Correlation Between Protection and *ex vivo* Neutralization in the Context of Pre-exposure Prophylaxis

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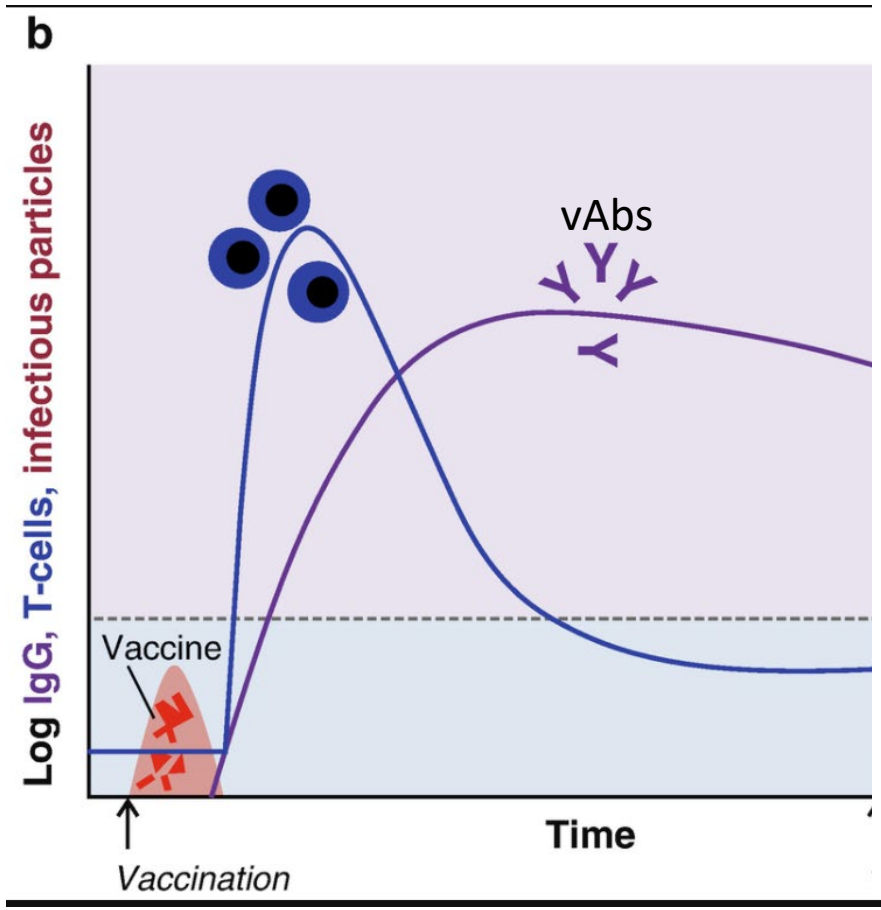
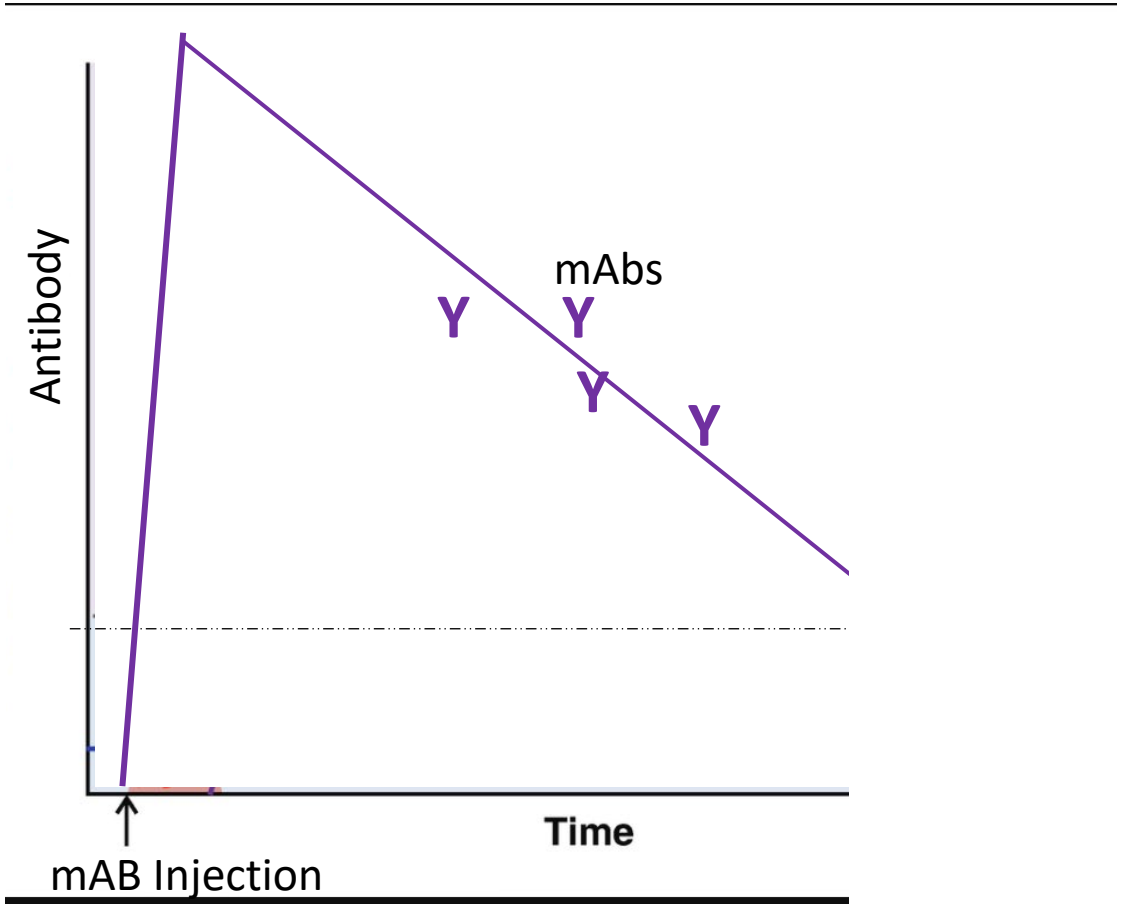
Motivation

- Monoclonal antibody (mAb) protective efficacy (PE) is due entirely to antibody
  - Estimate efficacy as a function of neutralization titer at exposure
- Vaccine efficacy (VE) is due to antibody and other things
  - Estimate efficacy as a function of neutralization titer at exposure
- Use same pseudo-virus neutralization assay for both trials
- Compare VE and PE curves to assess relative contribution of antibody to total vaccine effect.
- *Evaluate neutralization titer as a Correlate of Protection (CoP) for mAbs*

Vax Complex



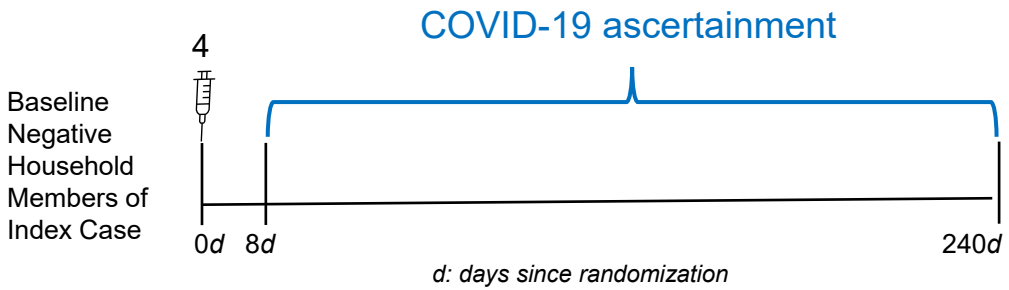
mAbs Simple

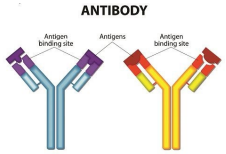


Jiskoot W., Kersten G.F.A., Mastrobattista E., Slütter B. (2019) Vaccines. In: Crommelin D., Sindelar R., Meibohm B. (eds) Pharmaceutical Biotechnology. Springer, Cham. https://doi.org/10.1007/978-3-030-00710-2_14

Two Trials

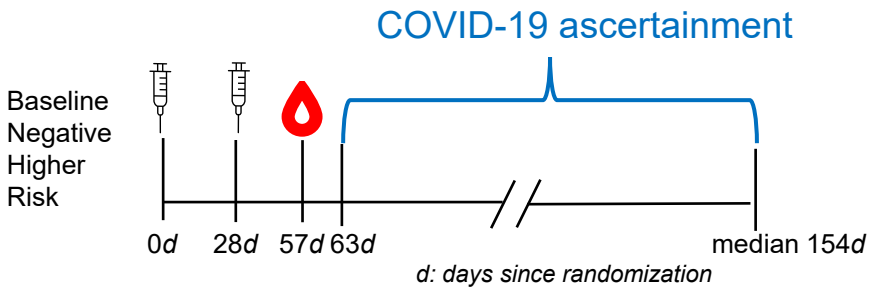
COV-2069 mAb Prevention Trial: CAS+imb Injection or Placebo





Timeline: July 2020 – October 2021
Location: U.S., Moldova, Romania
Events: 11 mAb; 63 placebo
Number of Particpants: 1630

mRNA-1273 Vaccine Trial : mRNA-1273 Vaccination or Placebo



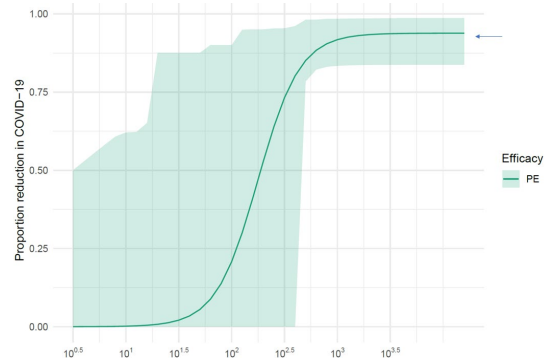
Timeline: August 2020 - March 2021
Location: U.S.
Events: 47 Vaccine; 659 Placebo
Number of Participants: 28281

CAS + imb: casirivimab and imdevimab; mAb: monoclonal antibody; PCR: polymerase chain reaction

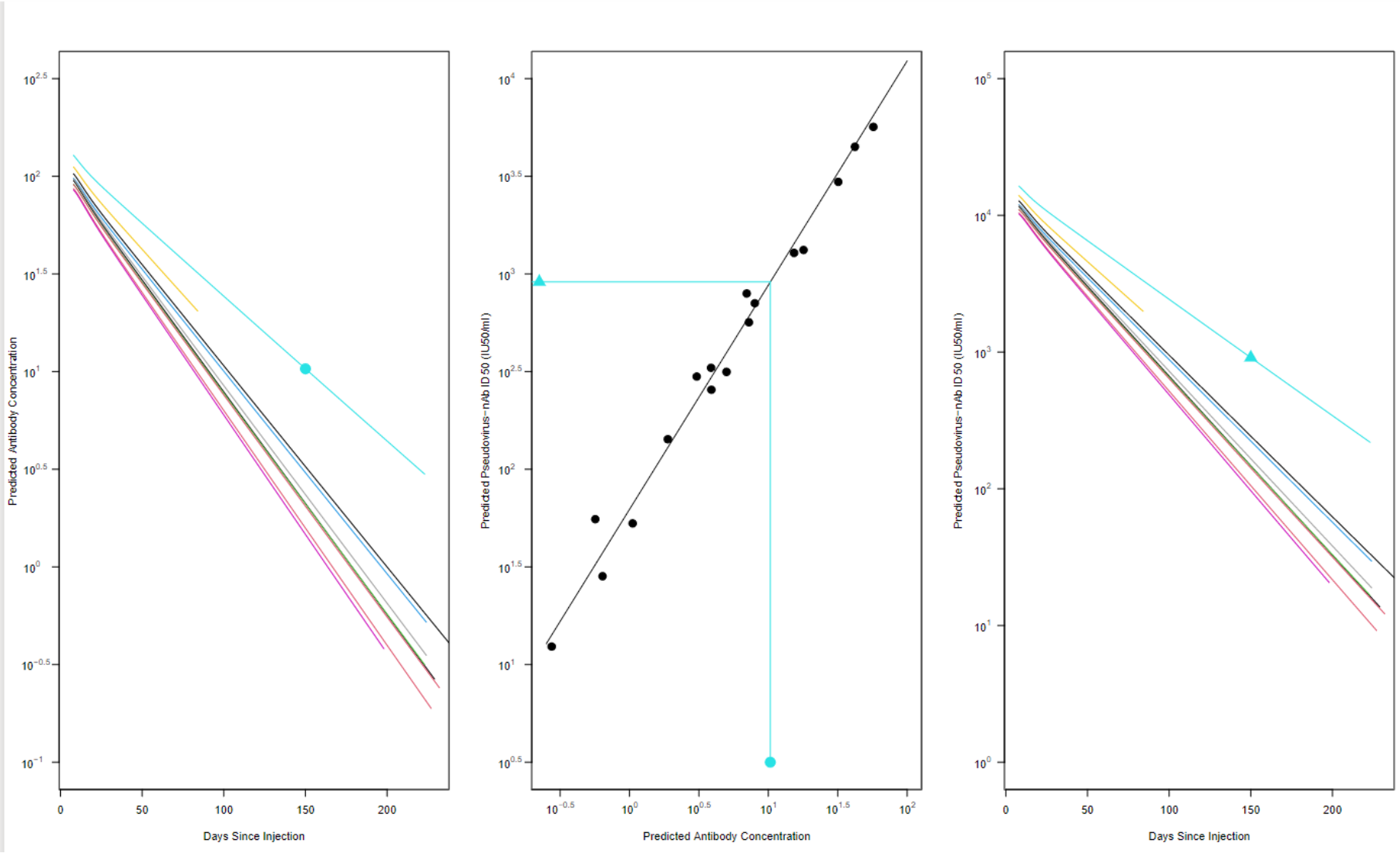
Outline of Approach

- Derive *individual* predicted titer for each day of follow-up
  - mAb trial: Use PK modeling & map to neutralization titer
  - Vaccine trial: Use measured peak antibody titer and estimated decay
- Use regression modeling to correlate COVID-19 with predicted titer

