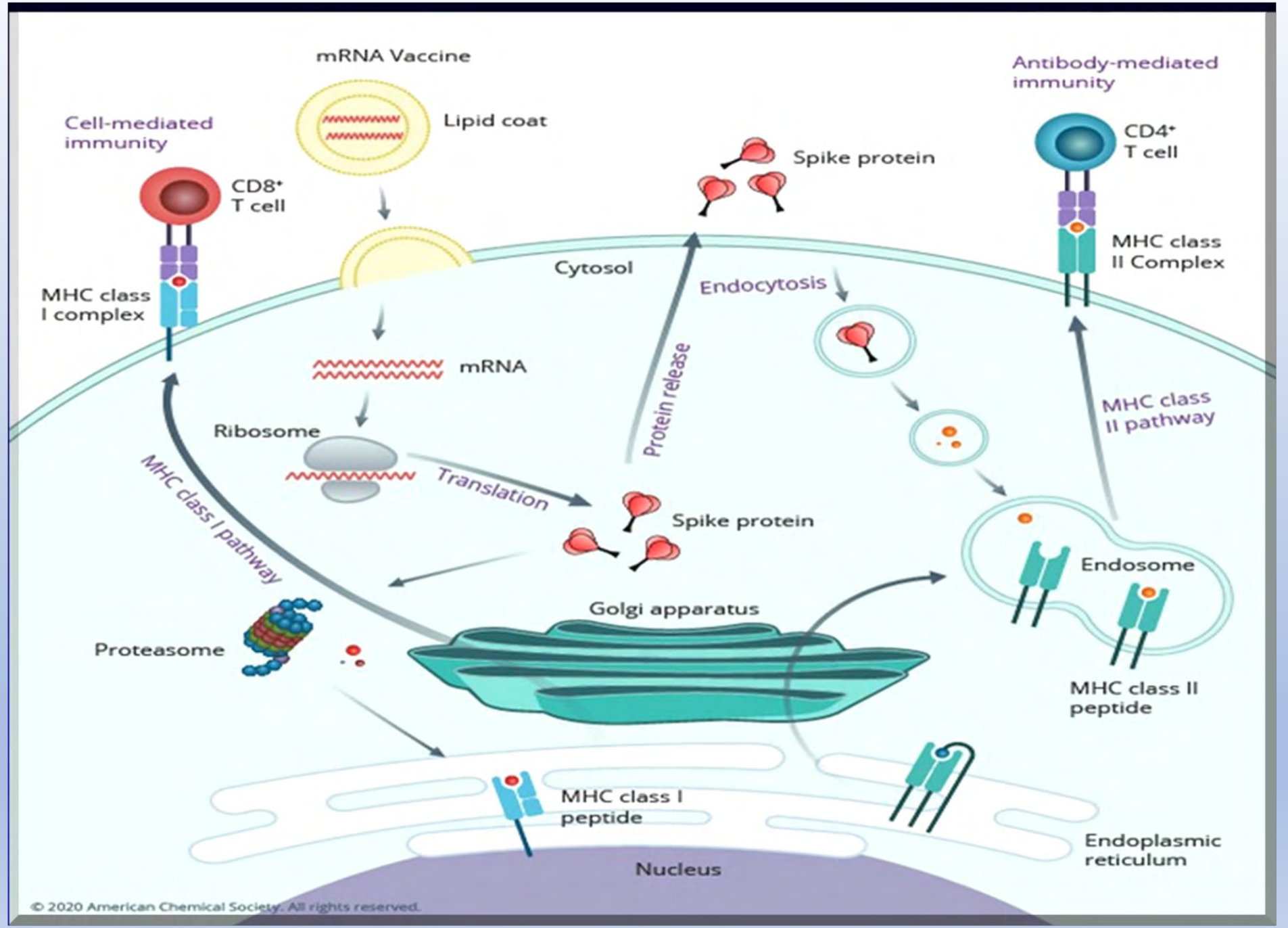
Moderna
SARS and MERS

How the mRNA vaccine works



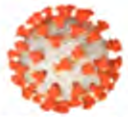
- Both Moderna and Pfizer's vaccines rely on messenger RNA, also known as mRNA. It's a genetic molecule that a cell uses to "read" the instructions needed to build proteins. The mRNA in these vaccines contains instructions to build the spike protein (for which the coronavirus gets its name). That protein helps the virus enter human cells

- The vaccines allow our cells to make the spike protein. Our immune system can then make antibodies to latch onto those spike proteins. Those antibodies may later prevent the real virus from infecting us.


mRNA Vaccine
Lipid coat
Cell-mediated immunity
CD8+ T cell
MHC class I complex
Cytosol
mRNA
Ribosome
Translation
Protein release
Spike protein
Endocytosis
Antibody-mediated immunity
CD4+ T cell
MHC class II Complex
MHC class II pathway
MHC class I pathway
Spike protein
Endosome
Golgi apparatus
Proteasome
MHC class II peptide
MHC class I peptide
Endoplasmic reticulum
Nucleus
© 2020 American Chemical Society. All rights reserved.

Phase 3: Evaluate Efficacy, Safety, and Immunogenicity of mRNA-1273 Vaccine in Adults to Prevent COVID-19

- N= 30,000
  - 1:1 vaccine: Placebo
    - Double blind, placebo controlled
    - 2 vaccinations (d1 and d29), follow-up 2 years
  - High risk for SARS-CoV-2 infection and increased risk for complications from infection
  - Population studied needs to represent the country and those disproportionately impacted
- Primary Outcomes
  - Efficacy
    - COVID-19 starting 14 days after second dose (d42)
  - Safety
- Key Statistical Assumptions
  - COVID-19 incidence rate over 6 months 0.75% in placebo group
  - Target Vaccine Efficacy (VE) 60% with lower bound 95% CI >30%



COVID-19
Prevention Network

CoVPN 3001, NIH-Moderna mRNA-1273-P301, NCT04470427

ORIGINAL ARTICLE

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, D. Diemert, S.A. Spector, N. Rouphael, C.B. Creech, J. McGettigan, S. Khetan, N. Segall, J. Solis, A. Brosz, C. Fierro, H. Schwartz, K. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, J. Mascola, L. Polakowski, J. Ledgerwood, B.S. Graham, H. Bennett, R. Pajon, C. Knightly, B. Leav, W. Deng, H. Zhou, S. Han, M. Ivarsson, J. Miller, and T. Zaks, for the COVE Study Group*

- Enrollment: July 27 – Oct 23
- N= 30,420 randomized
  - 30,351 received dose 1
    - >96% received dose 2
  - 29,148 (95.8%) mITT
  - 28,207 (92.9%) per-protocol

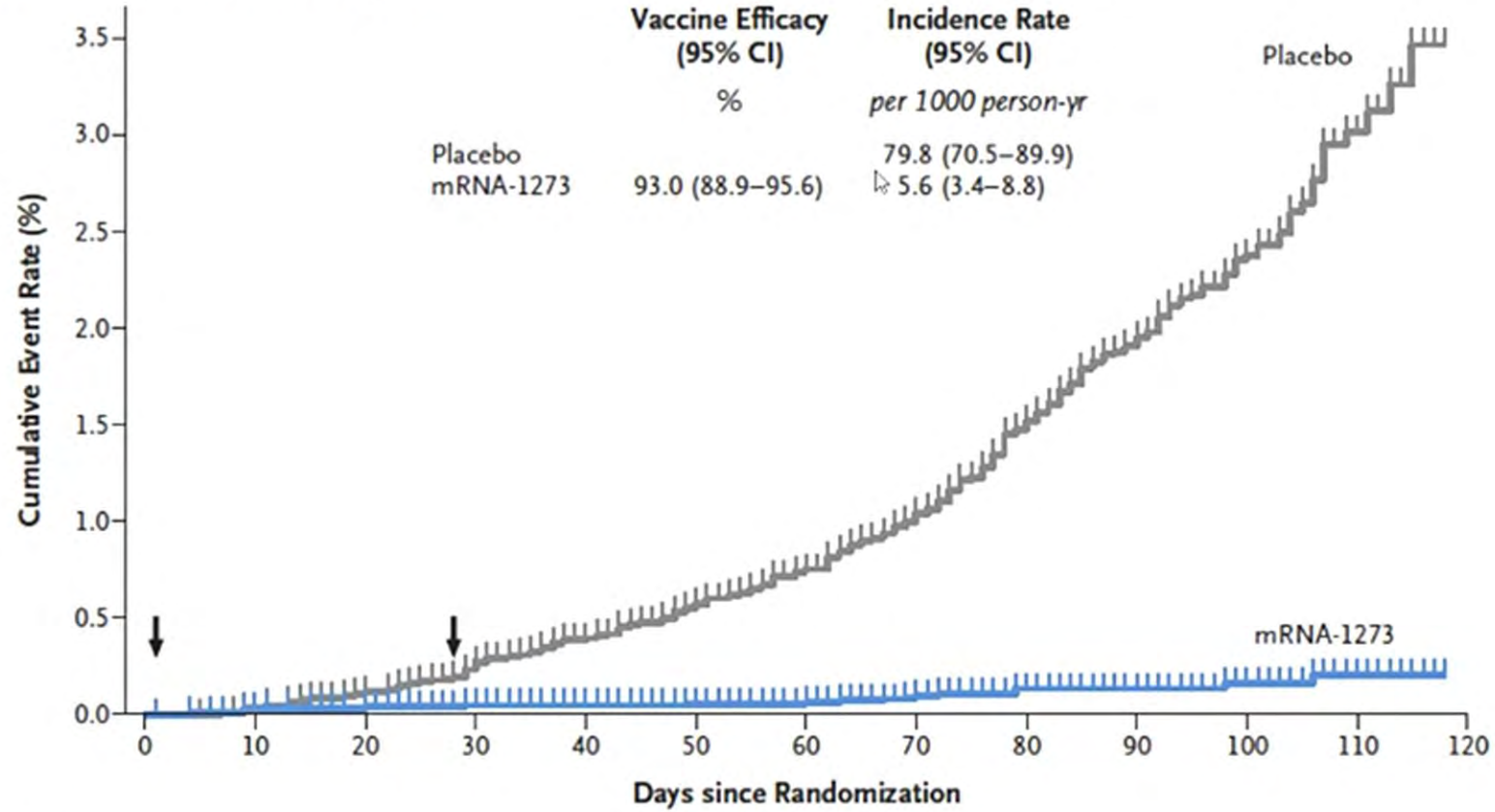
- As of Nov 25 (data cut off)
  - Median f/u 63 days post dose 2 (range 0-97)

COVID-19
Prevention Network

Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristics	Placebo (N=15,170)	mRNA-1273 (N=15,181)	Total (N=30,351)
Sex — no. of participants (%)			
Male	8,062 (53.1)	7,923 (52.2)	15,985 (52.7)
Female	7,108 (46.9)	7,258 (47.8)	14,366 (47.3)
Mean age (range) — yr	51.3 (18–95)	51.4 (18–95)	51.4 (18–95)
Age category and risk for severe Covid-19 — no. of participants (%)†			
18 to <65 yr, not at risk	8,886 (58.6)	8,888 (58.5)	17,774 (58.6)
18 to <65 yr, at risk	2,535 (16.7)	2,530 (16.7)	5,065 (16.7)
≥65 yr	3,749 (24.7)	3,763 (24.8)	7,512 (24.8)
Hispanic or Latino ethnicity — no. of participants (%)‡			
Hispanic or Latino	3,114 (20.5)	3,121 (20.6)	6,235 (20.5)
Not Hispanic or Latino	11,917 (78.6)	11,918 (78.5)	23,835 (78.5)
Not reported and unknown	139 (0.9)	142 (0.9)	281 (0.9)
Race or ethnic group — no. of participants (%)‡			
White	11,995 (79.1)	12,029 (79.2)	24,024 (79.2)
Black or African American	1,527 (10.1)	1,563 (10.3)	3,090 (10.2)
Asian	731 (4.8)	651 (4.3)	1,382 (4.6)
American Indian or Alaska Native	121 (0.8)	112 (0.7)	233 (0.8)
Native Hawaiian or Other Pacific Islander	32 (0.2)	35 (0.2)	67 (0.2)
Multiracial	321 (2.1)	315 (2.1)	636 (2.1)
Other	316 (2.1)	321 (2.1)	637 (2.1)
Not reported and unknown	127 (0.8)	155 (1.0)	282 (0.9)
Baseline SARS-CoV-2 status — no. of participants (%)§			
Negative	14,598 (96.2)	14,550 (95.8)	29,148 (96.0)
Positive	337 (2.2)	343 (2.3)	680 (2.2)
Missing data	235 (1.5)	288 (1.9)	523 (1.7)
Baseline RT-PCR test — no. of participants (%)			
Negative	14,923 (98.4)	14,917 (98.3)	29,840 (98.3)
Positive	95 (0.6)	87 (0.6)	182 (0.6)
Missing data	152 (1.0)	177 (1.2)	329 (1.1)
Baseline bAb anti–SARS-CoV-2 assay — no. of participants (%)			
Negative	14,726 (97.1)	14,690 (96.8)	29,416 (96.9)
Positive	303 (2.0)	305 (2.0)	608 (2.0)
Missing data	141 (0.9)	186 (1.2)	327 (1.1)

