COVID-19 vaccine efficacy studies: challenges and successes

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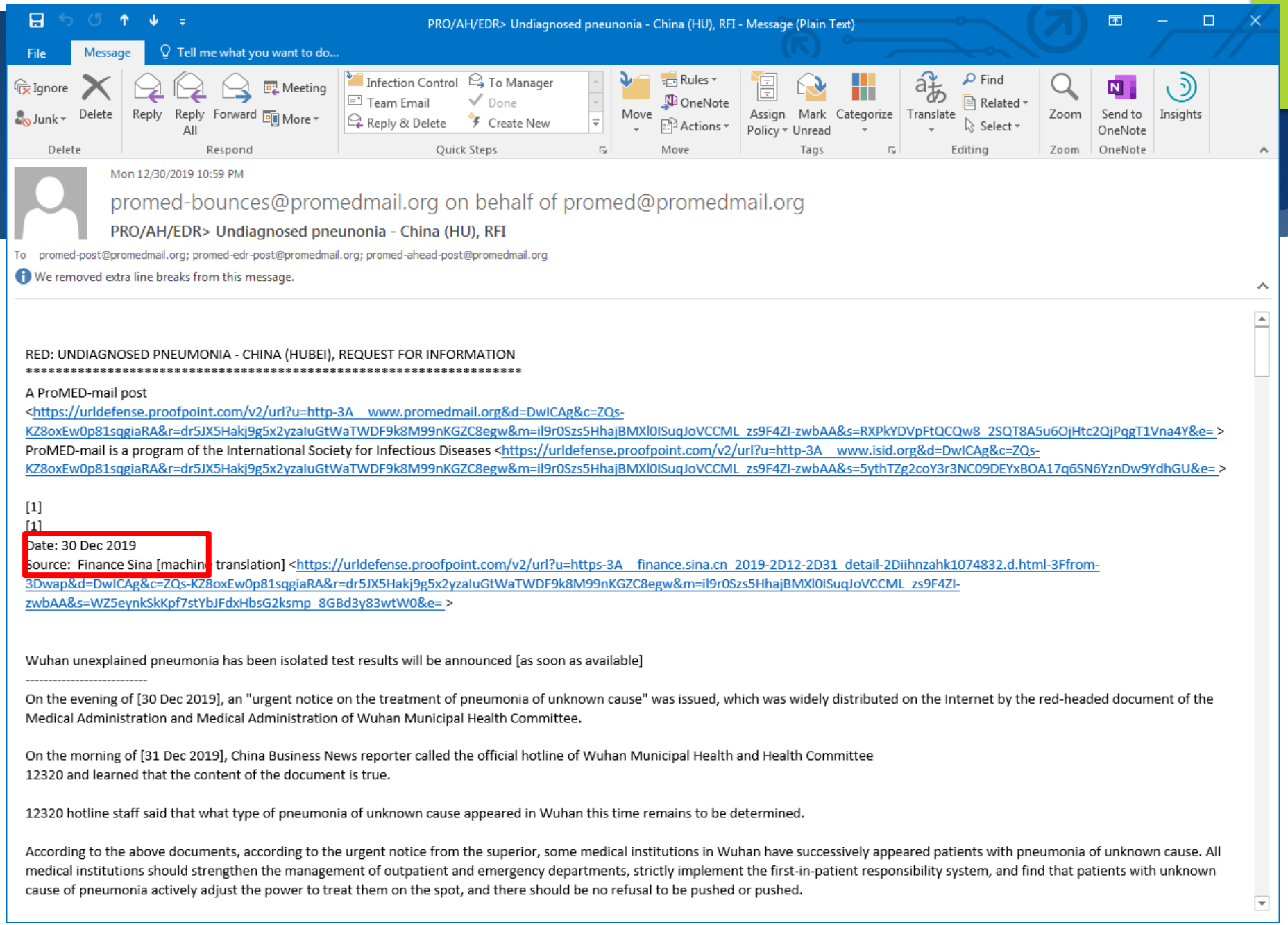
Disclosures

- I received funding from the NIH for the design and implementation of the Phase 3 clinical trial evaluating mRNA-1273 COVID-19 vaccine and the implementation of the SARS-CoV-2 rS with Matrix-M1™ COVID-19 vaccine



PRO/AH/EDR> Undiagnosed pneunonia - China (HU), RFI - Message (Plain Text)

File Message Tell me what you want to do...

Ignore Junk Delete | Reply Reply All Forward Meeting More | Infection Control Team Email Reply & Delete To Manager Done Create New | Move Rules OneNote Actions | Assign Policy Mark Unread Categorize | Translate Find Related Select | Zoom | Send to OneNote | Insights

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Mon 12/30/2019 10:59 PM

promed-bounces@promedmail.org on behalf of promed@promedmail.org

PRO/AH/EDR> Undiagnosed pneunonia - China (HU), RFI

To promed-post@promedmail.org; promed-edr-post@promedmail.org; promed-ahead-post@promedmail.org

We removed extra line breaks from this message.

RED: UNDIAGNOSED PNEUMONIA - CHINA (HUBEI), REQUEST FOR INFORMATION
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A ProMED-mail post
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ProMED-mail is a program of the International Society for Infectious Diseases <https://urldefense.proofpoint.com/v2/url?u=http-3A__www.isid.org&d=DwICAg&c=ZQs-KZ8oxEw0p81sqgiaRA&r=dr5JX5Hakj9g5x2yzaIuGtWaTWDF9k8M99nKGZC8egw&m=il9r0Szs5HhajBMXl0ISuqJoVCCML_zs9F4ZI-zwbAA&s=5ythTZg2coY3r3NC09DEYxBOA17q6SN6YznDw9YdhGU&e= >

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Date: 30 Dec 2019
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Wuhan unexplained pneumonia has been isolated test results will be announced [as soon as available]

On the evening of [30 Dec 2019], an "urgent notice on the treatment of pneumonia of unknown cause" was issued, which was widely distributed on the Internet by the red-headed document of the Medical Administration and Medical Administration of Wuhan Municipal Health Committee.

On the morning of [31 Dec 2019], China Business News reporter called the official hotline of Wuhan Municipal Health and Health Committee 12320 and learned that the content of the document is true.

12320 hotline staff said that what type of pneumonia of unknown cause appeared in Wuhan this time remains to be determined.

According to the above documents, according to the urgent notice from the superior, some medical institutions in Wuhan have successively appeared patients with pneumonia of unknown cause. All medical institutions should strengthen the management of outpatient and emergency departments, strictly implement the first-in-patient responsibility system, and find that patients with unknown cause of pneumonia actively adjust the power to treat them on the spot, and there should be no refusal to be pushed or pushed.

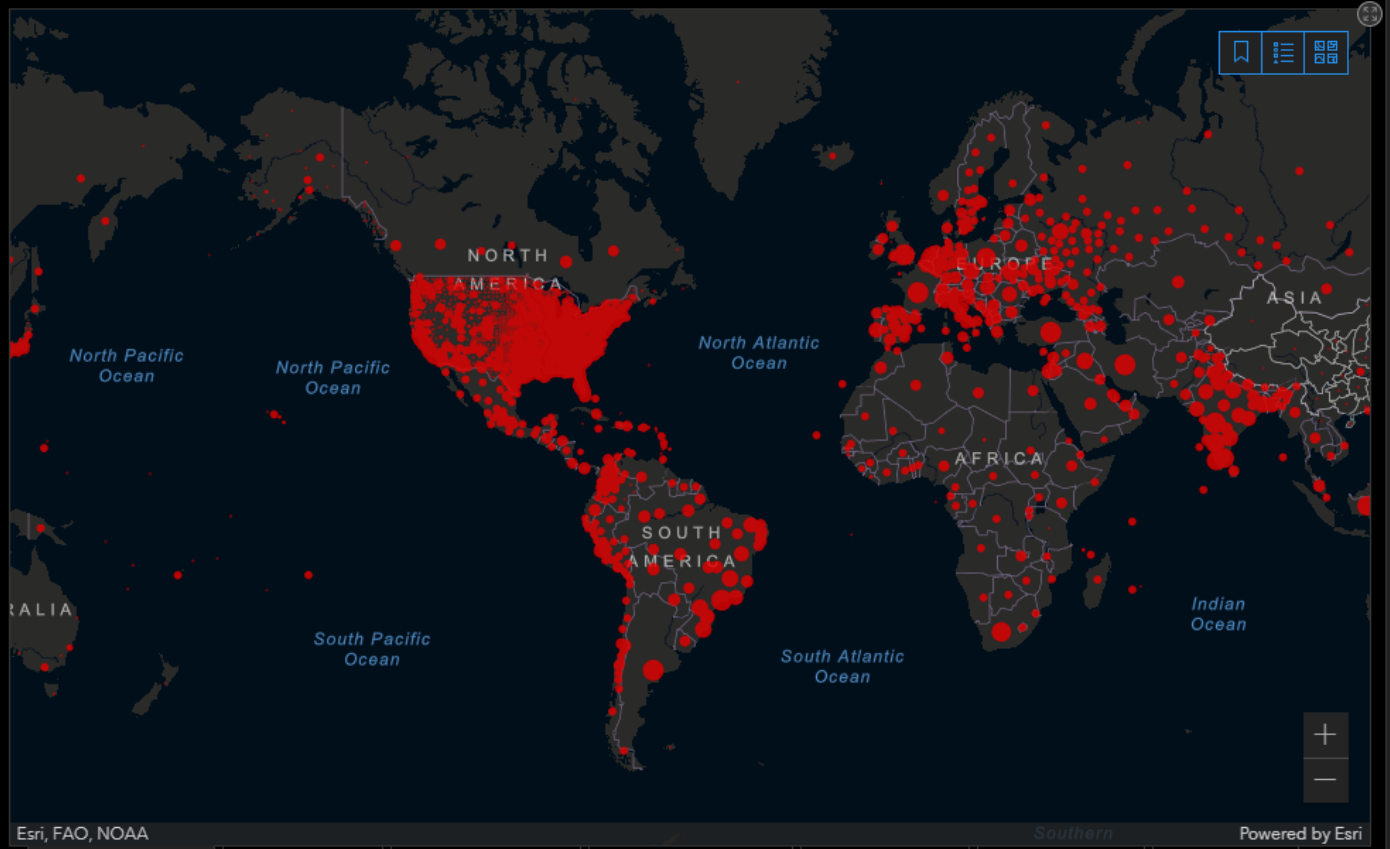
COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)

