Identifying A Correlate of Protection for COVID-19

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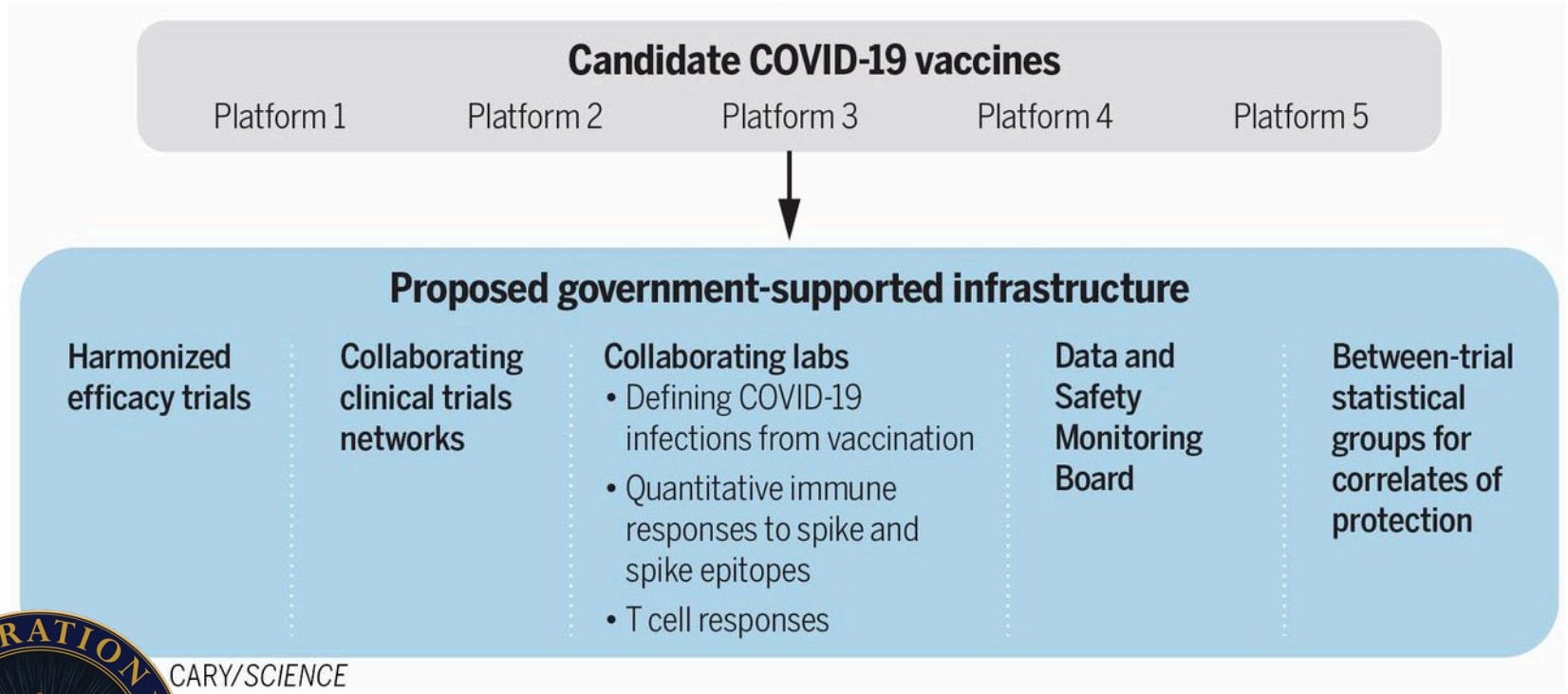
Outline

- Operation Warp Speed
- What/Why of correlates
- Pseudo-Virus neutralization assay
- Illustration and issues with correlates of risk and protection
- Analysis of the Moderna Phase III clinical trial

Operation Warp Speed Overview

- Five randomized, placebo-controlled phase 3 vaccine efficacy trials
- A key objective is harmonized evaluation of immune correlates of protection for the 5 trials



<u>CoVPN Statistical Group</u>
NIAID Biostatistics
Fred Hutch and UW Biostatistics,
Colleagues at other departments (e.g., UW Statistics, Emory Biostatistics)

Corey, Mascola, Fauci, Collins. *Science* (2020)

Correlates for COVID-19: Ecosystem

- Correlates analysis central tenet of USG trials
  - Common assays, endpoints, analysis
- Goal: antibody for immuno-bridging
- Large open access collaboration
  - Synergy & uptake
- Refined/developed new methods

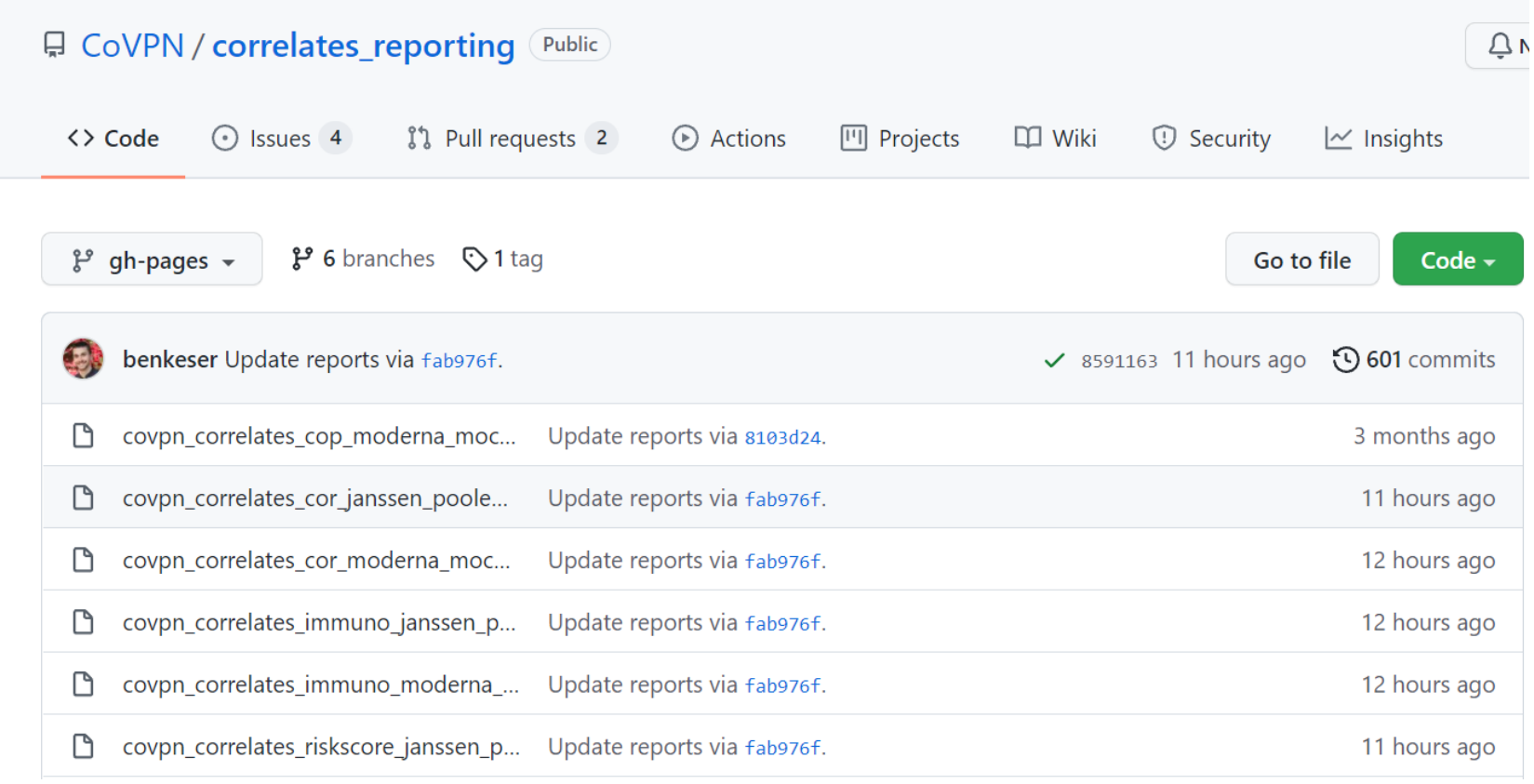
USG COVID-19 Response Team / CoVPN Vaccine Efficacy Trial Immune Correlates Statistical Analysis Plan

USG COVID-19 Response Team / Coronavirus Prevention Network (CoVPN) Biostatistics Team

Peter B. Gilbert[1,2*], Youyi Fong[1,2], David Benkeser[3], Jessica Andriesen[1], Bhavesh Borate[1], Marco Carone[2], Lindsay N. Carpp[1], Iván Díaz[4], Michael P. Fay[5], Andrew Fiore-Gartland[1], Nima S. Hejazi[6], Ying Huang[1,2], Yunda Huang[1], Ollivier Hyrien[1], Holly E. Janes[1,2], Michal Juraska[1], Kendrick Li[2], Alex Luedtke[7], Martha Nason[5], April K. Randhawa[1], Lars van der Laan[6], Brian D. Williamson[1], Wenbo Zhang[2], Dean Follmann[5]

CoVPN Biostatistics Immune Correlates SAP and Open-Source Implementation

- Developed a Statistical Analysis Plan for immune correlates assessment for a prototype phase 3 trial, publicly posted at Figshare with version-controlled updates
  https://figshare.com/articles/online_resource/CoVPN_COVID-19_Vaccine_Efficacy_Trial_Immune_Correlates_SAP/13198595
- SAP implemented with R code on Github



What are Correlates?

- Correlate of Risk : An immune marker that is statistically related to an efficacy endpoint
  - Those with higher influenza antibody titers have lower *Risk of Disease*
  - Don’t need a control group to assess
- Correlate of Protection: An immune marker that is statistically related to vaccine efficacy
  - Those with higher influenza antibody titers have higher *Vaccine Efficacy*
  - Do need a control group to assess

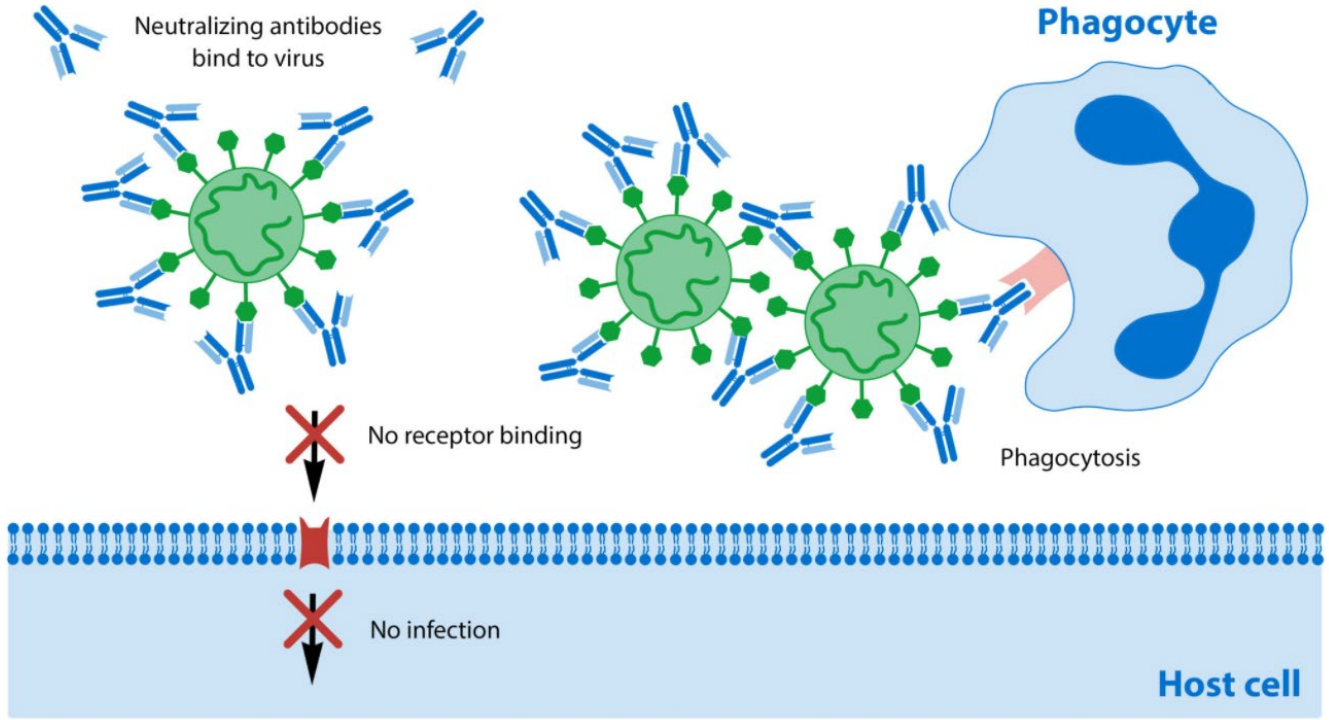
Gilbert & Plotkin CID 2012

Why Correlates of Protection?

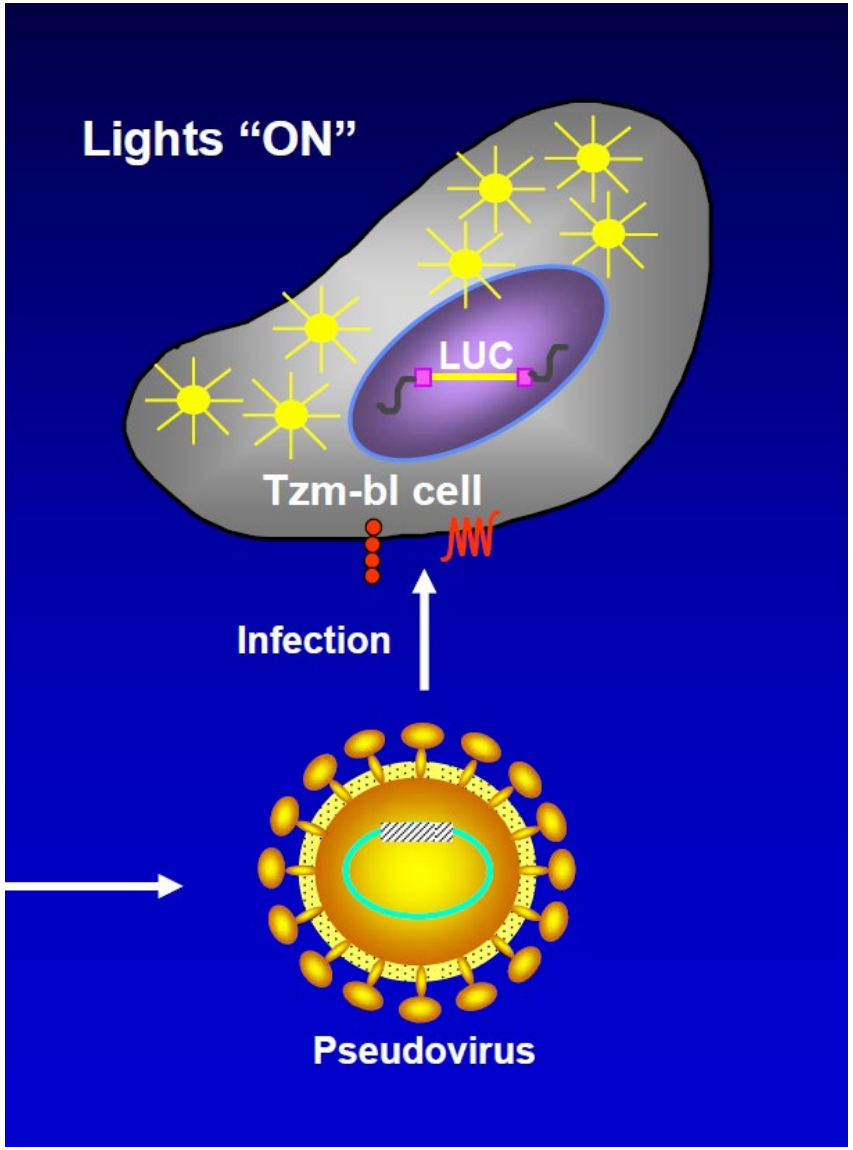
- Understanding of mechanism
- Assess potency of new lots of vaccines
- Bridge to other groups, e.g. kids
- Evaluate variants of concern in the test tube *is vaccine likely to work*?
- Assess impact of modified vaccines with variant inserts
- Possible trigger for boosting
- License modified or totally new vaccines with small immunogenicity studies