B Modified Intention-to-Treat Analysis



No. at Risk

Placebo	14,598	14,590	14,567	14,515	13,806	12,352	12,694	11,450	9736	6729	4067	1200	0
mRNA-1273	14,550	14,543	14,532	14,504	13,825	13,398	12,791	11,573	9911	6871	4179	1238	0

Covid-19 Onset	Placebo (N=14,598)	mRNA-1273 (N=14,550)
Randomization to 14 days after dose 1	11	5
14 Days after dose 1 to dose 2	35	2
Dose 2 to 14 days after dose 2	19	0
Starting 14 days after dose 2	204	12
Total (any time after randomization)	269	19

Severe Infection efficacy 100%

Severe illness 30 vs 0 cases

D29 NP swab+ 39 vs 15 cases

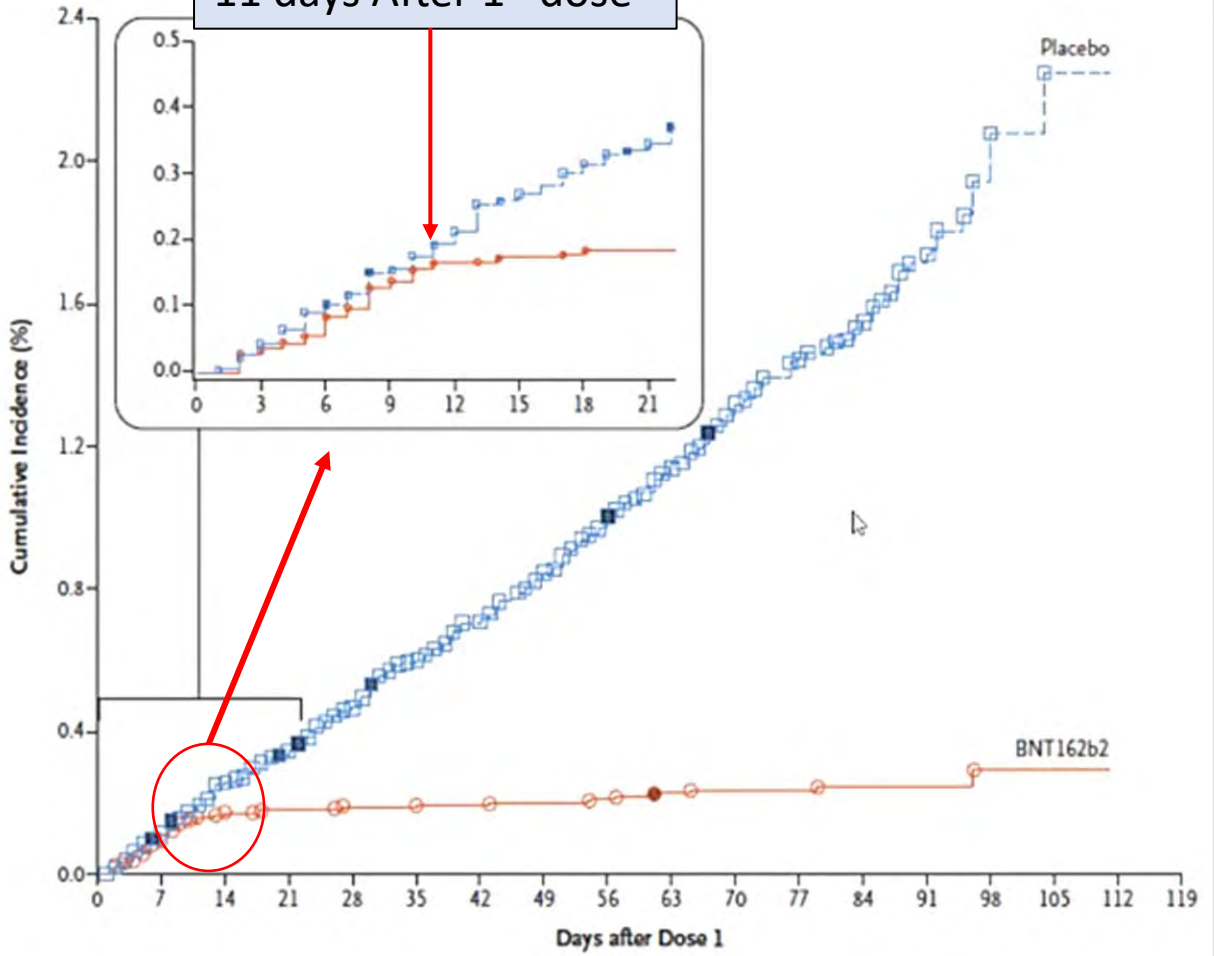
COVID-19

ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzalo Pérez Marc, M.D., Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D., Robert W. Frenck, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., Haylene Nell, M.D., Axel Schaefer, M.D., Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

11 days After 1st dose



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669) No. of participants	BNT162b2, 30 μg (N=21,669) Surveillance time *person-yr (no. at risk)*	Placebo (N=21,686) No. of participants	Placebo (N=21,686) Surveillance time *person-yr (no. at risk)*	VE (95% CI) *percent*
Covid-19 occurrence					
After dose 1	50	4,015 (21,314)	275	3,982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

Figure 3. Efficacy of BNT162b2 against Covid-19 after the First Dose.

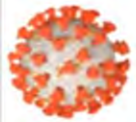
COVID-19 Prevention Network

US FDA: Emergency Use Authorization

- Nov 15: NIAID DSMB meeting
- Nov 16: Press release
- Dec 18: VRBPAC meeting
- Dec 19: FDA action – EUA
- Dec 20: ACIP/CDC Guidance
- Dec 21: Vaccine shipped

Key question:

- What to do with study volunteers
  - Study is NOT over (yet EUA/clinical vaccine available)
    - Asymptomatic infection, viral shedding/carriage, durability/waning immunity, protection in sub-groups



COVID-19
Prevention Network

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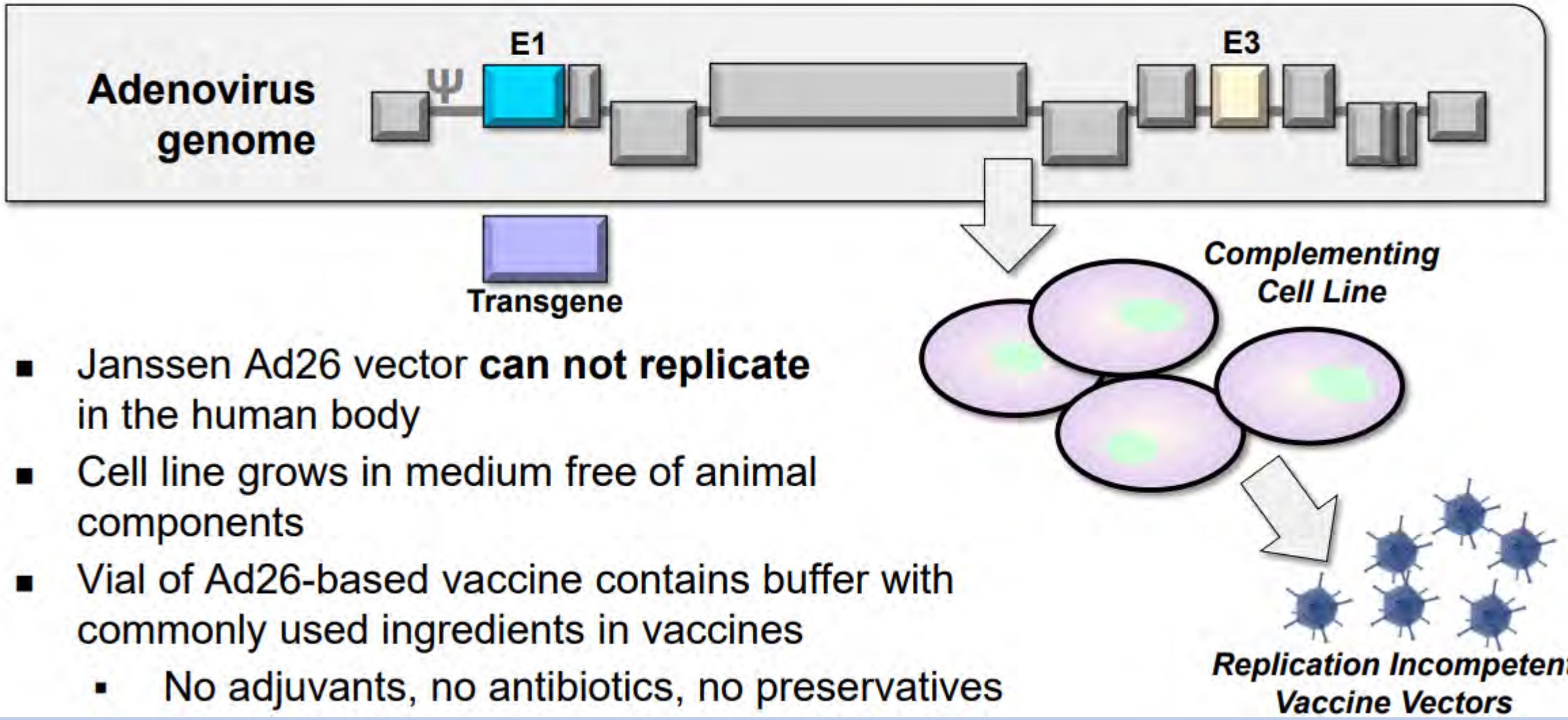
BIONTECH Pfizer	 mRNA	mRNA: encodes stabilized SARS-CoV-2 Spike	2 doses at 30µg (0, 21 days)	27July2020
OXFORD AstraZeneca	 Ad Vector	Replication incompetent ChAdOx1 wild type Spike; ΔF; TM	2 doses at 5 × 10^{10} vp, (0, 28 days)	28Aug2020
janssen	 Ad Vector	Replication Incompetent Ad26; stabilized Spike; ΔF; TM	1 dose at 5 × 10^{10} vp	23Sept2020
NOVAVAX	 Recombinant protein Adjuvanted	Baculovirus Expressed trimeric Stabilized Spike, ΔF; TM; trimerization domain; Matrix M	2 doses at 5 µg with Matrix M (0, 21 days)	27Dec2020
gsk SANOFI	 Recombinant protein Adjuvanted	Baculovirus Expressed trimeric Stabilized Spike, ΔF; TM; trimerization domain; AS03	5/15 µg +AS03 (0, 21 days)	2Q2021