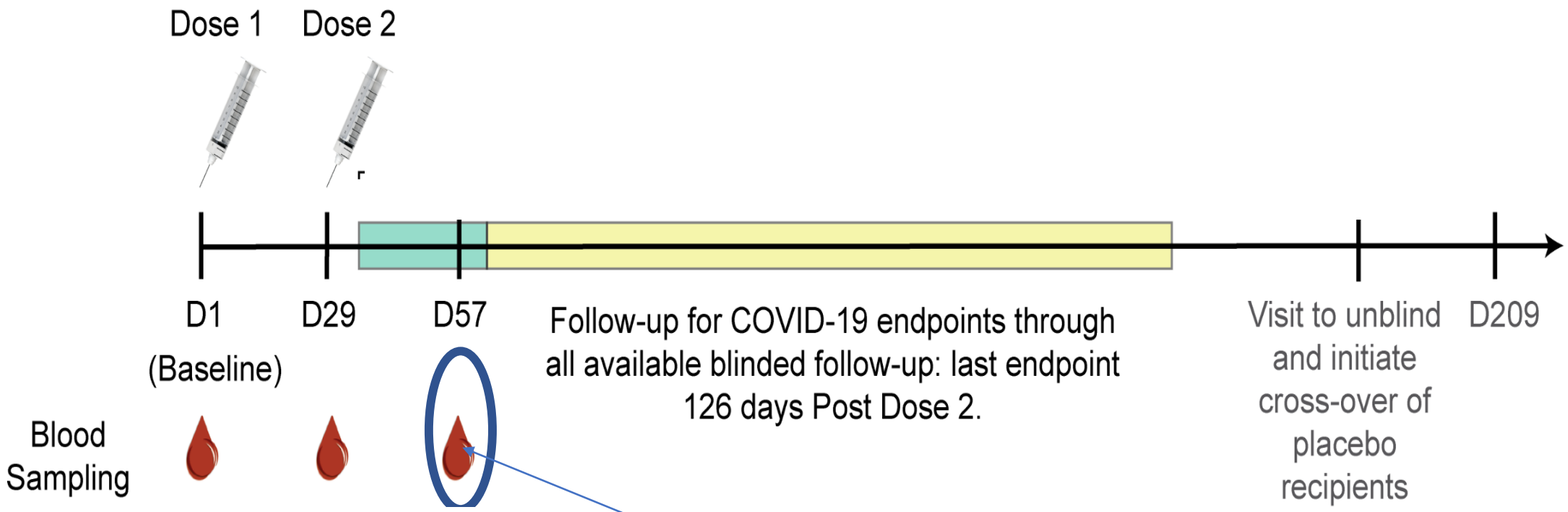
Subject	Day post injection	Arm	Predicted mAb titer	COVID-19 case?
1417	8	mAb	10000	No
1417	9	mAb	9727	No
1417	10	mAb	9462	Yes
…	….		…	….