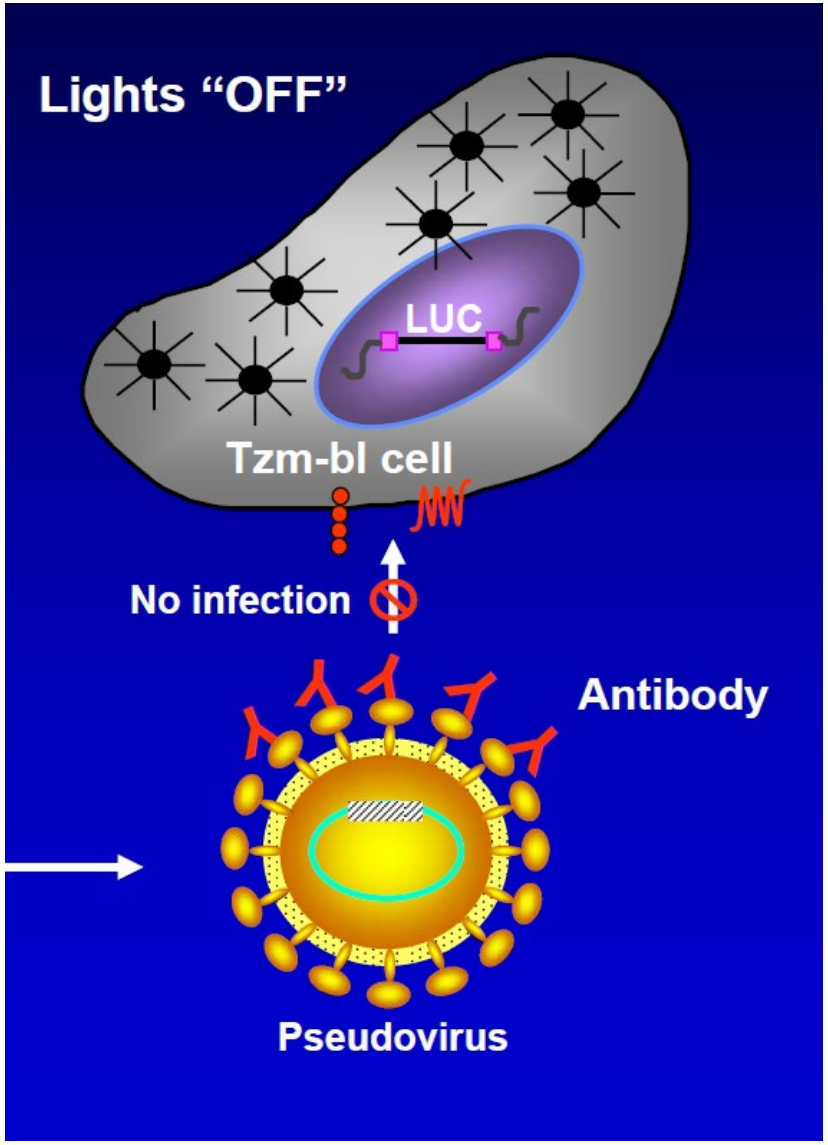
Neutralizing Antibodies

- Vaccines induce immune system to make antibodies to parts SARS-CoV-2 and other things too
- Antibodies block/thwart SARS-CoV-2 from infecting cells



How the Pseudo-Virus Neutralization Assay works





In each well a cage fight

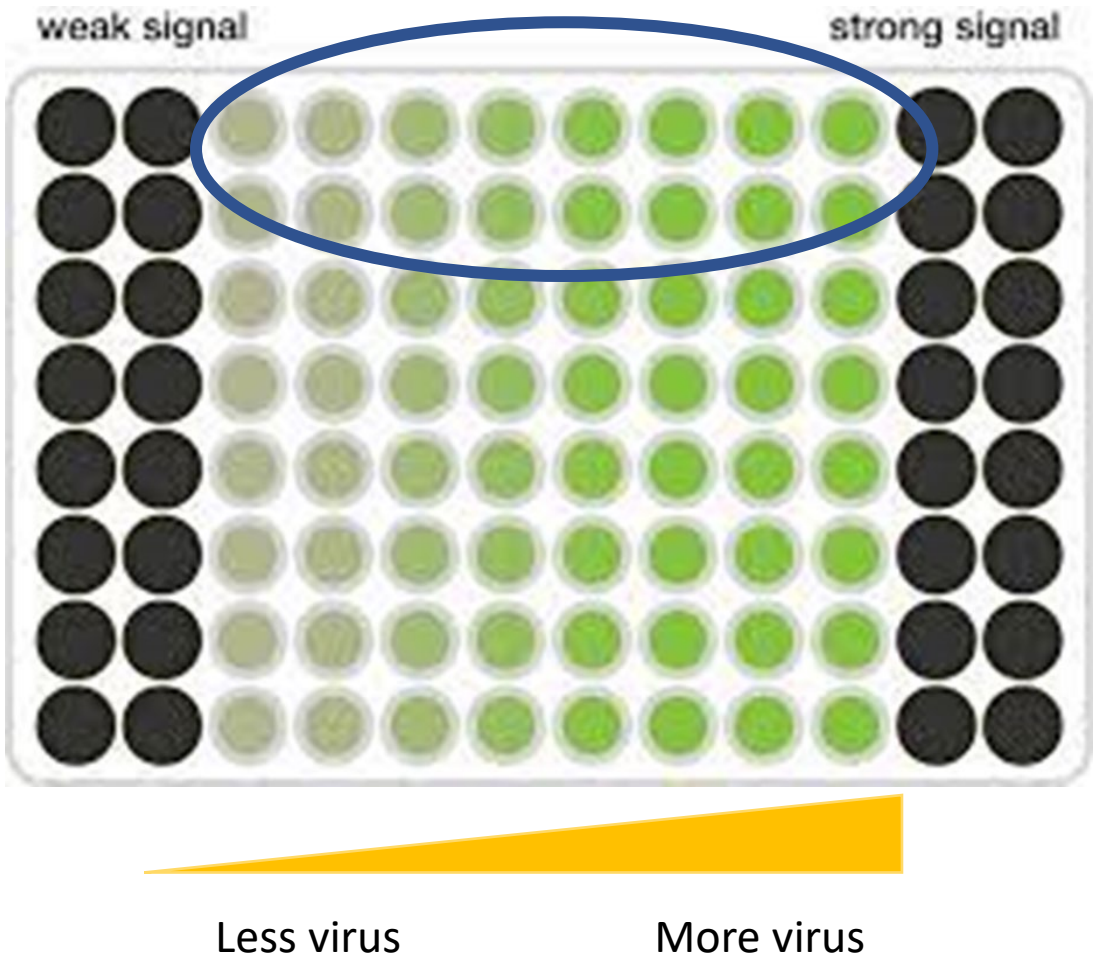
Mix

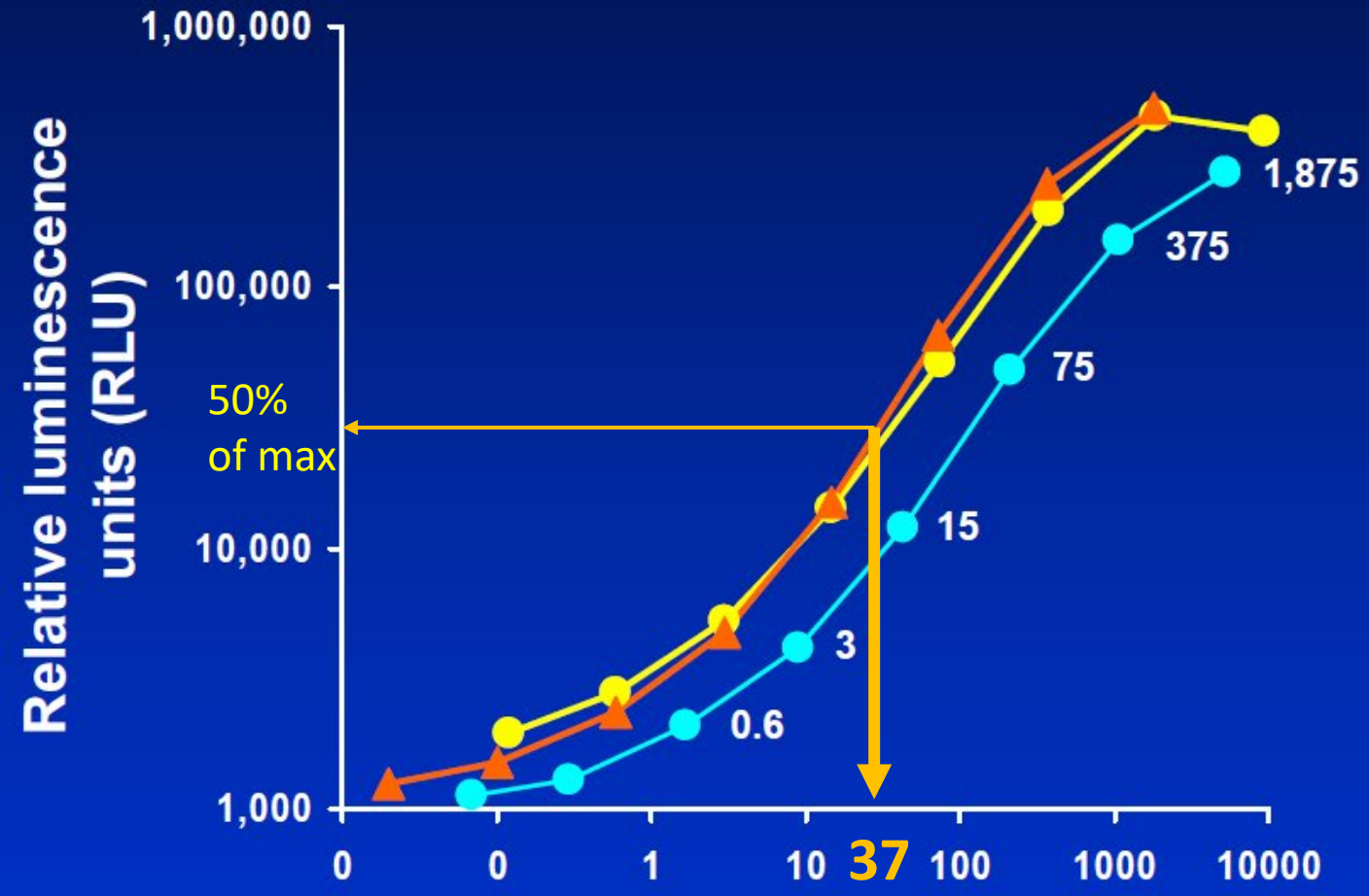
- infectable cells
- **person's serum w/antibodies**
- pseudo-virus

Lights out=> antibody wins!

Pseudo-Virus neutralization assay in a 96-well plate

- Put infectable cells in well
- Fill up 16 wells with serum/antibody from a person
- Put in different concentrations of virus
- Record light intensity





Concentration of Virions

ID50
infectious dose
that achieves 50%
of max light

$\log_{10}(37) = 1.57$

Correlates of Risk Analysis

antibody	# Vaccinees	# Infections	P(Disease)
10	100	20	0.20
100	800	80	0.10
1000	100	5	0.05

Risk is 4-fold larger for antibody at 10 vs 1000
Something's going on

Naïve Correlates of Protection Analysis

antibody	# Vaccinees	# Infections	P(Disease)	Vaccine Efficacy
10	100	20	0.20	0.500
100	800	80	0.10	0.750
1000	100	5	0.05	0.875

Suppose: Placebo Group attack Rate 40%

Vaccine Efficacy at antibody =10 is $100\% \times \left(1 - \frac{0.20}{0.40} \right) = 0.50$

Confounding And A Fix

Young: Good Immune Response Low Risk

Antibody	# Vaccinees	# Infections	P(Disease)
10	20	2	0.10
100	400	20	0.05
1000	80	3	0.04

Old: Bad Immune Response High Risk

Antibody	# Vaccinees	# Infections	P(Disease)
10	80	18	0.23
100	400	60	0.15
1000	20	2	0.10

Make a trial with 50:50 young & old at each Ab level

Adjusted
0.165
0.100
0.070

Now antibody doesn't depend on age

Proper Correlates of Protection

antibody	# Vaccinees	# Infections	Adjusted P(disease)*	Vaccine Efficacy
10	100	20	0.165	0.59
100	800	80	0.100	0.75
1000	100	5	0.070	0.83

Suppose: Placebo Group attack Rate 40%

Predicted Vaccine Efficacy at Antibody = 10 is 100% x (1 - $\frac{0.165}{0.40}$) = 0.59

*- Disease rate for a trial with equal young and old at each Ab level
Like randomizing 1000 to vaccine and then 3 levels of antibody 1:8:1

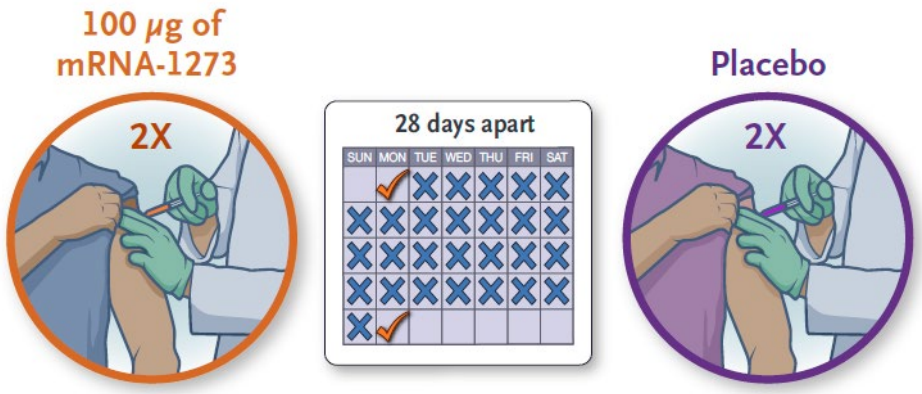
Correlate of Protection Summary

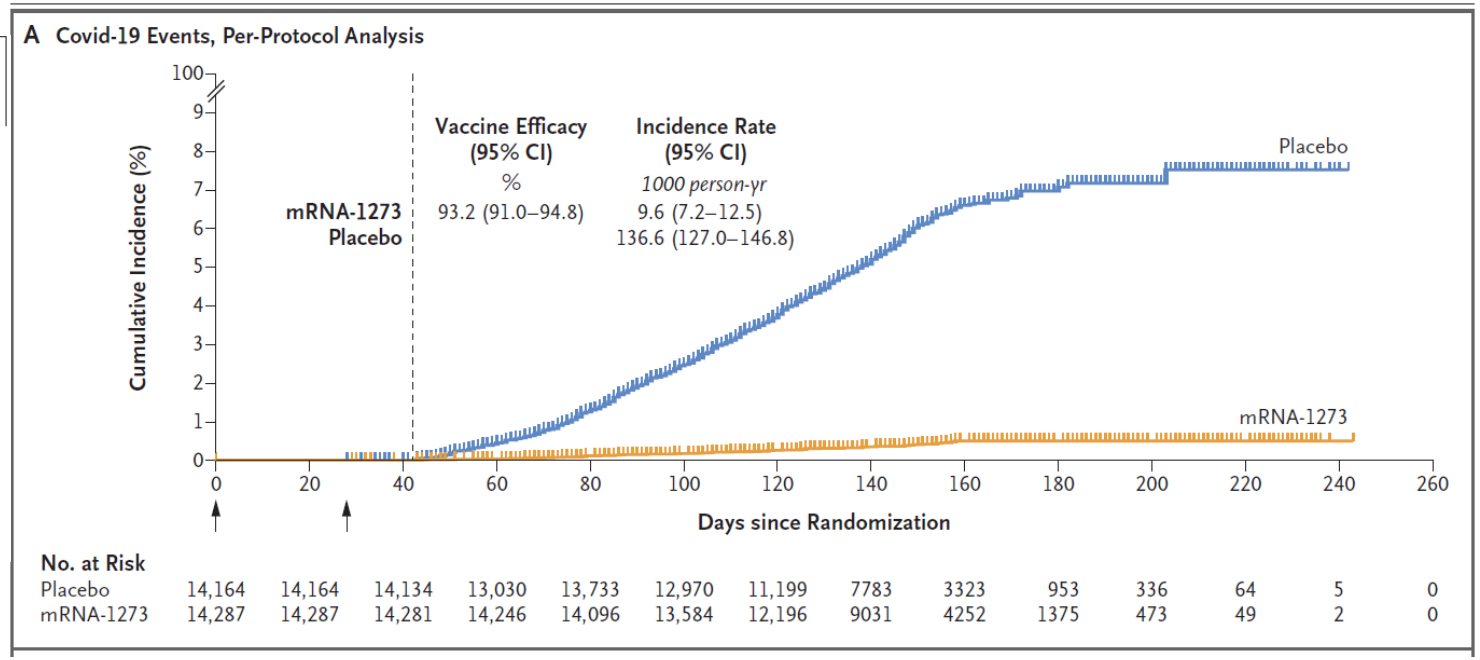
- Antibody level is not randomized so use statistical methods for observational data
- Assume we measure all factors (age, sex, etc) that predict both antibody level and risk of disease
- *Statistically create a trial where we randomize to placebo or vaccine then randomize to levels of antibody*
- VE of 0.83 at ID50 = 1000 is caused by the 'intervention'
  - Intervention = antibody at 1000 plus other vaccinal effects