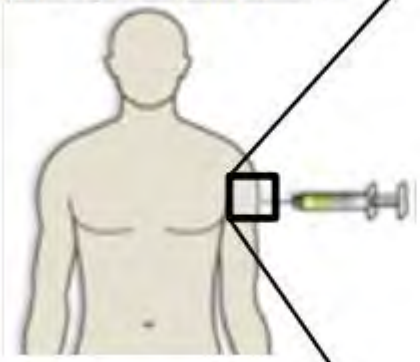
Ad26 Vector is Replication Incompetent



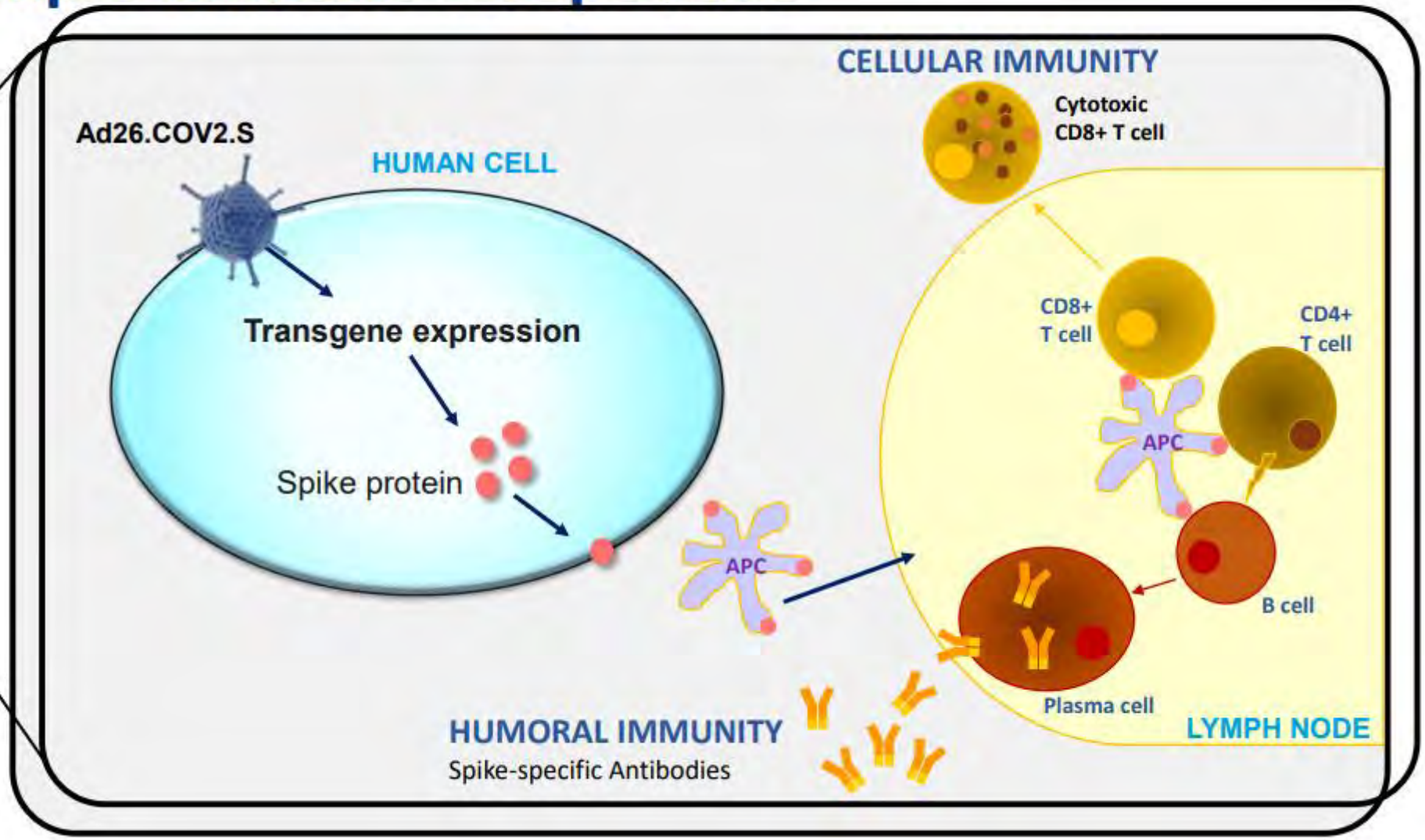
- Janssen Ad26 vector **can not replicate** in the human body
- Cell line grows in medium free of animal components
- Vial of Ad26-based vaccine contains buffer with commonly used ingredients in vaccines
  - No adjuvants, no antibiotics, no preservatives

Ad26.COV2.S Expresses SARS-CoV-2 Spike Protein, Eliciting Multiple Immune Responses

I.M. injection of Ad26.COV2.S



Adenoviral vectors classified as non-integrating*



Substantial Experience with Adenovirus 26-based Vaccines

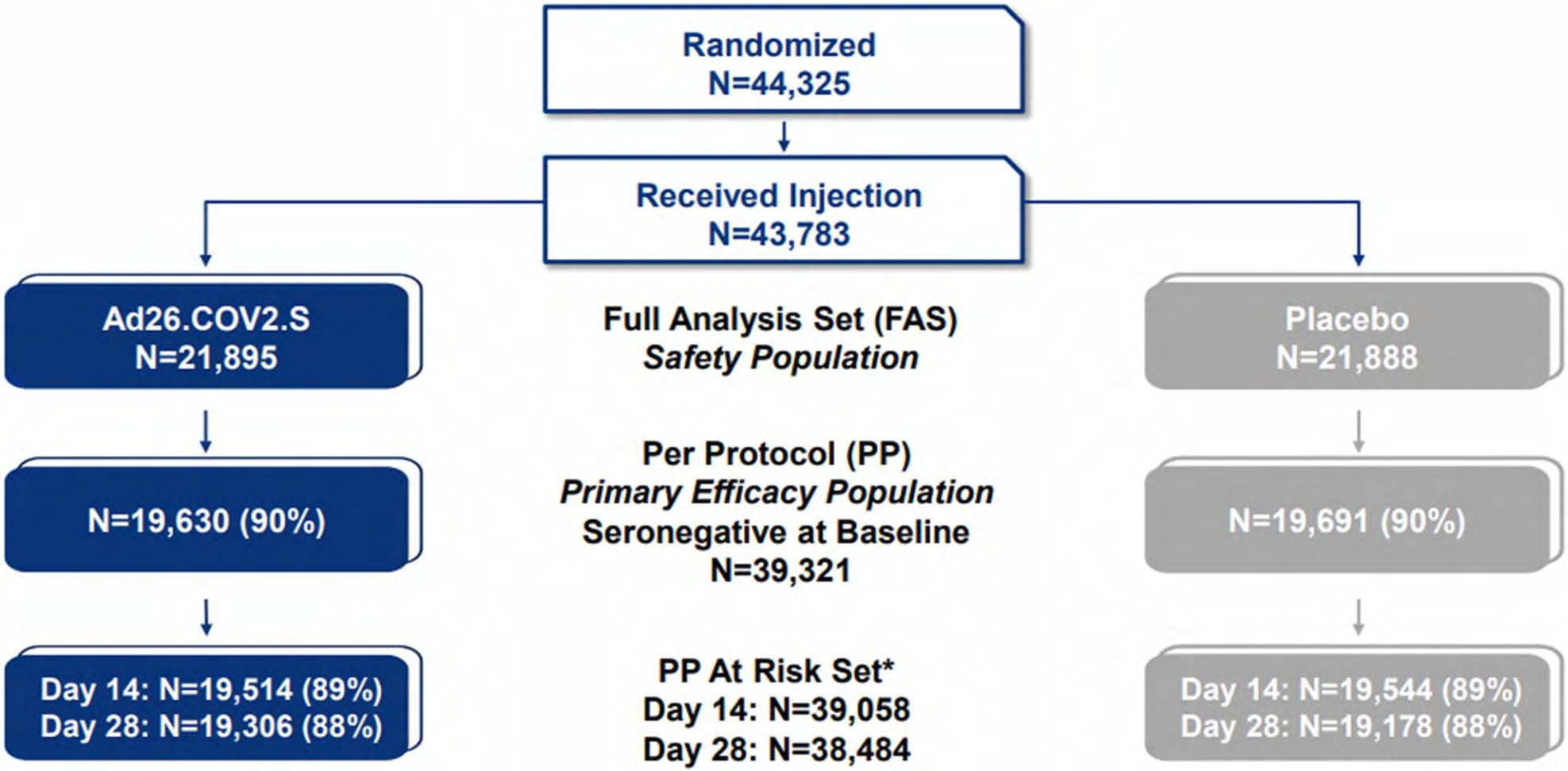
Substantial clinical experience with Ad26-based vaccines (N > 193,000)

- Across continents
- Various races, ethnicities
- Healthy adults
- Infants ≥ 4 months
- Elderly > 65 years
- People with HIV
- Breastfeeding, pregnant women within Ebola program

Regular database reviews show good tolerability, safety

- Local, systemic reactogenicity in line with other licensed vaccines
- Database searches for AESIs revealed no safety signals

COV3001 Disposition of Participants



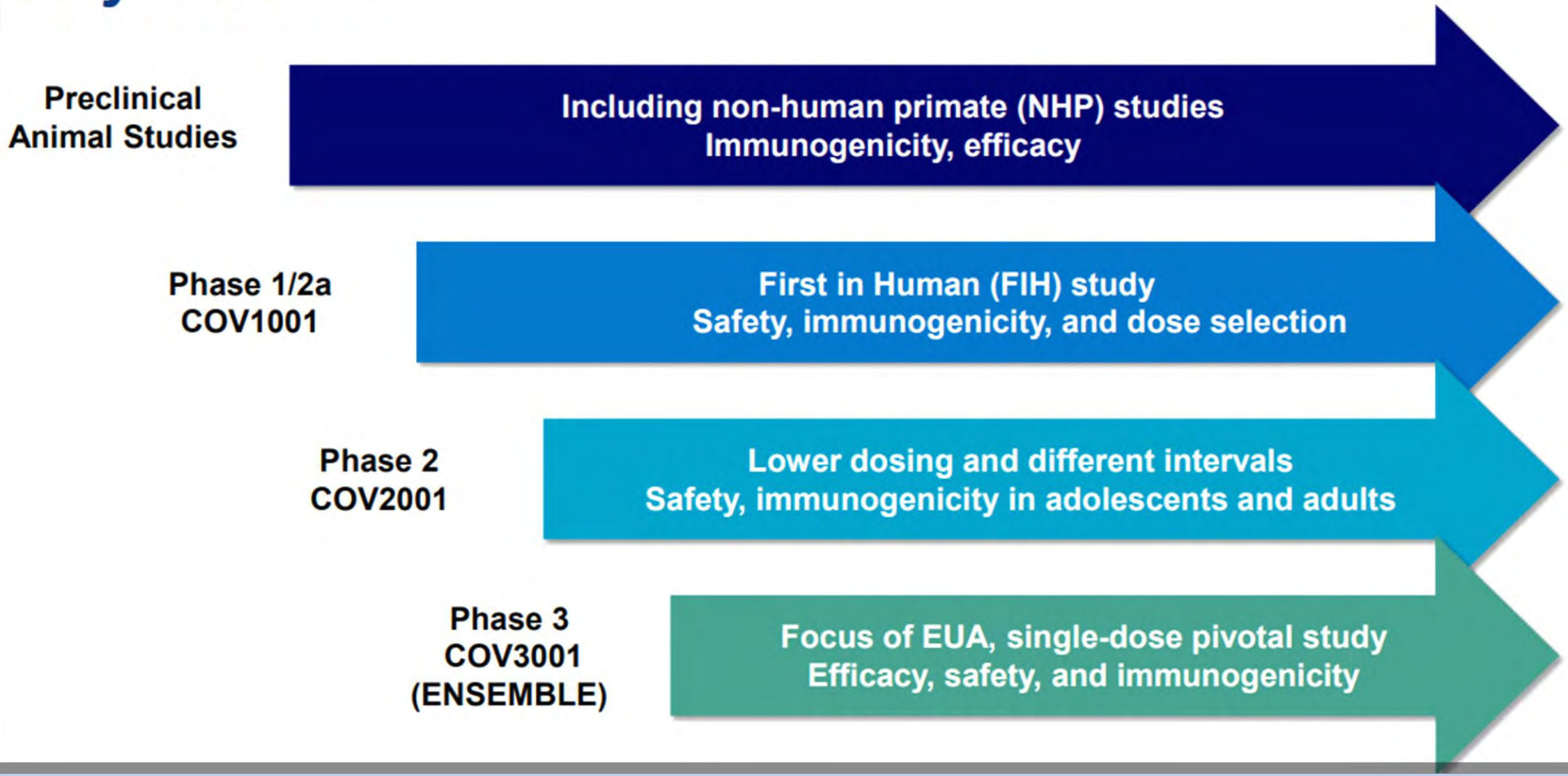
COV3001: No Relevant Differences at Baseline Between Vaccine and Placebo Groups Globally

Full Analysis Set	Ad26.COV2.S N = 21,895		Placebo N = 21,888	
	n	%	n	%
Sex, female	9,820	45%	9,902	45%
Mean Age (SD), years	50.7 (15.0)		50.7 (15.0)	
Age group				
18-59	14,564	67%	14,547	66%
≥ 60	7,331	33%	7,341	34%
≥ 65	4,259	19%	4,302	20%
≥ 75	809	4%	732	3%
Race				
American Indian or Alaska Native	2,083	10%	2,060	9%
Asian	743	3%	687	3%
Black or African American	4,251	19%	4,264	20%
Native Hawaiian or other Pacific Islander	58	0.3%	48	0.2%
White	12,858	59%	12,838	59%
Multiple, unknown, not reported	1,901	9%	1,989	9%
Ethnicity				
Hispanic or Latino	9,874	45%	9,963	46%

COV3001: Global Participants with Comorbidities Similar Between Vaccine and Placebo Groups

Full Analysis Set	Ad26.COV2.S N = 21,895		Placebo N = 21,888	
Baseline Comorbidity* Category, ≥ 2%	**n**	**%**	**n**	**%**
≥ 1 risk factor	8,936	40.8%	8,922	40.8%
Obesity ≥ 30 kg/m²	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%
Serious heart conditions	497	2.3%	511	2.3%

Comprehensive Development Program
Key Studies



Key Efficacy Findings from Ad26.COV2.S Single-Dose Study Demonstrate Protection Against Symptomatic COVID-19

85% vaccine efficacy* against severe COVID-19 globally, including the United States

- Consistent vaccine efficacy against severe disease across all regions
- Equally high protection in South Africa (n > 6,500) where B.1.351 is highly prevalent (> 95%)
- Complete protection against COVID-19 related hospitalizations as of day 28 and no COVID-19 related deaths in the Ad26 group compared to 5 in the placebo group

72% vaccine efficacy* against moderate to severe/critical COVID-19 in the United States