From concentration to titer for mAb trial



Peak Titer and Decay for Vaccine Trial

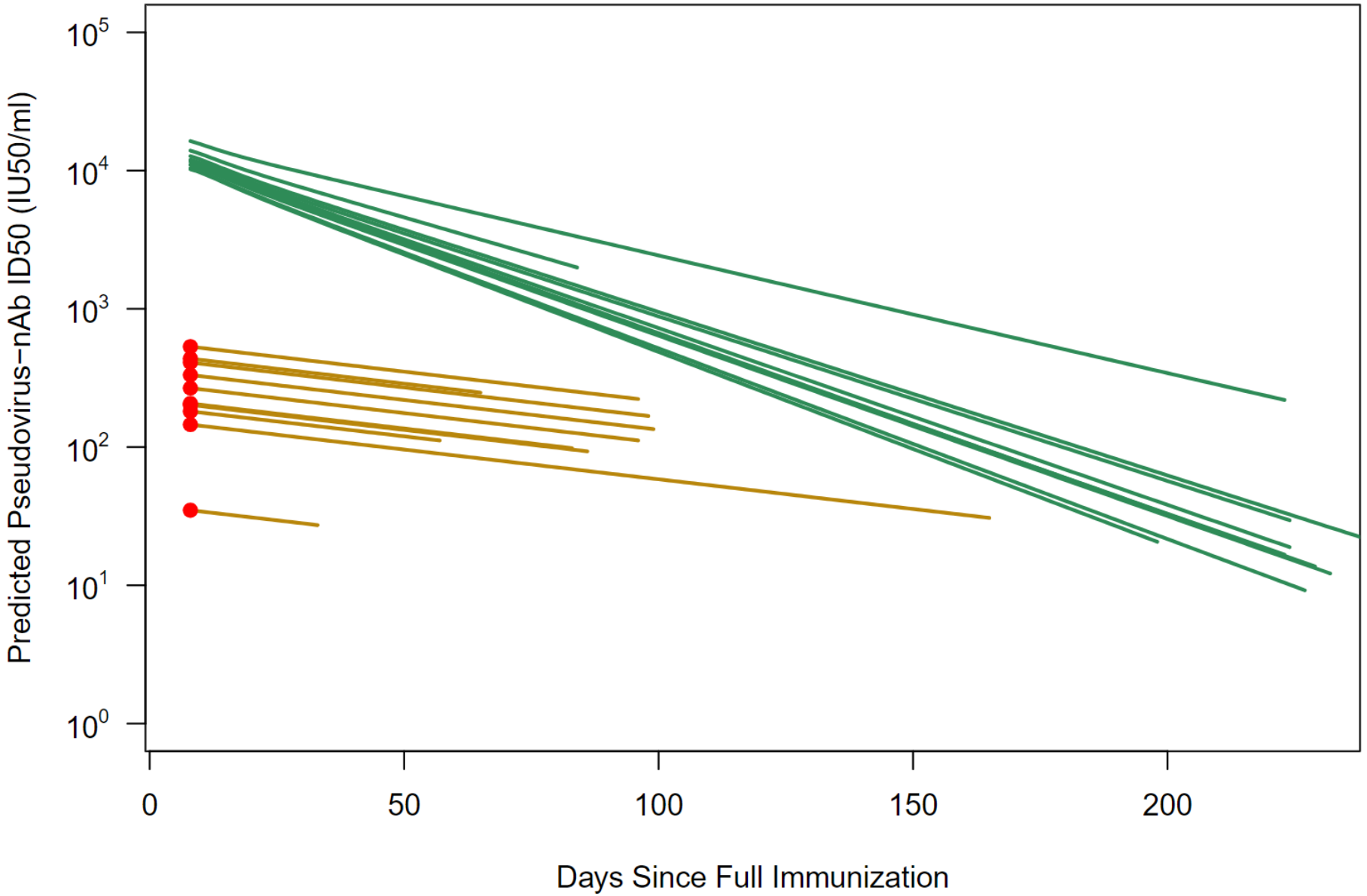


Draw Serum, determine D57 = day 57 neutralization titer

At day t post D57: Ab(t) = D57 – 0.0043 t

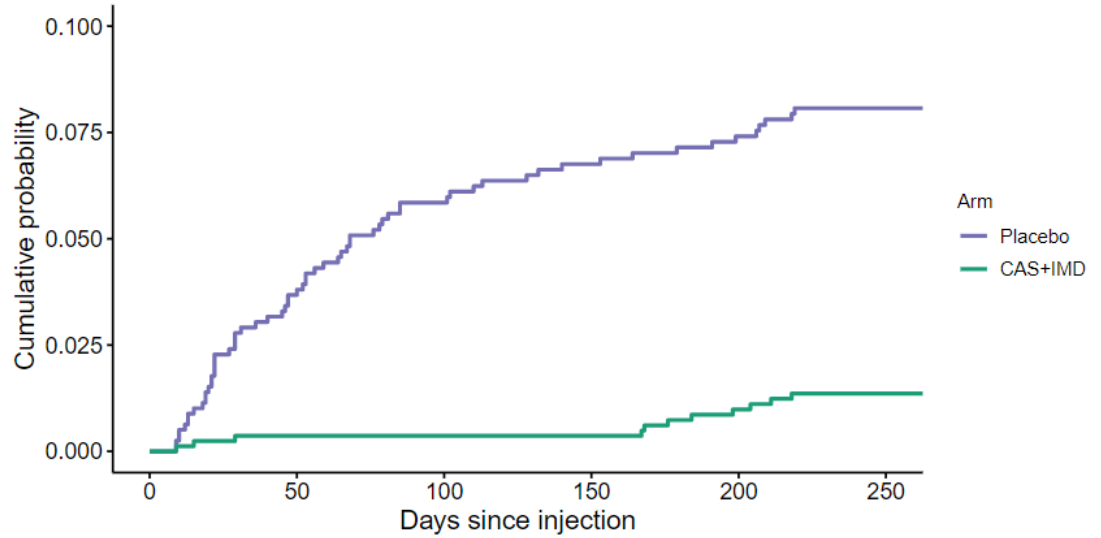
From Longitudinal Immunogenicity Study

mAbs and vAbs by time since full immunization

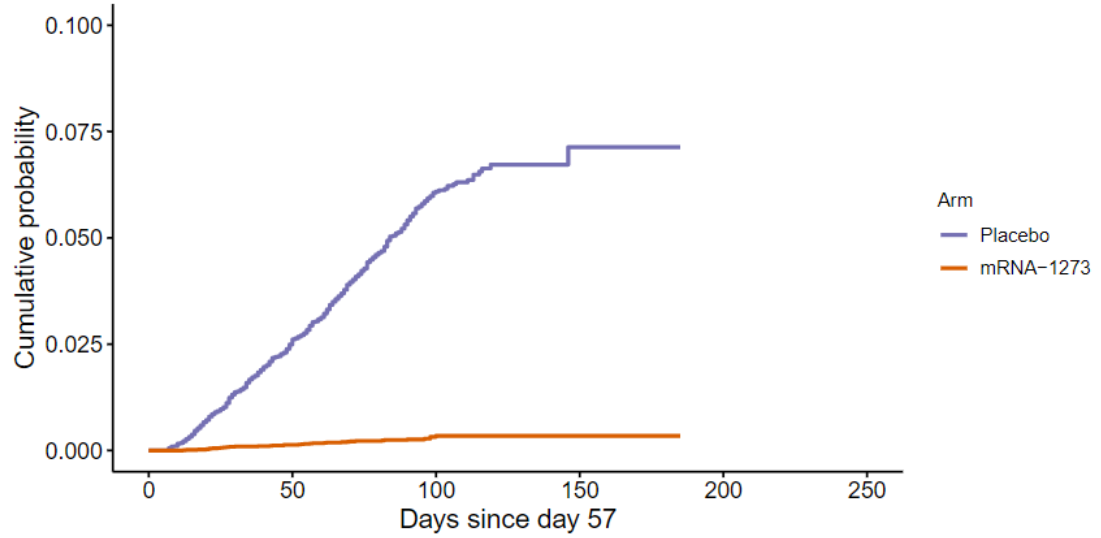


mAbs
vAbs

Cumulative Incidence of COVID-19

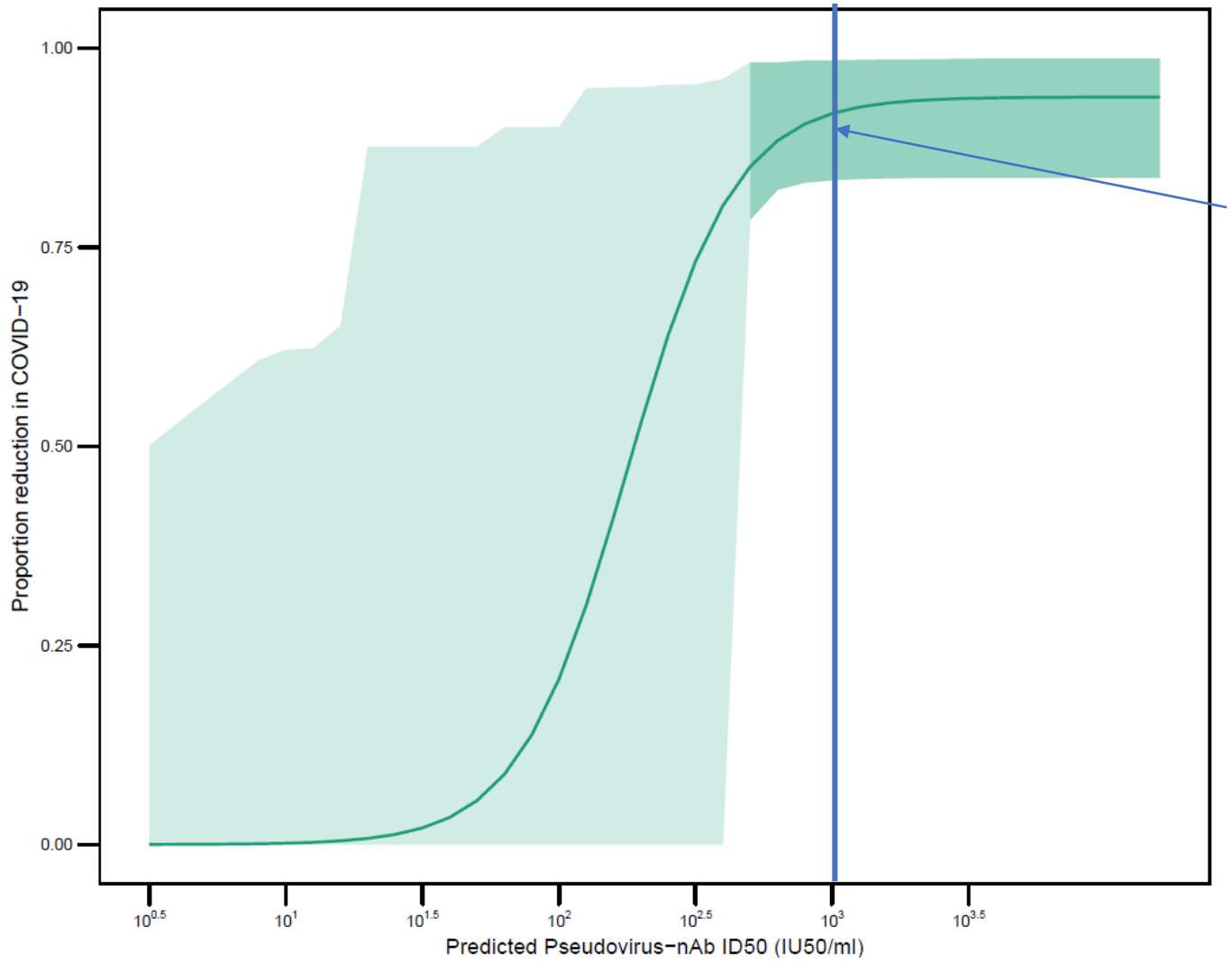


COV2069: mAb trial



COVE: Vaccine Trial

Correlate of Protection curve for mAb



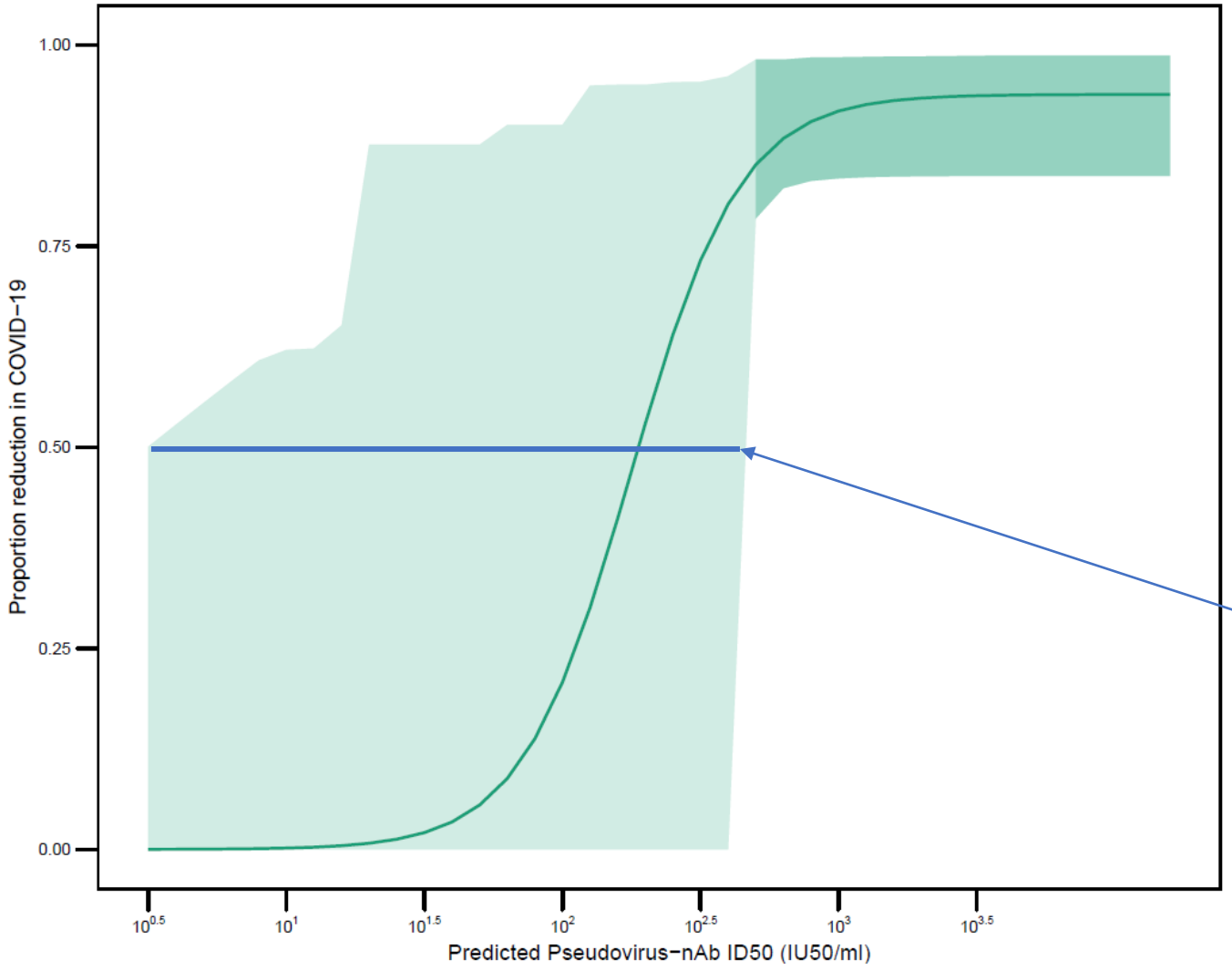
At a titer of 1000 IU50/ml:
92% Reduction in COVID-19

(95% CI: 84%, 98%)

Test of Association p<0.01

1000 IU50/ml =
reciprocal dilution of 4132.24

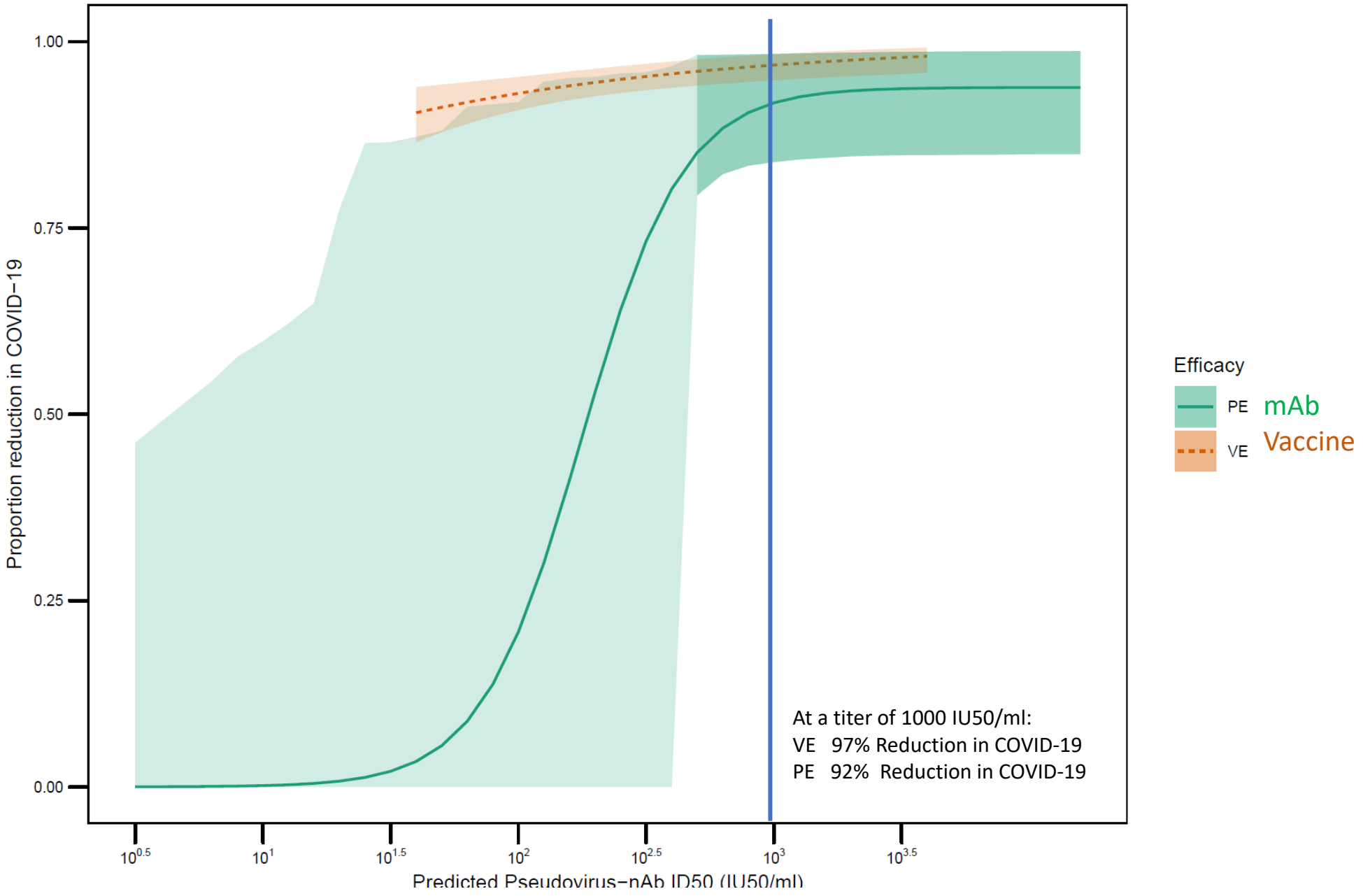
Correlate of Protection Curve for mAb



Titer for 50% PE: :
200 IU50/ml
(95% CI: 5 IU50/ml, 501 IU50/ml)