ORIGINAL ARTICLE

Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase

H.M. El Sahly, L.R. Baden, B. Essink, S. Doblecki-Lewis, J.M. Martin, E.J. Anderson, T.B. Campbell, J. Clark, L.A. Jackson, C.J. Fichtenbaum, M. Zervos, B. Rankin, F. Eder, G. Feldman, C. Kennelly, L. Han-Conrad, M. Levin, K.M. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, L. Polakowski, J.R. Mascola, J.E. Ledgerwood, B.S. Graham, A. August, H. Clouting, W. Deng, S. Han, B. Leav, D. Manzo, R. Pajon, F. Schödel, J.E. Tomassini, H. Zhou, and J. Miller, for the COVE Study Group*





N=30,415 participants enrolled
July 27, 2020 to October 23, 2020

Primary endpoint is COVID-19:

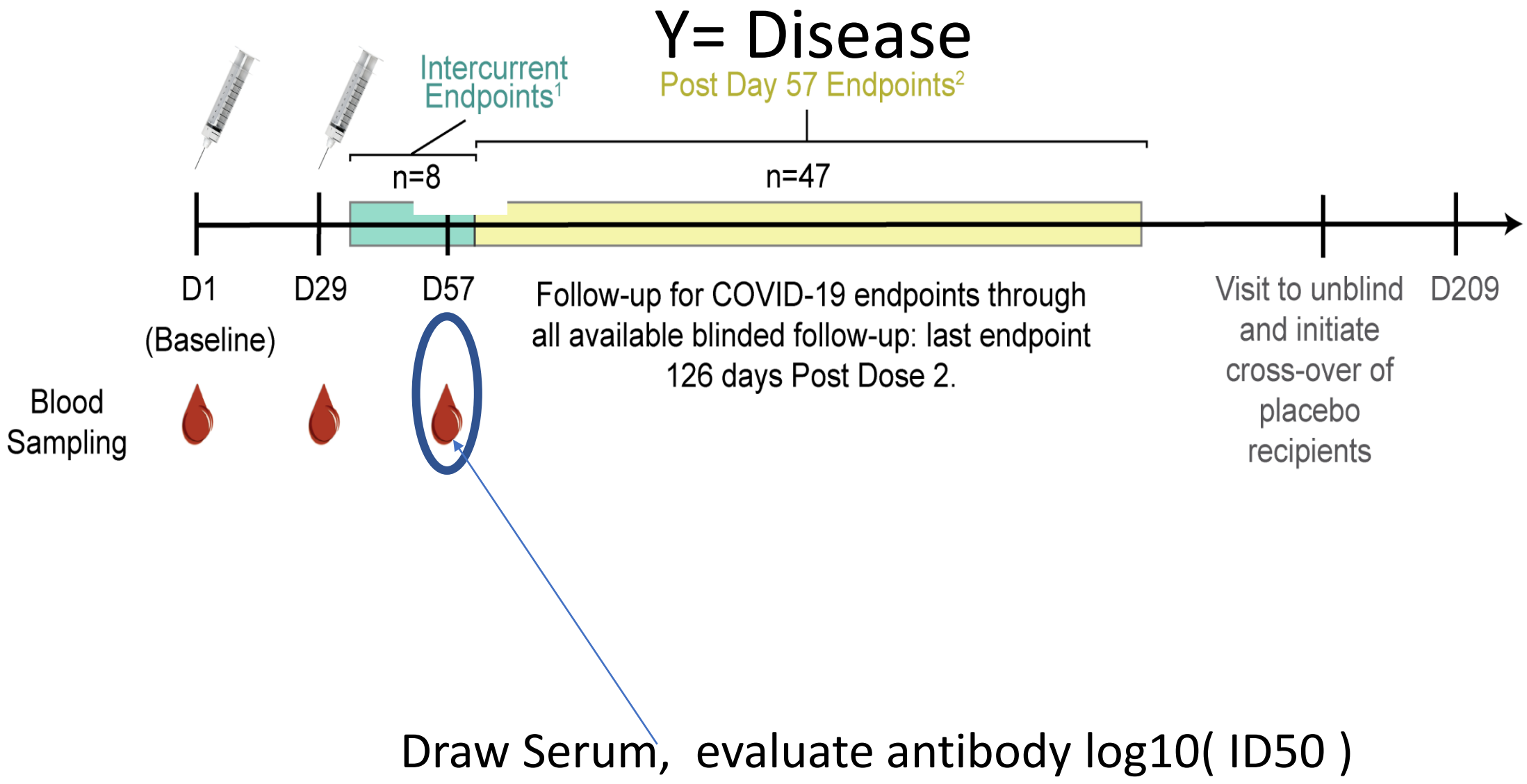
First occurrence of symptomatic COVID-19 with virologically-confirmed SARS-CoV-2 infection in participants with no evidence of previous SARS-CoV-2 infection

Per-protocol cohort analysis
VE = 93.2% (95% CI 91.0 to 94.8%)

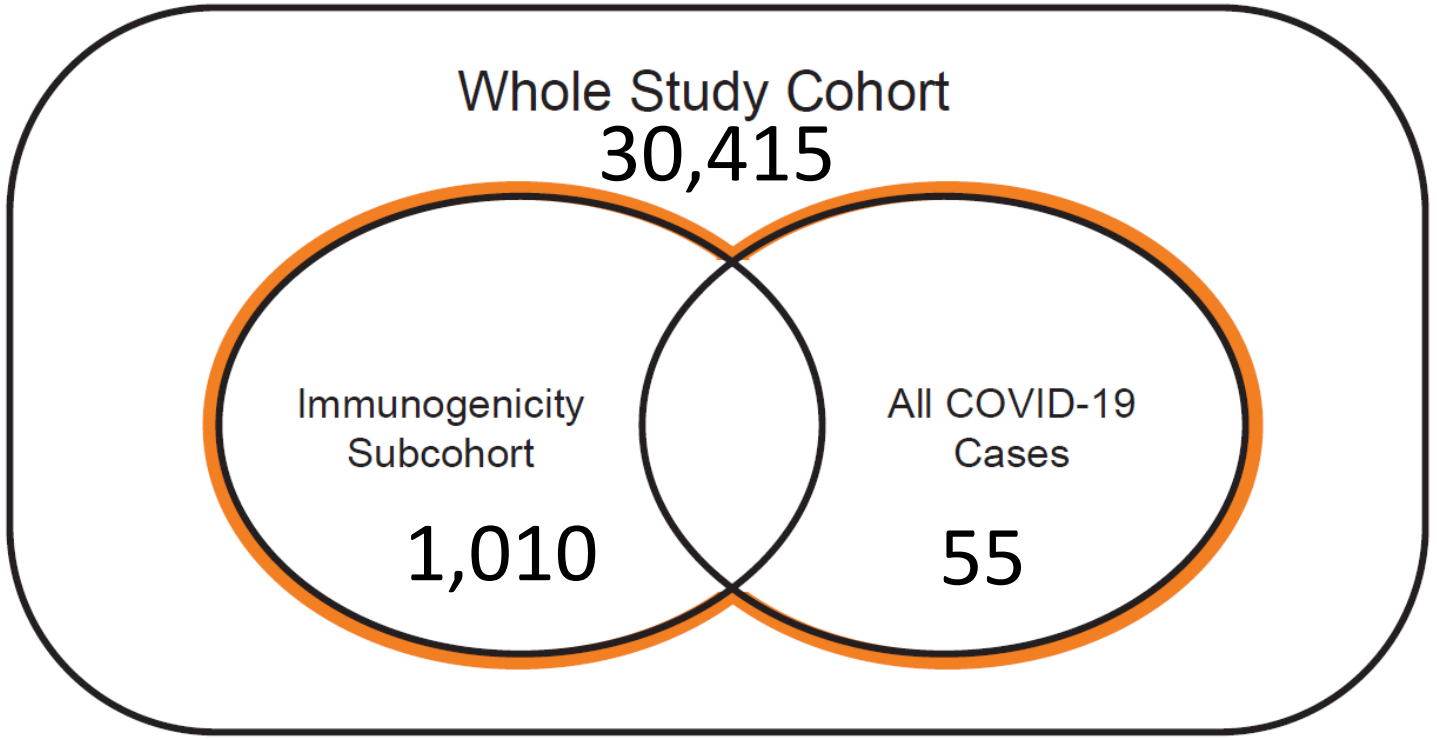
Median Follow-up 5.3 months

Measure antibody and disease

For Baseline Negative Per-Protocol recipients of two doses of mRNA-1273:



Measure Antibody in all Cases and Some non-cases



Case-cohort set = Immunogenicity subcohort plus COVID-19 cases outside the subcohort, excluding participants with missing antibody marker data.

- Immune correlates analyses in the **per-protocol baseline negative cohort**
  - Per-protocol = received both doses without major protocol violations

- Sampling stratified by baseline covariates

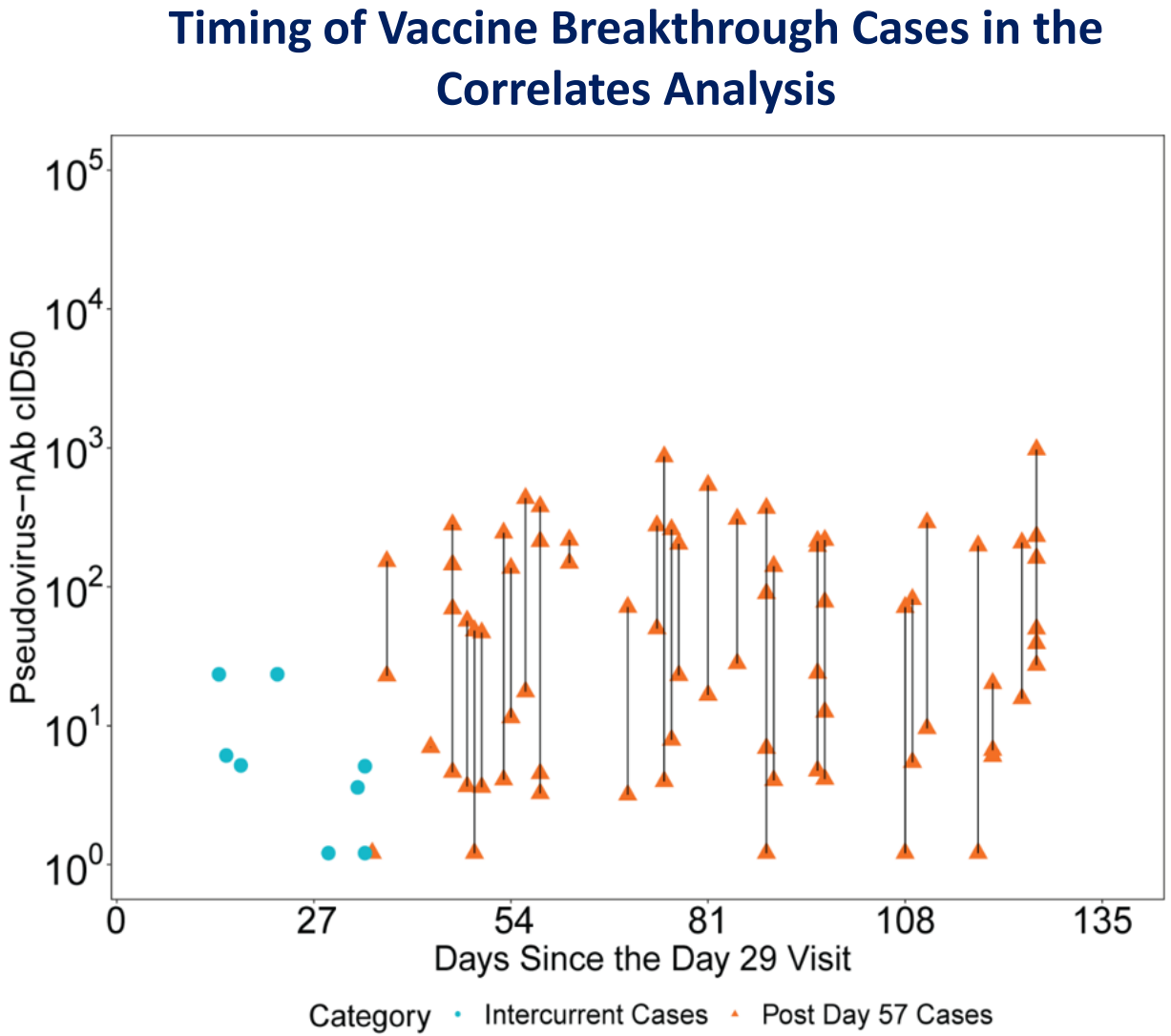
  (Vaccine, Placebo)
  x (SARS-CoV-2 Neg, Pos)
  x (Baseline demographics)

Per-Protocol Baseline Negative Vaccine Recipients in the Immunogenicity Subcohort by Randomization Strata and Demographics (N=1010)

Characteristic	Number (%)
Age < 65	670 (67%)
Age >= 65	340 (34%)
At-Risk	396 (39%)
Not At-Risk	614 (61%)
Female	476 (47%)
Male	534 (53%)

Characteristic	Number (%)
Hispanic or Latino	322 (32%)
Not Hispanic or Latino	685 (68%)
White Non-Hispanic	465 (46%)
Communities of Color	545 (54%)
Black or African American	182 (18%)
Asian	25 (2%)
American Indian or Alaska Native	17 (2%)
Native Hawaiian or Other Pacific Islander	5 (0.5%)
Multiracial	12 (1%)

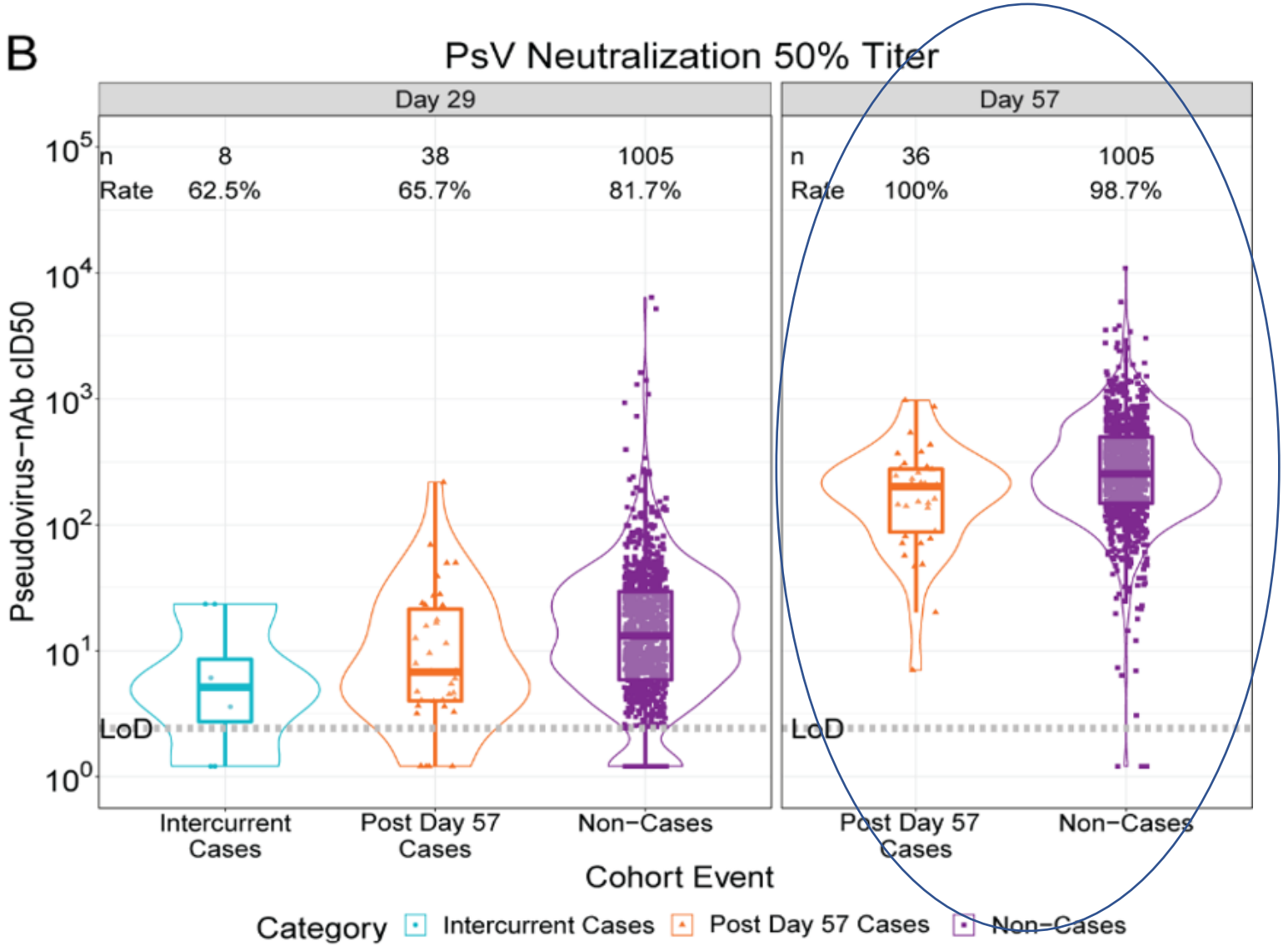
Antibody and timing of vaccine breakthroughs



