AstraZeneca

Threshold of Protection

Seth Seegobin
Sam Matthews
Rhiannon Edge

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A SARS-CoV-2 variant-adjusted threshold of protection model for monoclonal antibody pre-exposure prophylaxis against COVID-19

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Rhiannon Edge[1,10], Sam Matthews[1,10], Bahar Ahani[2], Anastasia A. Aksyuk[3], Lindsay Clegg[4], John L. Perez[5], Mark T. Esser[5], Lee-Jah Chang[5], Ian Hirsch[1], Tonya Villafana[5], John Pura[6], Oleg Stepanov[7], Katie Streicher[3], Tom White[1], Taylor S. Cohen[5], Dean Follmann[8], Peter B. Gilbert[9] & Seth Seegobin[1]

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A Statistical Immune Correlates of Protection Model for Predicting Efficacy from Neutralizing Antibody Titers to Establish Immunobridging of Monoclonal Antibodies for Prevention of COVID-19

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The Problem

- **Immunocompromised populations** may have a limited vaccine response, creating an urgent need for alternative preventive strategies such as **long-acting monoclonal antibodies (mAbs)**.
- **Rapid SARS-CoV-2 variant evolution** means efficacy against newly circulating strains must be assessed quickly.
- **Traditional efficacy trials are too slow** → by the time results are available, the dominant circulating variants may already have changed.
- **Limitations of current immunobridging approaches**:
  - They are often anchored to a single historical variant and efficacy estimate.
  - They do not easily accommodate multiple co-circulating variants.
  - They provide limited flexibility for setting and comparing efficacy targets across different protection levels.

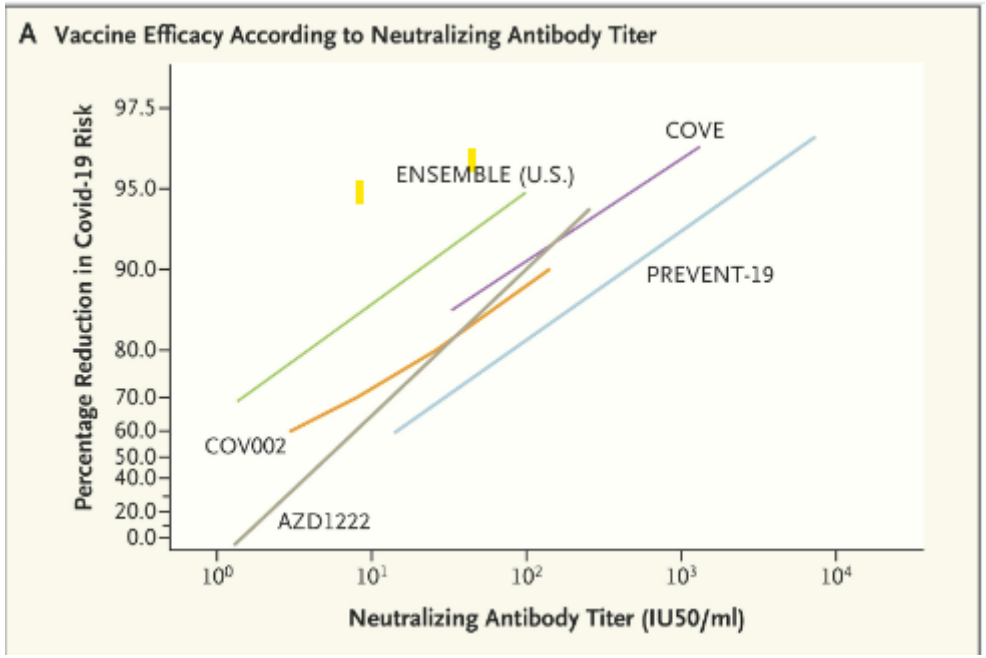
SARS-CoV-2 vaccines: neutralising antibody titres as a correlate of protection

nAb as Correlate of Protection

- Higher neutralising antibody titres are associated with lower risk of symptomatic COVID-19.
- Evidence from **five randomised controlled trials** of COVID-19 vaccines supports a relationship between neutralising antibody level and vaccine efficacy. Across different vaccine platforms, neutralising antibody levels have shown a consistent association with protection, although a universal protective threshold has not been established.

Gilbert et al., NEJM 387:24 (2022).

Higher neutralising antibody titres associated with reduced COVID-19 risk



This motivates evaluation of whether an analogous neutralisation-based framework can be applied to mAbs.