200 IU50/ml = 826 reciprocal dilution

Comparison of VE and PE as a function of titer at exposure



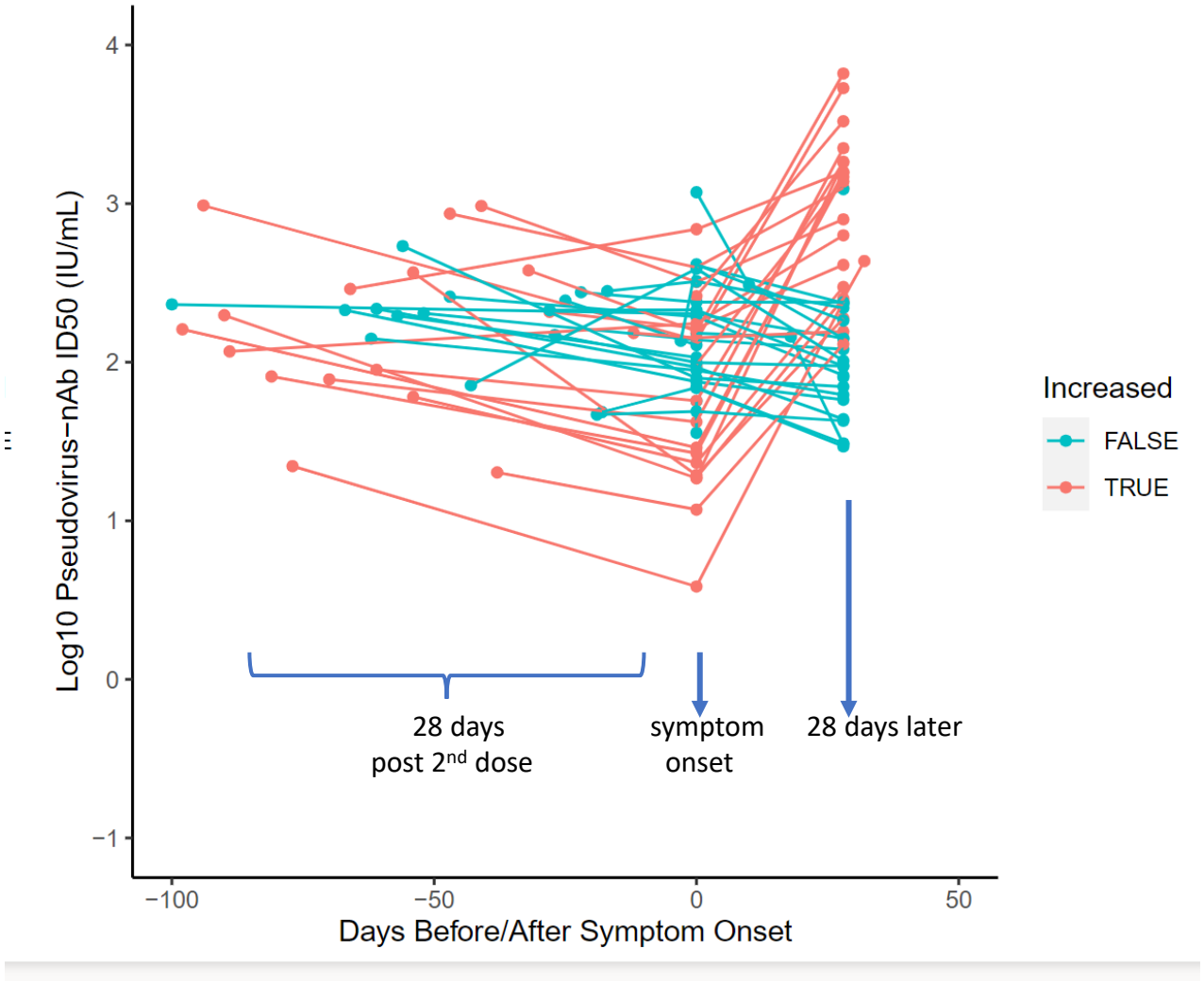
Quantifying The Difference in Efficacy

Neutralization Titer	mRNA-1273 Vaccine Efficacy VE	REGEN-COV Protective Efficacy PE	% Total Vaccine Effect Mediated by *Extant** Antibody	Probability a Protected Vaccinee Would be Protected by mAb
100 IU/ml	91% (87,94)	21% (0%, 90%)	9% (0%, 88%)	0.22 (0.00, 0.97)
1000 IU50/ml	97% (95%,98%)	92% (83%, 99%)	72% (51%,100%)	0.95 (0.87, 1.00)

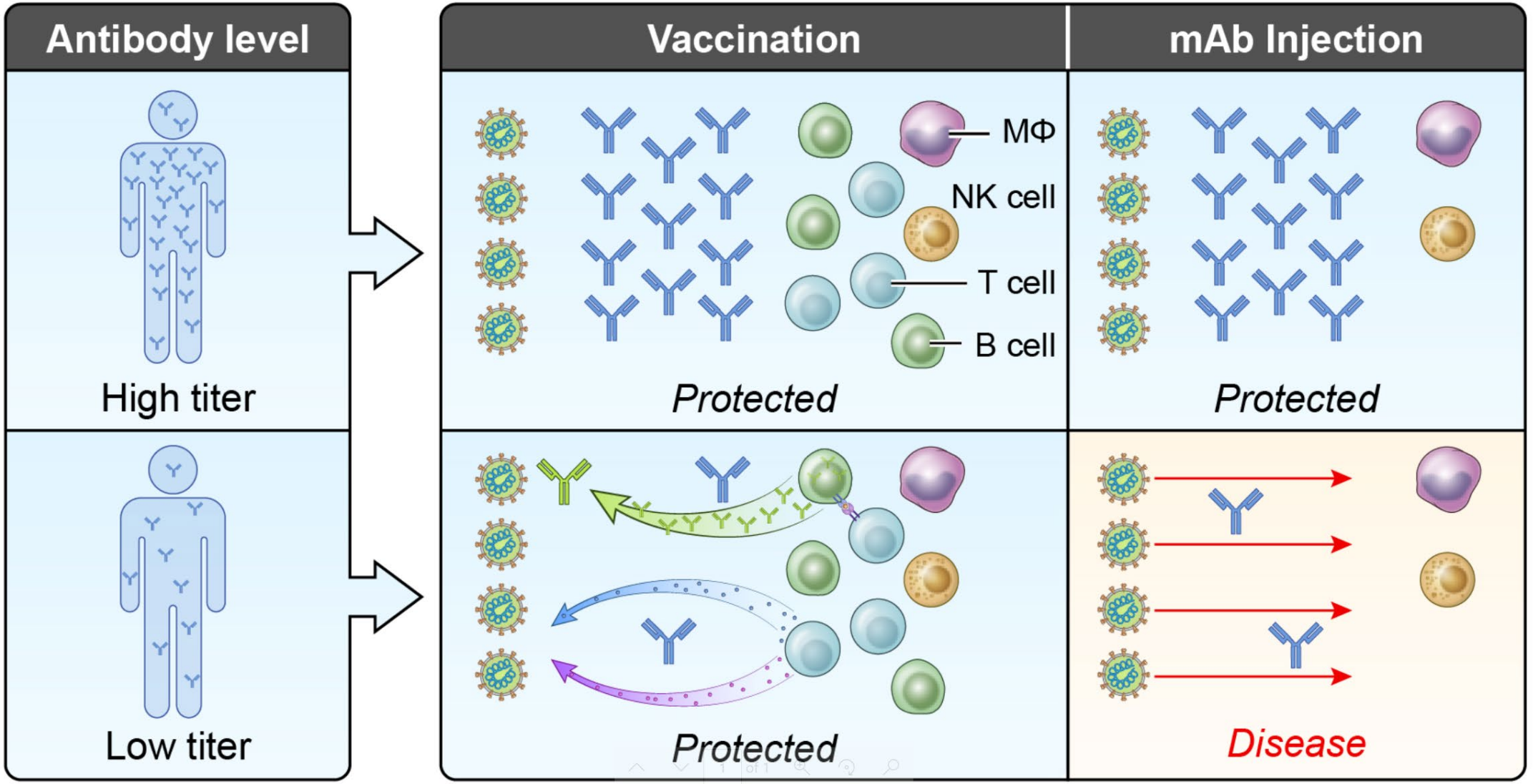
*Circulating and mucosal antibody at exposure, excludes anamnestic responses from B-cells

Mediation formula is log(1-PE)/log(1-VE) x 100%.
The probability that vaccine protection is due to antibody is PE/VE.

Low Titer Vaccinated Disease Cases Get Boosted



Vaccine vs mAb Protection



Conclusions

- Vaccine induced protection at higher titers mostly driven by extant antibody, less so at lower titers
- Strong correlation between titer and protection for mAbs supports titer as a mechanistic correlate of protection for mAbs
- Titer can aid in approval decisions for next generation mAbs
  - Trust but verify with post-approval endpoint studies?
- Ideal to get CoP curves for other mAbs

Collaborators

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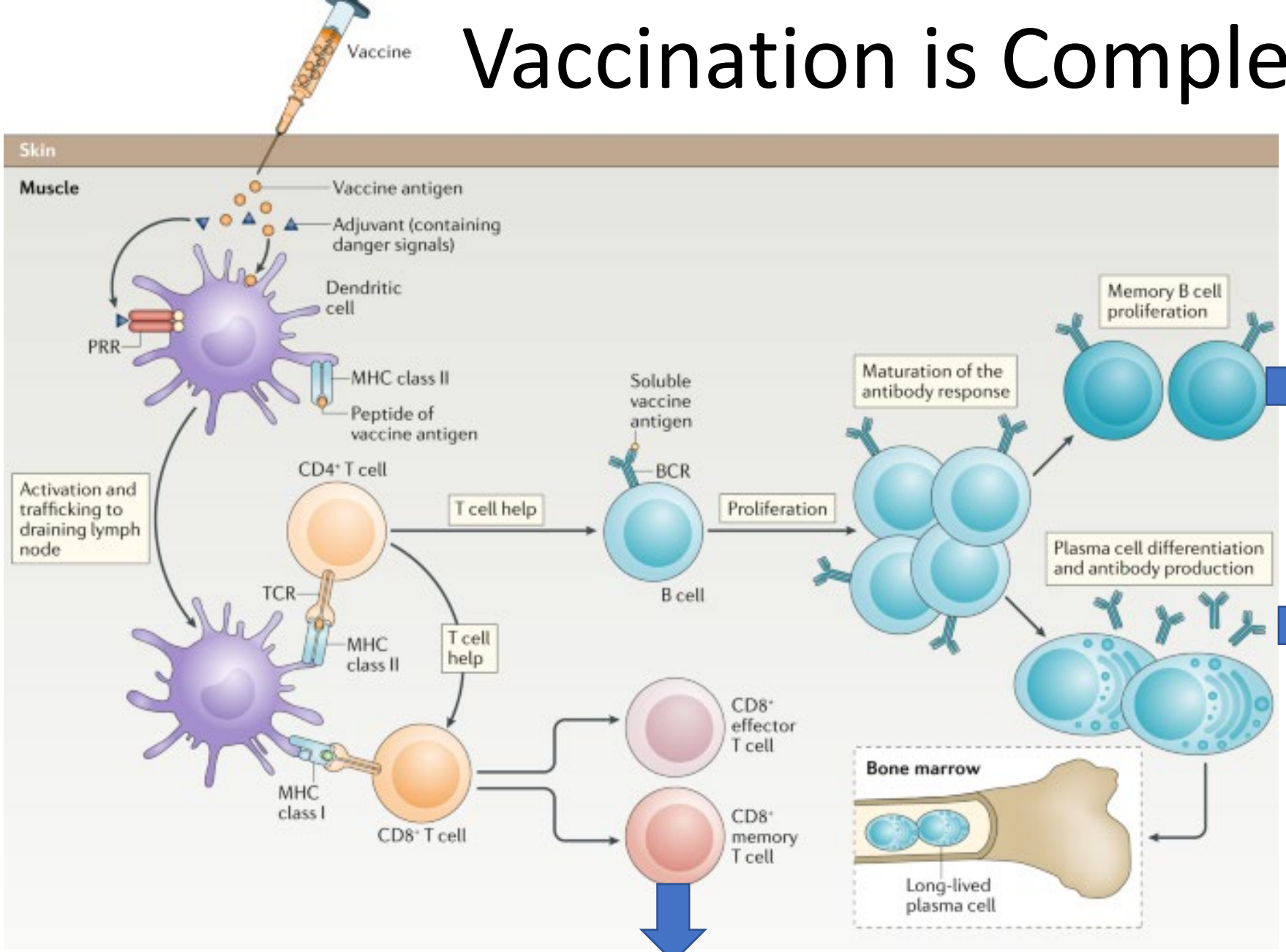
- Duke University: David Montefiori[3]
- Moderna: Jacqueline Miller[9], Honghong Zhou[9], Weiping Dang[9]
- Brigham and Women's Hospital: Lindsey R Baden[5],
- Baylor College of Medicine: Hana M El Sahly[6]
- Fred Hutch: Holly Janes[7] Youyi Fong Peter B. Gilbert[7,11,12]
- Emory University: David Benkeser[10]
- UNC: Myron S. Cohen[13]

Backup Slides

Vaccination is Complex



B cells

(make antibodies if infected enough)