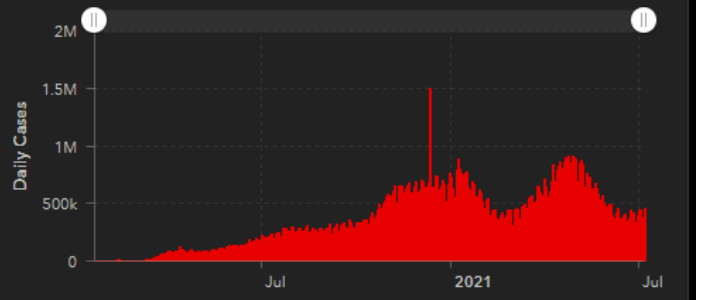
Last Updated at (M/D/YYYY)
7/7/2021, 1:21 PM

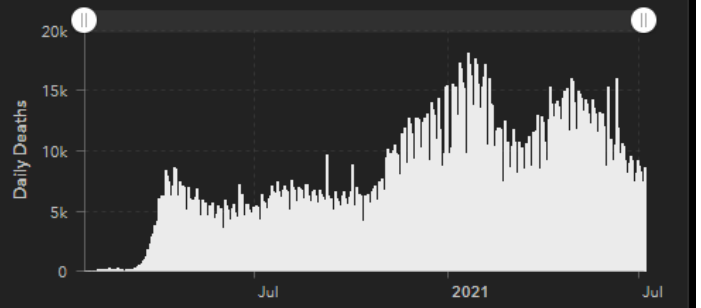
Cases	Deaths	Vaccine Doses Administered
184,852,183	3,996,863	3,319,048,509

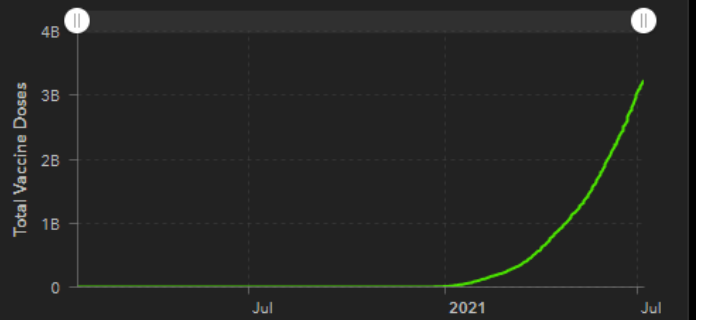
Cases and Deaths by Country/Region/Sovereignty

	Cases	Deaths
US	33,758,605	606,086
India	30,663,665	404,211
Brazil	18,855,015	526,892
France	5,856,680	111,448
Russia	5,614,540	137,718
Turkey	5,454,763	49,996
United Kingdom	5,007,964	128,565
Argentina	4,574,340	96,983
Colombia	4,402,582	110,019
Italy	4,265,714	127,718
Spain	3,897,996	80,969









Admin0 | Admin1 | Admin2

Cumulative Cases | Incidence Rate | Case-Fatality Ratio | Global Vaccinations | US Vaccinations | US Testing Rate | Terms of Use

A vaccine is/was needed

SARS-CoV-2 Vaccine Development

Any lessons from seasonal coronaviruses?

	Avian-Infectious-Bronchitis-like		Rhinoviruses	
	229–E	B814*	Type 2 (HGP or PK)	DC*
No. of volunteers inoculated	26	75	213	251
No. getting colds	13 (50%)	34 (45%)	78 (37%)	77 (31%)
Incubation period (days):				
Mean	3·3	3·2	2·1	2·1
Range	2–4	2–5	1–5	1–4
Duration (days):				
Mean	7	6	9	10
Range	3–18	2–17	3–19	2–26
Maximum No. of handkerchiefs used daily:				
Mean	23	21	14	18
Range	8–105	8–120	3–38	3–60
Malaise (%)	46	47	28	25
Headache (%)	85	53	56	56
Chill (%)	31	18	28	15
Pyrexia (%)	23	21	14	18
Mucopurulent nasal discharge (%)	0	62	83	80
Sore throat (%)	54	79	87	73
Cough (%)	31	44	68	56
No. of volunteers with colds of indicated severity:				
Mild	10 (77%)	24 (71%)	63 (80%)	36 (47%)
Moderate	2 (15%)	7 (20%)	12 (15%)	28 (36%)
Severe	1 (8%)	3 (9%)	4 (5%)	13 (17%)

TABLE IV.—*Relation Between Antibody Titre and the Response to Inoculation*

Titre of Neutralizing Antibody in Serum Before Inoculation	No. of Volunteers in Indicated Category Who			Total
	Excreted Virus	Developed Colds	Developed Rising Antibody Titres	
⩽5	7	6	4	8
5–	4	3	2	6
10–	6	3	1	8
40–160	1	1	0	4

Bradburne et al. BMJ 1967

SARS-CoV-2 Vaccine Development

Any lessons from seasonal coronaviruses?

- Previous infections partially protective against disease
- Previous infections not protective against re-infection
- Neutralizing Abs wane over time

COVID-19 vaccine development
Which Antigen? Which Platform?

- First generation COVID-19 vaccine: most are S-based, some are whole inactivated virus
- WHO: 105 vaccines in clinical testing and 184 vaccines are in pre-clinical testing
- In the US: Six constructs reached Phase 3 clinical testing.

m-RNA based

↓

Pfizer
Moderna

Adenovirus vector

↓

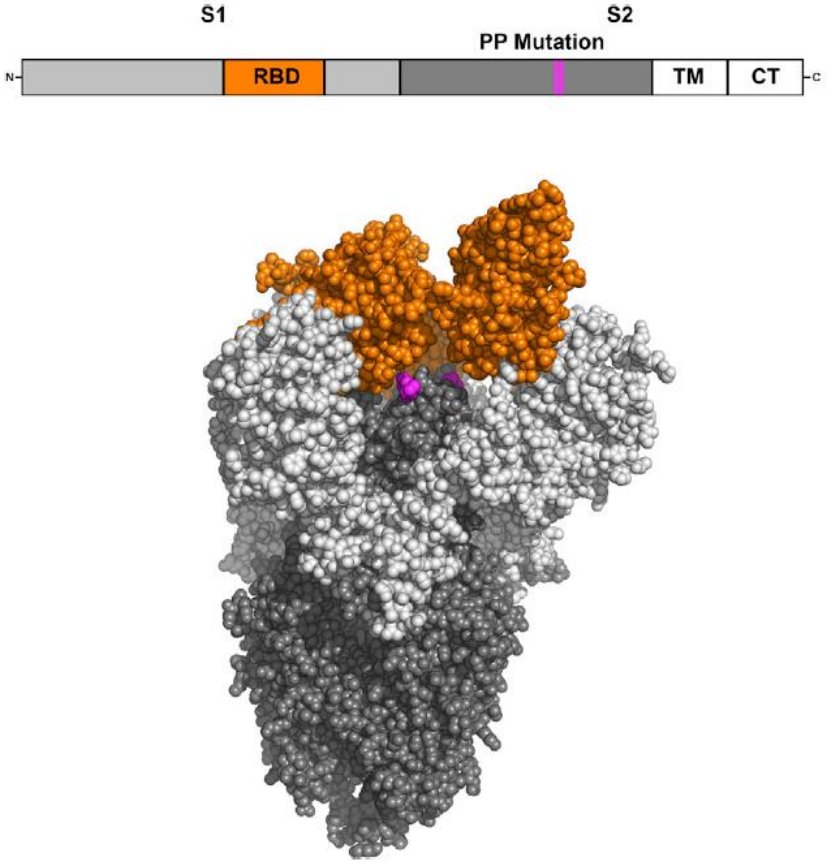
Janssen
AstraZeneca

S-Protein+adjuvant

↓

Novavax
Sanofi
Pasteur/GSK

COVID-19 vaccine development
Why the S protein?