Proposed Solution: Variant-Adjusted Threshold of Protection (ToP) Model

Core idea: Link predicted neutralising antibody (nAb) titres — adjusted for variant prevalence and potency — to clinical efficacy

Data sources:

- PROVENT trial (tixagevimab–cilgavimab) – largely non-immunocompromised, against early variants
- SUPERNOVA trial (sipavibart) – immunocompromised, more complex variant landscape

Method:

- Predict daily serum mAb concentrations using **population PK models**
- Combine concentration with **variant-specific in vitro IC50** values
- Weight potency by **circulating variant prevalence** over calendar time
- Derive a daily prevalence-adjusted predicted neutralising antibody (nAb) titres
- Model its association with symptomatic COVID-19 hazard using a time-varying Cox model

The PROVENT clinical trial demonstrated the efficacy of 300-mg IM AZD7442 for prevention of COVID-19 over 6 months[1]

Study design

Phase 3, multi-centre, double-blind study (NCT04625725)

Dosing

300-mg IM

Participants

Adults at increased risk for inadequate response to vaccination or SARS-CoV-2 infection, with no history of laboratory-confirmed SARS-CoV-2

N = 5197

randomised 2:1

- **AZD7442 Single dose (n=3441)**
- **Placebo Single dose (n=1731)**

Primary endpoints

Efficacy:
First episode of symptomatic Covid-19, confirmed by a positive RT-PCR test, post-dosing and on or before day 183

Safety:
Incidence of AEs, SAEs, MAAEs, and AESIs

Primary Analysis (3 May 2021)

Median (range) follow-up was **83 (4–166) days**

77% RRR

~12-Month Follow-Up (13 Apr 22)

All ongoing participants had completed ≥183 days follow-up

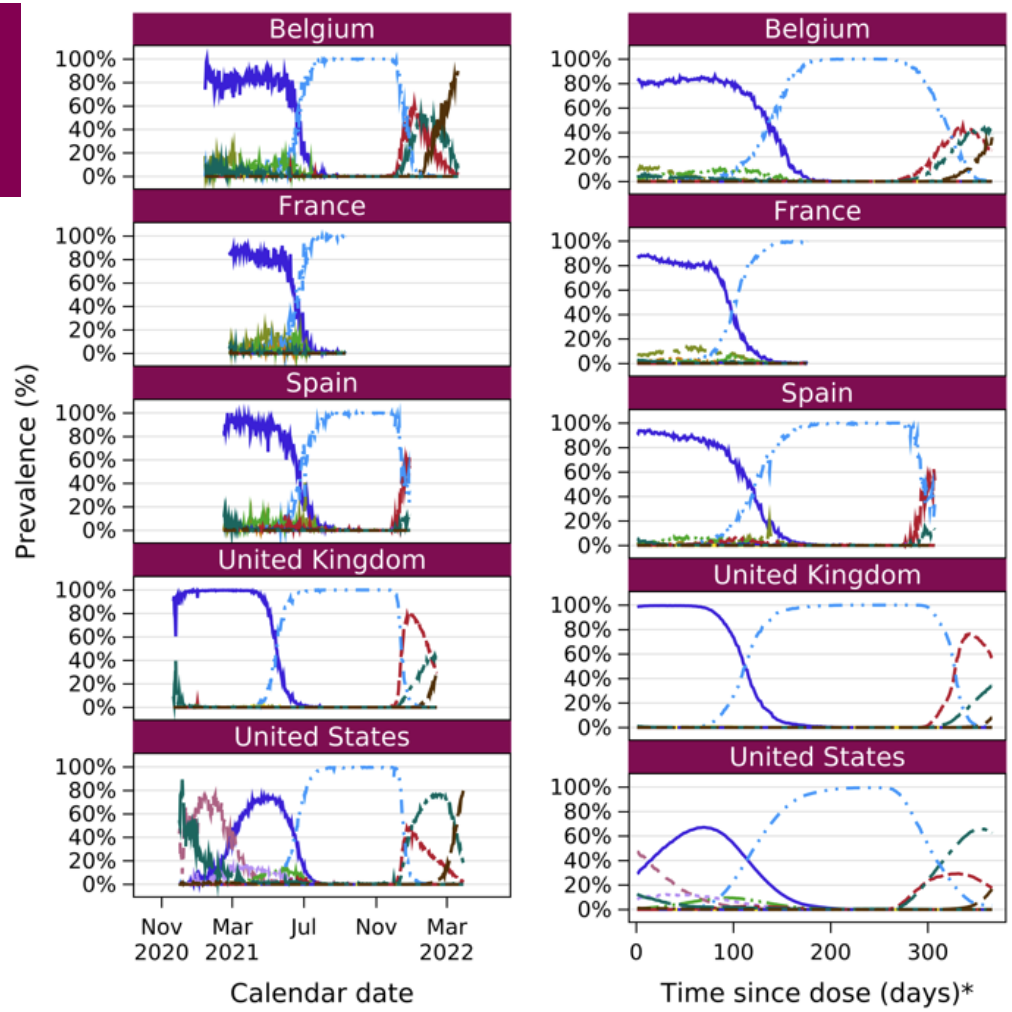
83% RRR

COVID-19, coronavirus disease 2019; IM, intramuscular; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. 1. Levin M et al. *N Engl J Med*. 2022;386:2188-2200.

