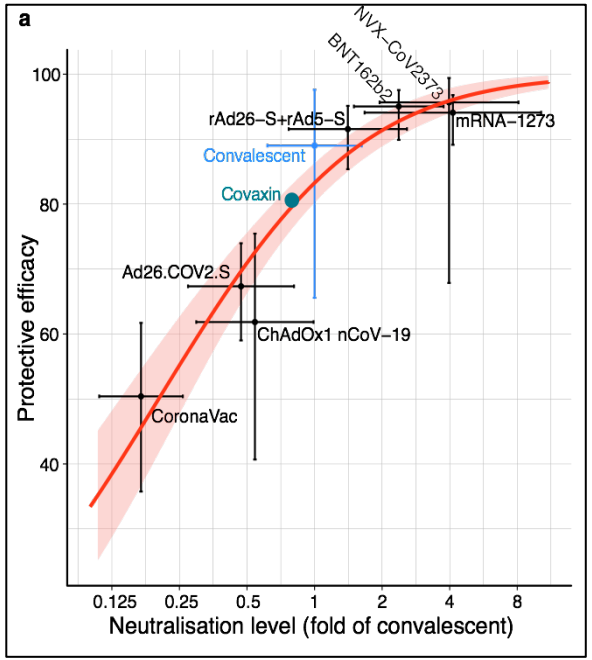
Correlates of protection using a neutralisation approach

Miles Davenport

Professor Davenport receives grants from:
- National Health and Medical Research Fund (Australia),
- Medical Research Futures Fund (Australia)
- National Institutes of Health (USA).

He declares no conflicts.

Basic question: *What is the relationship between antibodies and protection?*



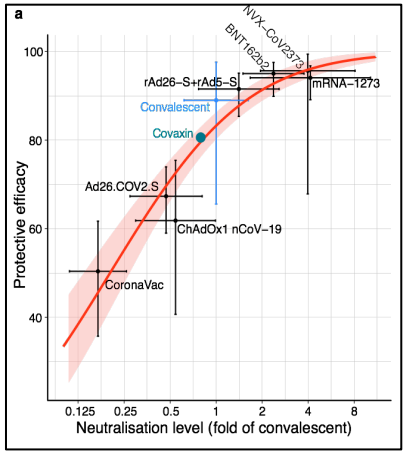
Khoury et al, Nature Med 2021
https://www.nature.com/articles/s41591-021-01377-8

mAb level

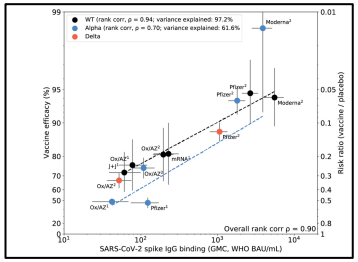
Outline:

- Vaccines - validating the relationship between neutralization and protection
- A dose response curve for therapeutic mAbs
- A dose response curve for prophylactic mAbs

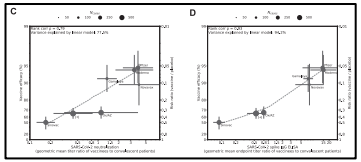
Comparing vaccines.



Khoury, et al, *Nature Medicine* 2021



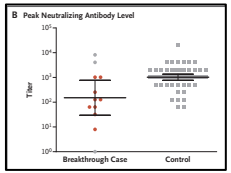
Goldblatt et al, *Vaccine* 2021



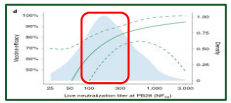
Earle et al, *Vaccine* 2021

- Identify **vaccinated groups** with **different GMT**
- Find relationship between neutralization and protection