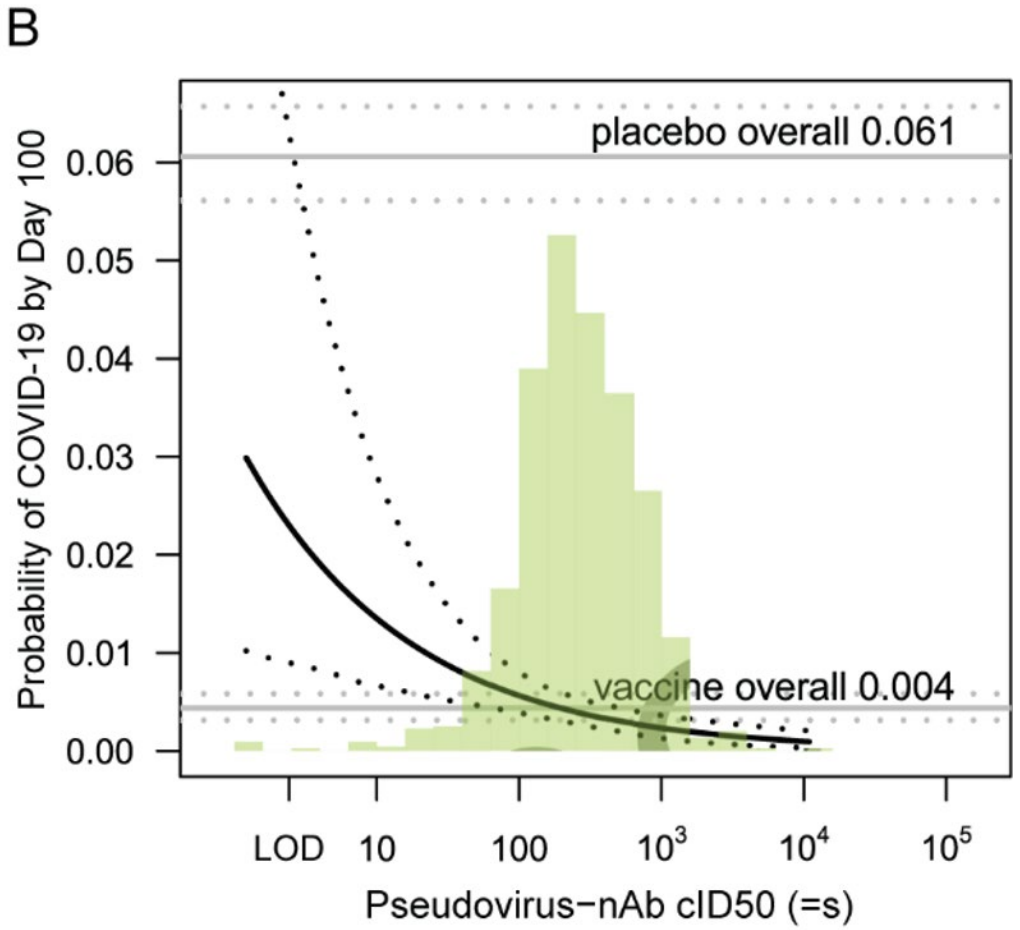
Upper triangle: Day 57 ID50 titer

Lower triangle: Day 29 ID50 titer

Antibody Levels Lower in Vaccine Breakthrough Cases than Vaccine Non-Cases



Correlate of Risk Curve



Cox Model with covariates
- Antibody
- logit(Risk Score)
- minority yes/no
- high risk yes/no

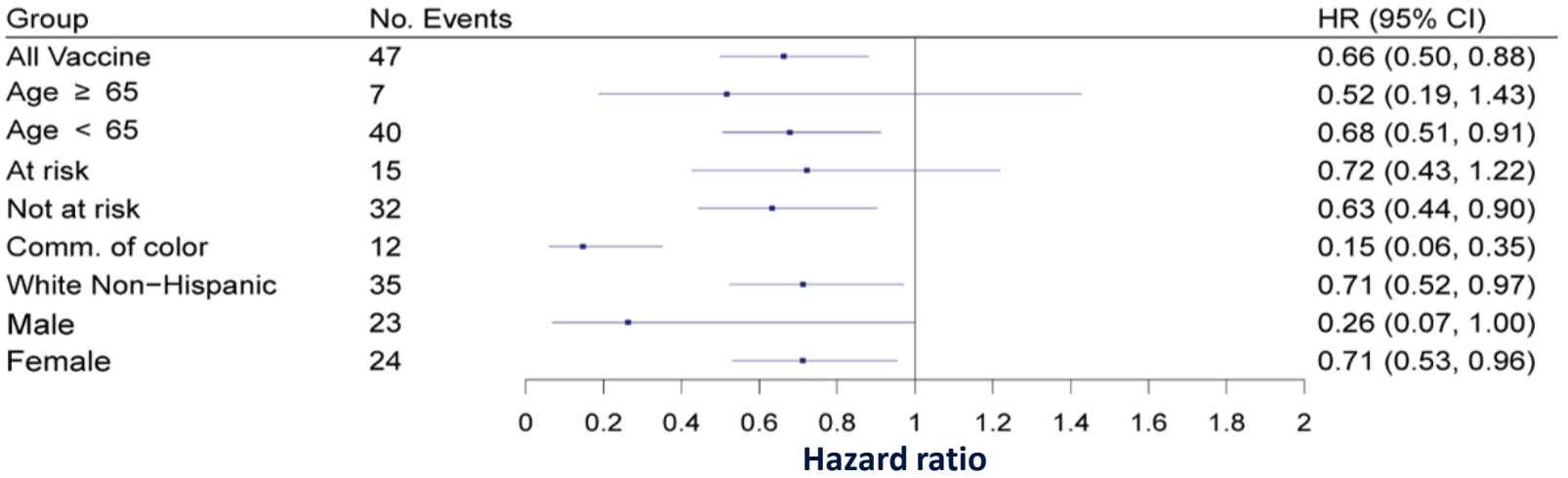
Weighted to reflect case-cohort design

At each Ab level, average
P(T<100|Ab,covariates) over covariates

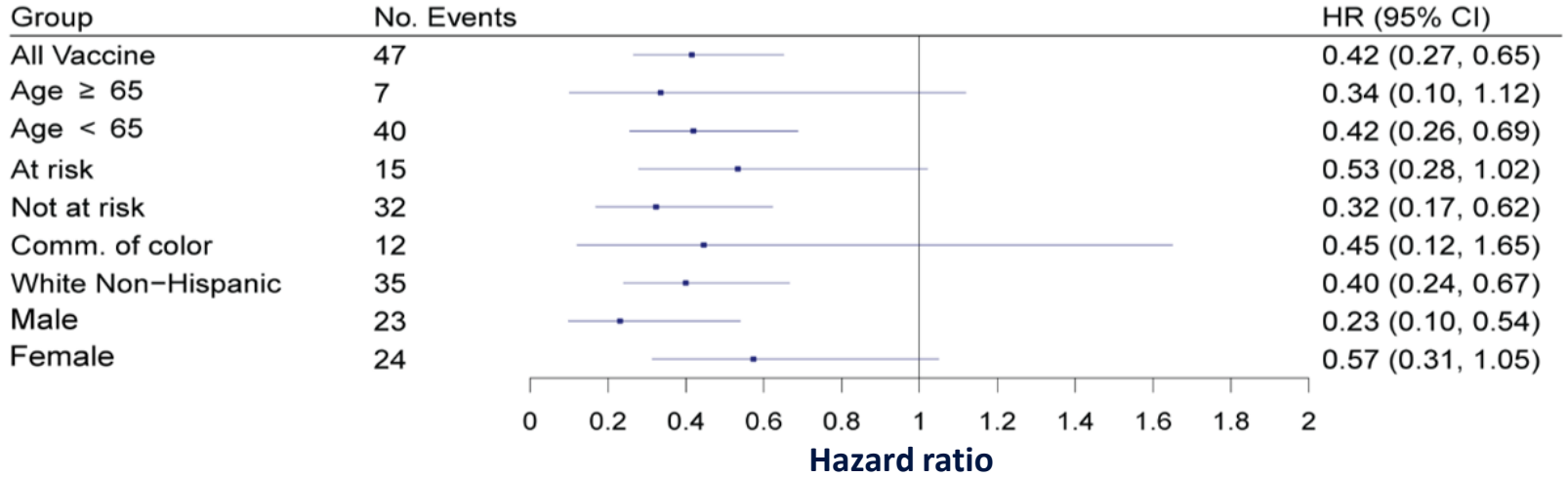
Risk by ID50: Varies from 0.030 at undetectable to 0.0009 at titer 10,000 (33x)

Day 57 Correlates of Risk By Subgroups

Spike IgG

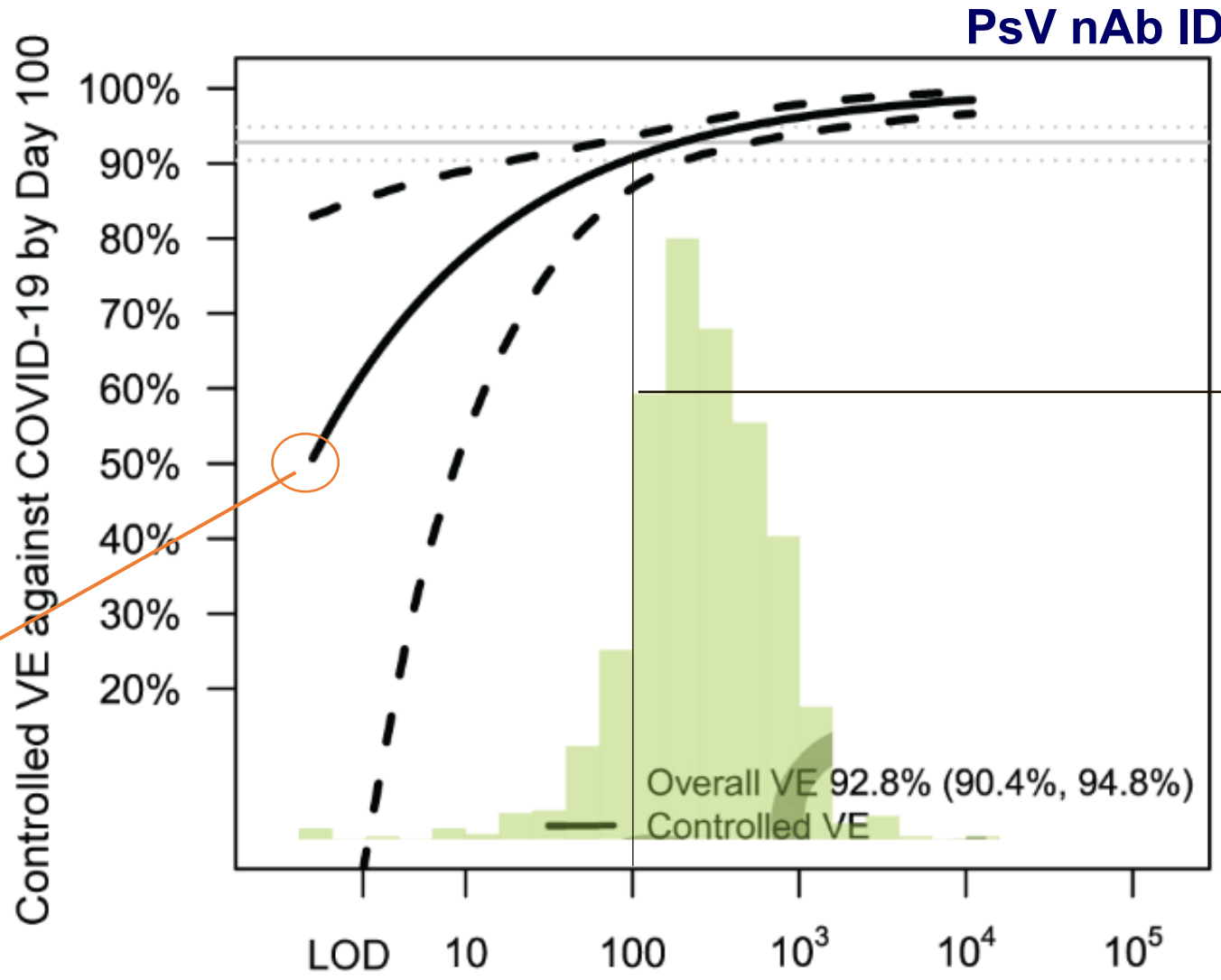


PsV nAb ID50



1000 ID50 versus 100 ID50

Correlate of Protection Curve

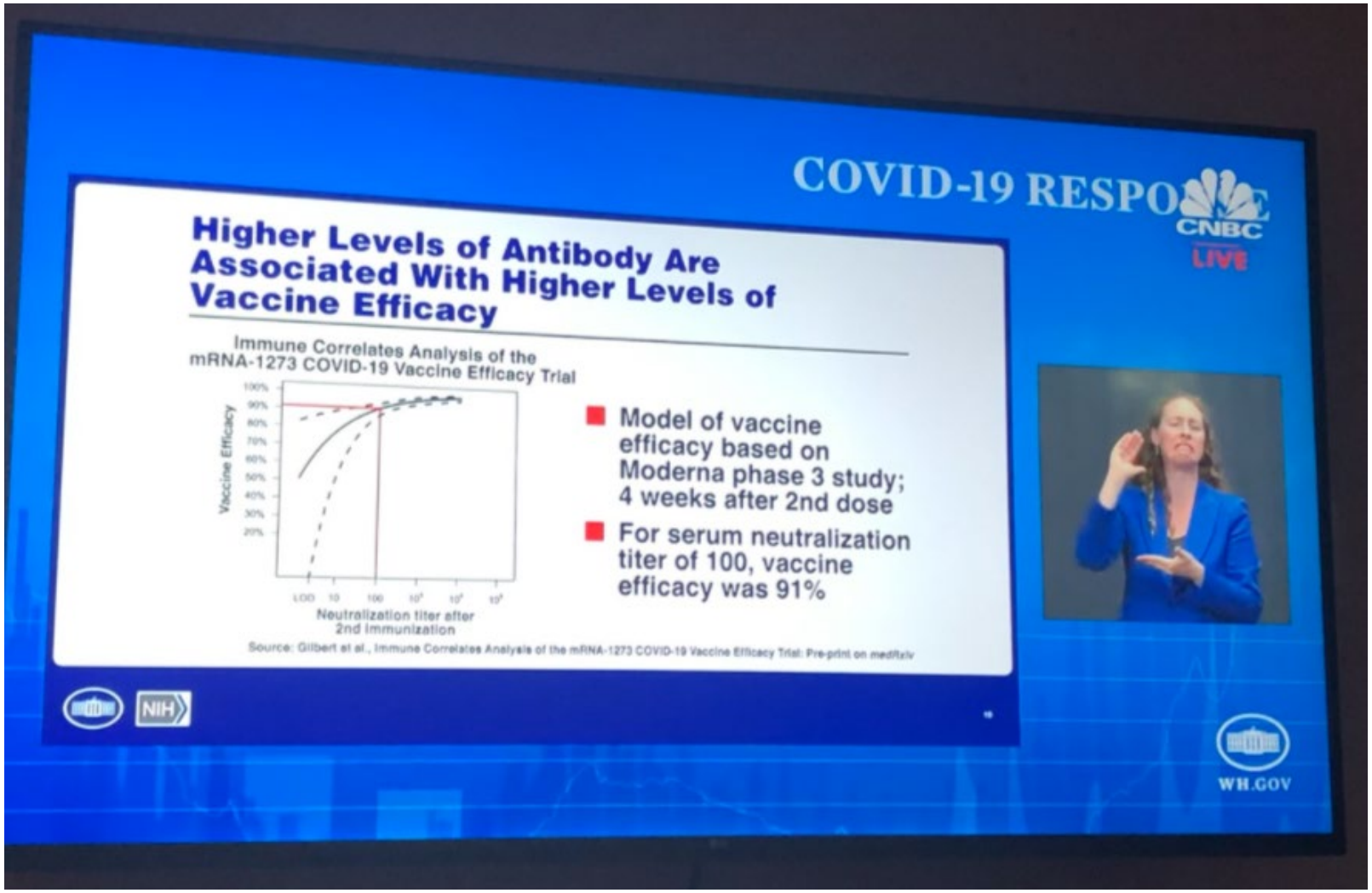


Estimated VE at
< LOD = 50%

90% vaccine efficacy at
50% neutralization titer >
100 IU50/ml

*Gilbert, Fong, Carone (2021, *arXiv*)