SARS-CoV-2 country-specific variant prevalence - PROVENT

Country-specific surveillance data were aligned to participant follow-up time across the PROVENT study period

Study	WHO SARS-CoV-2 name	Pango lineage (Hedgehog)[a]	In vitro IC_{50} (ng/mL)
PROVENT	Alpha	B.1.1.7	2.1
	Beta	B.1.351	5.6
	Wuhan	–	2.2
	BA.1	B.1.1.529.1	171.1
	BA.2	B.1.1.529.2	9.8
	Delta	B.1.617.2	2.2
	BA.1.1	B.1.1.529.1.1	466.0
	Eta	B.1.525	9.5
	Gamma	P.1	1.3
	Kappa	B.1.617.1	1.9
	Lambda	C.37	1.2
	Mu	B.1.621	17.2
	BA.4/5	B.1.1.529.4	69.4
	Iota	B.1.526	3.3
	Zeta	P.2	5.4
	Epsilon	B.1.427/B.1.429	1.3



The SUPERNOVA clinical trial demonstrated the efficacy of 300-mg IM AZD3152 for prevention of COVID-19

Study design

Phase 3, multi-centre, double-blind study (**NCT05648110**)

Dosing

300-mg IM with repeat dosing at Day 181

Participants

Adults and adolescents with immune impairment conditions

N = 3280

randomised 1:1

- **AZD3152 (n=1649)**
- **AZD7442 Initial dose (n=1082)**
- **Placebo Initial dose (n=549)**

Primary endpoints

Efficacy:
First episode of symptomatic Covid-19, confirmed by a positive RT-PCR test

Safety:
Incidence of AEs, SAEs, MAAEs, and AESIs

Primary Analysis (29 March 2024)[1]

All events analysis (irrespective of variant) ~ **34.9% RRR**

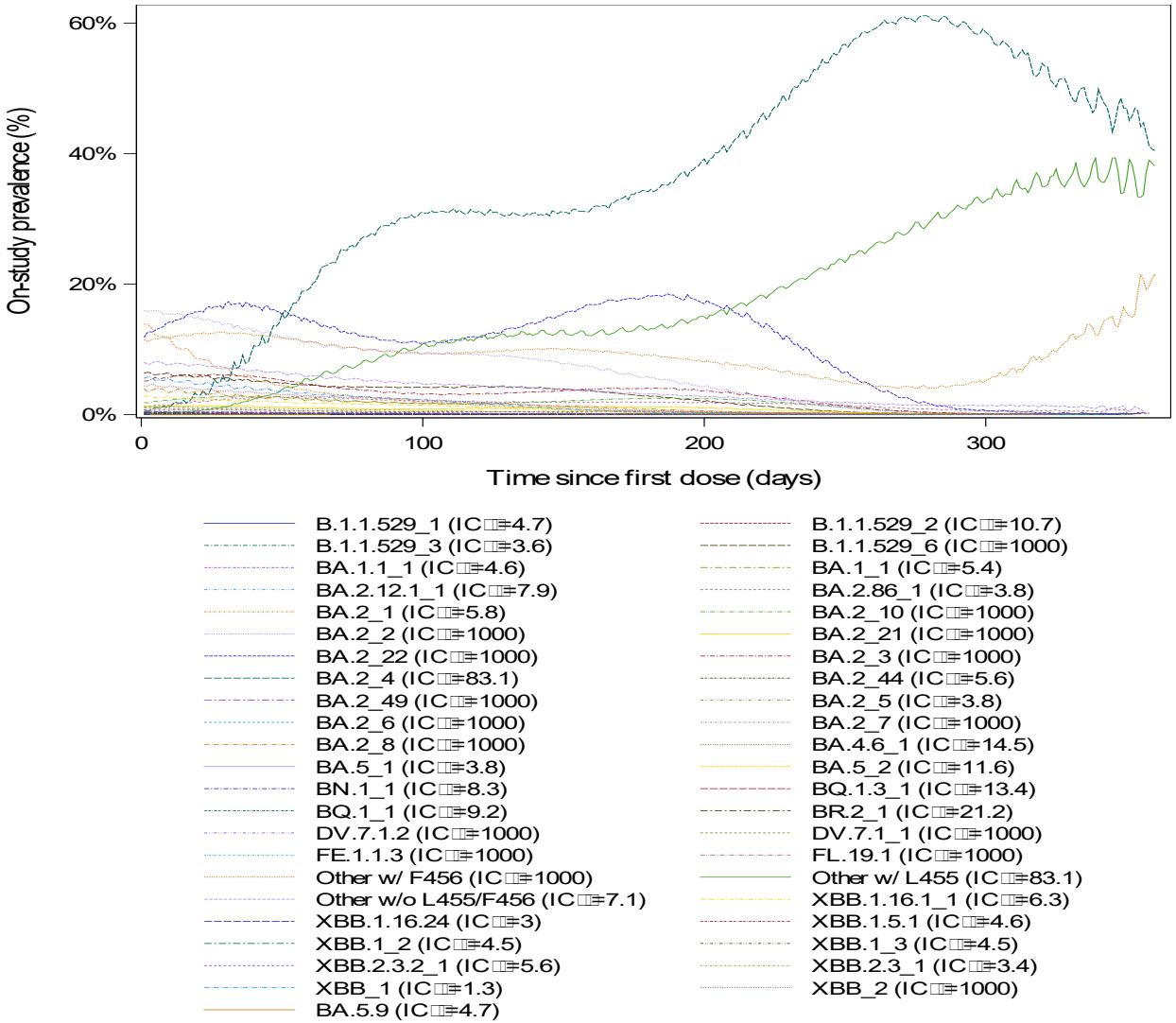
Matched analysis (non-456L mutation events) ~ **42.9% RRR**