- SARS-CoV: S protein is primary target of neutralizing Ab
- Passive transfer and vaccines against S: Protect mice from SARS-CoV challenge
- Passive transfer and vaccine against N protein: not protective and ? enhancing disease
- Similar findings with MERS CoV
- SARS-CoV-2 Pandemic: Humans develop robust Neut Ab against S and specifically its Receptor Binding Domain (RBD)

Wrapp et al, Science 2020

Covid-19 vaccine development Funding Source

Accelerated research and development

Time

January 13, 2020
Sequence for mRNA-1273 against the novel coronavirus finalized

Total of 63 days from sequence selection to first human dosing

March 16, 2020
First participant in NIH-led Phase 1 study was dosed

April 16, 2020
Award from U.S. government agency BARDA for up to $483 million to accelerate development

April 27, 2020
IND submitted to US FDA for Phase 2 study

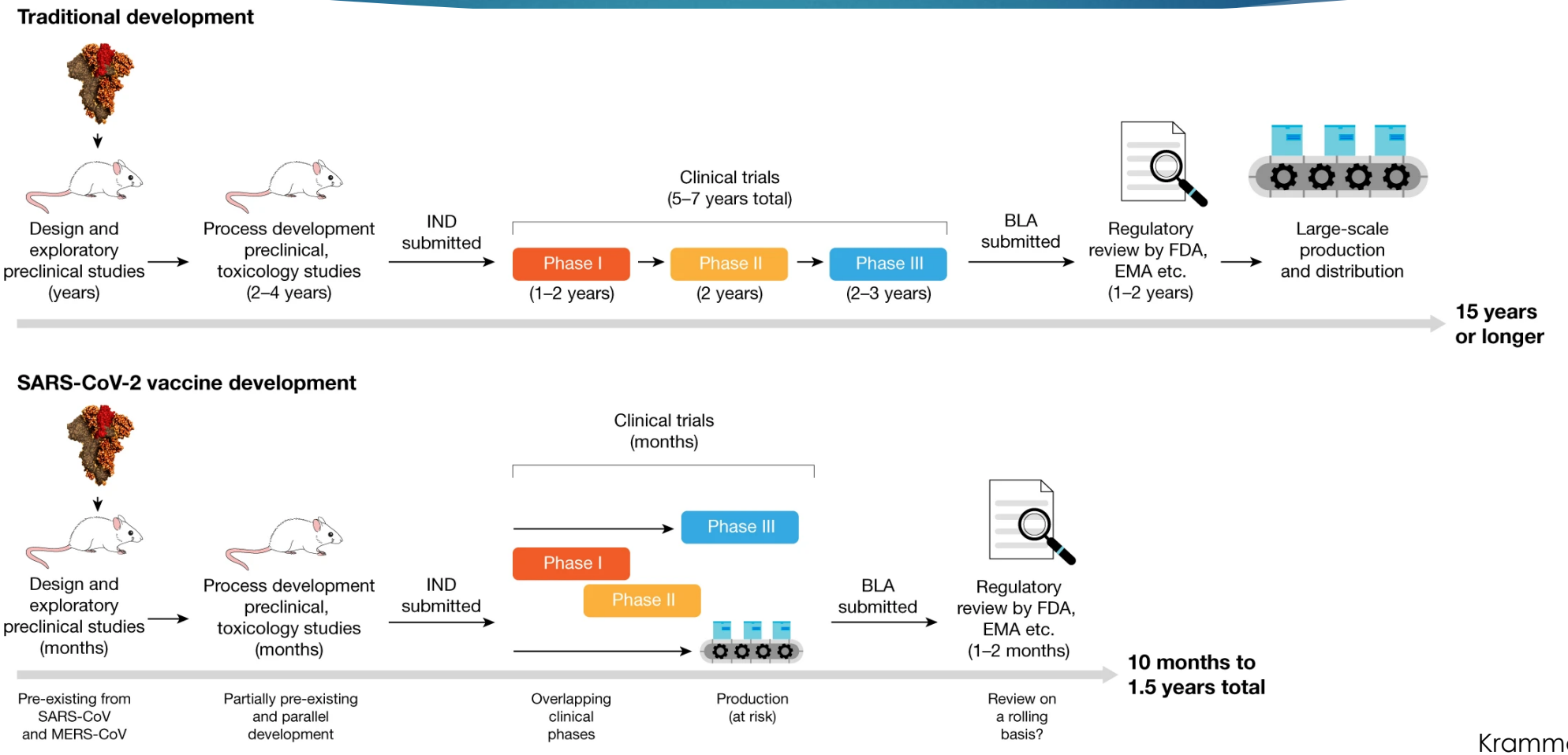
May 1, 2020
Collaboration announced with Lonza Ltd to manufacture mRNA-1273

May 18, 2020
Positive interim Phase 1 data announced

May 29, 2020
First participants dosed in Phase 2 study

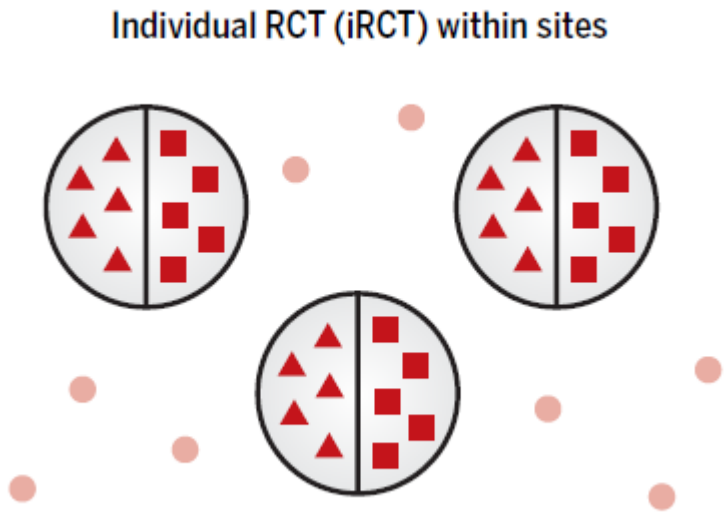
July 2020
Phase 3 start

Vaccine Clinical Trial Phases



Krammer F, Nature 2020

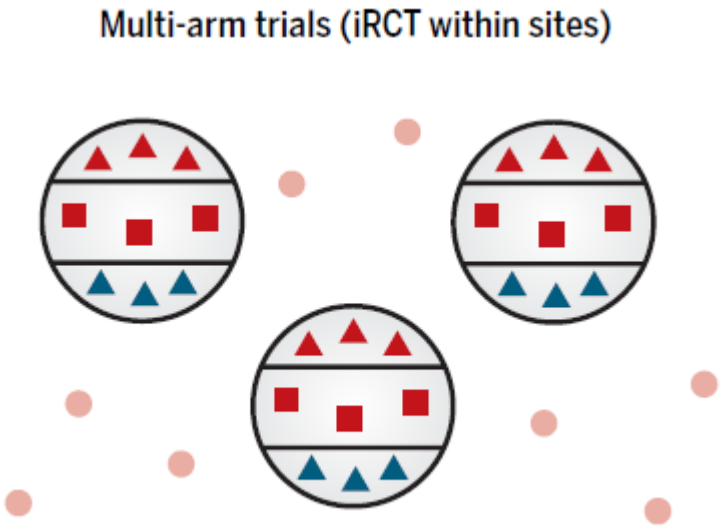
Phase 3 clinical Trial Study Design: What are the options?



- Statistically efficient
- Randomization at the subject level within site
- Of value when there is heterogeneity in disease incidence
- If the vaccine has indirect effect then there maybe reduction in disease incidence in comparator arm: *impact efficacy assessment*

Dean et al. Sci Transl Med 2019

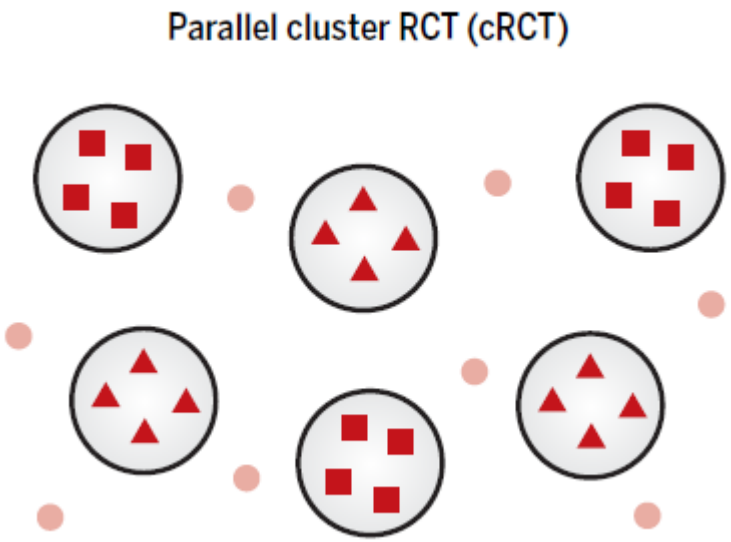
Phase 3 clinical Trial Study Design: What are the options?