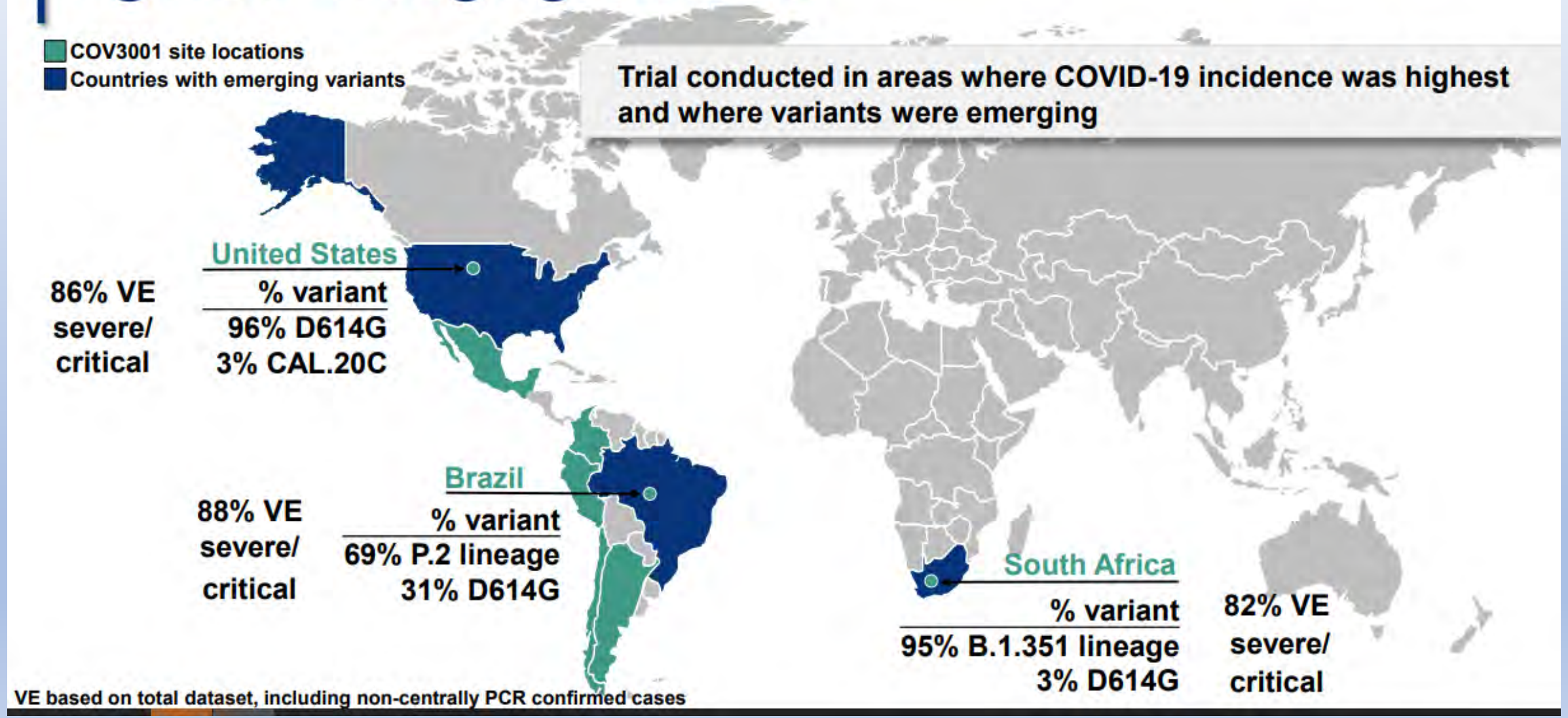
- Participants reflected diversity of US population (n > 19,000)

66% vaccine efficacy* against moderate to severe/critical COVID-19 across all countries

- Protection as of 2 weeks after vaccination

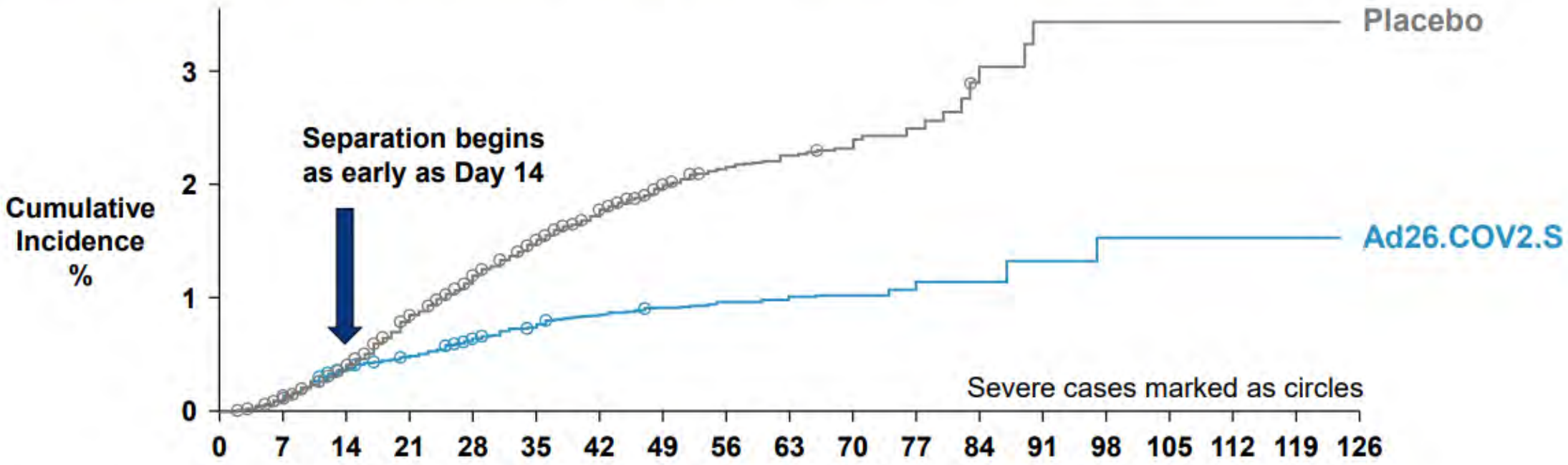
Similar vaccine efficacy demonstrated by age, comorbidities status, sex, race, and ethnicity

Vaccine Efficacy (VE) Results Support Protection Against Emerging Variants



VE based on total dataset, including non-centrally PCR confirmed cases

Kaplan Meier Shows Early Onset of Protection Against Moderate to Severe/Critical COVID-19



Participants at risk

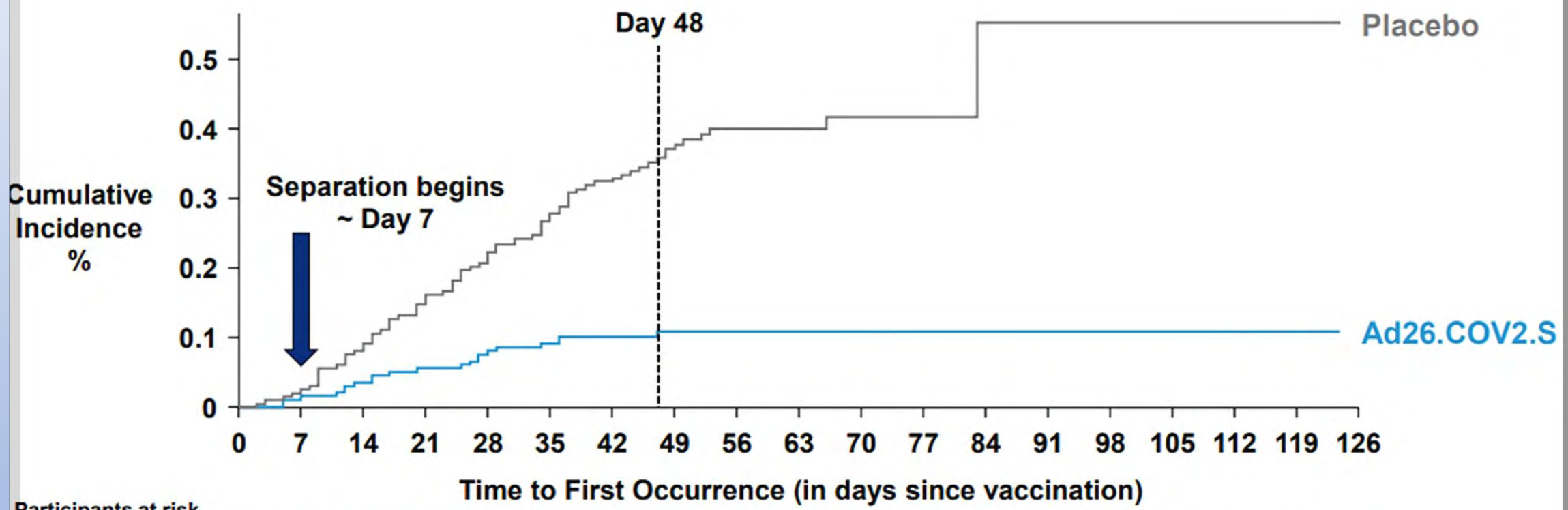
Ad26.COV2.S	19744	19725	19669	19642	19612	19578	18541	14909	10930	7831	3998	1468	713	484	483	482	142	31	0
Placebo	19822	19804	19745	19652	19579	19488	18411	14814	10823	7740	3876	1439	708	485	482	480	133	27	0

Cumulative number of cases

Ad26.COV2.S	0	27	76	96	126	151	168	178	184	188	189	191	191	192	193	193	193	193	193
Placebo	0	22	81	168	237	299	351	387	407	416	423	425	430	432	432	432	432	432	432

COV3001; Full Analysis Set; baseline seronegative; confirmed: positive PCR centrally confirmed COVID-19 cases

Time to First Occurrence of Severe/Critical COVID-19 Demonstrates Early Onset of Protection



Participants at risk																			
Ad26.COV2.S	19744	19741	19734	19725	19718	19705	18685	15043	11046	7919	4039	1481	720	490	490	489	146	31	0
Placebo	19822	19817	19799	19779	19760	19725	18682	15088	11069	7939	3995	1485	732	500	497	495	137	29	0
Number of cases																			
Ad26.COV2.S	0	3	7	11	16	18	20	21	21	21	21	21	21	21	21	21	21	21	21
Placebo	0	5	18	32	44	55	65	73	76	76	77	77	78	78	78	78	78	78	78

Data Support Substantial Effect on Prevention of COVID-19 Related Hospitalizations

PP At Risk Set	**Ad26.COV2.S** Cases, n	**Placebo** Cases, n	**VE** (95% CI)
> Day 14			
PCR+ cases from any source, regardless of central confirmation	**2**	**29**	**93.1% (72.7, 99.2)**
> Day 28			
PCR+ cases from any source, regardless of central confirmation	**0**	**16**	**100.0% (74.3, 100.0)**

Ad26.COV2.S Data Support Protection Against COVID-19-Related Deaths

Full Analysis Set *Through January 22, 2021*	Ad26.COV2.S N = 21,895	Placebo N = 21,888
All cause mortality	3	16
COVID-19 confirmed death > Day 1	0	5*

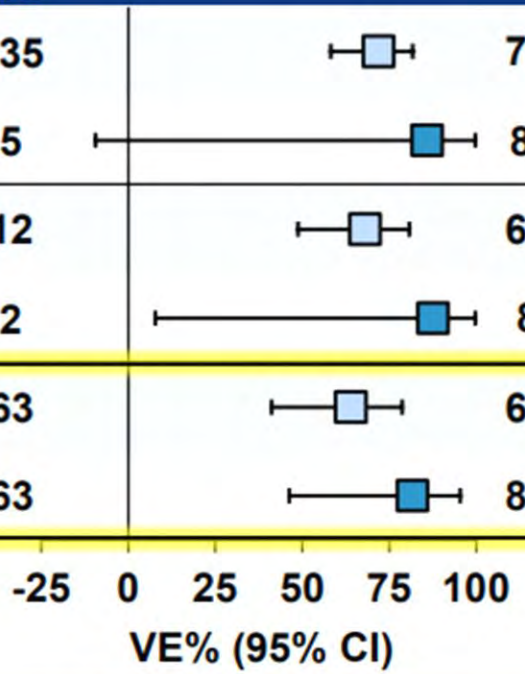
*One PCR+ participant at baseline, not included

Full Analysis Set *From January 22, 2021 to February 5, 2021*	Ad26.COV2.S N = 21,895	Placebo N = 21,888
Additional deaths reported	2	4
COVID-19 confirmed death > Day 1	0	1