Extant Antibodies

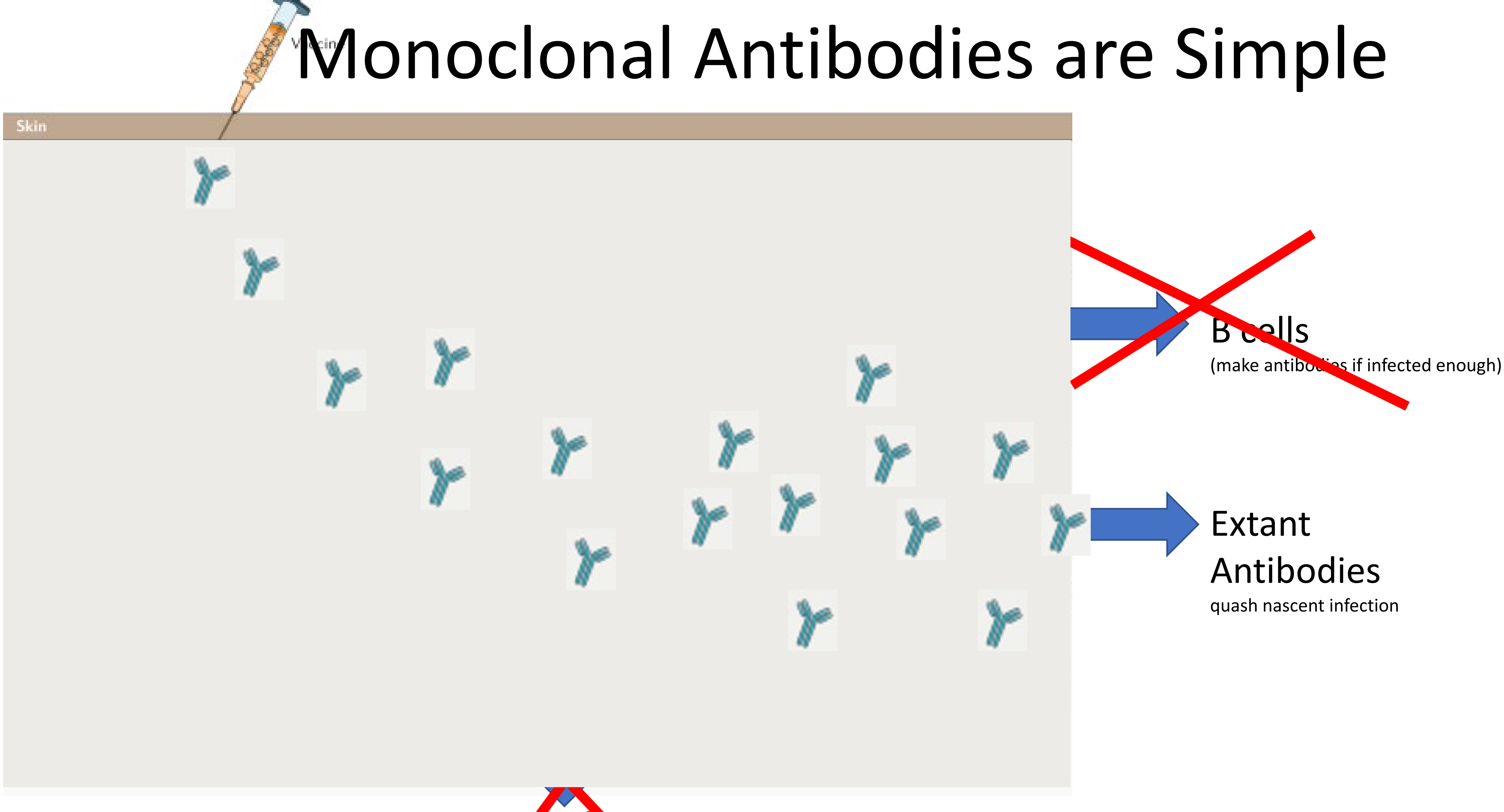
quash nascent infection

T cells

(kill infected cells, help out)

Pollard AJ. Nat Rev Immunol. 2021 Feb;21(2):83-100.

Monoclonal Antibodies are Simple



Pollard AJ. Nat Rev Immunol. 2021 Feb;21(2):83-100.

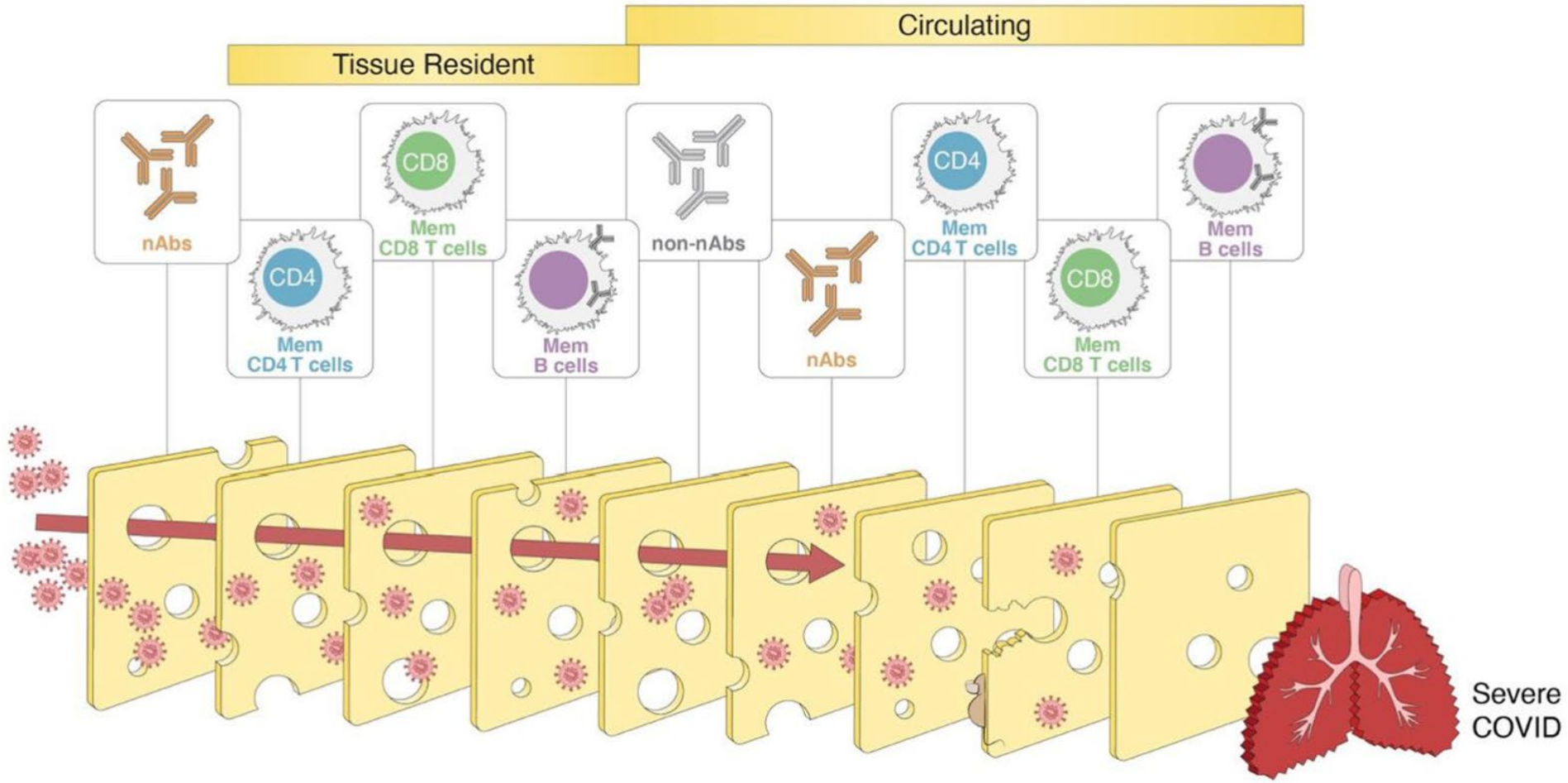
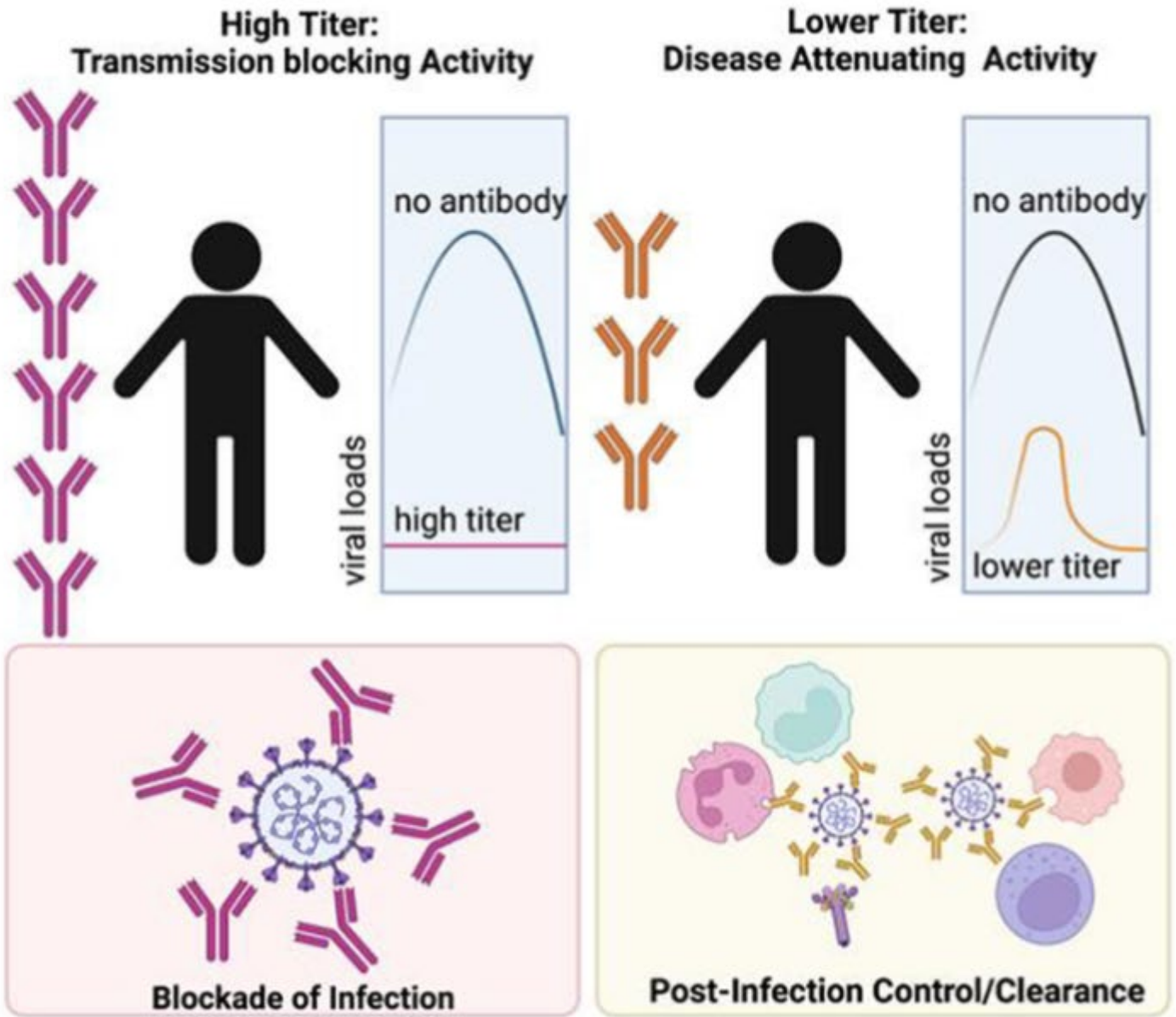


FIGURE 3 Layered defenses against SARS-CoV-2, or the "Swiss cheese" model of immunity. Multiple types of adaptive immunity with diverse mechanisms and locations likely provide layers of defense against COVID-19. Conceptually, layered defenses are like a "Swiss cheese model": even though each layer is imperfect, all together they make it highly unlikely that the pathogen breaches all of the layers of defense. Graphic inspired by the masking and public health layered defenses Swiss cheese model of Ian M. Mackay