- Efficient when more than one candidate is to be tested simultaneously
- Resource-saving approach
- Potential to diversify the vaccine candidates reaching the market
- Minimizes the effects of temporal trends in disease epidemiology on vaccine efficacy estimates.

Dean et al. Sci Transl Med 2019

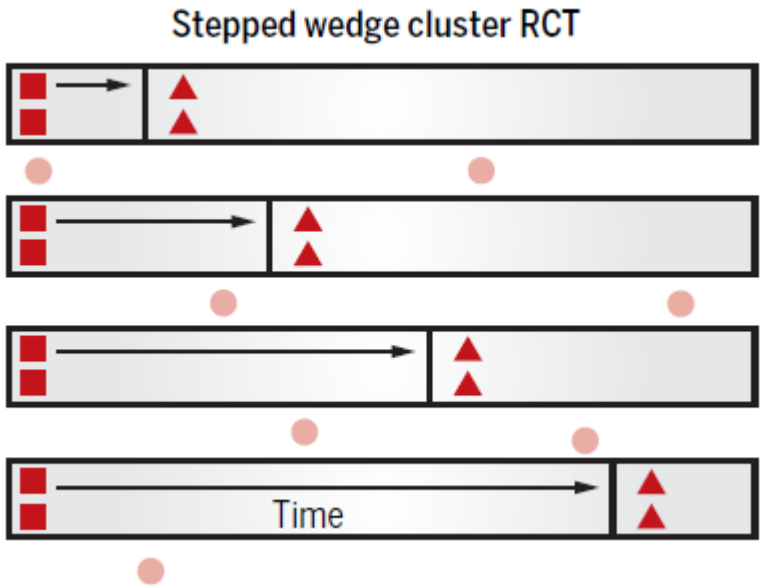
Phase 3 clinical Trial Study Design: What are the options?



- All subjects in a cluster receive the same intervention.
- Randomization occurs at the unit level: household, high-risk communities, town, transmission network (ring)
- Allows measurement of total (direct and indirect) effect.
- Less efficient than iRCT

Dean et al. Sci Transl Med 2019

Phase 3 clinical Trial Study Design: What are the options?



- The vaccine is given to all subjects in a randomized order.
- Complex planning and analysis
- All subjects and units are to be enrolled/randomized before vaccination.
- Slow to perform

Dean et al. Sci Transl Med 2019

Phase 3 clinical Trial Study Design: What are the options?

- Six constructs were moving to Phase 3 clinical testing in Apr-May.
- A multi-arm RCT is most efficient at testing the VE.
- It would require collaboration and planning between various pharmaceuticals.
- There was variability in the readiness of some of the constructs to launch within a similar timeframe.

iRCT

Phase 3 clinical Trial Primary Endpoint: What are the options?

- Infection
- Disease
- Severe Disease

A study with a primary endpoint that captures all the endpoints of public health importance is likely not feasible

Phase 3 clinical Trial Infection as endpoint

- Detecting infection with and without symptoms requires frequent sampling and surveillance.
- Seroconversion as an endpoint: can be a proxy for infection. Requires validated tests.
- Many vaccines of public health importance do not prevent infection but prevent disease: setting up the vaccine for failure and not helping public health

Phase 3 clinical Trial
Severe disease as endpoint

- Severe disease is the most clinically meaningful outcome to prevent
- Lower frequency indicates the need for even larger sample sizes
- For most vaccines, preventing mild disease also prevents severe disease
- Inactivated measles, Formalin inactivated RSV vaccine resulted in worsening/severe disease

At a minimum severe disease should be assessed.

Phase 3 clinical Trial Symptomatic COVID-19 as endpoint

- Virologically confirmed symptomatic disease: represents a disease outcome of interest
- precedent with other viruses.
- Improved feasibility: sample size consideration.

- Another good compromise: Burden of disease as endpoint (weighing severe cases more than mild-moderate cases)

Phase 3 clinical Trial
Symptomatic COVID-19 as endpoint

- Vaccine efficacy of mRNA-1273 to prevent the first occurrence of COVID-19 starting 14 days after the second dose of study product.

COVID-19

TWO of: Fever (≥ 38°C), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s)

OR

ONE of : cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia;

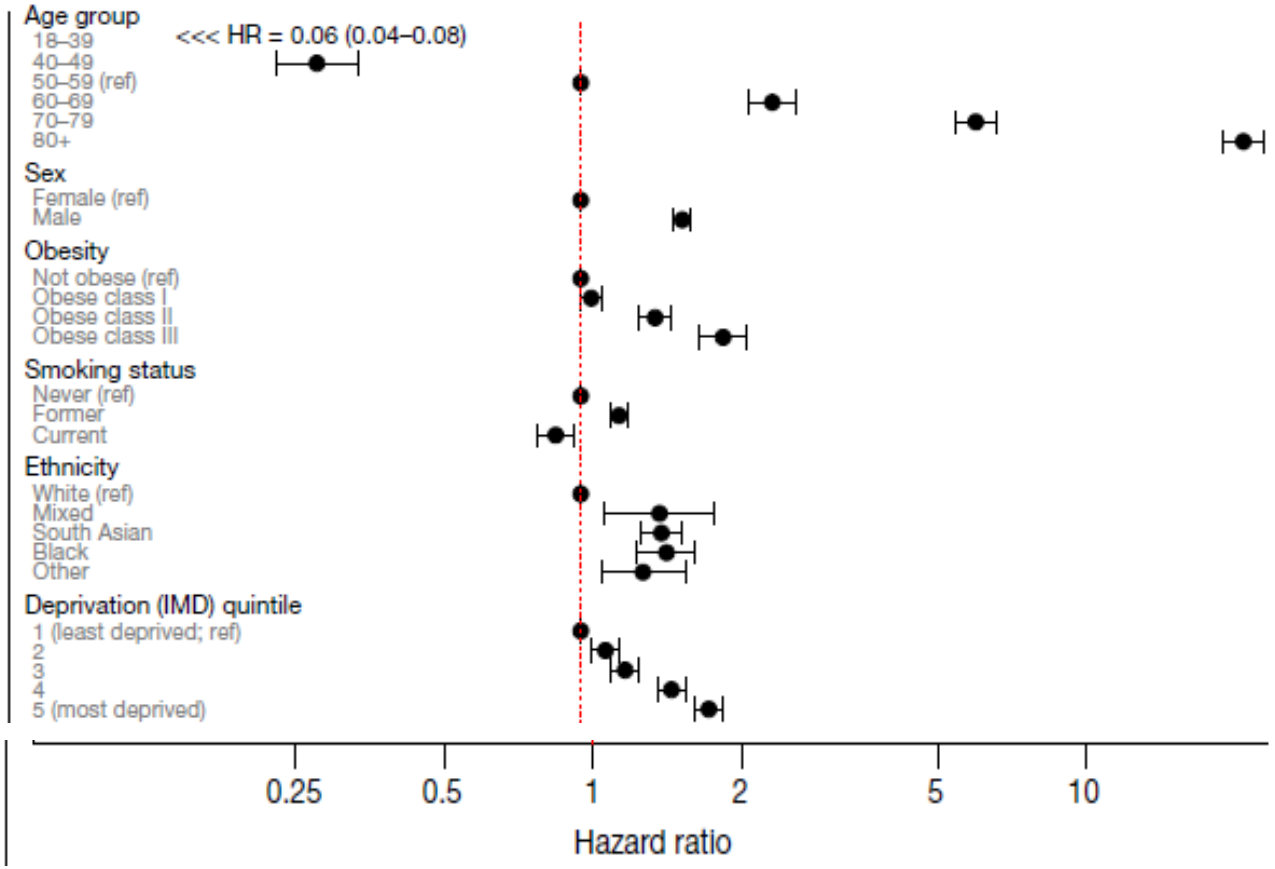
AND

Respiratory Sample positive for SARS-CoV-2 by RT-PCR

Phase 3 COVID-19 vaccine efficacy study mRNA-1273-P301

- Clinical trial principle: the study population should represent the vaccine target population
- Problem: clinical trial participation is traditionally predominantly Caucasians.
- COVID-19 disproportionately affects minorities: higher incidence and higher mortality.