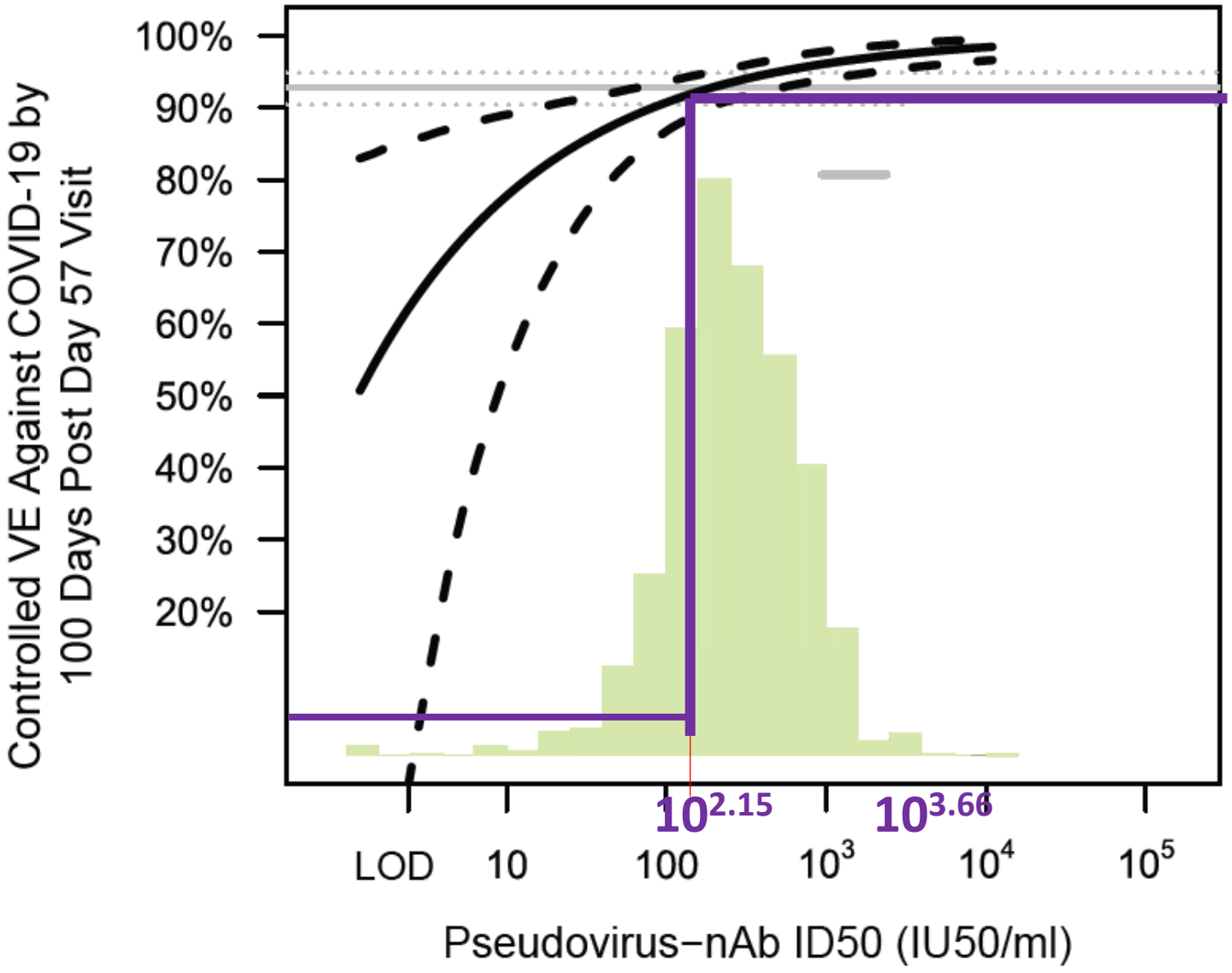
CoP Curve on TV



18 August 2021 7:34 pm

Briefing to Outline Rationale for a Booster Dose

C Protective Efficacy of Monoclonal Antibodies



At time of exposure

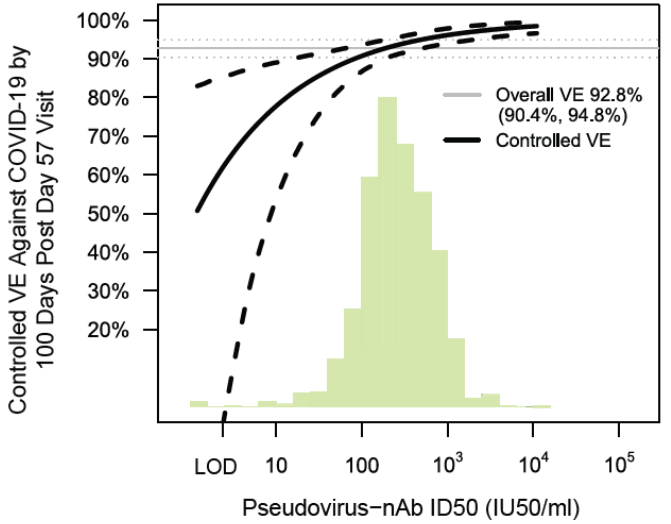
The REGN-COV trial demonstrated high efficacy of monoclonal antibodies relative to placebo

We will draw a Protective Efficacy curve using the same assay

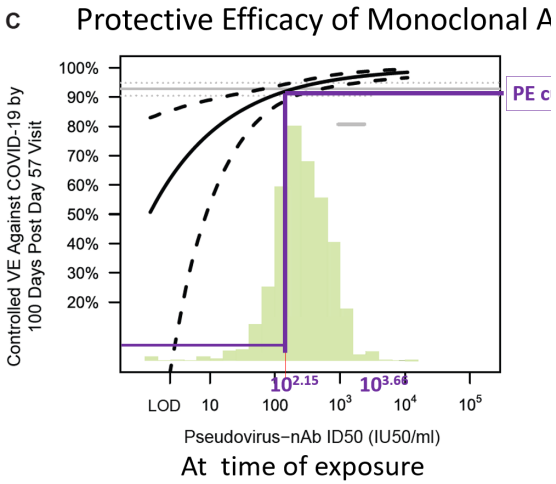
Further supports causative role of antibody

Correlates of Protection: COVID-19

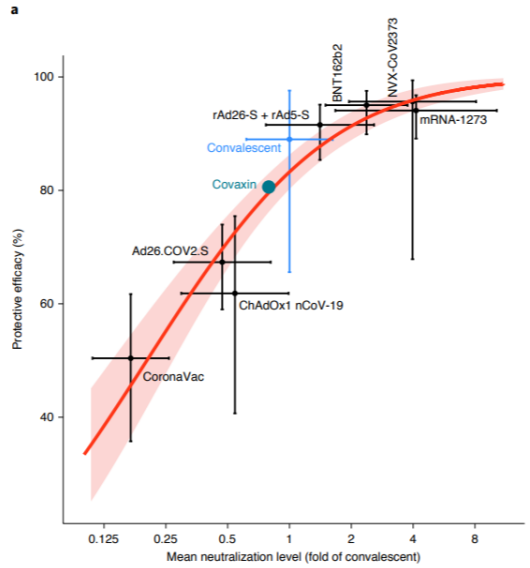
- Diverse streams of evidence support a causal role of
  - Individual Trials
    - Similarity of curves across platforms
  - Protection by passive immunization
  - Animal Studies
  - Meta-analysis



Moderna Trial: Gilbert et al 2021



At time of exposure



Meta-Analysis: Khoury et al 2021

Decision

Access Consortium: Alignment with ICMRA consensus on immunobridging for authorising new COVID-19 vaccines

Published 15 September 2021

*The Access Consortium considers that the weight of evidence from studies with authorised COVID-19 vaccines is sufficient to support using neutralising antibody titres as a primary endpoint **in cross-platform immunobridging** trials.*

https://www.gov.uk/government/publications/access-consortium-alignment-with-icmra-consensus-on-immunobridging-for-authorising-new-covid-19-vaccines/access-consortium-alignment-with-icmra-consensus-on-immunobridging-for-authorising-new-covid-19-vaccines

What's Next?

- Do similar analyses for all OWS vaccine trials
- Combine analyses over all OWS vaccine trials
- **Correlates for Delta and Omicron infections**
- Perform risk proximal correlates
  - Correlate day 87 antibody with day 87 risk, etc
- Use mAb prevention trial data for improved mediation analysis

Domestic terror charges in Atlanta spa shootings case

Prosecutors also signal they intend to seek hate crime charges against the suspect. In News

Celine Dion talks about her return to Las Vegas stage

Pop icon also shares about lockdowns and 30th anniversary of "Beauty and the Beast." In Life

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CORONAVIRUS PANDEMIC

When are we truly immune to the virus?

McCarth in spot as Chen fate dec

House minority lea serious tests in po

Jeanine Santucci and Matth
USA TODAY

WASHINGTON – House oust conference chair Liz day that will serve as a be party.

Wyoming Rep. Cheney institution in Republica run afoul of the party fo Donald Trump and con tion Trump lost was st

Peter Gilbert
Leadership, Advice, Support and many slides

Science

RESEARCH ARTICLES

Cite as: P. B. Gilbert *et al.*, *Science* 10.1126/science.abm3425 (2021).

Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial

Peter B. Gilbert[1,2,3*†], David C. Montefiori[4†], Adrian B. McDermott[5†], Youyi Fong[1,2], David Benkeser[6], Weiping Deng[7], Honghong Zhou[7], Christopher R. Houchens[8], Karen Martins[8], Lakshmi Jayashankar[8], Flora Castellino[8], Britta Flach[5], Bob C. Lin[5], Sarah O'Connell[5], Charlene McDanal[4], Amanda Eaton[4], Marcella Sarzotti-Kelsoe[4], Yiwen Lu[1], Chenchen Yu[1], Bhavesh Borate[1], Lars W. P. van der Laan[1], Nima S. Hejazi[1,9], Chuong Huynh[8], Jacqueline Miller[7], Hana M. El Sahly[10], Lindsey R. Baden[11], Mira Baron[12], Luis De La Cruz[13], Cynthia Gay[14], Spyros Kalams[15], Colleen F. Kelley[16], Michele P. Andrasik[1], James G. Kublin[1], Lawrence Corey[1,17], Kathleen M. Neuzil[18], Lindsay N. Carpp[1], Rolando Pajon[7], Dean Follmann[19], Ruben O. Donis[8‡], Richard A. Koup[5‡], on behalf of the Immune Assays Team§, Moderna, Inc. Team§, Coronavirus Vaccine Prevention Network (CoVPN)/Coronavirus Efficacy (COVE) Team§, and United States Government (USG)/CoVPN Biostatistics Team§

COVID-19
Prevention Network

David

USG / CoVPN Biostatistics Implementation Team

- **David Benkeser**
- Bhavesh Borate
- **Youyi Fong**
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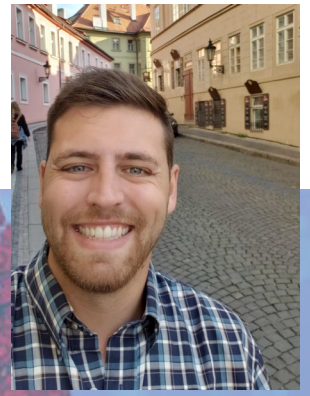
- Kendrick Li
- Di Lu
- Yiwen Lu
- Brian Simpkins
- Chenchen Yu
- Lars van der Laan

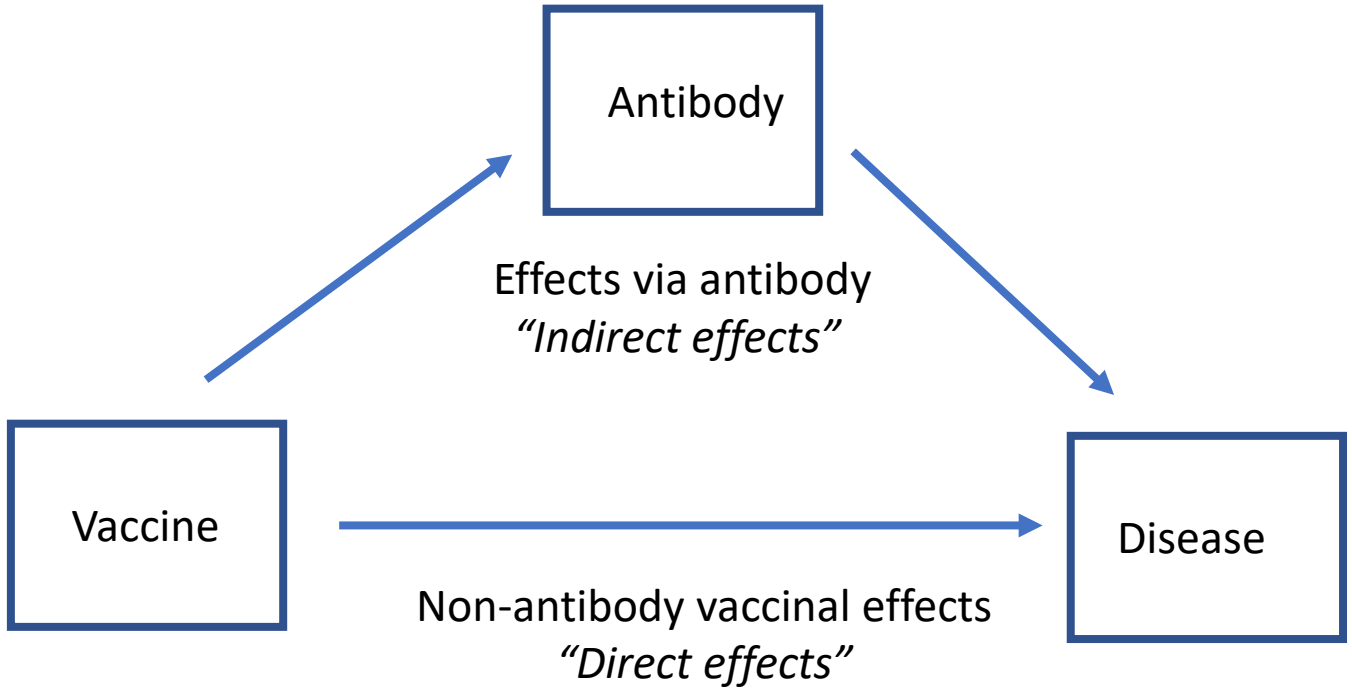
Youyi



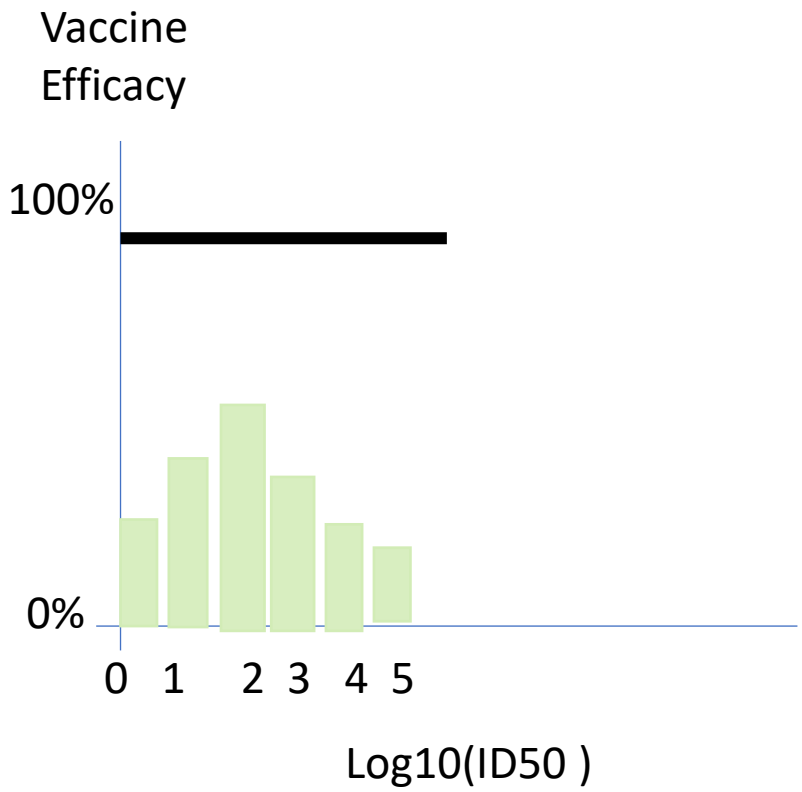
Statistical Details for Correlates Model