0-3 months – 41.9% Overall
0-3 months – 60.0% matched

~12-Month Follow-Up (Feb 2024)

All ongoing participants had complete study follow-up

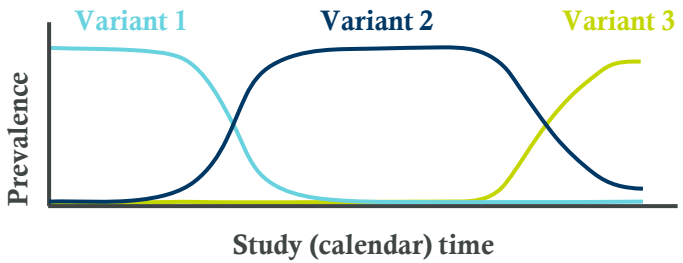
SUPERNOVA: no overlapping variants with a more complex variant landscape



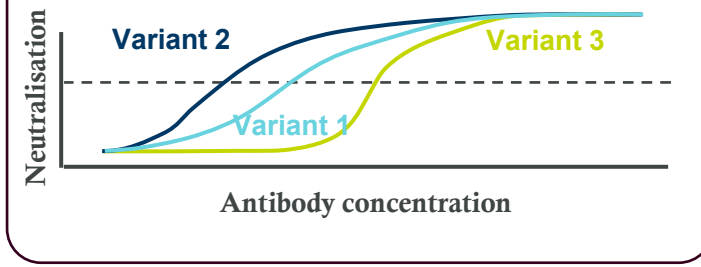
- The landscape of SARS-CoV-2 has evolved into a complex ecosystem with the emergence of numerous variants, signaling a departure from the early stages of the pandemic where a single or a few dominant variants prevailed.
- This makes SUPERNOVA a strong test case for evaluating transportability of the PROVENT-derived model

Prevalence-adjusted nAb titres as time-varying exposure

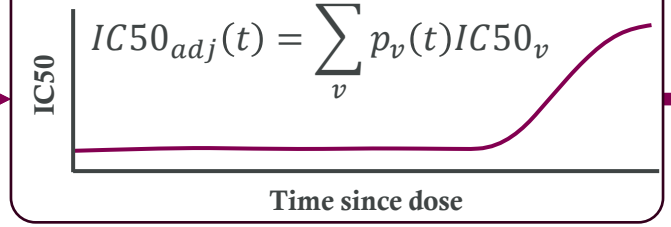
Variant Surveillance



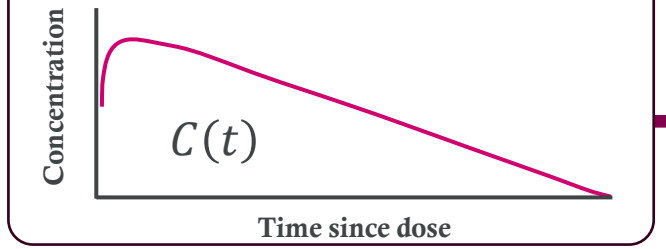
In vitro IC50s



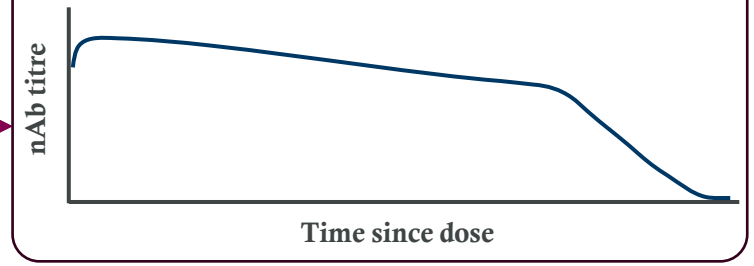
Prevalence Adjusted IC50



Daily serum mAb Concentration



Daily prevalence adjusted nAb titre



$$nAb(t) = \frac{C(t)}{IC50_{adj}(t)}$$

PROVENT ToP Cox Model

Time-varying Cox model linking daily prevalence-adjusted neutralisation metric to hazard of symptomatic COVID-19