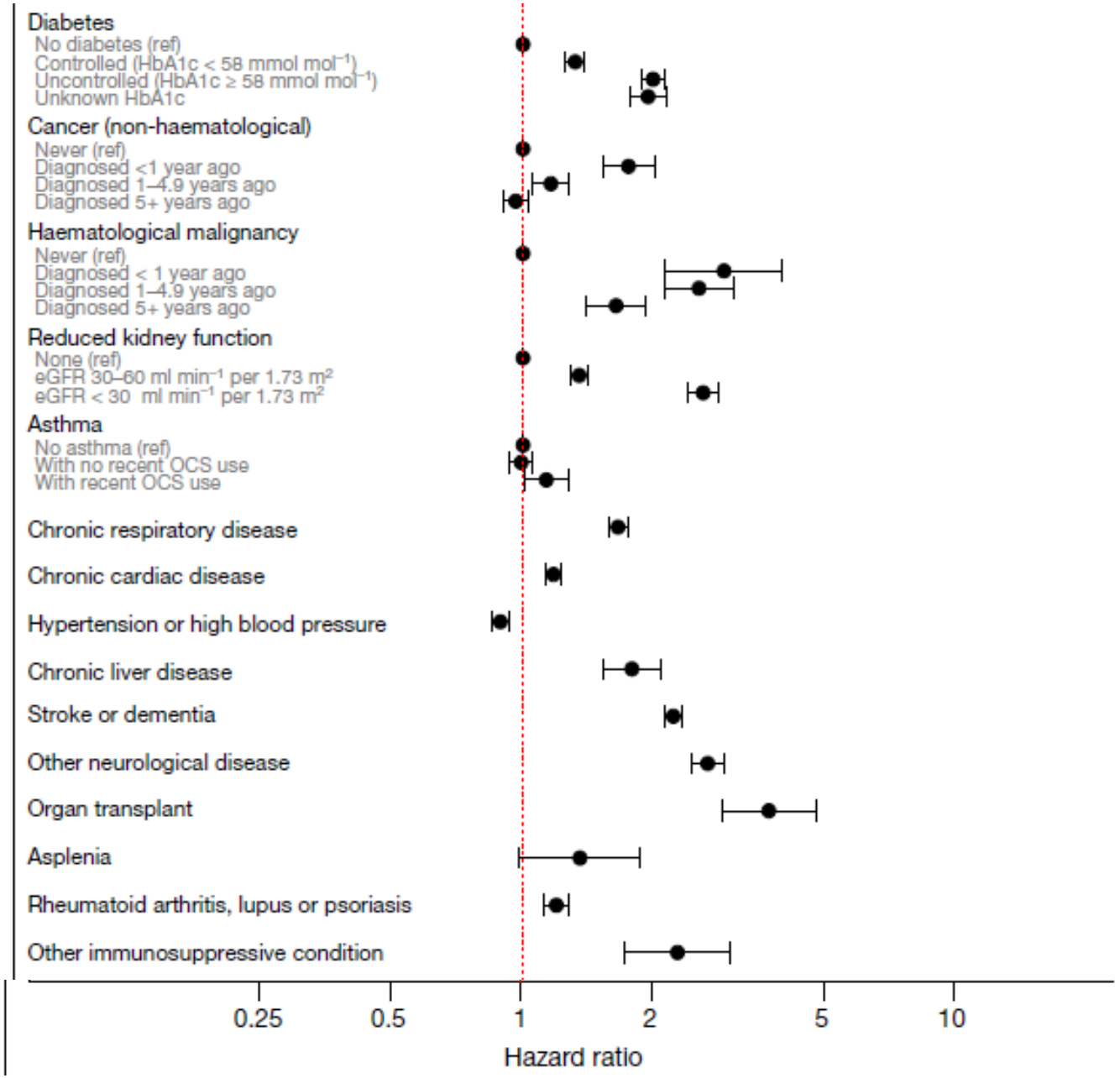
COVID-19: Mortality by key demographics



Williamson EJ, et al. Nature 2020

COVID-19: Race/Ethnicity differences in mortality

www.cdc.gov



Mortality by COVID-19 by underlying co-morbidity

Williamson EJ, et al. Nature 2020

Phase 3 clinical Trial
Symptomatic COVID-19 as endpoint

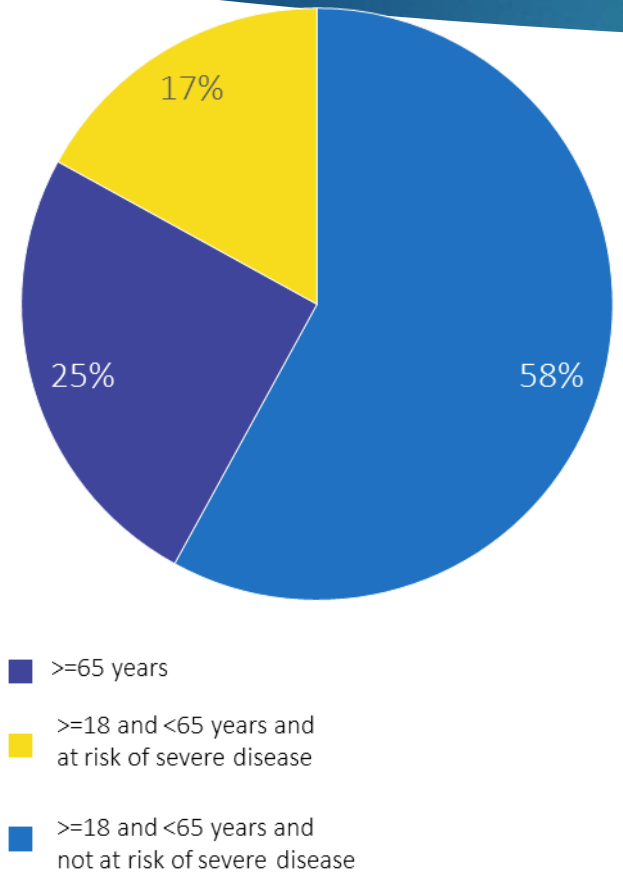
- Stratification: usually pre-specified to account for variables that affect the outcome in a predictable fashion

AGE<65

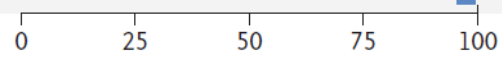
AGE of 65 and older

Presence of severe disease risk criteria

mRNA1273 Efficacy in older persons and persons with co-morbidities



Subgroup	Placebo (N=14,073)	mRNA-1273 (N=14,134)	Vaccine Efficacy (95% CI)
	no. of events/total no.		
All patients	185/14,073	11/14,134	94.1 (89.3–96.8)
Age			
≥18 to <65 yr	156/10,521	7/10,551	95.6 (90.6–97.9)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Age, risk for severe Covid-19			
18 to <65 yr, not at risk	121/8403	5/8396	95.9 (90.0–98.3)
18 to <65 yr, at risk	35/2118	2/2155	94.4 (76.9–98.7)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Sex			
Male	87/7462	4/7366	95.4 (87.4–98.3)
Female	98/6611	7/6768	93.1 (85.2–96.8)
At risk for severe Covid-19			
Yes	43/3167	4/3206	90.9 (74.7–96.7)
No	142/10,906	7/10,928	95.1 (89.6–97.7)
Race and ethnic group			
White	144/8916	10/9023	93.2 (87.1–96.4)
Communities of color	41/5132	1/5088	97.5 (82.2–99.7)