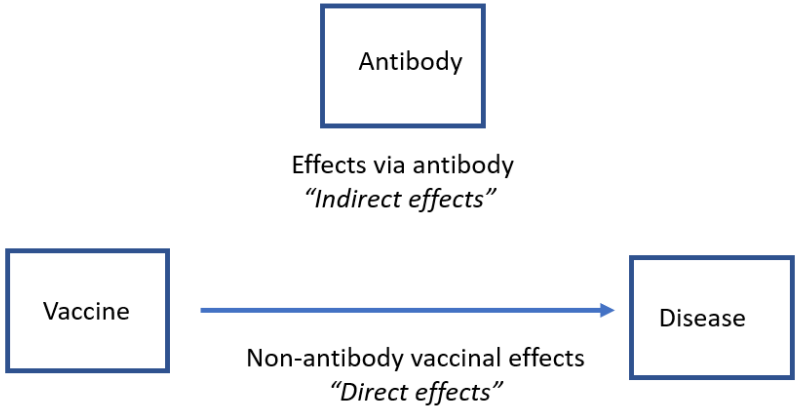
- Correlates of Risk Model: Cox regression in the vaccine group alone
  - Specify h(t) = h0(t) exp{ B1 Ab + B2 X }
  - X – logit(risk score), minority, high risk
  - t is days post peak
  - Fit using weighted Cox regression
  - Get P(T<t | Ab, X) from Cox output
  - Average over empirical dbn of X to get P(T<100 days|A=1,Ab)
- Correlates of Protection: Above plus the placebo event rate
  - Use P(T<t|Ab) from the above
  - Form 1 – P(T<100 days | A=1,Ab)/ P(T<100 days| A=0)
  - A=1 vaccine A=0 placebo

How *much* does antibody contribute to protection?

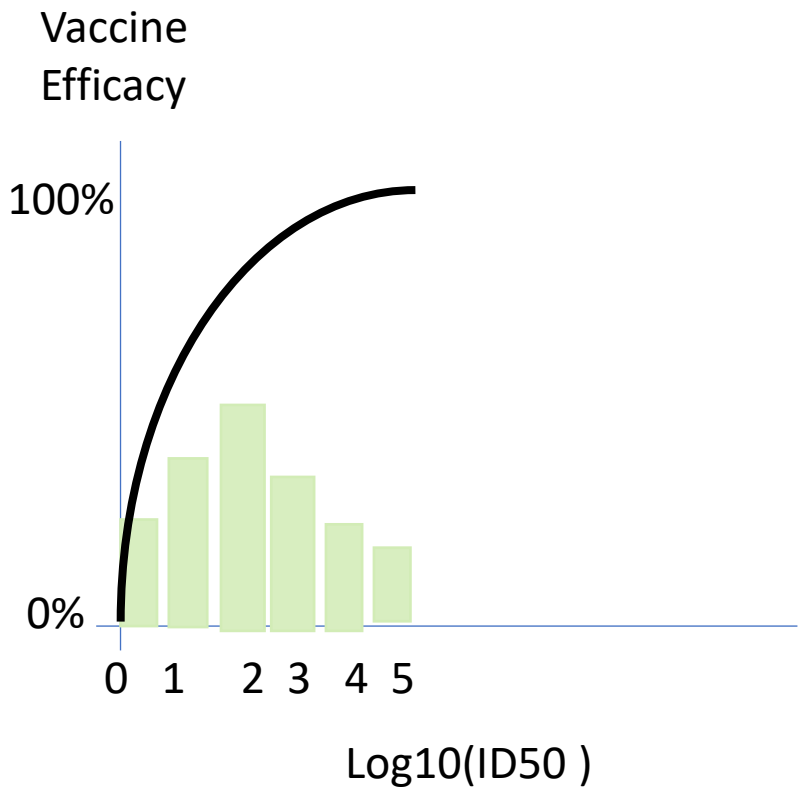


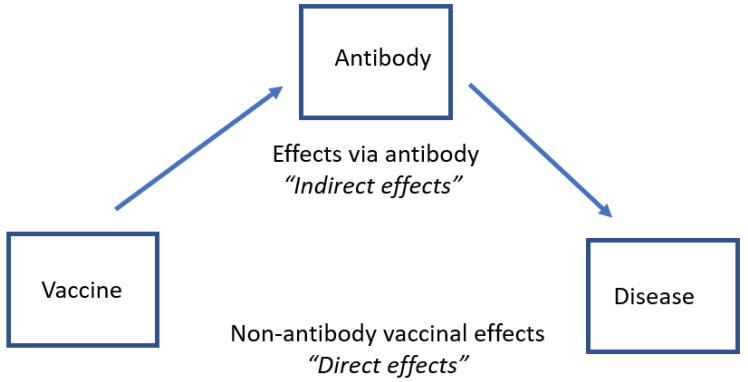
Example 1: Antibody has no effect



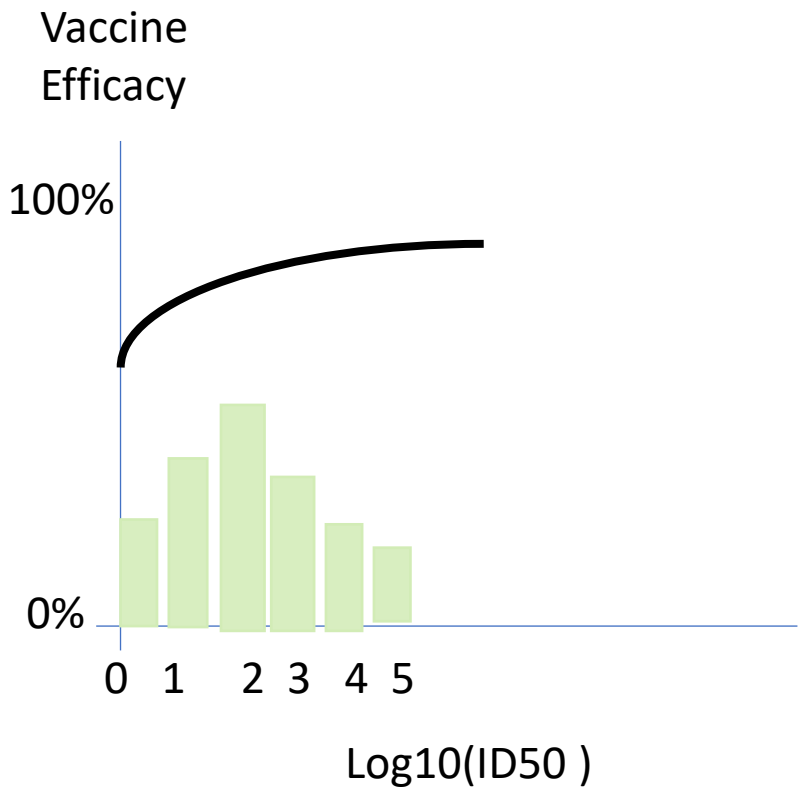


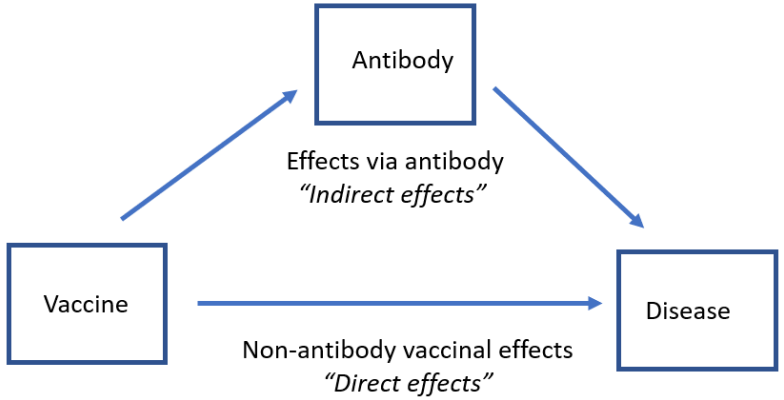
Example 2: Antibody has the entire effect



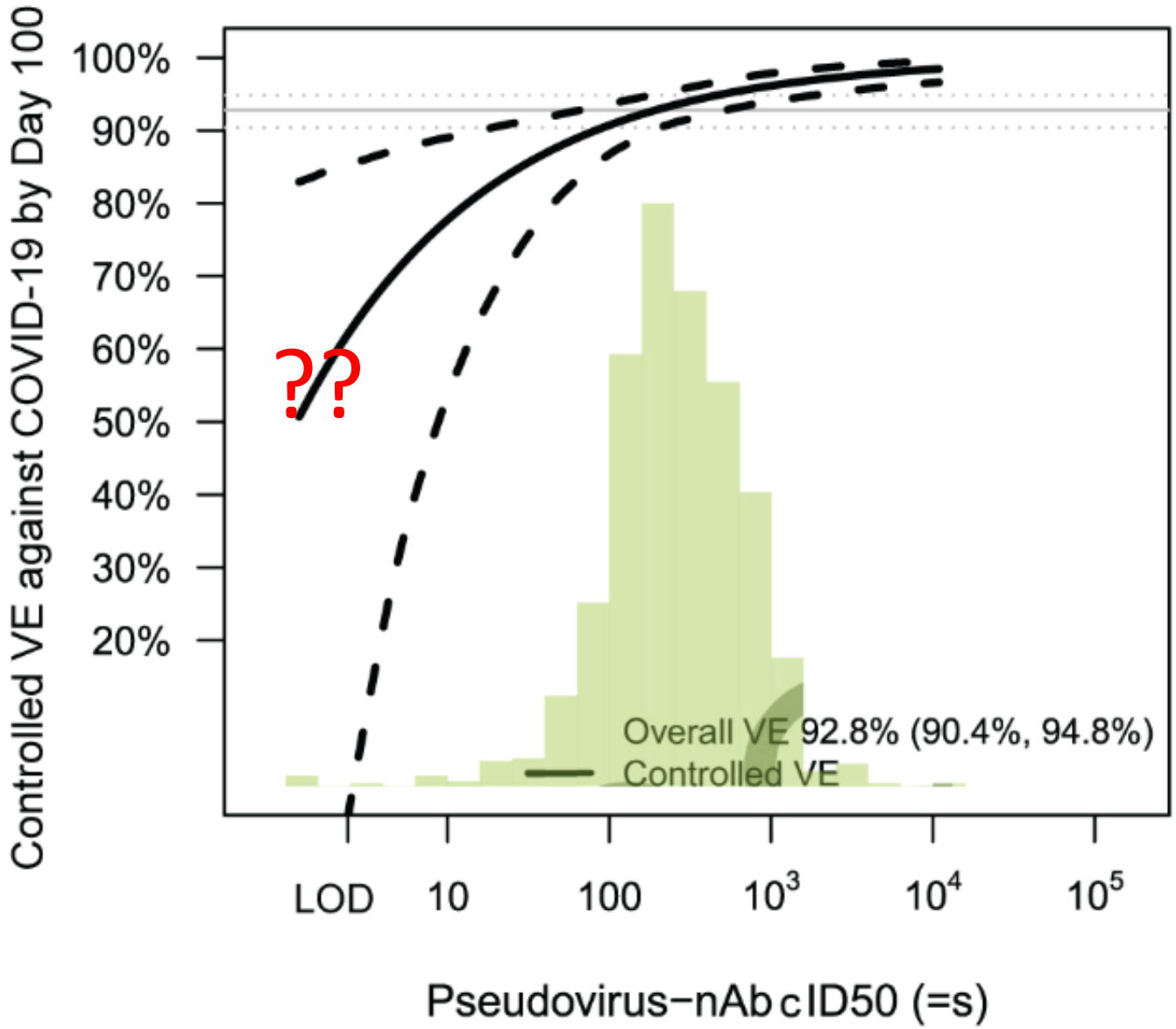


Example 3: It's complicated





It’s impossible



Crude Mediation Analysis *Day 29 ID80* Marker

- VE with no antibody is about 75% = (1 – 1/4) x 100%
- Overall VE is about 95% = (1 - 1/20) x 100%
- Fold reduction in risk is

$$20 = 4 \times 5$$

$$5^{1.86} = 5^{0.86} \times 5^{1.00}$$

Total reduction = not via antibody x via antibody

- Crude proportion mediated is

$$100\% \ \frac{1.00}{1.86} = 54\%$$

Mediation of VE Through Day 29 Neutralization Titers*

Point Estimates (95% Confidence Intervals)			
	Direct VE	Indirect VE	Proportion Mediated
Day 29 nAb ID50	56.0% (42.2, 66.5%)	83.2% (76.9, 87.8%)	68.5% (58.5, 78.4%)
Day 29 nAb ID80	73.9% (60.1, 82.9%)	71.7% (59.7, 80.1%)	48.5% (34.5, 62.4%)

Direct VE: VE comparing vaccine vs. placebo with marker set to undetectable

Indirect VE: VE in vaccinated at observed marker vs. at marker deactivated to be undetectable

Prop. Mediated: Fraction of total risk reduction from vaccine attributed to the marker

- Interpretation of nAb ID50 titer result: If circulating neutralizing antibodies at Day 29 could be removed but the other consequences of vaccination remained, overall VE would be expected to reduce by 68.5% from 92.3% to 56.0% (on the log scale)

*TMLE method of Benkeser, Diaz, Ran (2021, *arXiv*)

Domestic terror charges in Atlanta spa shootings case

Prosecutors also signal they intend to seek hate crime charges against the suspect. In News

Celine Dion talks about her return to Las Vegas stage

Pop icon also shares about lockdowns and 30th anniversary of "Beauty and the Beast." In Life

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CORONAVIRUS PANDEMIC

When are we truly immune to the virus?

McCarth in spot as Chen fate dec

House minority lea serious tests in po

Jeanine Santucci and Matth
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WASHINGTON – House oust conference chair Liz day that will serve as a be party.

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Peter Gilbert
Leadership, Advice, Support and many slides

Science

RESEARCH ARTICLES

Cite as: P. B. Gilbert *et al.*, *Science* 10.1126/science.abm3425 (2021).

Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial

Peter B. Gilbert[1,2,3*†], David C. Montefiori[4†], Adrian B. McDermott[5†], Youyi Fong[1,2], David Benkeser[6], Weiping Deng[7], Honghong Zhou[7], Christopher R. Houchens[8], Karen Martins[8], Lakshmi Jayashankar[8], Flora Castellino[8], Britta Flach[5], Bob C. Lin[5], Sarah O'Connell[5], Charlene McDanal[4], Amanda Eaton[4], Marcella Sarzotti-Kelsoe[4], Yiwen Lu[1], Chenchen Yu[1], Bhavesh Borate[1], Lars W. P. van der Laan[1], Nima S. Hejazi[1,9], Chuong Huynh[8], Jacqueline Miller[7], Hana M. El Sahly[10], Lindsey R. Baden[11], Mira Baron[12], Luis De La Cruz[13], Cynthia Gay[14], Spyros Kalams[15], Colleen F. Kelley[16], Michele P. Andrasik[1], James G. Kublin[1], Lawrence Corey[1,17], Kathleen M. Neuzil[18], Lindsay N. Carpp[1], Rolando Pajon[7], Dean Follmann[19], Ruben O. Donis[8‡], Richard A. Koup[5‡], on behalf of the Immune Assays Team§, Moderna, Inc. Team§, Coronavirus Vaccine Prevention Network (CoVPN)/Coronavirus Efficacy (COVE) Team§, and United States Government (USG)/CoVPN Biostatistics Team§

COVID-19
Prevention Network

David

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- **David Benkeser**
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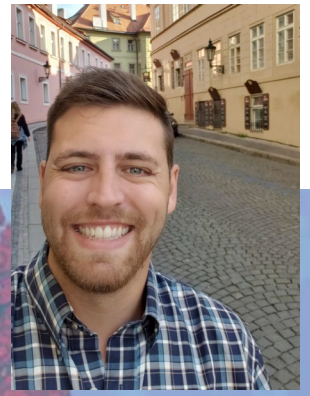
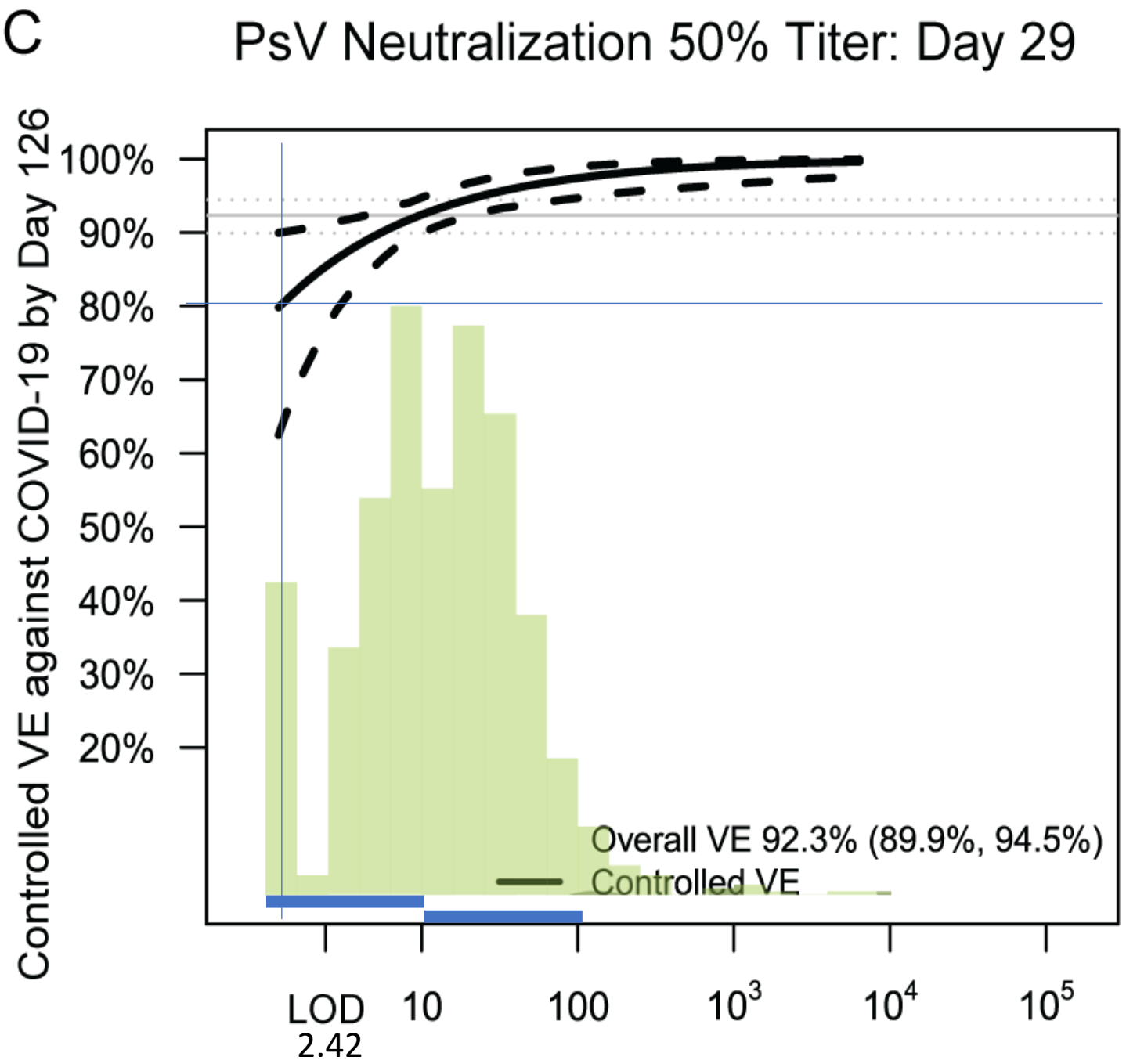
- Kendrick Li
- Di Lu
- Yiwen Lu
- Brian Simpkins
- Chenchen Yu
- Lars van der Laan

Youyi



BACKUP SLIDES



Vaccine Efficacy with
No antibody is about 80%

“Direct Effect”

Crude Mediation Analysis of D29 ID50 antibody

- VE with no antibody is about 80% = (1 – 1/5) x 100%
- Overall VE is about 95% = (1 - 1/20) x 100%
- Fold reduction in risk is

$$20 = 5 \times 4$$

$$4^{2.16} = 4^{1.16} \times 4^{1}$$

Total reduction = not via antibody x via antibody

- Crude proportion mediated is

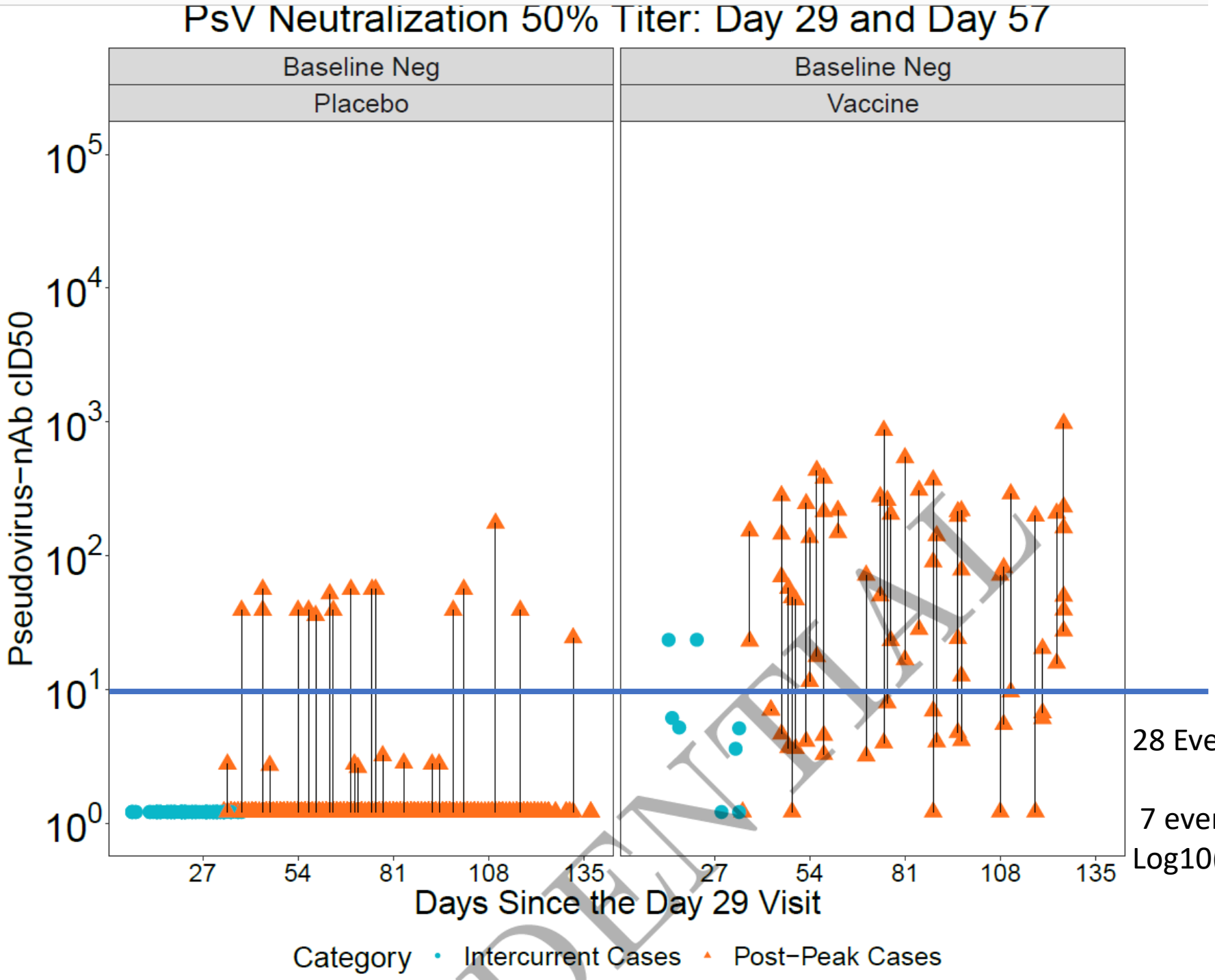
100% (1/2.16) = 46%

Table S8. Sensitivity analysis to assess Day 57 and Day 29 antibody markers categorized as upper vs. lower tertiles as controlled vaccine efficacy CoPs against COVID-19

	Marginalized Risk Ratio $RR_M(0,1)$[1]		Controlled Risk Ratio = (1-CVE(1))/(1-CVE(0))[2]		E-values[3]	
Antibody Marker	Point Est.	95% CI	Point Est.	95% CI	For Point Est.	For 95% CI UL
Day 57 Spike IgG	0.24	0.06, 0.56	0.32	0.09, 0.75	7.9	3.0
Day 57 RBD IgG	0.28	0.08, 0.62	0.38	0.11, 0.83	6.5	2.6
Day 57 PsV ID50	0.31	0.08, 0.72	0.42	0.11, 0.96	5.9	2.1
Day 57 PsV ID80	0.20	0.03, 0.51	0.27	0.05, 0.68	9.3	3.3
Day 29 Spike IgG	0.19	0.06, 0.40	0.26	0.08, 0.53	9.8	4.5
Day 29 RBD IgG	0.29	0.10, 0.59	0.38	0.13, 0.79	6.5	2.8
Day 29 PsV ID50	0.33	0.13, 0.65	0.44	0.17, 0.86	5.5	2.5
Day 29 PsV ID80	0.22	0.07, 0.46	0.30	0.10, 0.61	8.5	3.8

[1]This analysis estimates the Controlled Risk Ratio under the no-unmeasured confounding and positivity assumptions.

[2]Conservative (upper bound) estimate assuming unmeasured confounding at level $RR_{UD}(0, 1) = RR_{EU}(0, 1) = 2$ and thus $B(0, 1) = 4/3$ (notation as in Ding and vanderWeele (2016)).



28 Events below 10

7 events at LOD
Log10(2.42/2) = 0.08

Two Lines of Investigation Into Immune Correlates

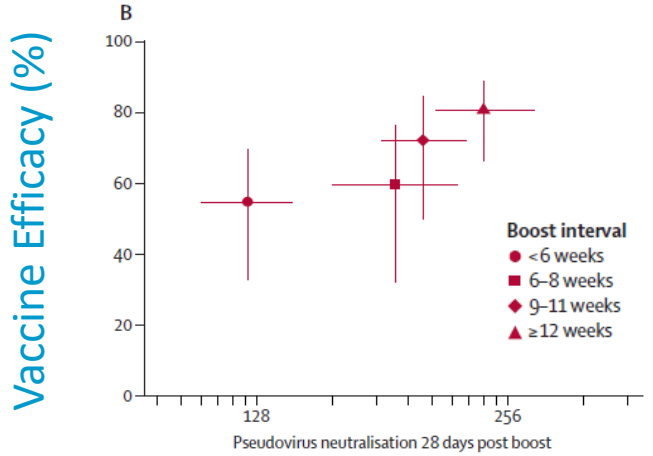
1. Correlates of Risk (CoR): How well do post-vaccination antibody markers predict COVID-19 occurrence?
   - Inference on statistical association parameters
2. Correlates of Protection (CoP): How well do post-vaccination antibody markers predict or cause vaccine efficacy (VE) against COVID-19?
   - Inference on causal effect parameters

- All analyses adjust for baseline prognostic factors in an effort to remove potential confounding
  - Baseline risk score built by superlearner of the placebo arm; communities of color; heightened at-risk

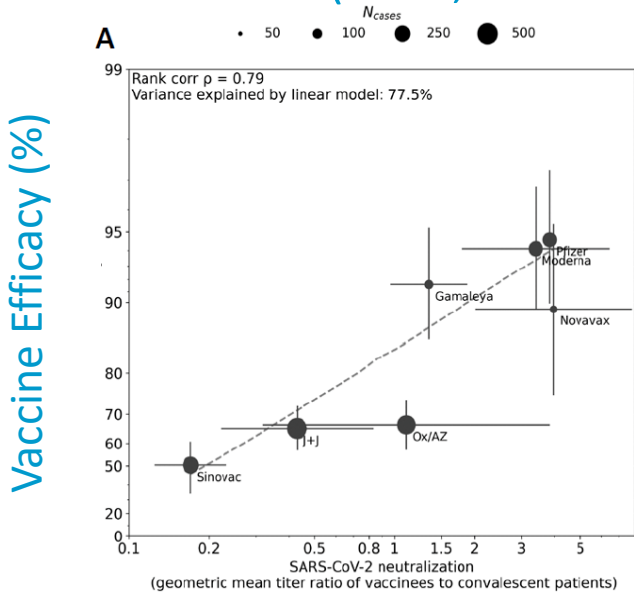
Pillars of Evidence for a Neutralizing Antibody Titer Immune Marker Surrogate Endpoint

- Meta-analysis of phase 3 VE trials[1]
- Similar correlates results in other phase 3 trials or observational studies[2]
- Nonhuman primate vaccine challenge studies[3]
- VE is lower against variants that reduce vaccine-elicited neutralizing antibody titers
- Natural history re-infection correlates studies
  - E.g., Jessie Bloom et al. fishing vessel study
- Prevention efficacy of broadly neutralizing monoclonal antibodies

Voysey et al. (2021, *Lancet*)

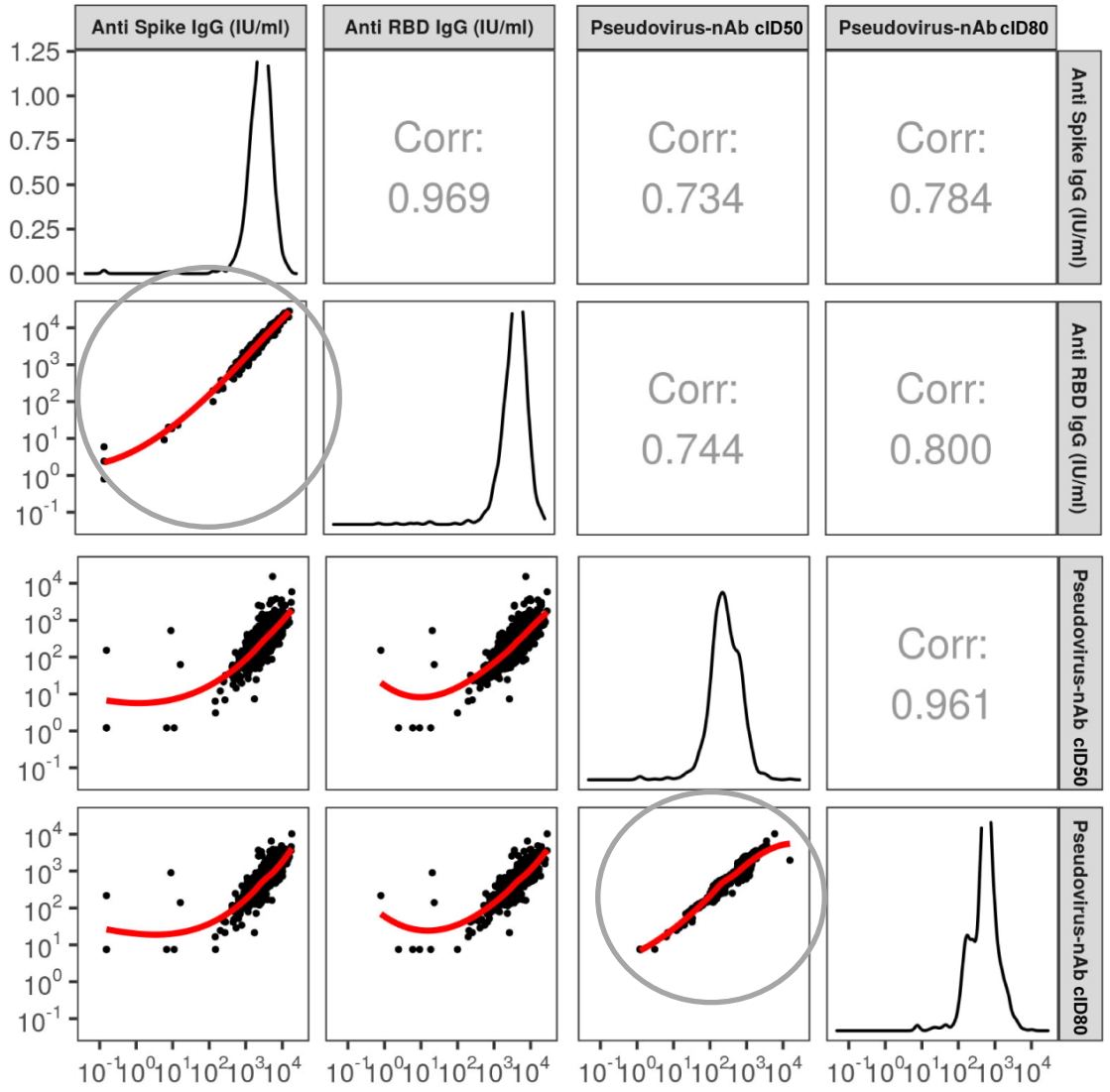


Earle et al. (2021, *Vaccines*)