- All COVID-19 associated deaths occurred in South Africa

Vaccine Efficacy Consistently High Across Key Countries > Day 28

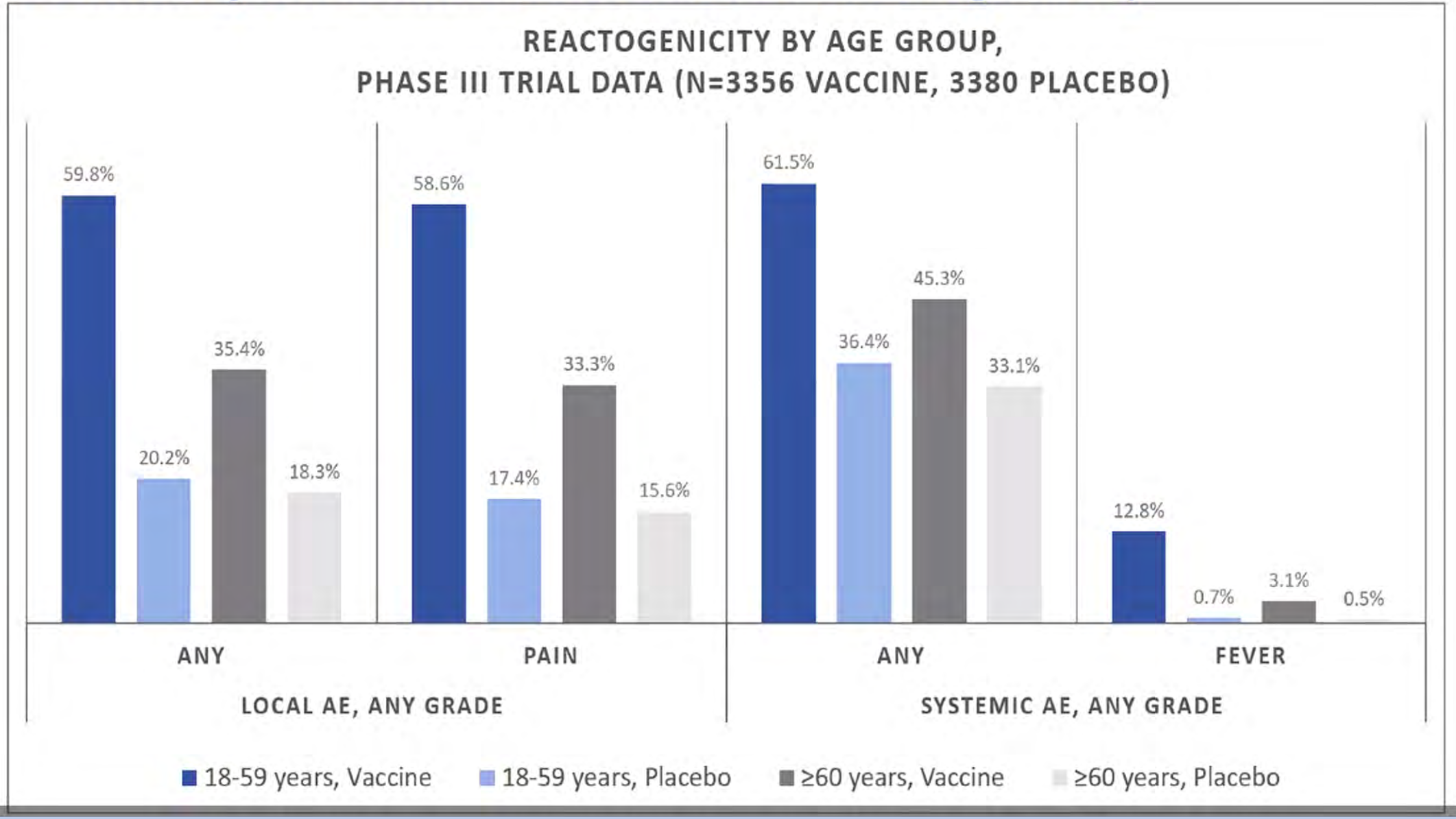
Country *% Variant*	Severity	# Events / N Ad26.COV2.S N = 19,306	# Events / N Placebo N = 19,178	> Day 28 Vaccine Efficacy (95%CI)
United States 96% D614G 3% CAL.20C	**Moderate-Severe/Critical**	**32 / 8,958**	**112 / 8,835**	**72.0% (58.2, 81.7)**
	Severe/Critical	**1 / 8,958**	**7 / 8,835**	**85.9% (-9.4, 99.7)**
Brazil 69% P.2 lineage 31% D614G	**Moderate-Severe/Critical**	**24 / 3,354**	**74 / 3,312**	**68.1% (48.8, 80.7)**
	Severe/Critical	**1 / 3,354**	**8 / 3,312**	**87.6% (7.8, 99.7)**
South Africa 95% B.1.351 lineage 3% D614G	**Moderate-Severe/Critical**	**23 / 2,449**	**64 / 2,463**	**64.0% (41.2, 78.7)**
	Severe/Critical	**4 / 2,449**	**22 / 2,463**	**81.7% (46.2, 95.4)**



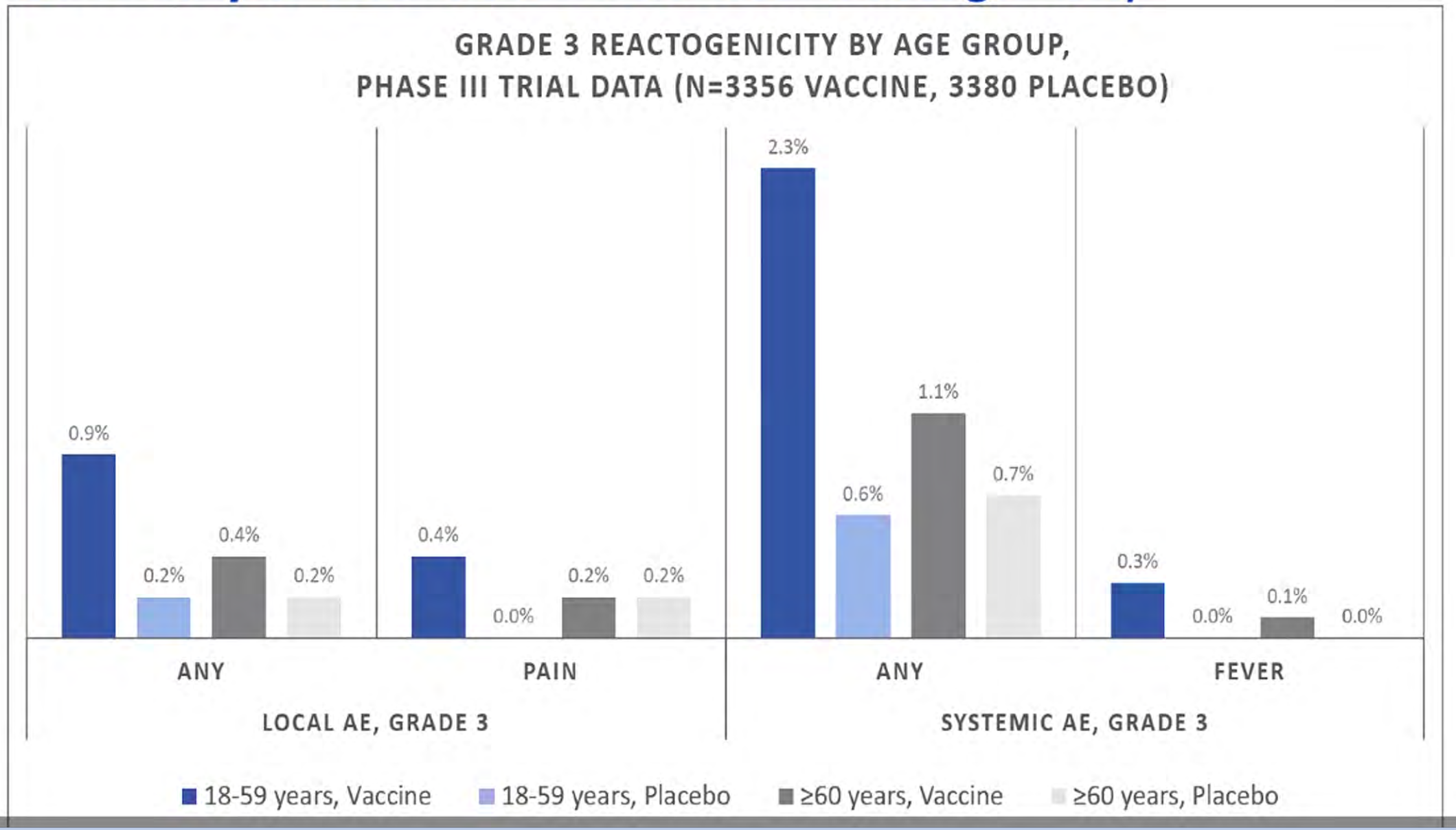
South Africa *PP At Risk Set (N = 4,912)* **Hospitalizations > Day 28*: 0 vs 6 (Ad26.COV2.S vs placebo)**

Full Analysis Set (N = 6,576) **COVID-related deaths: 0 vs 5** (Ad26.COV2.S vs placebo)

Summary of Available Evidence: Reactogenicity



Summary of Available Evidence: Reactogenicity



Thrombotic and Thromboembolic Events

Full Analysis Set	Ad26.COV2.S N = 21,895 n	Placebo N = 21,888 n
Total participants with any event	14	10
Venous thromboembolic events		
Deep vein thrombosis	6	2
Pulmonary embolism	4	1
Transverse sinus thrombosis	1	0
Thrombosed hemorrhoid	0	1
Total participants with venous events	11	4
Arterial thromboembolic events		
Cerebrovascular events	3*	3
Cardiovascular events	1	3
Total participants with arterial events	3	6

Single Dose of Ad26.COV2.S Offers Substantial Protection Against COVID-19

- 85% VE* against severe disease
  - Onset of protection as early as 7 days after vaccination
  - Complete protection against COVID-19 related hospitalizations* and deaths
- 66% VE* against moderate to severe disease across all countries
  - Onset evident as early as Day 14, and increased through Day 56
- 72% VE* against moderate to severe COVID-19 in US
  - Study participants reflected the diversity of the overall US population
- Protection against all symptomatic disease consistent with primary endpoint
- High-quality, robust data at a time when the incidence of SARS-CoV-2 was increasing, and new, highly transmissible variants were emerging
- High levels of protection consistent across subgroups, countries and regions*

Benefits of Ad26.COV2.S Outweigh Known and Potential Risks

- Demonstrated acceptable safety and reactogenicity profile
- Overall, reactogenicity mild and transient
  - Grade 3 reactogenicity rare
- Most AEs mild or moderate
  - Generally resolved 1 to 2 days post vaccination
- Safety further supported by > 193,000 individuals exposed to Janssen Ad26-based vaccines

Logistical, Practical Advantages to Help Simplify Distribution and Expand Vaccine Access of Single Dose Ad26.COV2.S

Single, 0.5ml dose offers ability to vaccinate population faster

5 doses per vial

No dilution required

Stored for 3 months at normal refrigerator temperatures, 2° to 8° C (36° to 46° F)

2-year shelf life when frozen, -25° to -15° C (-13° to 5° F)

Prepared for large-scale manufacturing

20 million doses by end of March

100 million doses to US in first half of 2021

Shipping fits into existing supply chain infrastructure

Summary of the Evidence:

All authorized COVID-19 vaccines

- No trials compared efficacy between vaccines in the **same** study at the **same** time
  - All Phase 3 trials differed by calendar time and geography
  - Vaccines were tested against different circulating variants and in settings with different background incidence
- All authorized COVID-19 vaccines demonstrated efficacy (range 65 to 95%) against symptomatic lab-confirmed COVID-19
- All authorized COVID-19 vaccines demonstrated **high** efficacy (≥89%) against COVID-19 severe enough to require **hospitalization**
- In the vaccine trials, **no** participants who received a COVID-19 vaccine **died** from COVID-19
  - The Moderna and Janssen trials each had COVID-19 deaths in the placebo arm

COVID-19 vaccination of persons with underlying medical conditions

- Any currently authorized COVID-19 vaccine can be administered to persons with underlying medical conditions who have no contraindications to vaccination, including:
  - Immunocompromised persons
  - People with autoimmune conditions
  - People with history of Guillain-Barré syndrome, Bell's palsy, dermal filler use

- Clinical trials demonstrate similar safety and efficacy profiles in persons with underlying medical conditions, including those that place them at increased risk for severe COVID-19, compared to persons without comorbidities

Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine-United States, Dec 14-23, 2020

Centers for Disease Control and Prevention
MMWR
Early Release / Vol. 70
January 6, 2020

- On December 11: EUA for Pfizer-BioNTech COVID-19 vaccine
- By December 23: 1,893,360 first doses administered
  - 4,393 adverse reactions reported to VAERS
  - 175 identified for further review as possible anaphylaxis
  - 83 cases of non-anaphylaxis allergic reactions
  - 21 determined to be anaphylaxis based on Brighton Collaboration Criteria
    - 17 with a history of allergies
    - 7 of those with a history of anaphylaxis
- Overall rate of 11.1 / million
  - Approximately 10x higher than the incidence of anaphylaxis with other vaccines

https://www.cdc.gov/mmwr/volumes/70/wr/mm7002e1.htm?s_cid=mm7002e1_w

Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine-United States, Dec 14-23, 2020

Centers for Disease Control and Prevention
MMWR
Early Release / Vol. 70
January 6, 2020

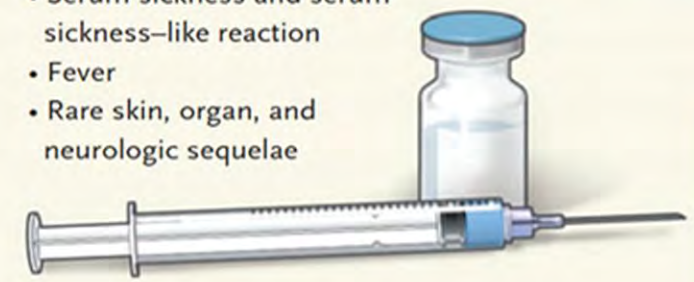
- Median age 40 (27-60)
- Female 90%
- Median interval to onset of symptoms 13 minutes (2-150)
  - Symptom onset <15 minutes 71%
  - Symptom onset <30 minutes 86%
- Prior history of allergies or allergic reactions 81%
  - Medication allergy 8
    - (Sulfa 4, Penicillin 1, Macrolides 2, Steroids 1, Hydrocodone 1, Prochlorperazine 1)
  - Food allergy 4
  - Insect stings 2
  - Vaccines 2 (rabies, influenza)
  - Radiocontrast Media 1