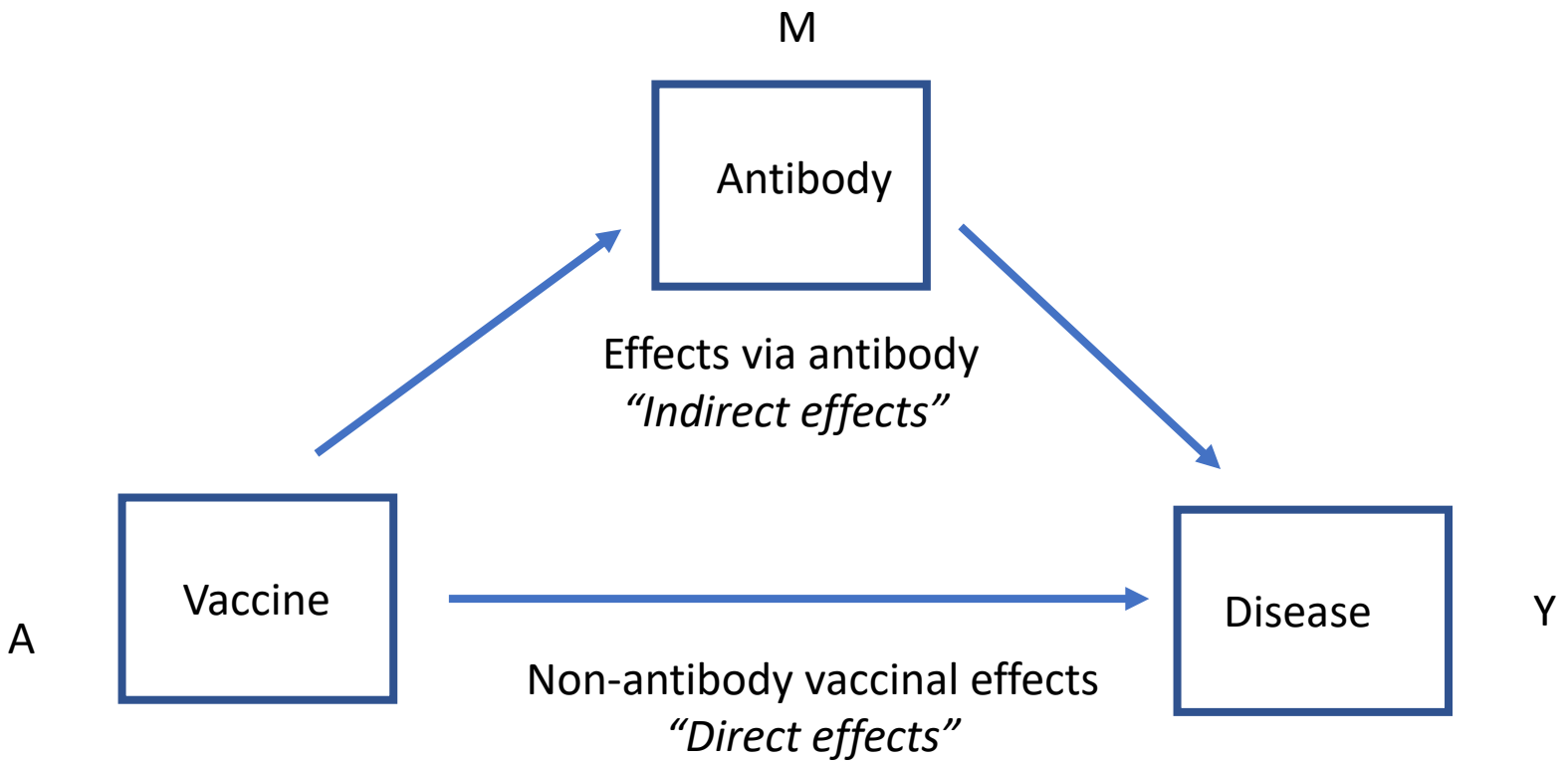
Goldblatt, Alter, Crotty, Plotkin 2022. Immunological Reviews. 2022;310:6–26.

FIGURE 6 Antibody mechanisms of action. The cartoon depicts that potential contribution of Fab versus Fc mediated antibody functions at different antibody titers. Where neutralization alone may be sufficient to block transmission at peak titers (left). However, as titers wane, or variants evade large fractions of antibodies, the ability of antibodies to leverage immune effector functions may be vital to protection from disease



Goldblatt, Alter, Crotty, Plotkin 2022. Immunological Reviews. 2022;310:6–26.

How *much* does antibody contribute to protection?



DAG applies conditional on X Assume no unmeasured confounders

Deconstruction for an idealized 3-arm trial

Arm	Cases
Placebo	100
vAbs	20
Vaccine = vAbs + B/T cells	5

80% reduction from vAbs

75% additional reduction from B/T cells

95% Total reduction from Vaccine

Total = vAbs x B/T cells

0.05 = 0.20 x 0.25

= $0.05^{0.54}$ x $0.05^{0.46}$ → 54% total effect via vAbs

Probability a protected vaccinee would be protected if assigned to mAb arm: Idealized Trial

Arm	Cases
Placebo	100
vAbs	20
Vaccine = vAbs + B/T cells	5

95 protected by Vaccine

80 protected by vAbs

Probability = 80/95

Proportion of total vaccine effect mediated by extant antibody at a titer of 10^3

- $1 - VE = \theta_I \; x \; \theta_D$
- $\text{Total Effect} = \text{Antibody “Indirect”} \; \text{x} \; \text{non-antibody “Direct”}$
- $0.03 = 0.03^{\text{P}} \; \text{x} \; 0.03^{(1-\text{P})}$
- $0.03 = 0.08 \; \text{x} \; 0.03^{(1-\text{P})}$
- $\log(0.03) = \log(0.08) + (1\text{-P}) \log(0.03)$

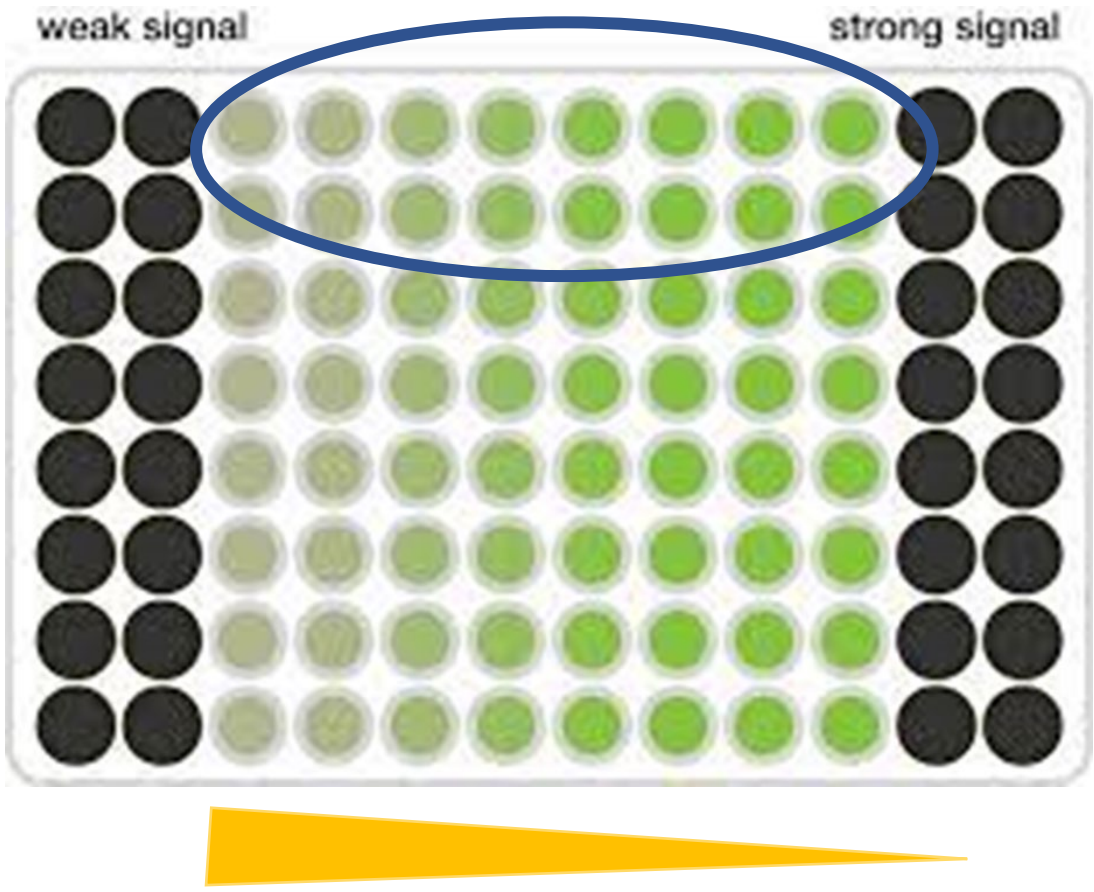
$\Rightarrow$P = log(0.03)/log(0.08) = 0.72

$\Rightarrow$At a titer of 1000 or 10^3 72% of the Total effect is mediated via antibody

Pseudo-Virus neutralization assay in a 96-well plate

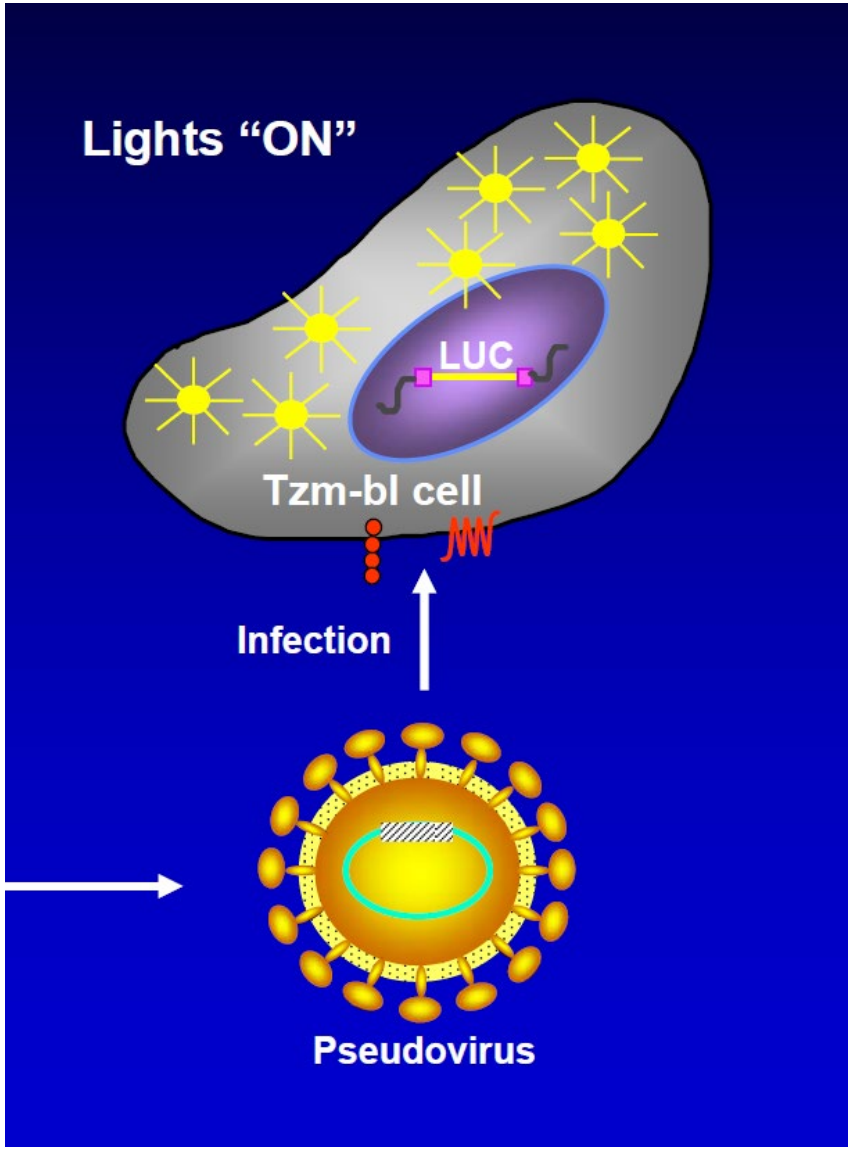
- Put infectable cells in well
- Fill up 16 wells with virus
- Mix with 8 5-fold dilutions of serum run in duplicate