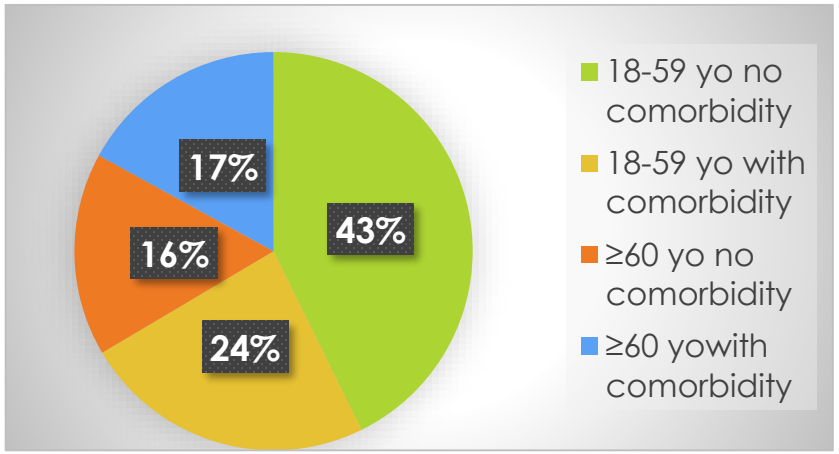


Vaccine Efficacy of mRNA-1273 to Prevent Covid-19 in Subgroups

Baden LR, et al. N Engl J Med 2

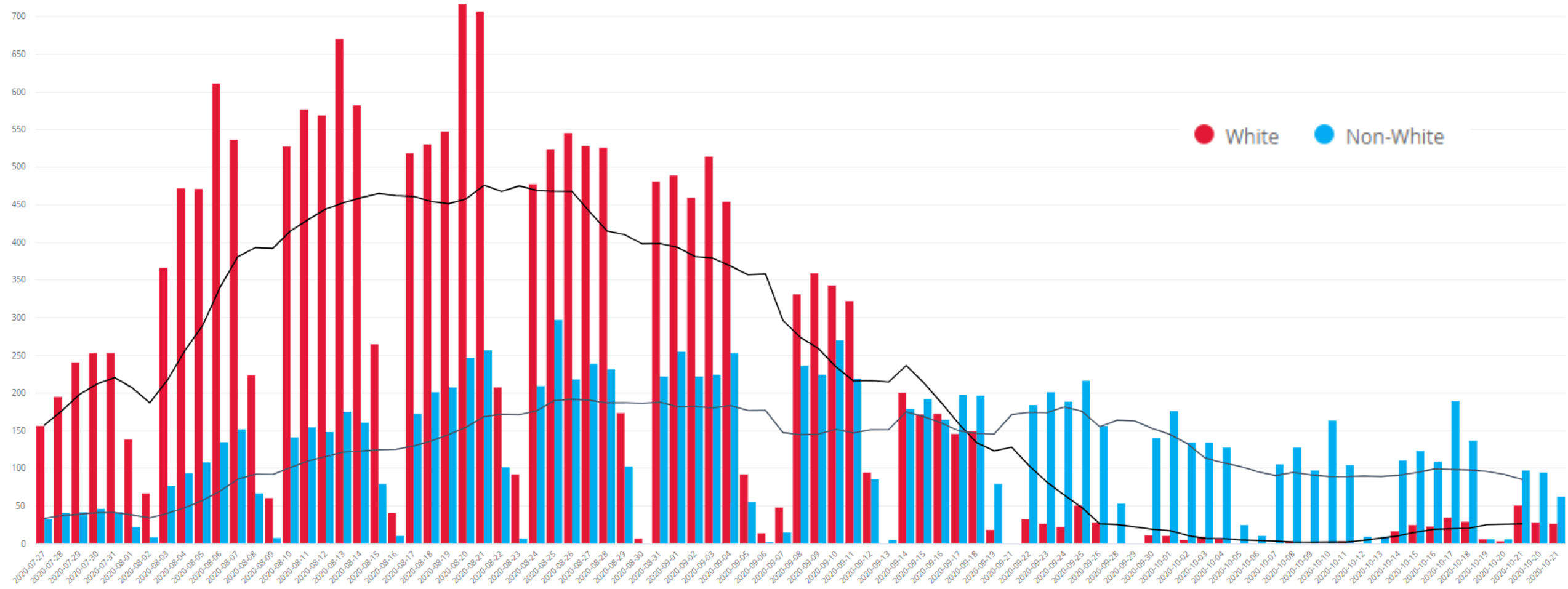
Janssen Vaccine Efficacy by age and co-morbidity

	Onset at Least 14 Days			Onset at Least 28 Days		
	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)	Ad26.COV2.S Cases (N) Person-yrs	Placebo Cases (N) Person-yrs	VE%[a] (95% CI)
Age group and comorbidity presence						
18-59, no	89 (8346) 1433.5	258 (8411) 1428.2	65.6% (56.1, 73.3)	58 (8267) 1428.2	180 (8254) 1418.3	68.0% (56.8, 76.6)
18-59, yes	48 (4404) 671.5	131 (4371) 661.0	63.9% (49.4, 74.7)	29 (4350) 668.1	79 (4273) 654.8	64.0% (44.3, 77.3)
≥60, no	14 (3391) 541.6	57 (3335) 530.0	76.0% (56.3, 87.6)	11 (3355) 539.0	39 (3298) 527.6	72.4% (45.0, 87.3)
≥60, yes	22 (3373) 467.4	63 (3427) 469.9	64.9% (42.2, 79.4)	15 (3334) 464.9	26 (3353) 465.2	42.3% (-13.1, 71.6)



VRBPAC FDA briefing book, 26FEB2021

Enrollment Diversity Over Time



How Did we turn the tide?

- Commitment from Operation Warp Speed leadership and beyond
- DSMB: Diversity as a primordial study metric
- Mobilization of the CoVPN Operations:

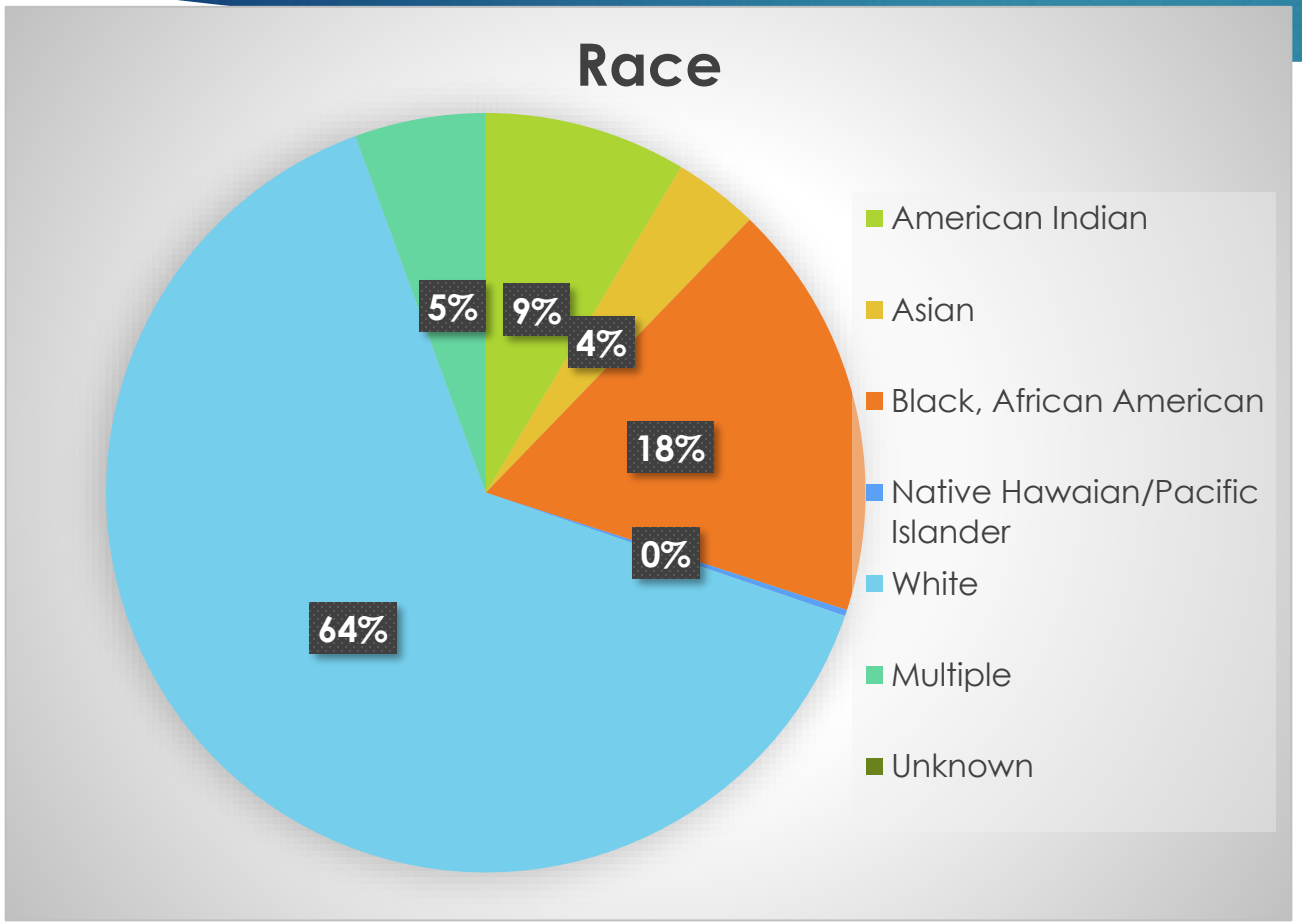
1. CoVPN Registry: rollout to CoVPN and non-COVPN sites
2. Educational and Promotional Material Production