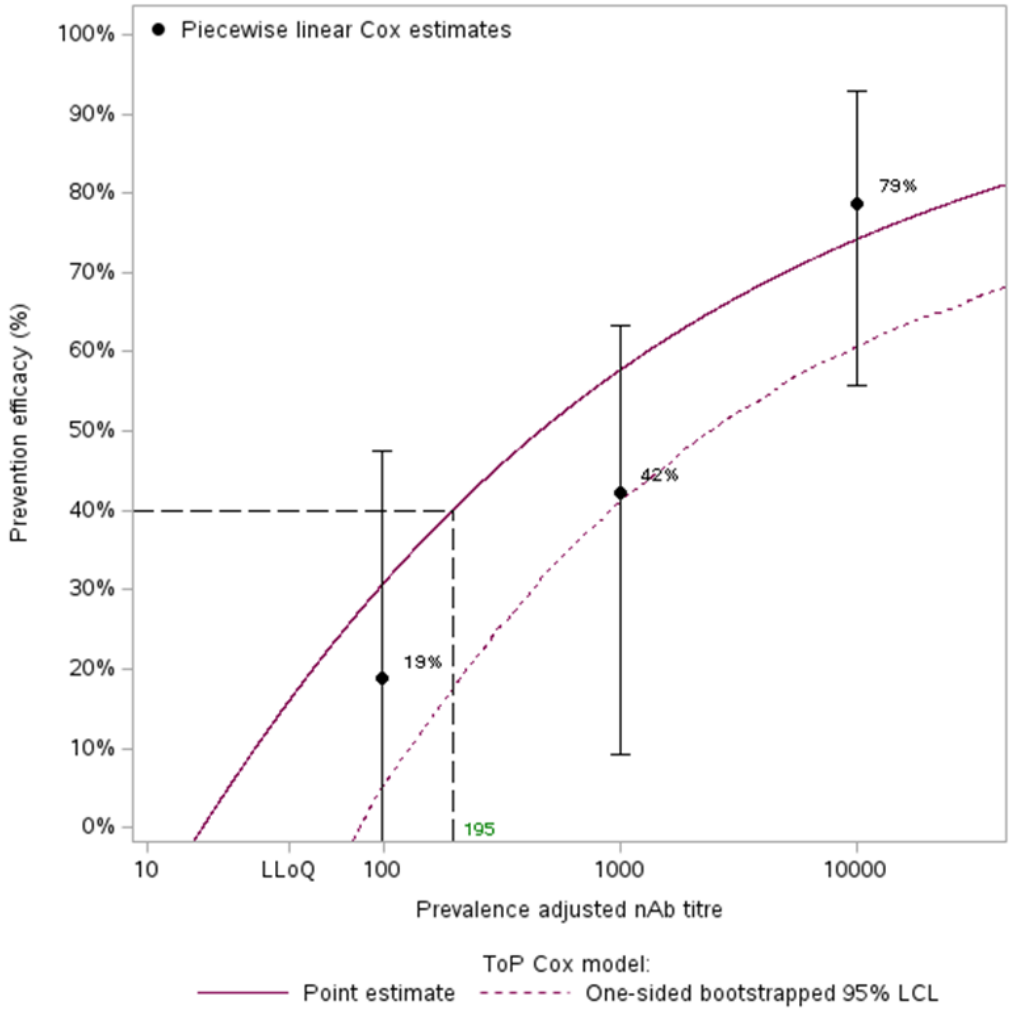
- The extended Cox model assumes the hazard for participant i at days since first dose t as:

$$h\left(t; Z_i, c_{i,t}, IC_{50_{i,t}}\right) = h_0(t)\exp\left(Z_i\left[\gamma_0 + \gamma_1\, log_{10}\left(\frac{c_{i,t}}{IC_{50_{i,t}}} + 1\right)\right]\right),$$

where:

- $h_0(t)$ represents the baseline hazard function,
- Z is the treatment indicator (equals one for individuals receiving AZD7442 and zero otherwise)
- $c_{i,t}$ and $IC_{50_{i,t}}$ are time-varying covariate for the daily serum mAb concentrations from the pop-PK model, and prevalence standardised IC_{50}(mAb potencies)
- $\frac{c_{i,t}}{IC_{50_{i,t}}}$ gives the expected daily nAb titres assuming no baseline level (i.e. estimates the nAb received as a biproduct of the drug)
- The log-10 transformation is appropriate given $c_{i,t}$ come from some multivariate log-normal distribution via the pop-PK model

Model Results with PROVENT



1. The solid line shows the model-based estimate of predicted efficacy as a function of the **prevalence adjusted nAb titre level**.
2. The dotted line shows **lower 95% bootstrap confidence bound**
3. Black points represent point estimates from a **piecewise-linear** Cox model based on observed efficacy, with 95% bootstrap confidence intervals.

Joint distribution of exposure and predicted efficacy

- The ToP model is a conditional on the serum mAb concentrations $c_{i,t}$, which come from the distribution defined by the pop-PK model
- Therefore, to obtain results from the joint distribution (accounting for heterogeneity in PK) there are two options, which can be shown to give similar results

i. Monte Carlo: first simulating from the pop-PK model, and then feeding these values into the ToP Cox model distribution