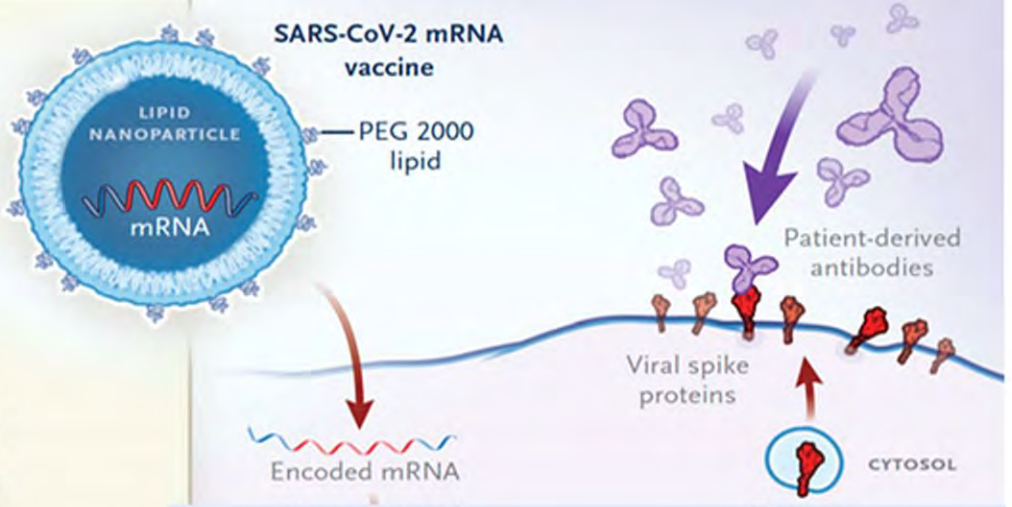
https://www.cdc.gov/mmwr/volumes/70/wr/mm7002e1.htm?s_cid=mm7002e1_w

SARS-CoV-2 mRNA Vaccines

Vaccine Reactions

- Immediate
  - IgE
  - Non-IgE
  - Nonimmune (vasovagal syncope)
- Delayed
  - Site reactions
  - Urticaria or benign exanthem
  - Serum sickness and serum sickness–like reaction
  - Fever
  - Rare skin, organ, and neurologic sequelae





Castells M, Phillips EJ NEJM 2020 Dec 30

Pfizer-BioNTech

- 30 mcg mRNA encoding spike protein
- lipids (0.43 mg (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate), 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine, and 0.2 mg cholesterol), 0.01 mg potassium chloride, 0.01 mg monobasic potassium phosphate, 0.36 mg sodium chloride, 0.07 mg dibasic sodium phosphate dihydrate, and 6 mg sucrose.

Moderna

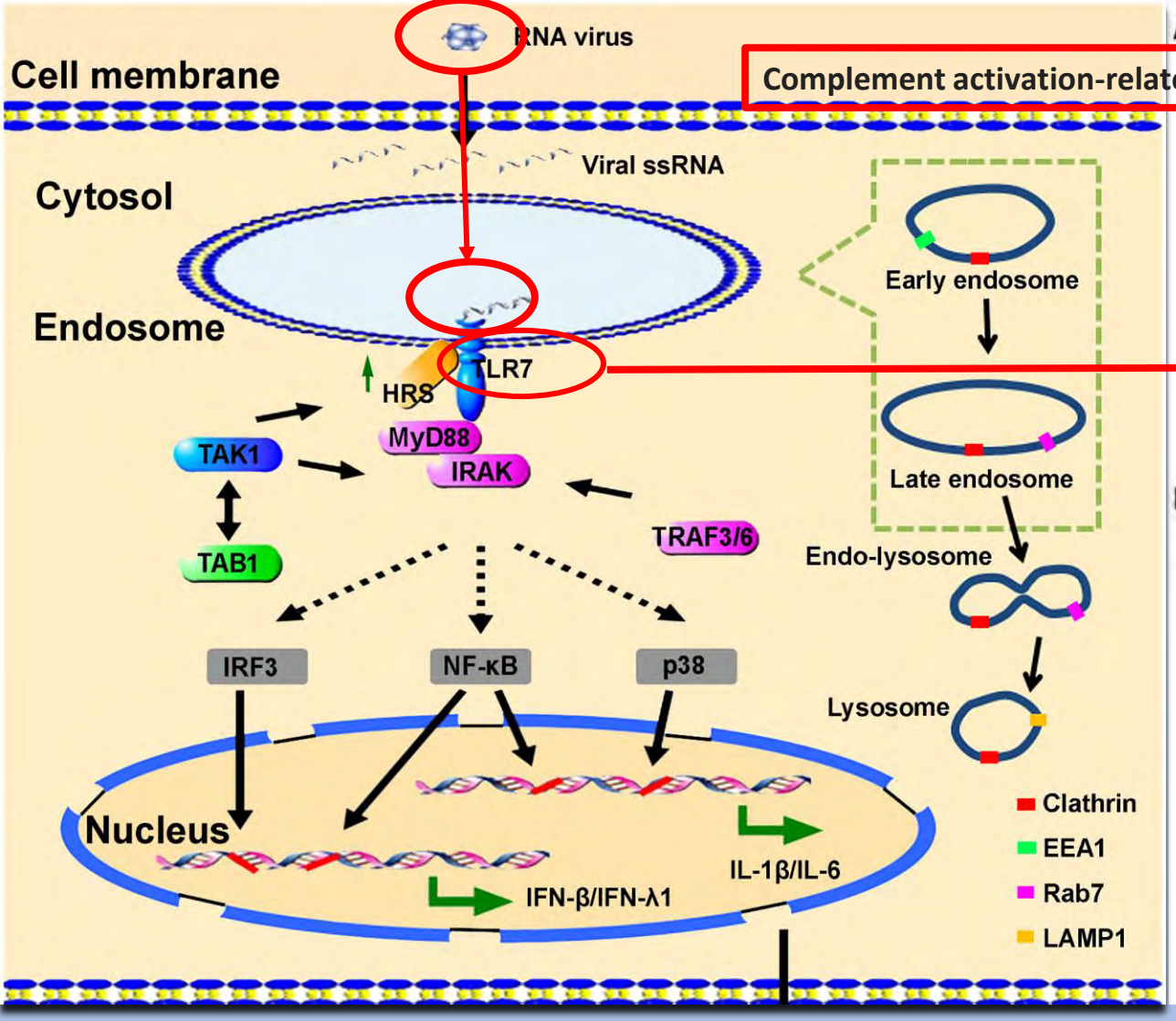
- 100 mg mRNA encoding spike protein
- lipids (SM-102; 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [PEG2000-DMG]; cholesterol; and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose.

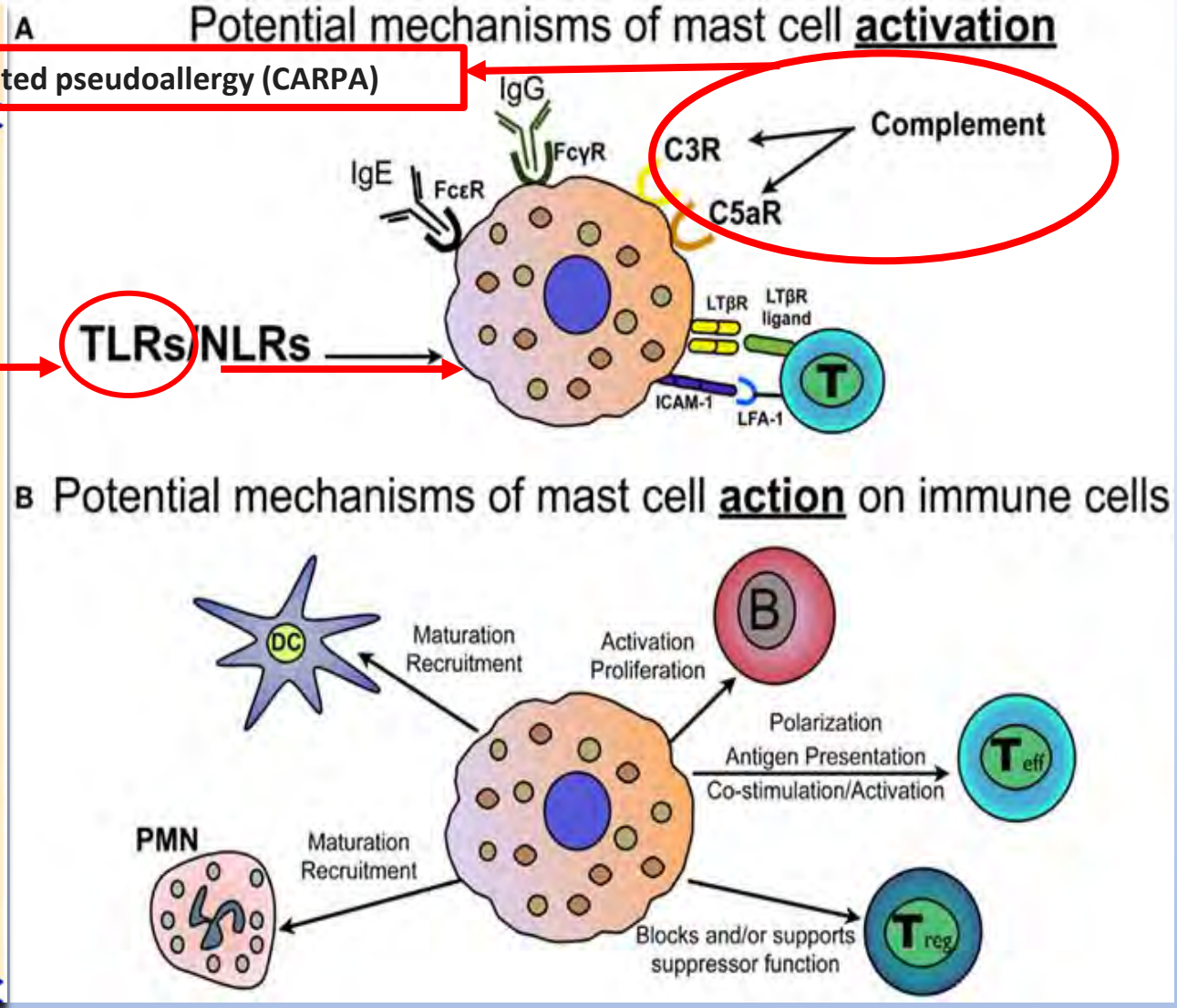
PEG/Polysorbate Vaccine Excipients

Excipient	Vaccine type	Vaccine	Amount per dose
Polysorbate 20	Influenza	Flublok&Flublock quad	<27.5 mcg (Tween20)
Polysorbate 20	Hepatitis A	Havrix	0.05 mg/ml
Polysorbate 20	Hepatitis A&B	Twinrix	unknown
Polysorbate 20	Sars-CoV-2 (Sanofi)		
Polysorbate 80	Tdap	Boostrix	<100 mcg (Tween 80)
Polysorbate 80	Influenza	Fluad	1.175 mg
Polysorbate 80	Influenza	Fluarix quad	<0.0550 mg (Tween 80)
Polysorbate 80	Influenza	Flucelvax quad	≤1500 mcg (Tween 80)
Polysorbate 80	Influenza	Flulaval Quad	≤887 mcg
Polysorbate 80	HPV	Gardasil and Gardasil -9	50 mcg
Polysorbate 80	Hepatitis B	Heplisav-B	0.1 mg/ml
Polysorbate 80	DTaP	Infanrix	<100 mcg (Tween 80)
Polysorbate 80	Japanese encephalitis	JE-Vax	<0.0007%
Polysorbate 80	DTaP + IPV	Kinrix	<100 mcg (Tween 80)
Polysorbate 80	DTaP+HepB+IPV	Pediarix	≤100 mcg (Tween 80)
Polysorbate 80	DTaP+IPV+Hib	Pentacel	10 ppm
Polysorbate 80	Pneumococcal 13-valent	Prevnar 13	100 mcg
Polysorbate 80	DTaP + IPV	Quadracel	10 ppm
Polysorbate 80	Rotavirus	RotaTeq	?
Polysorbate 80	Zoster	Shingrix	0.08 mg
Polysorbate 80	Meningococcal group B	Trumenba	0.018 mg
Polysorbate 80	Sars-CoV-2 (Astrazenica) Sars-CoV-2 (Janssen)		<0.007 mg/ml
PEG2000	Sars-CoV-2 (Moderna) Sars-CoV-2 (Pfizer)		0.05 mg