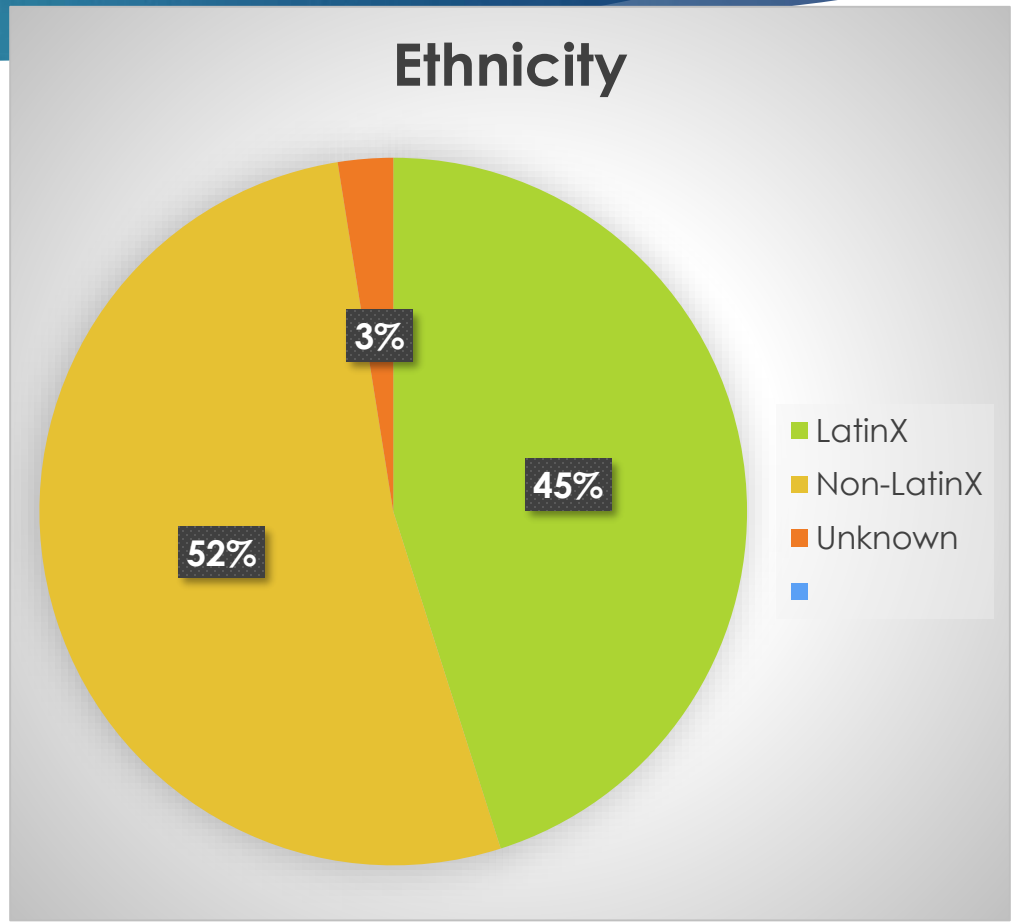
- CoVPN leadership: frequent communications to the sites “ keep the eye on the goal”
- Sponsor buy-in: send directive to slow (or stop) enrollment at sites with high % Caucasian participants

How Did we turn the tide?

- The study sites understood the importance of diversity and got busy and creative:
  1. Increasing utilization of CoVPN registry
  2. Sorting existing registries and prioritizing minorities
  3. Outreach to local communities' leaders: churches, community centers
  4. Outreach to fire department, police department, retail, post office
  5. Establish satellite sites in areas with high prevalence of minorities
  6. Establish flexible clinic hours to accommodate participants' needs
  7. Interviews in local media outlets catering to minorities
  8. Community trust/engagement based on previous experiences

Ethnic/Racial Representation
Janssen Phase 3





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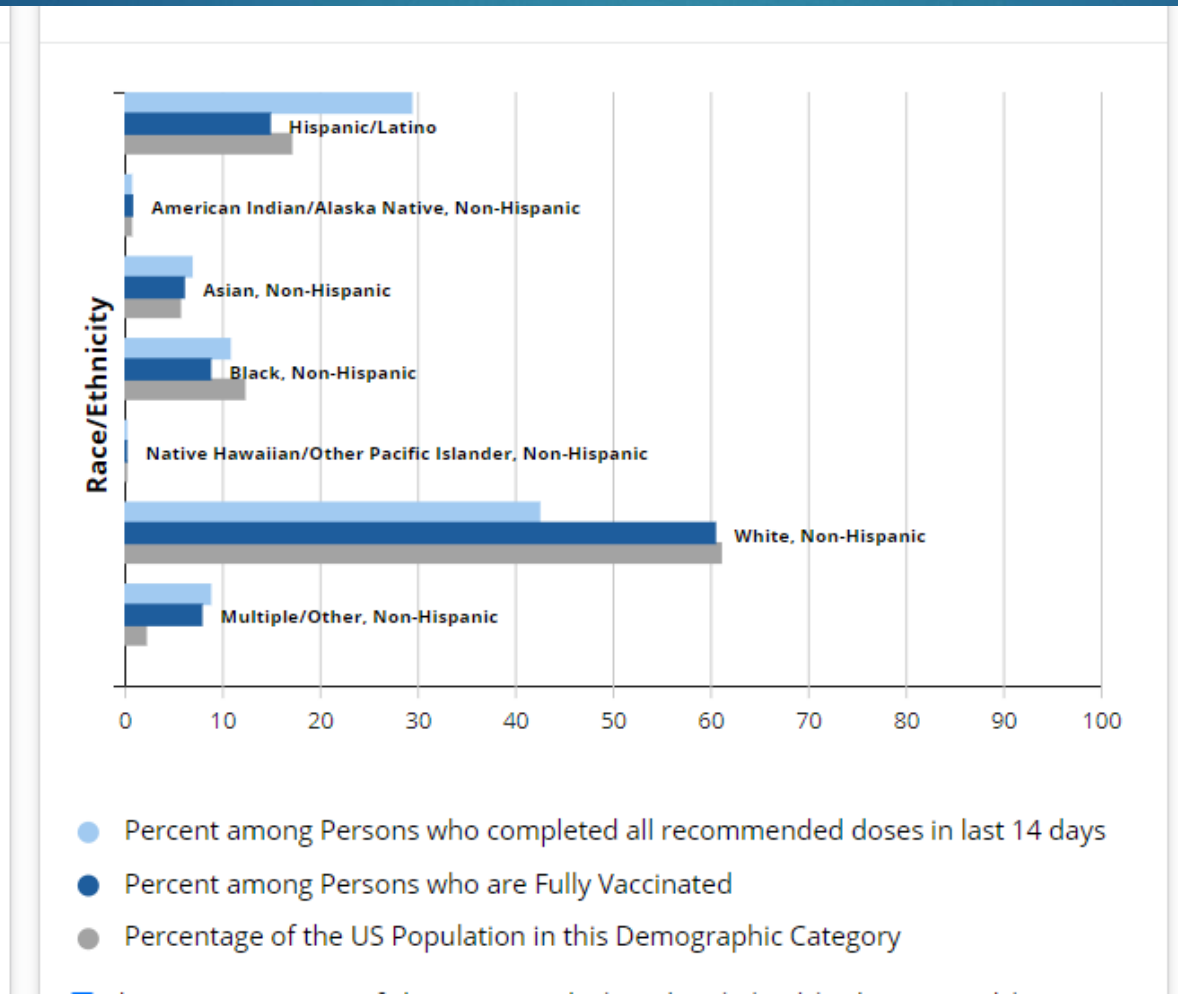
Ethnic/Racial Representation EUA Receipt



www.cdc.gov

CONCLUSIONS

- Representation of populations in whom the vaccine will be used is key:

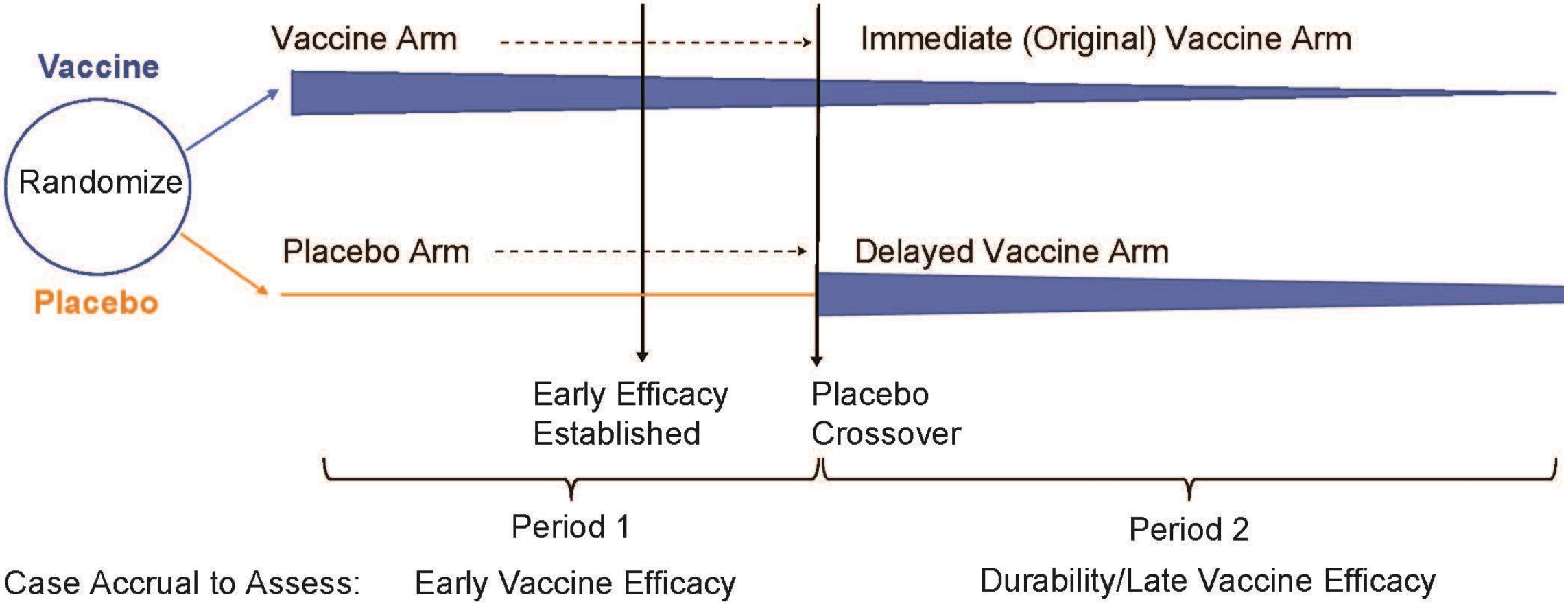
1. Predict responses and efficacy
2. Facilitate uptake
3. Inform policies

- Representation and progress are two different metrics

After EUA:
Questions that remain to be answered

- Need to detect less common or delayed safety events: Will there be enhanced disease severity as antibody levels wane?
- **Study Management: ethics of maintaining the blind**
- Durability of vaccine efficacy, over 2 years
- Correlate of protection
- **Efficacy against emerging strains**
- Is there need for a boost? If so, when?