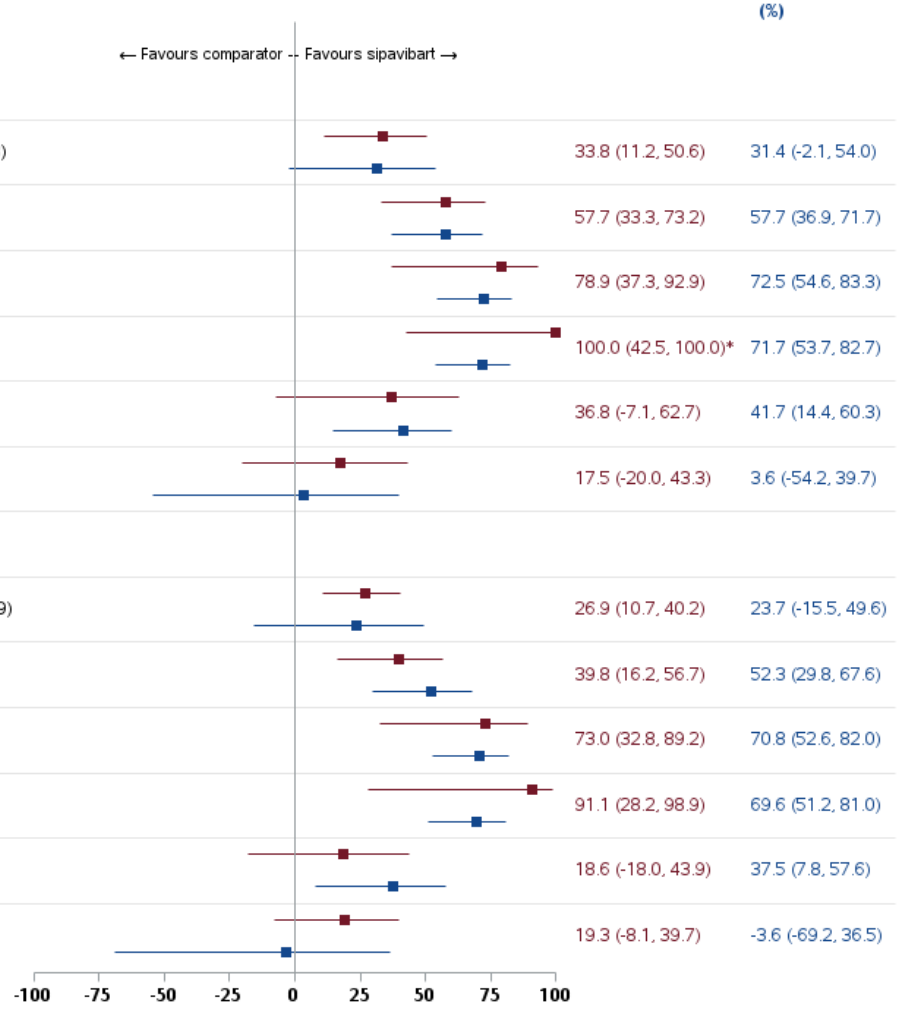
ii. Rubin's rule: first simulate from the pop-PK model and take the pooled average and calculate the total variance as a composite of the average within-simulation variance and between-simulation variance

We consider the second approach here

Model Validation with SUPERNOVA

- ToP model estimates from PROVENT along with SUPERNOVA prevalence adjusted nAb titers used to estimate efficacy in SUPERNOVA
- The PROVENT-derived model demonstrated encouraging external validity when applied to SUPERNOVA prevalence-adjusted neutralisation metrics.

Endpoint	Sipavibart N=1649 n (%)	Comparator N=1631 n (%)	Observed in SUPERNOVA (%)	PROVENT ToP model prediction (%)
3 months post any dose				
Any variant	100 (6.1)	144 (8.8)	33.8 (11.2, 50.6)	31.4 (-2.1, 54.0)
Matched non-F456L	27 (1.6)	61 (3.7)	57.7 (33.3, 73.2)	57.7 (36.9, 71.7)
XBB + subvariants	4 (0.2)	18 (1.1)	78.9 (37.3, 92.9)	72.5 (54.6, 83.3)
BA.2.86 + subvariants	0	8 (0.5)	100.0 (42.5, 100.0)*	71.7 (53.7, 82.7)
JN.1 + subvariants	23 (1.4)	35 (2.1)	36.8 (-7.1, 62.7)	41.7 (14.4, 60.3)
F456L	52 (3.2)	60 (3.7)	17.5 (-20.0, 43.3)	3.6 (-54.2, 39.7)
6 months post any dose				
Any variant	175 (10.6)	226 (13.9)	26.9 (10.7, 40.2)	23.7 (-15.5, 49.6)
Matched non-F456L	59 (3.6)	93 (5.7)	39.8 (16.2, 56.7)	52.3 (29.8, 67.6)
XBB + subvariants	6 (0.4)	21 (1.3)	73.0 (32.8, 89.2)	70.8 (52.6, 82.0)
BA.2.86 + subvariants	1 (0.1)	10 (0.6)	91.1 (28.2, 98.9)	69.6 (51.2, 81.0)
JN.1 + subvariants	52 (3.2)	61 (3.7)	18.6 (-18.0, 43.9)	37.5 (7.8, 57.6)
F456L	85 (5.2)	99 (6.1)	19.3 (-8.1, 39.7)	-3.6 (-69.2, 36.5)