*adapted from https://vacinesafety.edu/components-excipients.htm (Johns Hopkins Bloomberg School of Public Health)

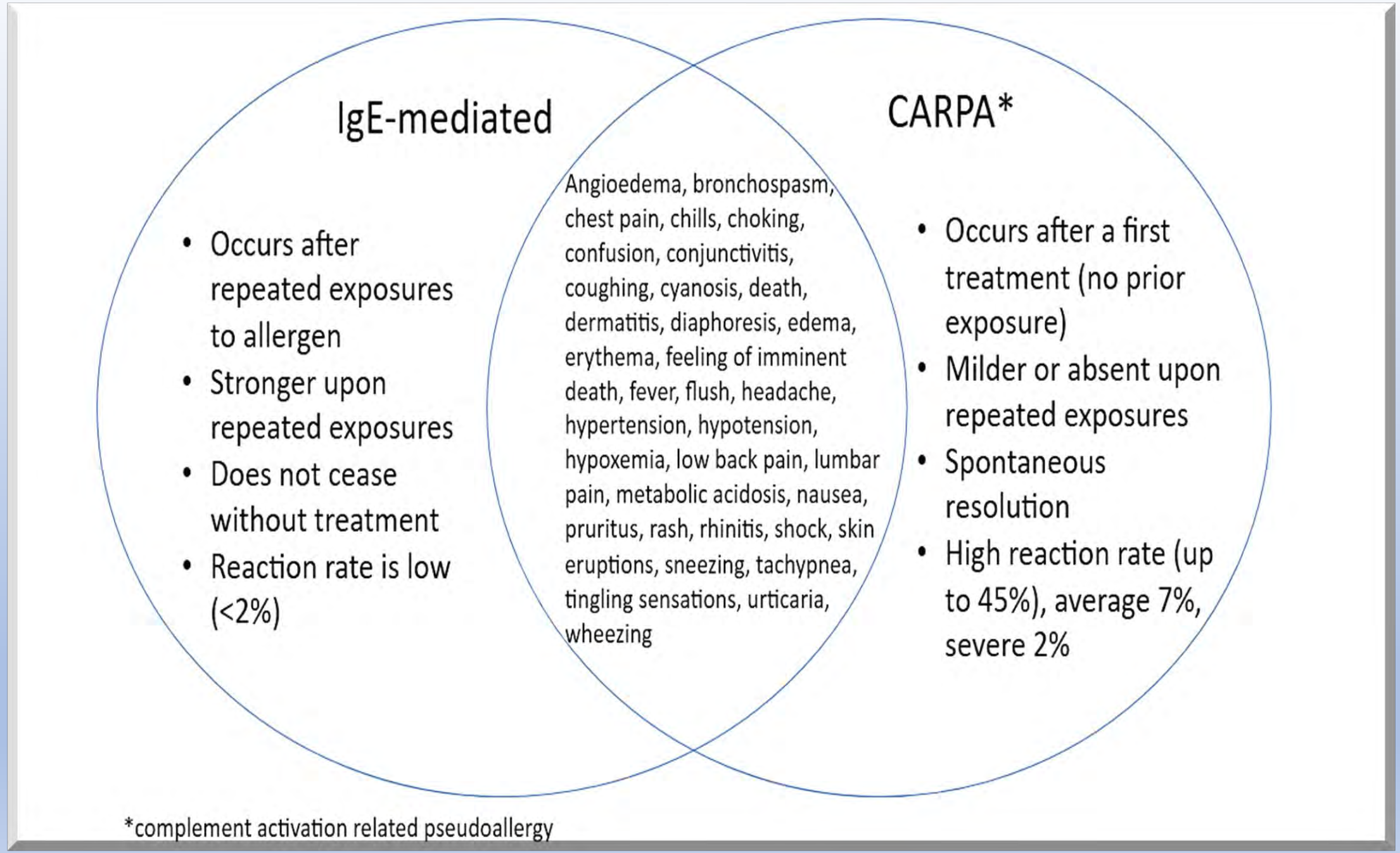
https://vaccinesafety.edu/components-excipients.htm





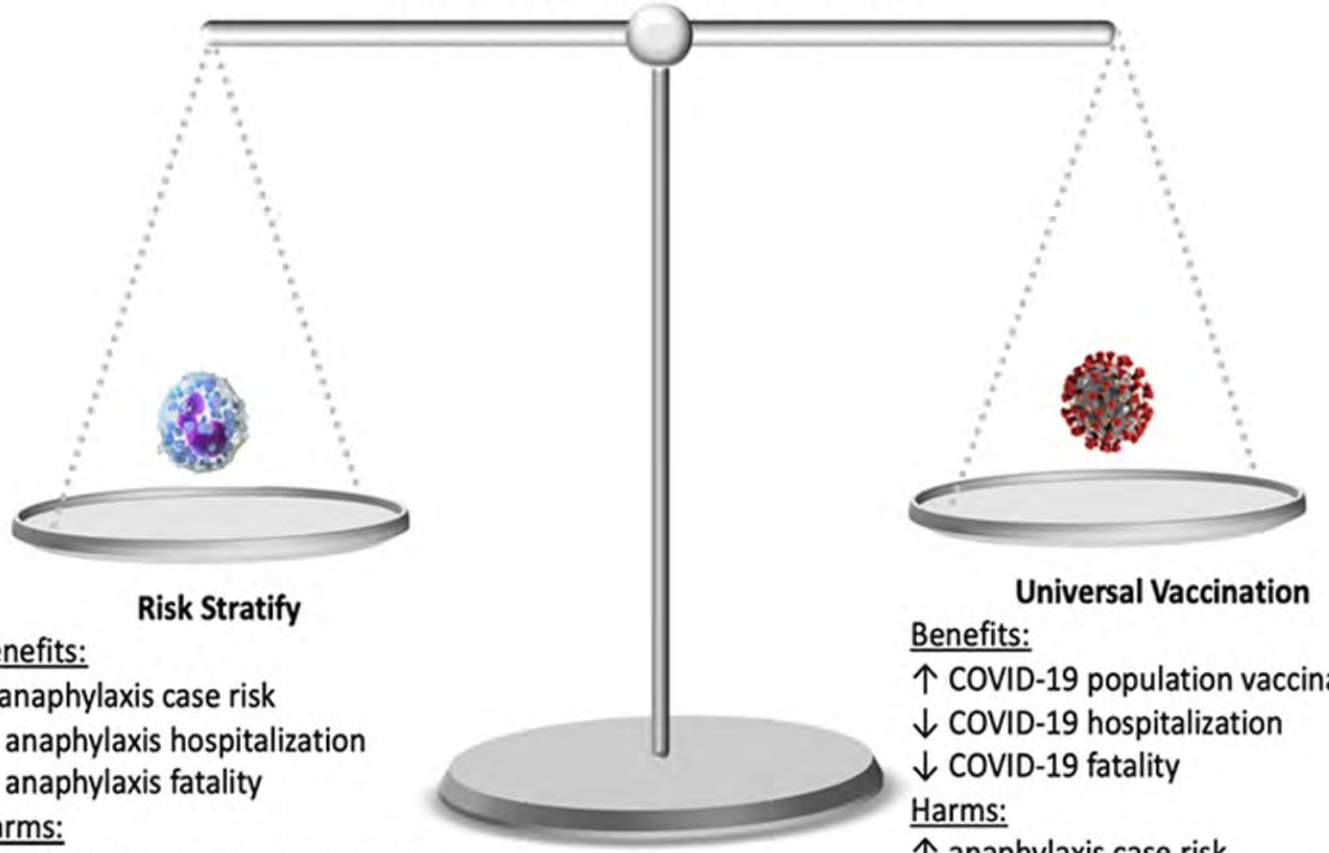
Mast cells have a broad set of TLR molecules, thus can recognize and bind bacterial, viral, and fungal PAMPs as well as various endogenous molecules generated in response to infection.

Sandig, H., & Bulfone-Paus, S. (2012). TLR signaling in mast cells: common and unique features. *Frontiers in immunology*, *3*, 185.


IgE-mediated
• Occurs after repeated exposures to allergen
• Stronger upon repeated exposures
• Does not cease without treatment
• Reaction rate is low (<2%)
Angioedema, bronchospasm, chest pain, chills, choking, confusion, conjunctivitis, coughing, cyanosis, death, dermatitis, diaphoresis, edema, erythema, feeling of imminent death, fever, flush, headache, hypertension, hypotension, hypoxemia, low back pain, lumbar pain, metabolic acidosis, nausea, pruritus, rash, rhinitis, shock, skin eruptions, sneezing, tachypnea, tingling sensations, urticaria, wheezing
CARPA*
• Occurs after a first treatment (no prior exposure)
• Milder or absent upon repeated exposures
• Spontaneous resolution
• High reaction rate (up to 45%), average 7%, severe 2%
*complement activation related pseudoallergy

Vaccination & Anaphylaxis Risk

Risk Stratify or Universal Vaccination?



Risk Stratify

Benefits:
- ↓anaphylaxis case risk
- ↓ anaphylaxis hospitalization
- ↓ anaphylaxis fatality

Harms:
- ↓ COVID-19 population vaccination
- ↑ COVID-19 hospitalization
- ↑ COVID-19 fatality

Universal Vaccination

Benefits:
- ↑ COVID-19 population vaccination
- ↓ COVID-19 hospitalization
- ↓ COVID-19 fatality

Harms:
- ↑ anaphylaxis case risk
- ↑ anaphylaxis hospitalization
- ↑ anaphylaxis fatality

Shaker MS, Abrams E, Greenhawt M. Submitted for Publication. 2021

Contraindications and precautions for COVID-19 vaccines

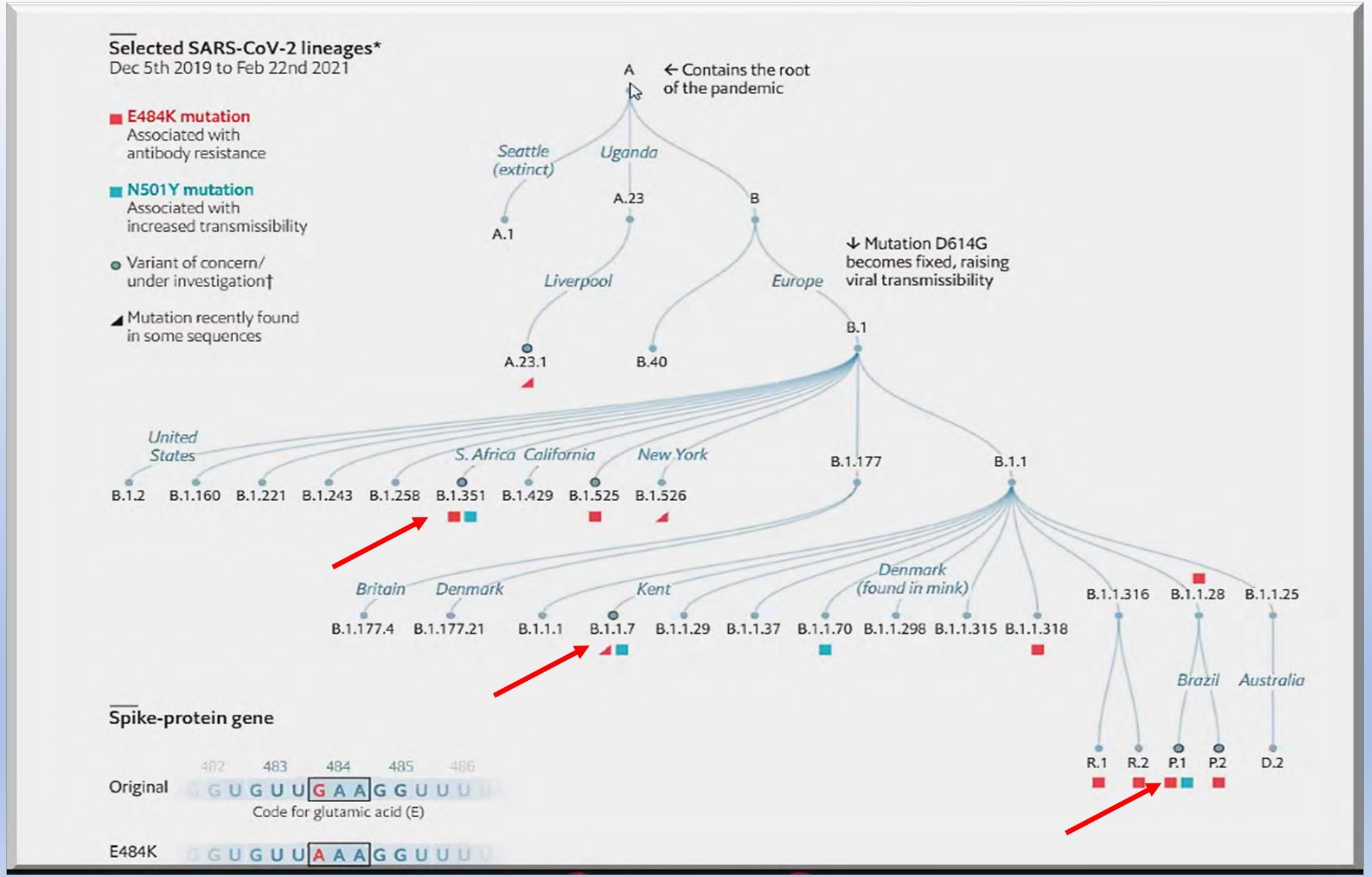
CONTRAINDICATION TO VACCINATION	PRECAUTION TO VACCINATION	MAY PROCEED WITH VACCINATION
History of the following: • Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to component of the vaccine† • Immediate allergic reaction* of any severity after a previous dose or known (diagnosed) allergy to a component of the vaccine† Actions: • Do not vaccinate. • Consider referral to allergist-immunologist. • Consider other vaccine alternative.†	Among persons without a contraindication, a history of: • Any immediate allergic reaction* to other vaccines or injectable therapies‡ Actions: • Risk assessment • Consider referral to allergist-immunologist • 30-minute observation period if vaccinated	Among persons without a contraindication or precaution, a history of: • Allergy to oral medications (including the oral equivalent of an injectable medication) • History of food, pet, insect, venom, environmental, latex, etc., allergies • Family history of allergies Actions: • 30-minute observation period: persons with history of anaphylaxis (due to any cause) • 15-minute observation period: all other persons