Moderna Vaccine Study
Placebo Cross Over/unblinded



Follman et al. Ann Intern Med 2021

Randomized Trial of Immediate vs Delayed Vaccination

Placebos Crossover to Vaccine

Randomized to	# cases August-November	# cases December-March	Randomized to
Vaccine	25	60	*Immediate Vaccine*
Placebo	125	30	*Delayed Vaccine*
		150	*Inferred Placebo*
	Vaccine Efficacy 80%		

cases on placebo
cases on vaccine

Based on estimated VE for newly vaccinated of 80%

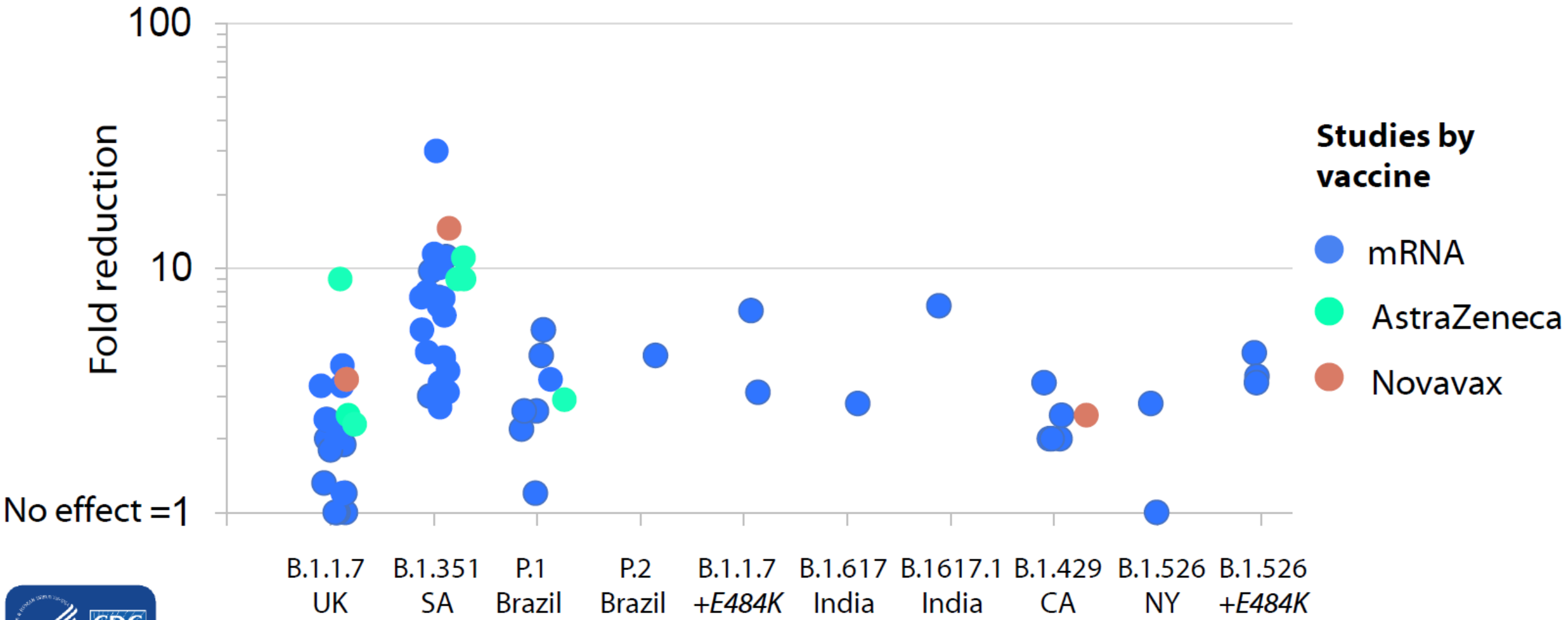
Estimated Vaccine Efficacy in Period 2 = 1 – 60/*150* = 60%

Adapted from Follman D 2021

In come the variants…

Variants of Concern		
Name	**Lineage**	**Location of emergence/prevalence**
Alpha	B.1.1.7	Britain
Beta	B.1.351	South Africa
Gamma	P.1	Brazil
Delta	B.1.617.2	India
Variants of Interest		
Name	**Lineage**	**Location of emergence/prevalence**
Epsilon	B.1.427, B.1.429	California
Zeta	P.2	Brazil
Eta	B.1.525	New York
Theta	P.3	Phillippines
Iota	B.1526	New York
Kappa	B.1.617.1	India

Reduced Neutralization Activity of Vaccine Sera Relative to Wildtype/Dominant Strain, by Study (n=31)



Type of Infection or Disease	PCR-Positive Persons		PCR-Negative Persons		Effectiveness (95% CI)*
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
	number of persons				*percent*
Infection					
PCR-confirmed infection with the B.1.1.7 variant†					
After one dose	892	18,075	1241	17,726	29.5 (22.9–35.5)
≥14 days after second dose	50	16,354	465	15,939	89.5 (85.9–92.3)
PCR-confirmed infection with the B.1.351 variant‡					
After one dose	1329	20,177	1580	19,926	16.9 (10.4–23.0)
≥14 days after second dose	179	19,396	698	18,877	75.0 (70.5–78.9)
Disease§					
Severe, critical, or fatal disease caused by the B.1.1.7 variant					
After one dose	30	468	61	437	54.1 (26.1–71.9)
≥14 days after second dose	0	401	20	381	100.0 (81.7–100.0)
Severe, critical, or fatal disease caused by the B.1.351 variant					
After one dose	45	348	35	358	0.0 (0.0–19.0)
≥14 days after second dose	0	300	14	286	100.0 (73.7–100.0)
Severe, critical, or fatal disease caused by any SARS-CoV-2					
After one dose	139	1,966	220	1,885	39.4 (24.0–51.8)
≥14 days after second dose	3	1,692	109	1,586	97.4 (92.2–99.5)

BnT1262b2 effectiveness against VARIANTS OF INTEREST

Abu Raddad et al. NEJM 2021

Vaccination status	Test negative controls	B.1.1.7 or S-gene target negative			B.1.617.2 or S-gene target positive		
		cases	cases:controls	aVE(%)	cases	cases:controls	aVE(%)
Unvaccinated	58253	4891	0.084	base	695	0.012	base
Any vaccine							
Dose 1	32703	1481	0.045	51.1 (47.3 to 54.7)	279	0.009	33.5 (20.6 to 44.3)
Dose 2	8483	74	0.009	86.8 (83.1 to 89.6)	27	0.003	80.9 (70.7 to 87.6)
BNT162b2							
Dose 1	7036	344	0.049	49.2 (42.6 to 55.0)	49	0.007	33.2 (8.3 to 51.4)
Dose 2	6412	28	0.004	93.4 (90.4 to 95.5)	13	0.002	87.9 (78.2 to 93.2)
ChAdOx1							
Dose 1	25667	1137	0.044	51.4 (47.3 to 55.2)	230	0.009	32.9 (19.3 to 44.3)
Dose 2	2071	46	0.022	66.1 (54.0 to 75.0)	14	0.007	59.8 (28.9 to 77.3)

Effectiveness of BNT1262b2 and ChAdOx1 vaccine against Delta Variant

Bernal et al. medRxiv 2021

Vaccination status	Number of cases		Ratio B.1.617.2 to B.1.1.7	aOR
	B.1.1.7	B.1.617.2		
Unvaccinated	8268	691	0.084	base
Any vaccine				
Dose 1	2237	272	0.122	1.38 (1.10-1.72)
Dose 2	81	25	0.309	1.60 (0.87-2.97)
Dose 1 or 2	2511	322	0.128	1.40 (1.13-1.75)
Vaccine type (dose 1 or 2)				
BNT162b2	720	68	0.094	1.17 (0.82-1.67)
ChAdOx1	1791	254	0.142	1.48 (1.18-1.87)

Odds ratios for detection of B.1.617.2 relative to B.1.1.7 in vaccinated compared to unvaccinated individuals

Bernal et al. medrxiv 2021

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