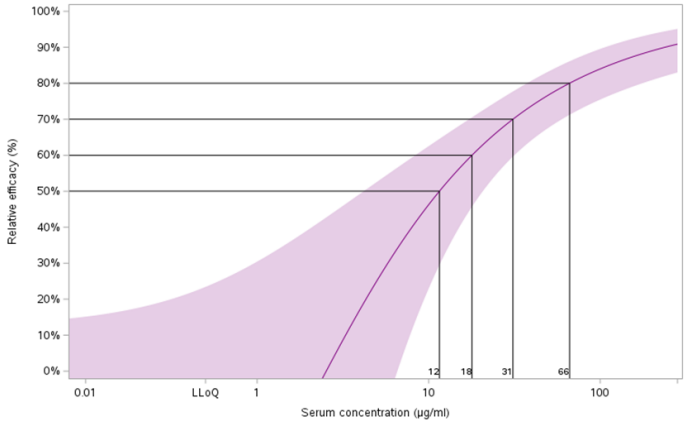


Rubin's rule was applied to the PROVENT ToP model predictions

Application

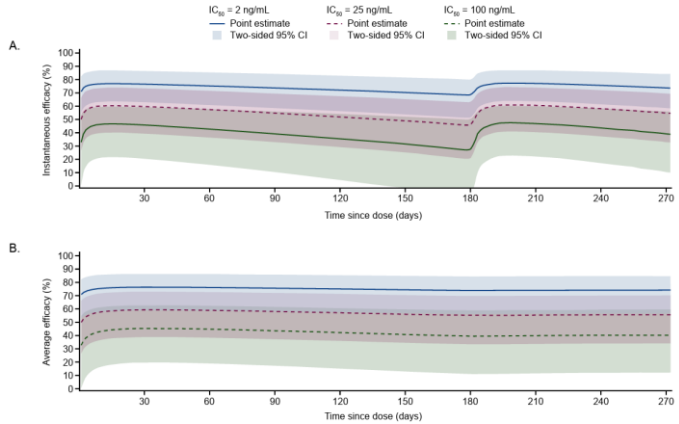
Predict Efficacy

Use a pop-PK model and the ToP model to estimate clinical efficacy against new variants.



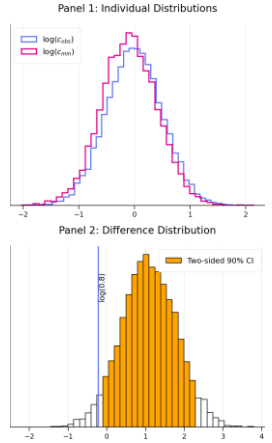
Predict Duration of Protection

Estimate how long predicted nAb titres remain above the required efficacy based on instantaneous or average efficacy projections.



Immunobridge based on Threshold

Assess non-inferiority of the observed serum mAb concentration to the distribution of the minimal effective concentration



Predict Efficacy

Prespecify:
- mAb of interest
- Dosing regimen
- IC_{50} for variant of concern
- Time period for average efficacy, P

i. Draw daily simulations $c_{i,t}$ from pop-PK model for the proposed dosing regimen and mAb of interest

ii. Compute $\bar{C}_i = \frac{1}{|P|}\sum_{t\in P}\log_{10}\left(\frac{c_{i,t}}{IC_{50}}+1\right)$

iii. Compute the average log hazard ratio estimate $\hat{\mu}_i$, and the corresponding $\widehat{SE}_i$ from each simulation, where

$$\hat{\mu}_i = \hat{\gamma}_0 + \hat{\gamma}_1\bar{C}_i$$

$$\widehat{SE}_i = \sqrt{\sigma^2_{\gamma_0} + \bar{C}_i^2\sigma^2_{\gamma_1} + 2\bar{C}_i\rho\sigma_{\gamma_0}\sigma_{\gamma_1}}$$

$\Sigma_\gamma = \begin{bmatrix} \sigma^2_{\gamma_0} & \rho\sigma_{\gamma_0}\sigma_{\gamma_1} \\ \rho\sigma_{\gamma_0}\sigma_{\gamma_1} & \sigma^2_{\gamma_1} \end{bmatrix}$ is the covariance matrix of the parameter estimates

iv. Use Rubin's rule to construct the pooled average log hazard ratio estimate $\bar{\mu}$, and corresponding total variance, T

v. Construct the CI for the log hazard ratio based on $\bar{\mu}$ and T

vi. Back transform $\bar{\mu}$ and the CI using $g(.) = 1 - \exp(.)$ to predict the efficacy

Predict Duration of Protection

Instantaneous efficacy:

i. Simulate $c_{i,t}$ from the pop-PK model

ii. Simulate $\theta_{i,t}$ from $N\left(\hat{\gamma}_0 + \hat{\gamma}_1\, log_{10}\left(\frac{c_{i,t}}{IC_{50}} + 1\right), \Sigma_{g_{i,t}}\right)$, where

$$\Sigma_{g_{i,t}} = \sigma_{\gamma_0}^2 + \left(log_{10}\left(\frac{c_{i,t}}{IC_{50}} + 1\right)\right)^2 \sigma_{\gamma_1}^2 + 2\, log_{10}\left(\frac{c_{i,t}}{IC_{50}} + 1\right)\rho\sigma_{\gamma_0}\sigma_{\gamma_1}$$

iii. For each timepoint t, use Rubin's rule to construct the pooled average log hazard ratio estimates $\bar{\mu}_t$, and corresponding total variances, T_t

iv. Construct the daily CIs for the log hazard ratio based on $\bar{\mu}_t$ and T_t

v. Back transform each $\bar{\mu}_t$ and the daily CIs using $g(.) = 1 - \exp(.)$ to predict the instantaneous efficacy

Average efficacy: Follow a similar approach to efficacy predictions, but update the period, P by one day at a time.