Interchangeability of COVID-19 vaccine products

- Any COVID-19 vaccine can be used when indicated; no product preference

- COVID-19 vaccines are **not** interchangeable
  - Safety and efficacy of a mixed series has not been evaluated

- If first dose of mRNA COVID-19 vaccine was received but patient unable to compete series with same or different mRNA vaccine
  - Single dose of Janssen COVID-19 vaccine may be administered at minimum interval of 28 days from mRNA dose*
  - Considered to have received valid, single-dose Janssen vaccination, not mixed vaccination series (mRNA/viral vector)


Selected SARS-CoV-2 lineages*
Dec 5th 2019 to Feb 22nd 2021
E484K mutation
Associated with antibody resistance
N501Y mutation
Associated with increased transmissibility
Variant of concern/ under investigation†
Mutation recently found in some sequences
A
← Contains the root of the pandemic
Seattle (extinct)
Uganda
A.1
A.23
B
Liverpool
Europe
A.23.1
B.40
↓ Mutation D614G becomes fixed, raising viral transmissibility
B.1
United States
S. Africa
California
New York
B.1.2
B.1.160
B.1.221
B.1.243
B.1.258
B.1.351
B.1.429
B.1.525
B.1.526
B.1.177
B.1.1
Britain
Denmark
Kent
Denmark (found in mink)
B.1.177.4
B.1.177.21
B.1.1.1
B.1.1.7
B.1.1.29
B.1.1.37
B.1.1.70
B.1.1.298
B.1.1.315
B.1.1.318
B.1.1.316
B.1.1.28
B.1.1.25
Brazil
Australia
R.1
R.2
P.1
P.2
D.2
Spike-protein gene
482 483 484 485 486
Original
G U G U U G A A G G U U U U
Code for glutamic acid (E)
E484K
G U G U U A A A G G U U U U

COVID-19 Variant Strains

Alaska – Feb. 24, 2021 Situation Report

Alaska Sequencing Consortium - Situation Report 24 February 2021

Genomic Sequencing Effort in Alaska

	Samples	Change from Previous Report
Genomes released on GISAID	403	+120
Genomes with sufficient phylogenetic information	389	+125

Variants of Concern Identified in Alaska

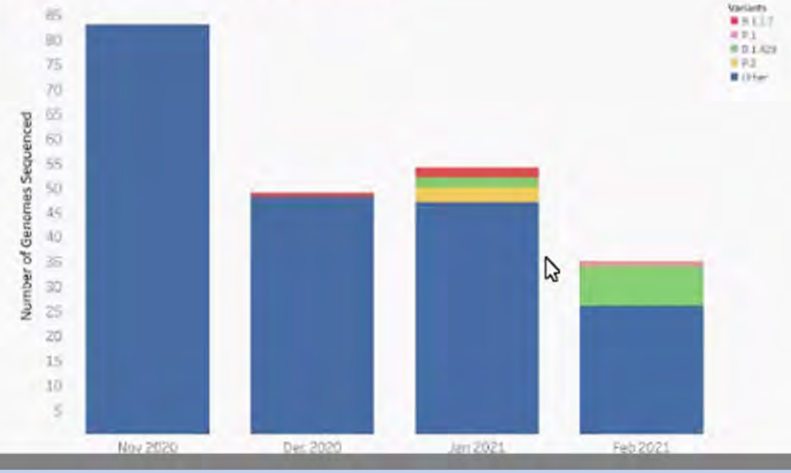
Lineage	Found	First Identified in Alaska
B.1.1.7	2	20 December 2020
B.1.351	0	Not detected
P.1	1	8 February 2021

B.1.1.7→2
B.1.35→ 0
P.1→ 1

Variants of Interest Identified in Alaska

Lineage	Found	First Identified in Alaska
B.1.429	10	8 January 2021
P.2	3	27 January 2021

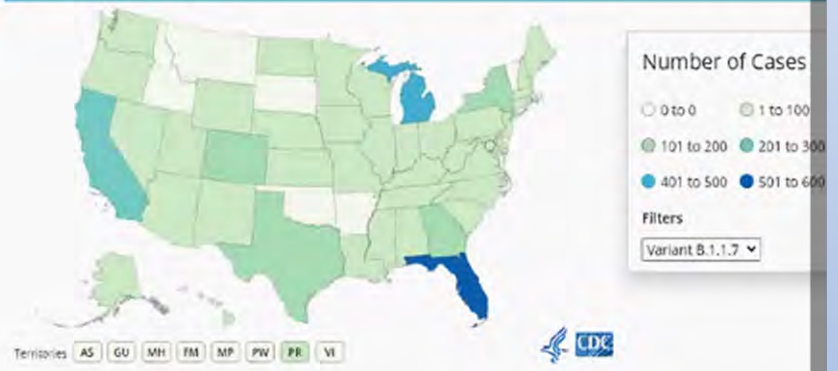
Recent Variants Identified in Alaska



U.S. – March 2, 2021

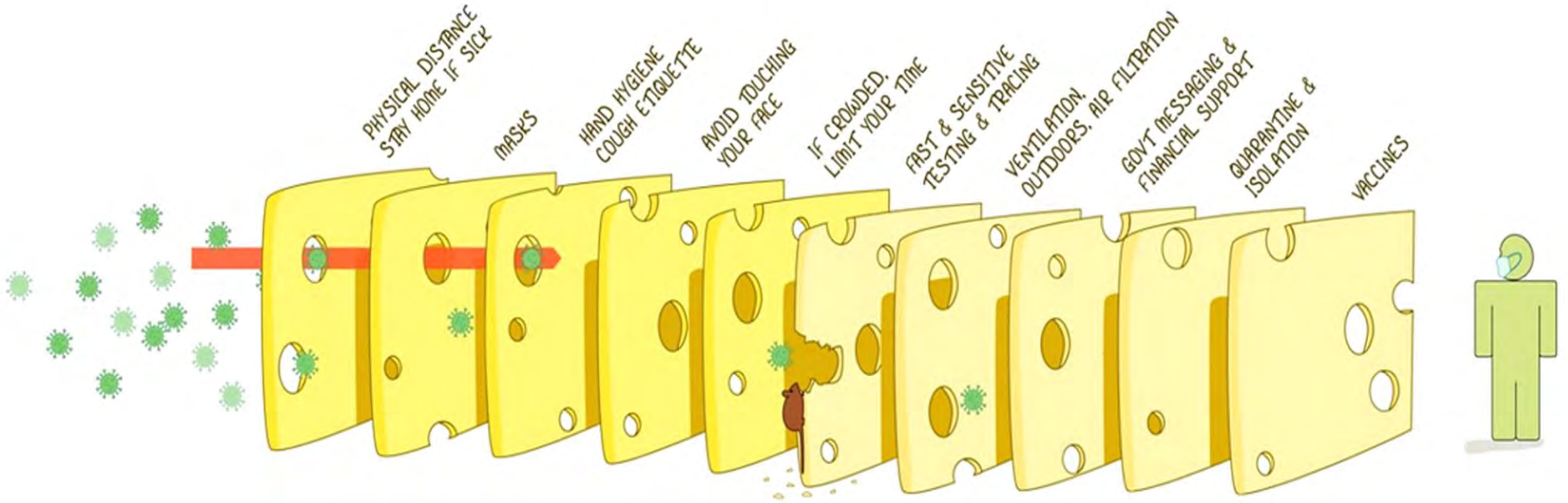
Variant	Reported Cases in US	Number of Jurisdictions Reporting
B.1.1.7	2506	46
B.1.351	65	17
P.1	10	5

Emerging Variant Cases in the United States*†



The Swiss Cheese Respiratory Virus Pandemic Defence

Recognising that no single intervention is perfect at preventing spread

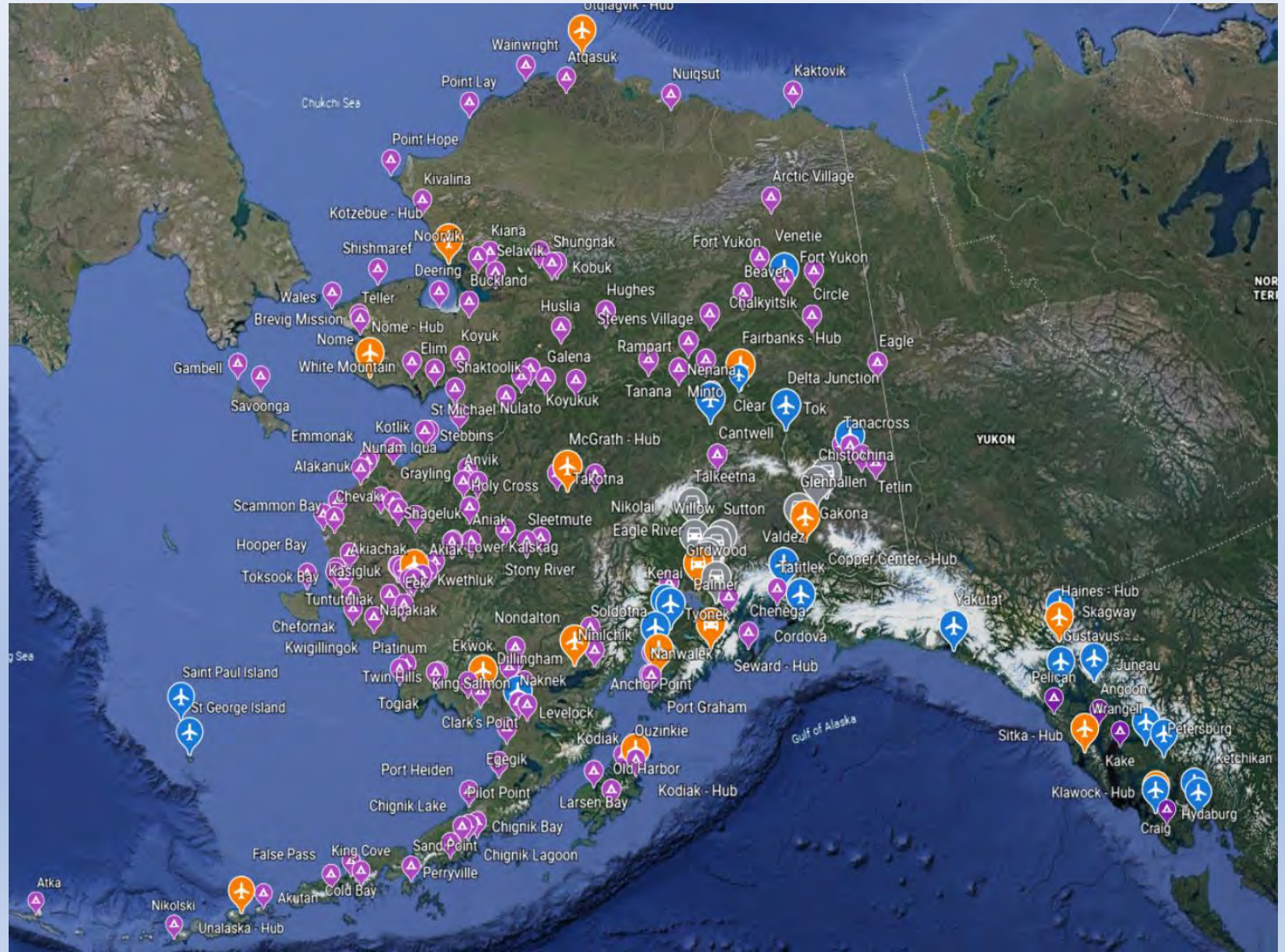


Each intervention (layer) has imperfections (holes).
Multiple layers improve success.

Ian M Mackay
virologydownunder.com

With thanks to Jody Lanard, Katherine Arden & the Uni of Qld
Based on the Swiss cheese model of accident causation, by James T Reason, 1990
version 3.0
update 24oct2020

Shipping the vaccine within Alaska



Questions ?