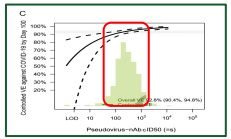
Breakthrough infection



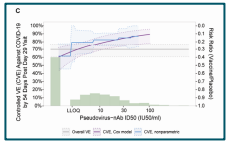
BNT162b2
Bergwerk, NEJM 2021



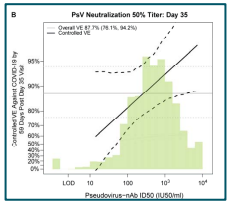
ChAdOx1
Feng, Nat Med, 2021



mRNA1273
Gilbert, Science 2021



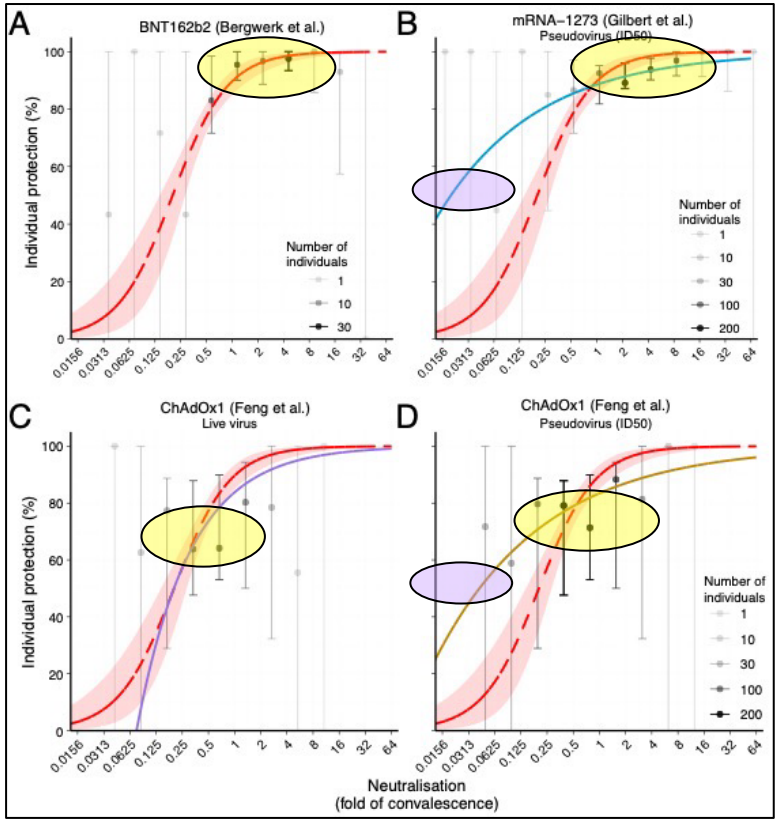
Ad26.COV2.S
Fong, Nat Comms 2022



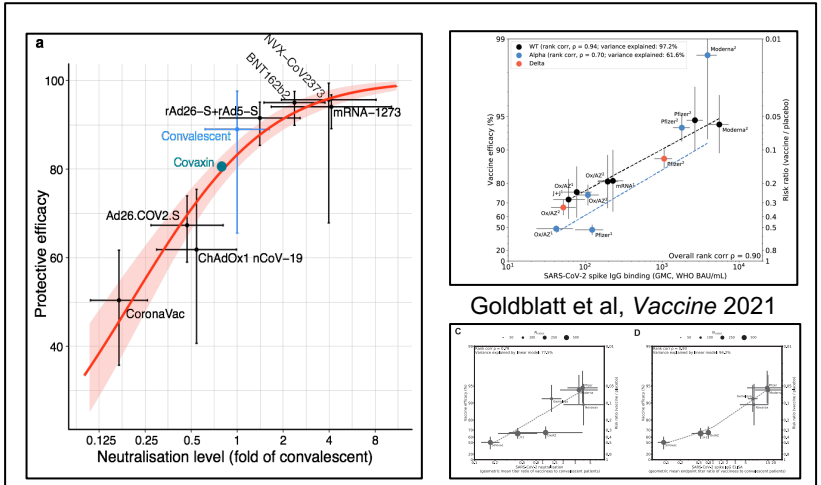
NVX-CoV2372
Fong, MedRxiv 2022

- Study **neutralization titers in subjects** with and without **breakthrough infection**
- Find relationship between neutralization and protection

Protection from phase 3 vs. breakthrough analysis



Khoury et al, MedRxiv 2022
https://www.medrxiv.org/content/10.1101/2022.06.05.22275943v1
(in press – EID)



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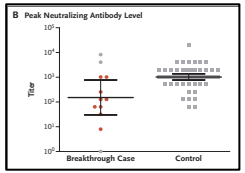
Yesterday's question:

- *Vaccine efficacy against symptomatic infection with ancestral virus soon after vaccination?*



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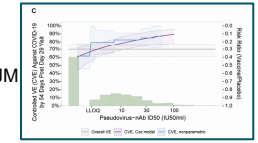

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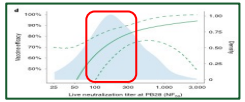

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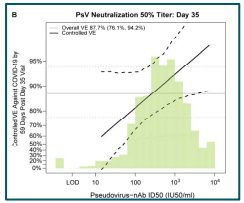
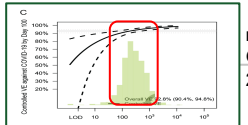