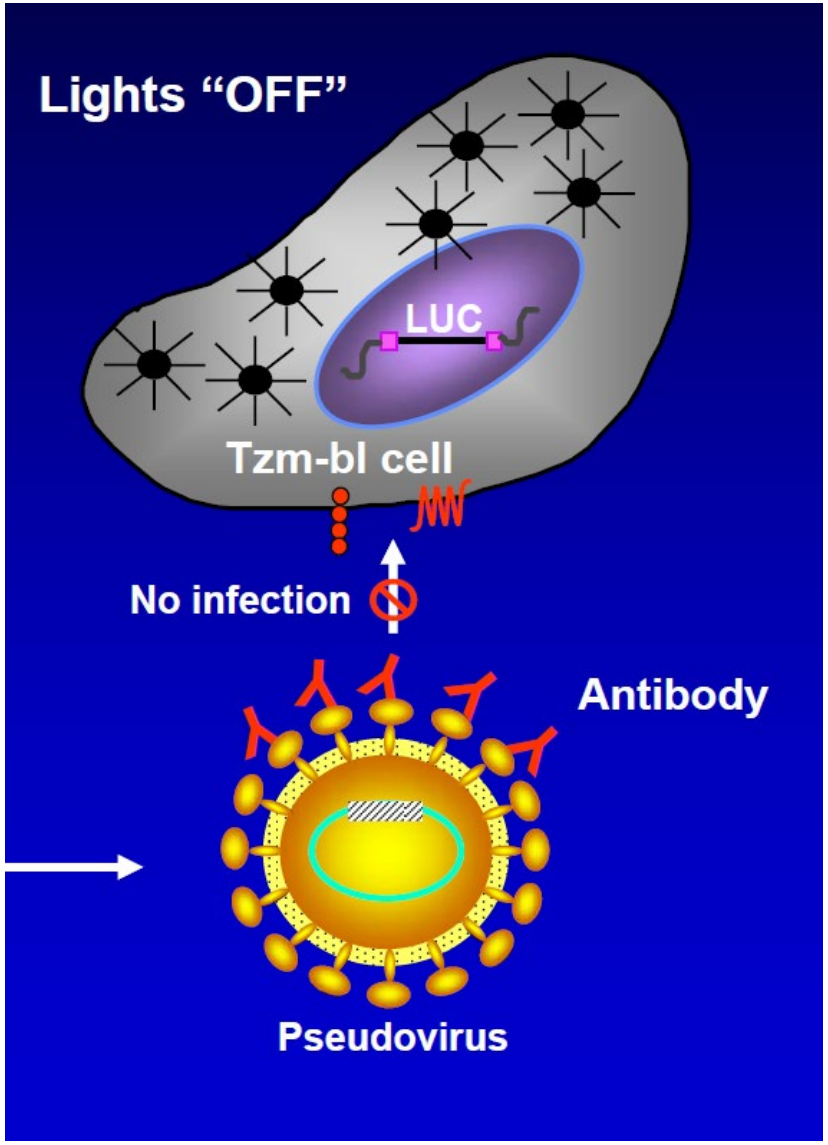
- Record light intensity



16 Wells
For Fred
Serum

How the Pseudo-Virus Neutralization Assay works



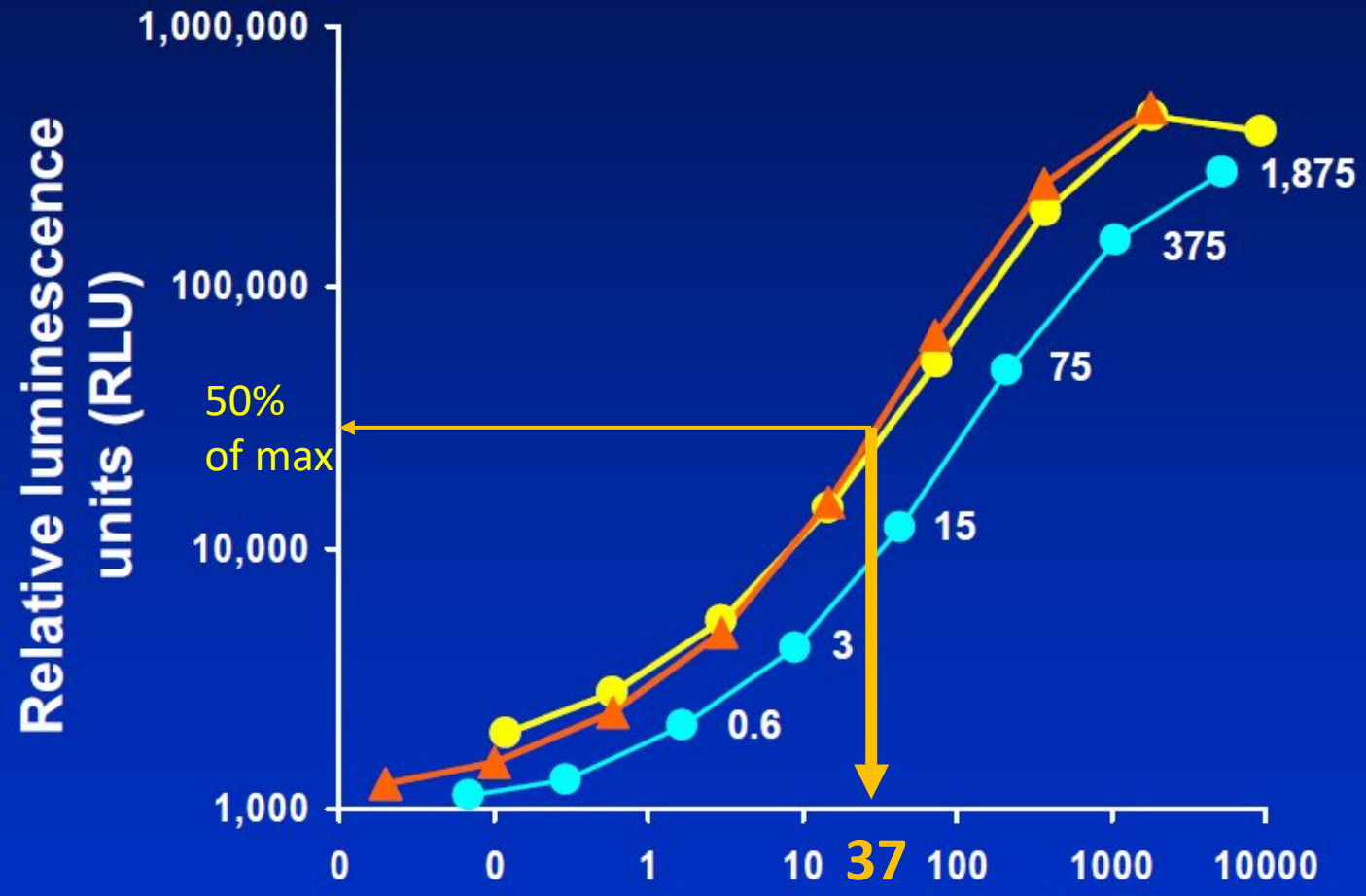


In each well a cage fight

Mix

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

Lights out=> antibody wins!

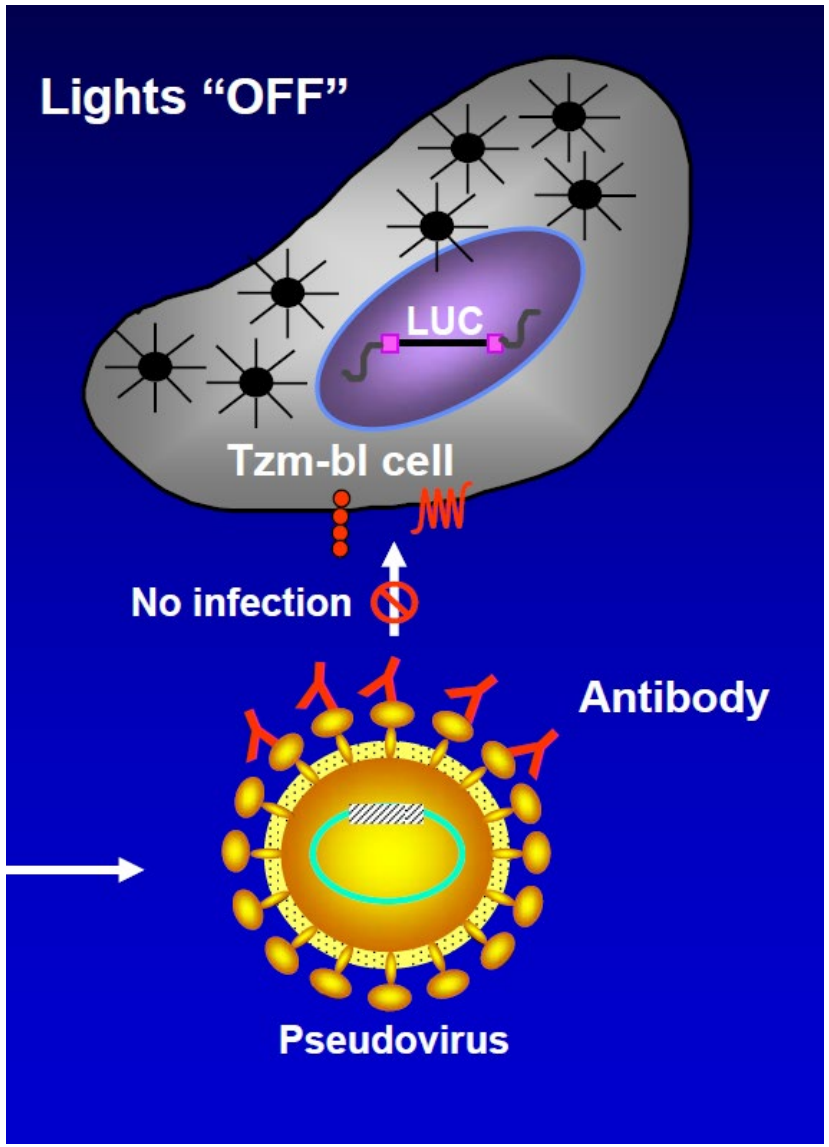


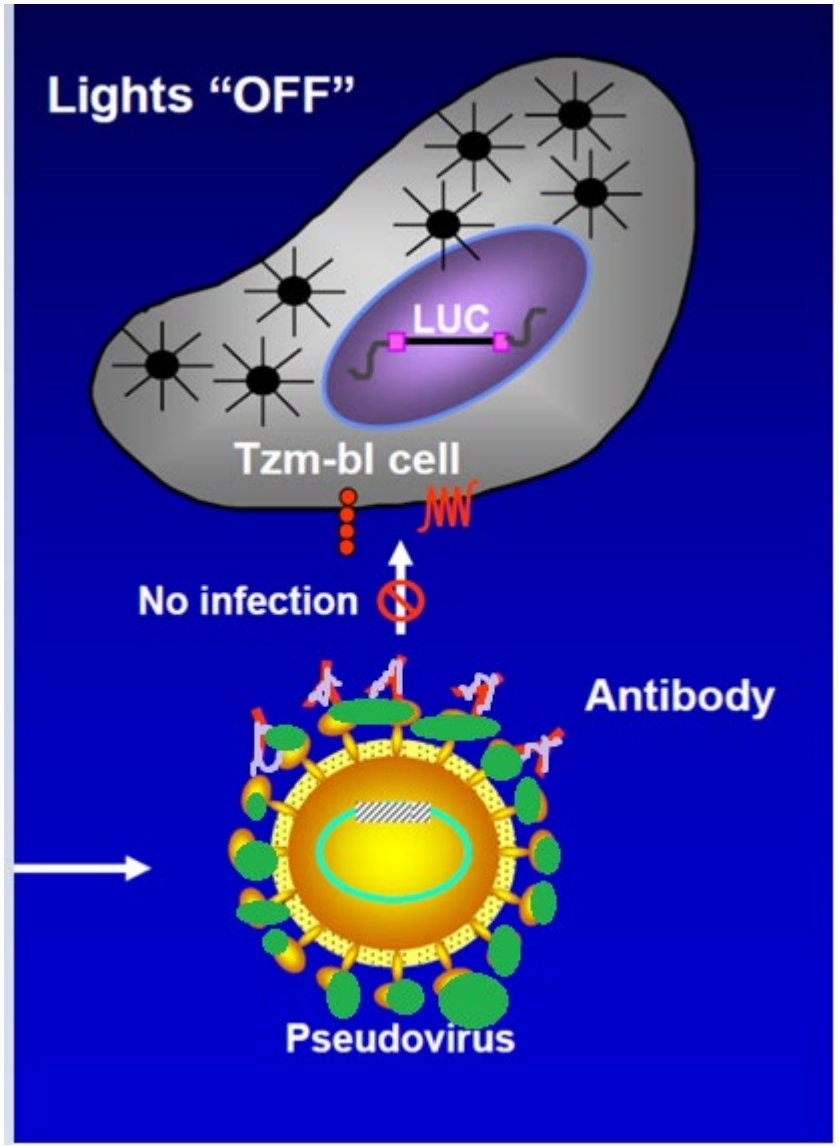
Concentration of Antibody

ID50
infectious dose
that achieves 50%
of max light

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

Strain Specific Neutralization Assay





Ancestral Virus, Ancestral Antibody Y

Omicron Virus Omicron Antibody Y

mAb CoP Model

- Cox model relates risk to neut titer at exposure time
- Use 3 parameter logistic curve: 0 effect if no Abs, <100% effect

$$h(t)=h0(t) \quad Z \quad [\, T + (1-T) \ \exp[A0+A1\ mAb(t)]/(1+\exp[A0+A1\ mAb(t)])$$

Placebo Risk of Disease On day d

1 if vaccine group
0 if placebo group

3 parameter logistic function

mAb(t) = an *individual's projected* ID50 titer on day t based on predicted concentration converted to ID50
3PL has 0 PE with zero antibody, asymptotes to PE = 1 – T with saturated antibody