Immunobridge Based on Threshold

- For a variant of concern k, the minimal serum mAb concentration c_{min} to achieve the desired efficacy level E is given by

$$g(\gamma_0, \gamma_1) = c_{min} = IC_{50_k}\left[10^{\left(\frac{\log(1-E)-\gamma_0}{\gamma_1}\right)-1}\right]$$

- From the delta rule $g(\gamma_0, \gamma_1) \sim N\left(g(\hat{\gamma}_0, \hat{\gamma}_1), \nabla g(\hat{\gamma}_0, \hat{\gamma}_1)\Sigma_\gamma \nabla g(\hat{\gamma}_0, \hat{\gamma}_1)^T\right)$, where $\nabla g(\hat{\gamma}_0, \hat{\gamma}_1) = \left[\frac{\partial g(\hat{\gamma}_0, \hat{\gamma}_1)}{\partial \gamma_0} \quad \frac{\partial g(\hat{\gamma}_0, \hat{\gamma}_1)}{\partial \gamma_1}\right]$

- Assume that at time t the serum mAb concentration, c_t for a new mAb is log-normally distributed as $\log_{10}(c_t) \sim N(\log_{10}(\mu_c), \sigma_c^2)$

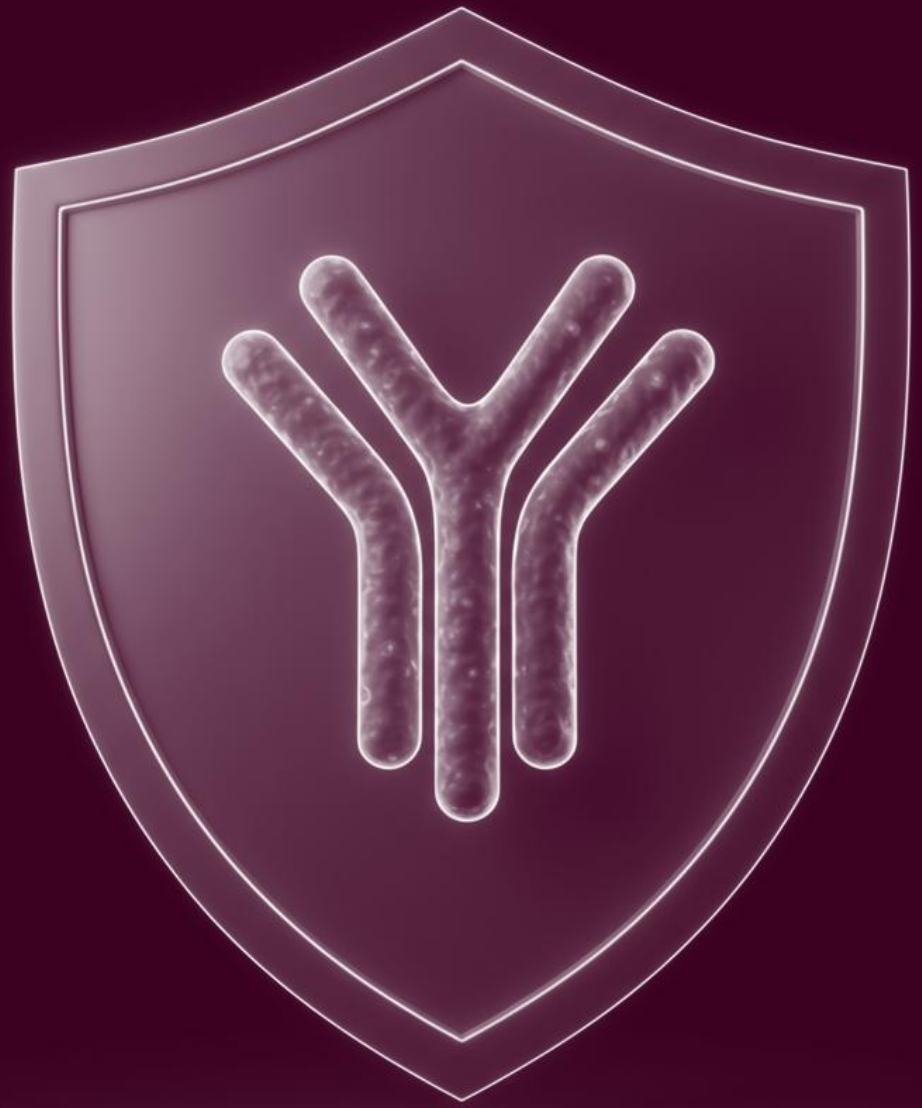
- Adapting the standard approach from PK bioequivalence trials, non-inferiority is declared when the two-sided 90% confidence limit comparing c_{t} to c_{min} is greater than 0.8

Conclusion

- This threshold-based framework provides a scalable and adaptable approach for evaluating candidate mAbs in a changing variant landscape.

- Integrating prevalence-adjusted neutralisation metrics with clinical efficacy models may enable more timely prediction of expected protection against emerging variants.

- Continued refinement, external validation, and explicit treatment of uncertainty will be important for applying this approach to future pathogens and evolving public health settings.



Thank you.