[1]Oxford/AZ analyses by dose interval (Voysey et al., 2021, *Lancet*) Khoury et al. (2021, *Nat Med*), Earle et al. (2021, *Vaccine*)
[2]Feng, Voysey et al. (2021, *Nat Med*); Bergwerk et al. (2021, *NEJM*)
[3]Corbett, Nason, Seder et al. (2021, *Science*)

Correlations of Day 57 Antibody Markers in Per-Protocol Baseline Negative Vaccine Recipients



- High correlation of bAb Spike and bAb RBD responses (r=0.969)
- High correlation of nAb cID50 and cID80 responses (r=0.961)
- Article focused on reporting results for bAb Spike and cID50
- Moderate-to-high correlation of bAb markers with nAb markers (0.734-0.800)

Serial Dilution for measurement

- Have an error prone scale that `reads` between 2 and 24 pounds
- Want to weigh water . . . but some buckets are >24 pounds

Dilution	Weight	Readout	Estimate
NEAT	48	>24	----
1/2	24	>24	----
1/4	12	12.7	50.8
1/8	6	5.4	43.2
1/16	3	2.8	44.8
1/32	1.5	<2	----
1/64	.75	<2	----
1/128	.375	<2	----

Average 46.3

Wait, readout isn't in pounds

- Suppose readout is light intensity, but varies by day

True weight in pounds	Day 1 lumens
20	2400
10	1200
5	600

- Make 3 buckets: 20, 10, 5 pounds. Calibrate lumens to weight each day. Then measure that day's buckets
  - e.g. if a ¼ dilution reads 1200 lumens +/- 4 x 10 pounds = 40 pounds

mRNA-1273 Vaccine Antibody Over Time

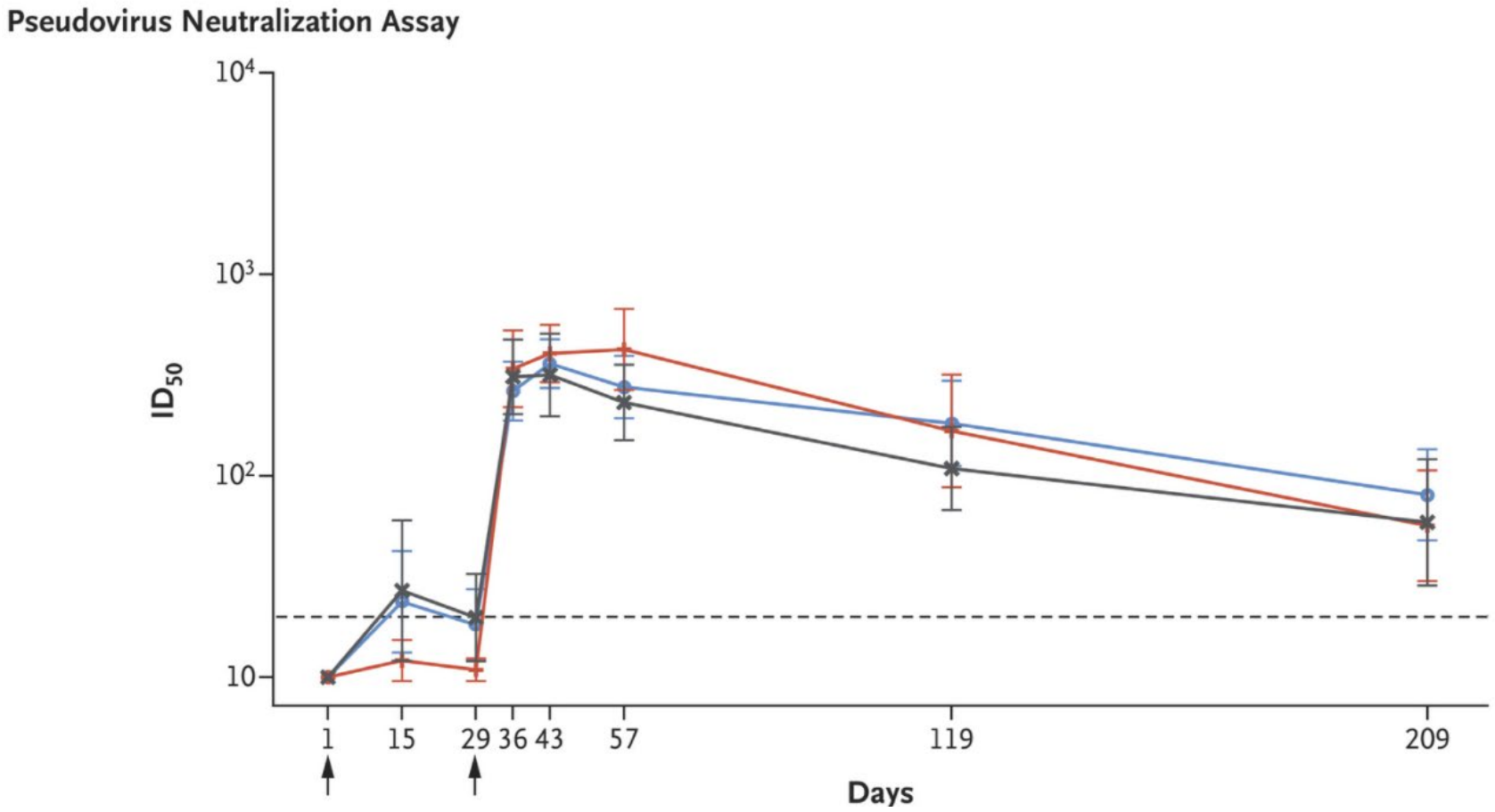
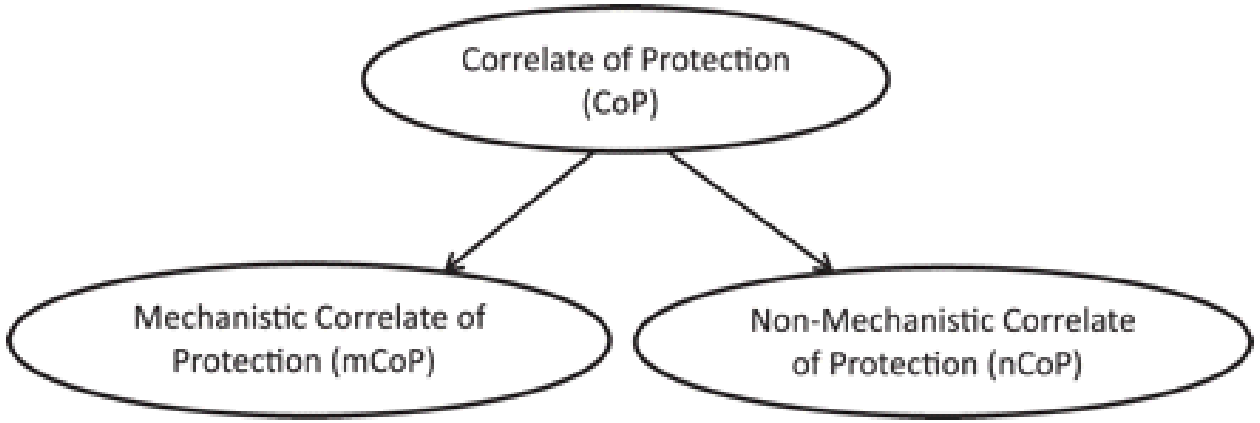


Figure 1. A correlate of protection (CoP) may be either a mechanism of protection, mCoP, or a nonmechanism of ...



e.g. Circulating antibody blocks virus from infecting cells

e.g. Circulating antibody in lockstep with cellular responses that stop disease

Clin Infect Dis, Volume 54, Issue 11, 1 June 2012, Pages 1615–1617, https://doi.org/10.1093/cid/cis238

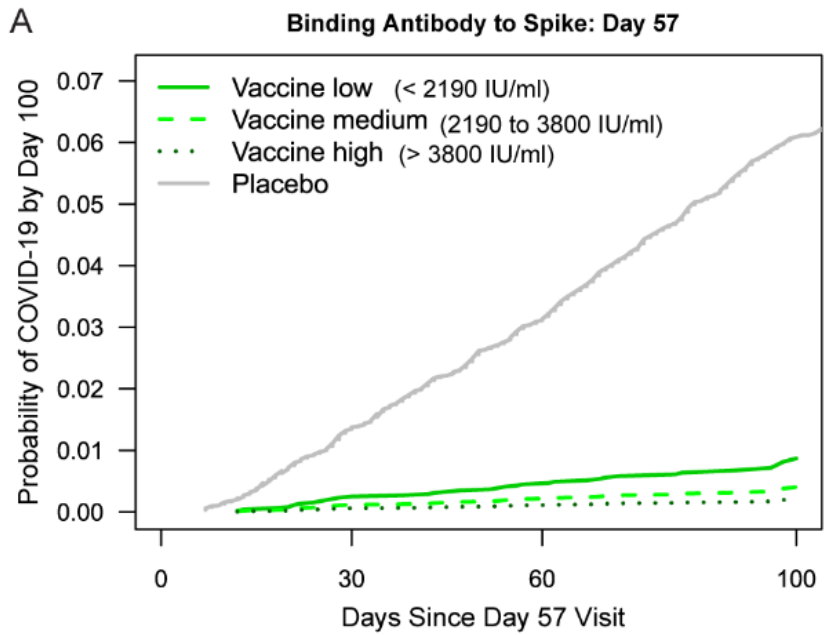
Gilbert & Plotkin CID 2021

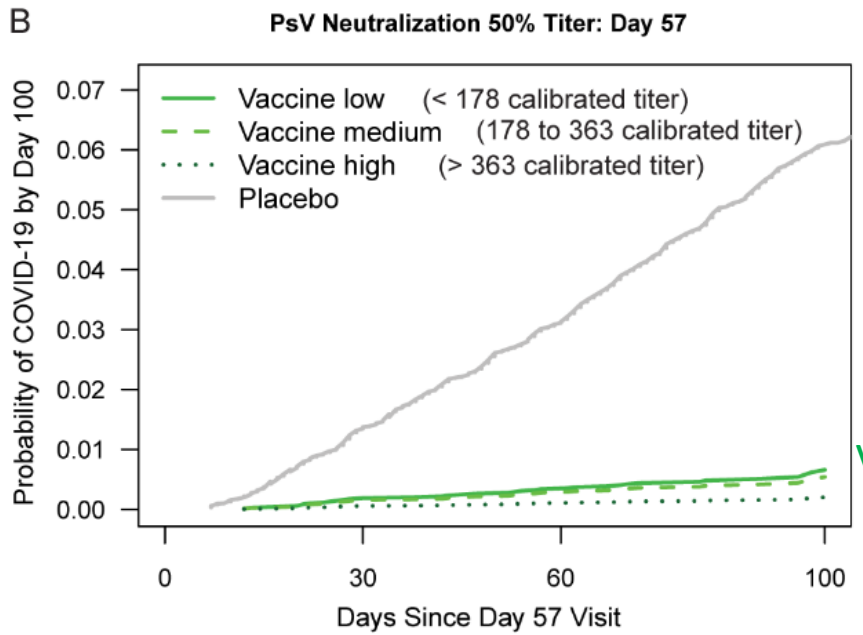
Baseline Demographics and Characteristics Based in the Per-Protocol Set

Characteristics n (%)	Placebo (N=14073)	mRNA-1273 (N=14134)	Total (N=28207)
Sex			
Male	7462 (53.0)	7366 (52.1)	14828 (52.6)
Female	6611 (47.0)	6768 (47.9)	13379 (47.4)
Age at Screening (yr)			
Mean (range)	51.6 (18- 95)	51.6 (18- 95)	51.6 (18- 95)
Age (yr) and health risk for severe Covid-19*			
≥18 and <65 and Not at Risk	8200 (58.3)	8189 (57.9)	16389 (58.1)
≥18 and <65 and at Risk	2324 (16.5)	2367 (16.7)	4691 (16.6)
≥65	3549 (25.2)	3578 (25.3)	7127 (25.3)
Ethnicity			
Hispanic or Latino	2780 (19.8)	2789 (19.7)	5569 (19.7)
Not Hispanic or Latino	11165 79.3)	11212 (79.3)	22377 (79.3)
Not reported and unknown	128 (0.9)	133 (1.0)	261 (0.9)
Race‡			
White	11174 (79.4)	11253 (79.6)	22427 (79.5)
Black or African American	1349 (9.6)	1385 (9.8)	2734 (9.7)
Asian	689 (4.9)	620 (4.4)	1309 (4.6)
American Indian or Alaska Native	111 (0.8)	108 (0.8)	219 (0.8)
Native Hawaiian or Other Pacific Islander	31 (0.2)	35 (0.2)	66 (0.2)
Multiracial	307 (2.2)	295 (2.1)	602 (2.1)
Other	295 (2.1)	299 (2.1)	594 (2.1)
Not reported and unknown	117 (0.9)	139 (1.0)	256 (0.9)
Baseline SARS-CoV-2 Status†			
Negative	14073 (100)	14134 (100)	28207 (100)
Positive	0	0	0
Missing	0	0	0
Baseline RT-PCR			
Negative	14073 (100)	14134 (100)	28207 (100)
Positive	0	0	0
Missing	0	0	0
Baseline bAb Anti-SARS-CoV-2			
Negative	14073 (100)	14134 (100)	28207 (100)
Positive	0	0	0
Missing	0	0	0
Risk Factor for Severe Covid-19 at Screening‡			
Chronic lung disease	688(4.9)	673 (4.8)	1361 (4.8)
Significant cardiac disease	694 (4.9)	711 (5.0)	1405 (5.0)
Severe obesity	936 (6.7)	956 (6.8)	1892 (6.7)
Diabetes	1345 (9.6)	1364 (9.7)	2709 (9.6)
Liver disease	90 (0.6)	95(0.7)	185(0.7)
HIV	77 (0.5)	82 (0.6)	159 (0.6)
Body Mass Index, (kg/m^2)			
Mean (SD)	29.27 (6.650)	29.28 (6.827)	29.28 (6.739)

bAb = binding antibody concentration; IRT = interactive response technology; RT-PCR = reverse transcription polymerase chain

Day 57 Marker Correlates of Risk: Cumulative Incidence by Tertiles





Placebo

Vaccine Tertiles

	No. At-Risk*			
Low:	4573	4552	4187	1411
Med:	4804	4741	4359	1843
High:	4687	4656	4326	1670
Plac:	13758	13218	11165	3364

	Cumulative No. of COVID-19 Endpoints**			
Low:	0	8	14	25
Med:	0	7	10	14
High:	0	3	5	8
Plac:	0	187	409	646

	No. At-Risk*			
Low:	4727	4705	4384	1391
Med:	4681	4635	4260	1669
High:	4656	4609	4228	1865
Plac:	13758	13218	11165	3364

	Cumulative No. of COVID-19 Endpoints**			
Low:	0	10	13	21
Med:	0	4	10	18
High:	0	3	7	8
Plac:	0	187	409	646

*No. At-Risk = estimated number in the population for analysis: baseline negative per-protocol vaccine recipients not experiencing the COVID-19 endpoint through 6 days post Day 57 visit.
**Cumulative No. of COVID-19 Endpoints = estimated cumulative number of this cohort with a COVID-19 endpoint.

Proper Correlates of Protection

antibody	# Vaccinees	# Infections	Adjusted P(disease)*	Vaccine Efficacy
10	100	20	0.165	0.59
100	800	80	0.100	0.75
1000	100	5	0.070	0.83

Naive Vaccine Efficacy
0.500
0.750
0.875

Suppose: Placebo Group attack Rate 40%

Predicted Vaccine Efficacy at Antibody = 10 is 100% x (1 - $\frac{0.165}{0.40}$) = 0.59

*- Disease rate for a trial with equal young and old at each Ab level
Like randomizing 1000 to vaccine and then 3 levels of antibody 1:8:1