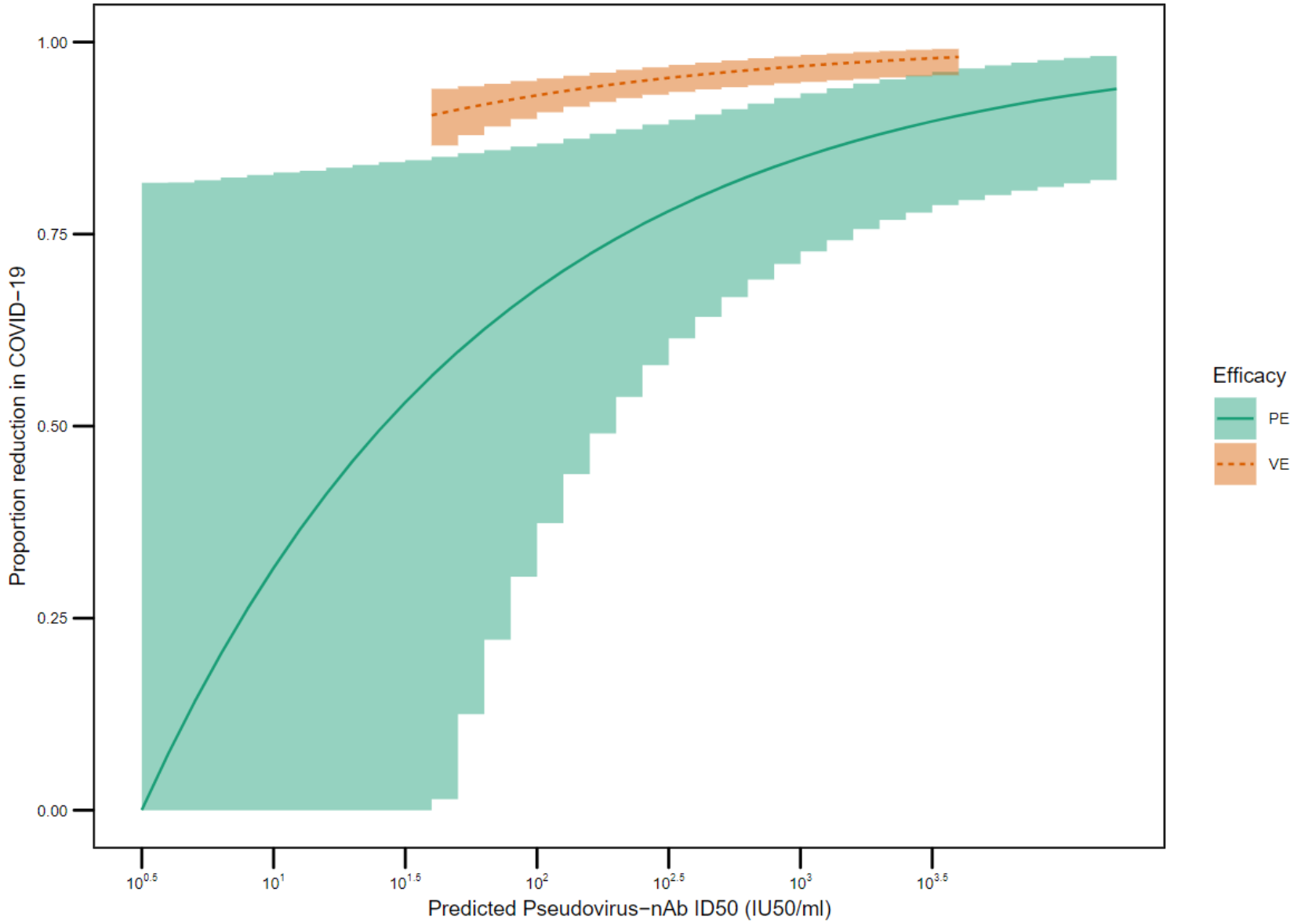
Vaccine CoP model

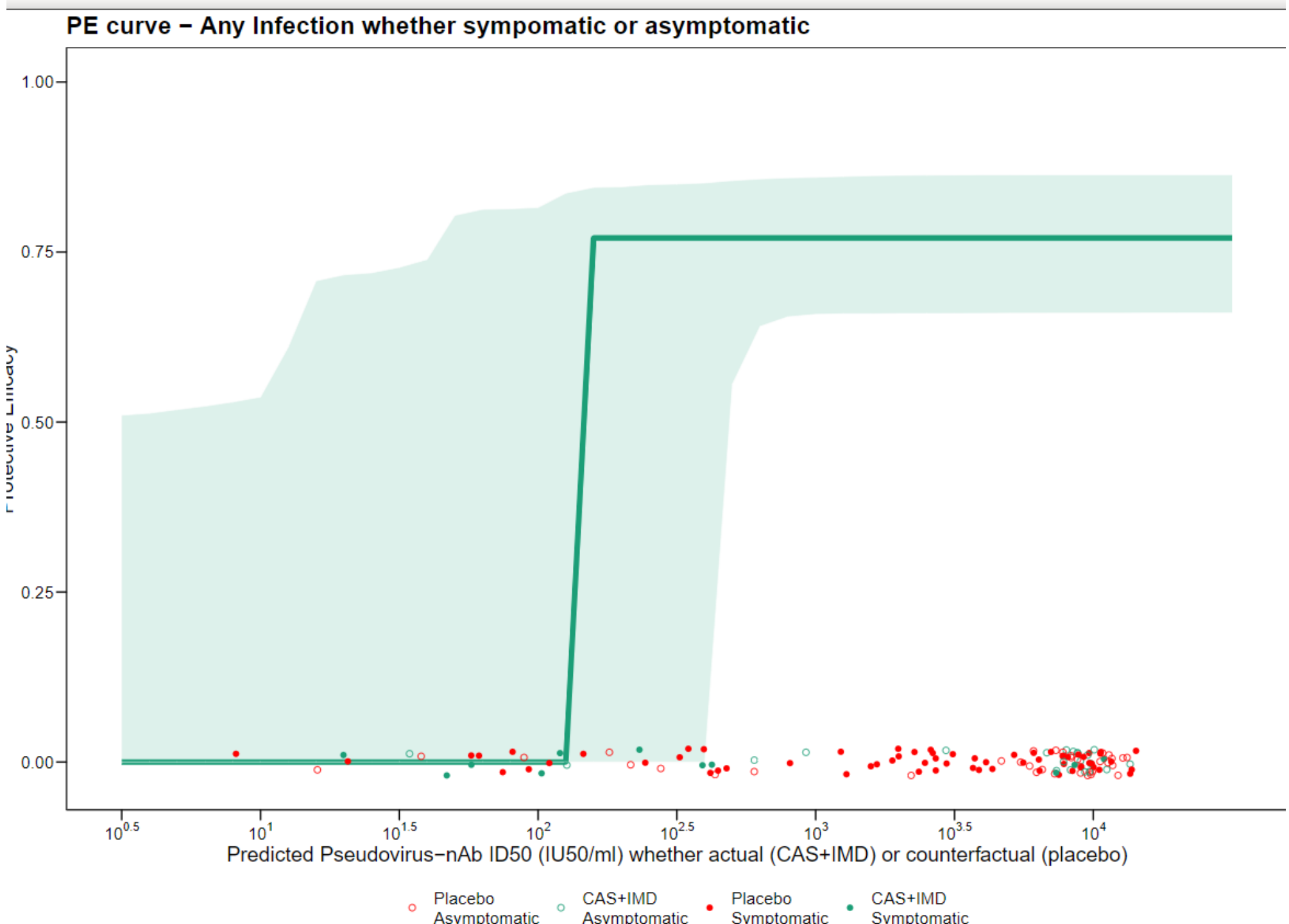
- Cox model for vaccine study
  - $h(t) = h_0(t) \exp\{ A [B0 + B1\ Ab(t)] + B2\ X \}\ I(t> E)$
  - A – vaccine indicator
  - X – logit(risk score), minority status, High Risk
  - t - calendar time
  - E - entry time
  - Ab(t) – predicted neutralization titer at time t $Ab(t) = D57 – 0.0043\ t$

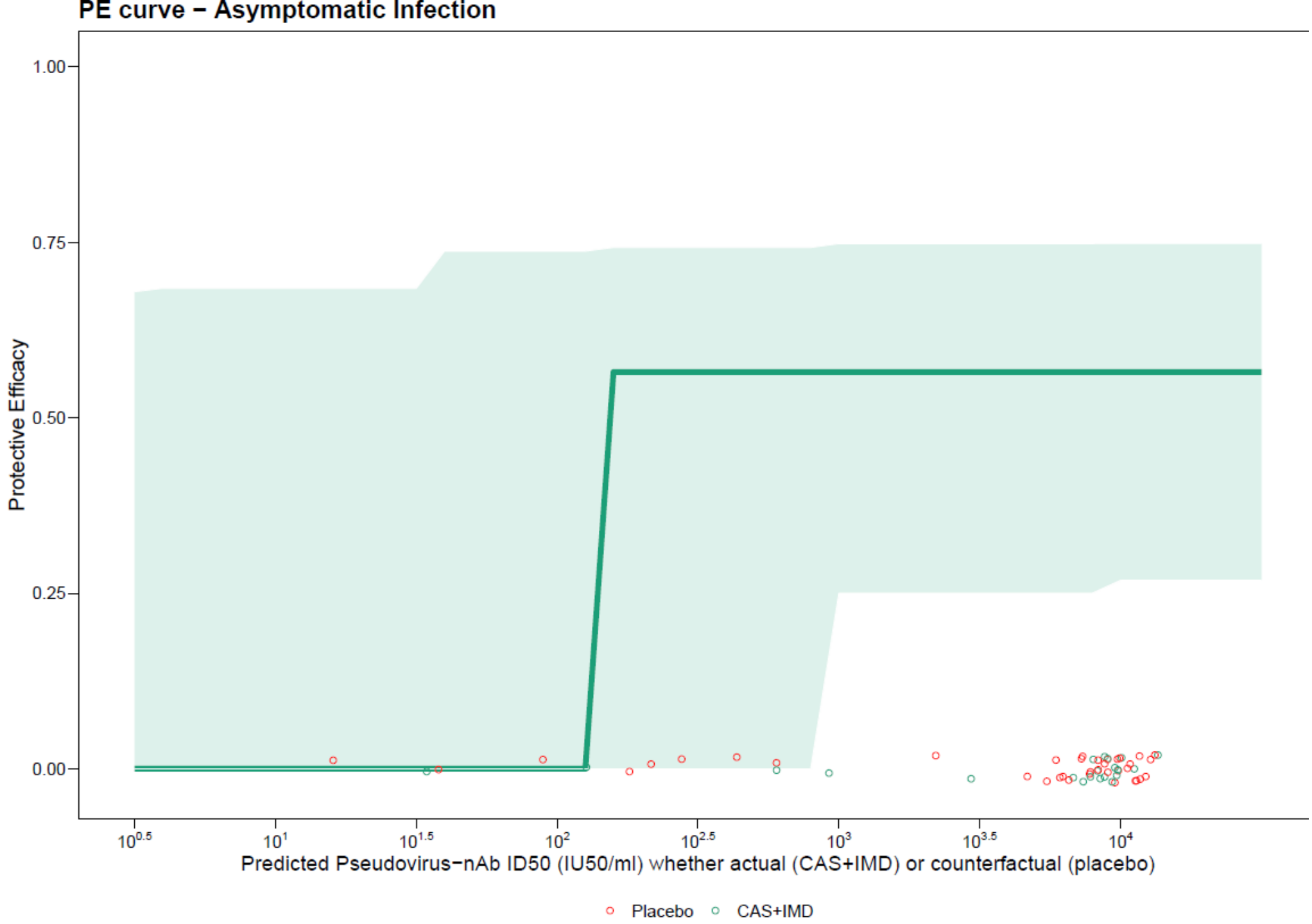
- $VE(Ab) = 1 – \exp(B0+B1\ Ab)$

Assume no unmeasured confounders

Cox model with log-linear hazard ratio




PE curve − Any Infection whether sympomatic or asymptomatic
1.00
0.75
0.50
0.25
0.00
Protective Efficacy
$10^{0.5}$
10^{1}
$10^{1.5}$
10^{2}
$10^{2.5}$
10^{3}
$10^{3.5}$
10^{4}
Predicted Pseudovirus−nAb ID50 (IU50/ml) whether actual (CAS+IMD) or counterfactual (placebo)
Placebo Asymptomatic
CAS+IMD Asymptomatic
Placebo Symptomatic
CAS+IMD Symptomatic


PE curve − Asymptomatic Infection
1.00
0.75
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0.00
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$10^{0.5}$
10^{1}
$10^{1.5}$
10^{2}
$10^{2.5}$
10^{3}
$10^{3.5}$
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Placebo
CAS+IMD