NVX-CoV2372
Fong, MedRxiv 2022



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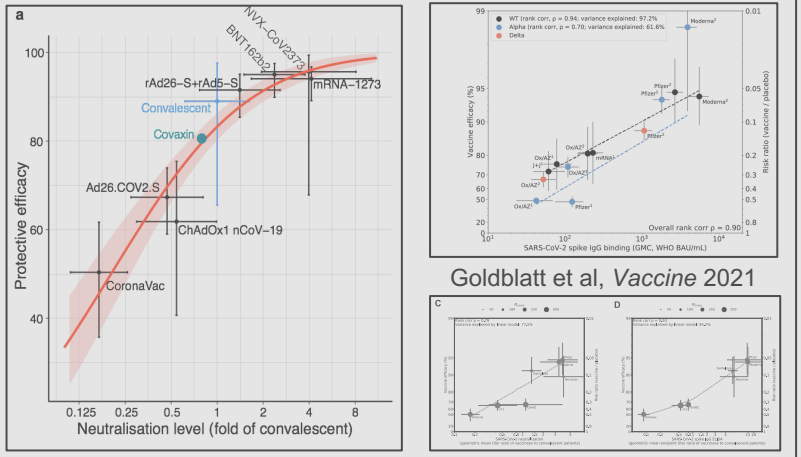

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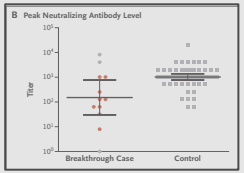

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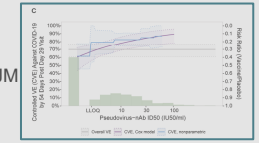

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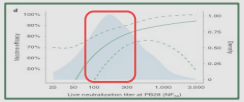

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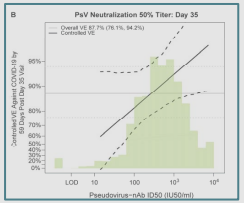

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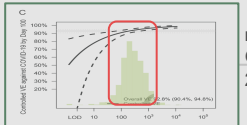


mRNA1273
Gilbert, Science 2021

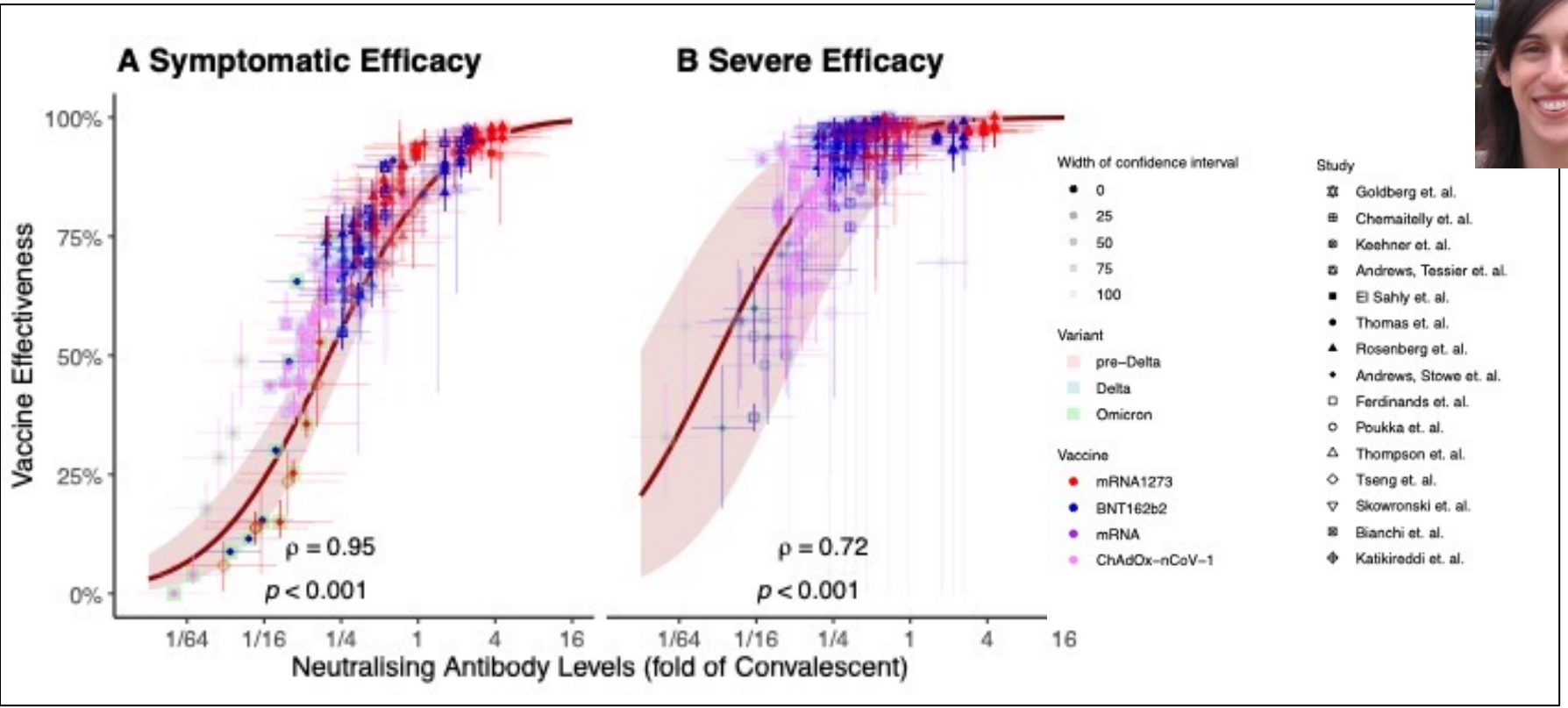
Yesterday's question:

- *Vaccine efficacy against symptomatic infection with ancestral virus soon after vaccination?*

Today's question:

Vaccine efficacy*:*

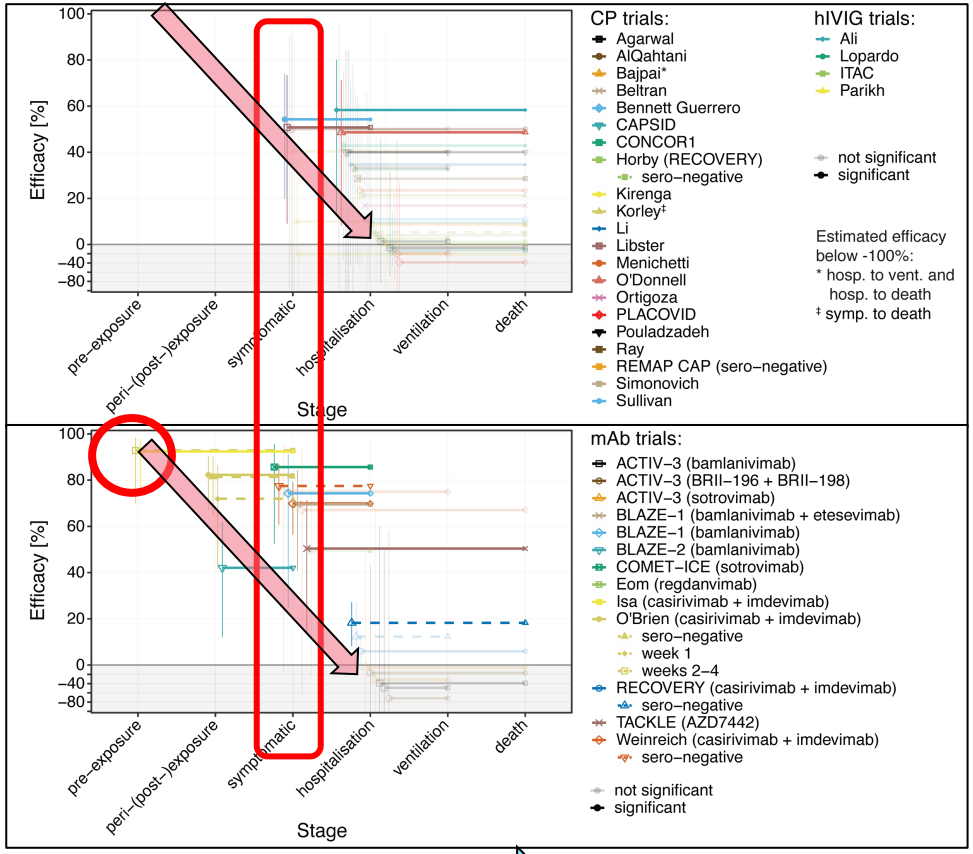
- *With waning antibody levels*
- *Against new variants*
- *Against severe infection*



Cromer, MedRxiv 2022:
https://www.medrxiv.org/content/10.1101/2022.06.09.22275942v1

Outline:

- Vaccines - validating the relationship between neutralization and protection
- A dose response curve for therapeutic mAbs
- A dose response curve for prophylactic mAbs

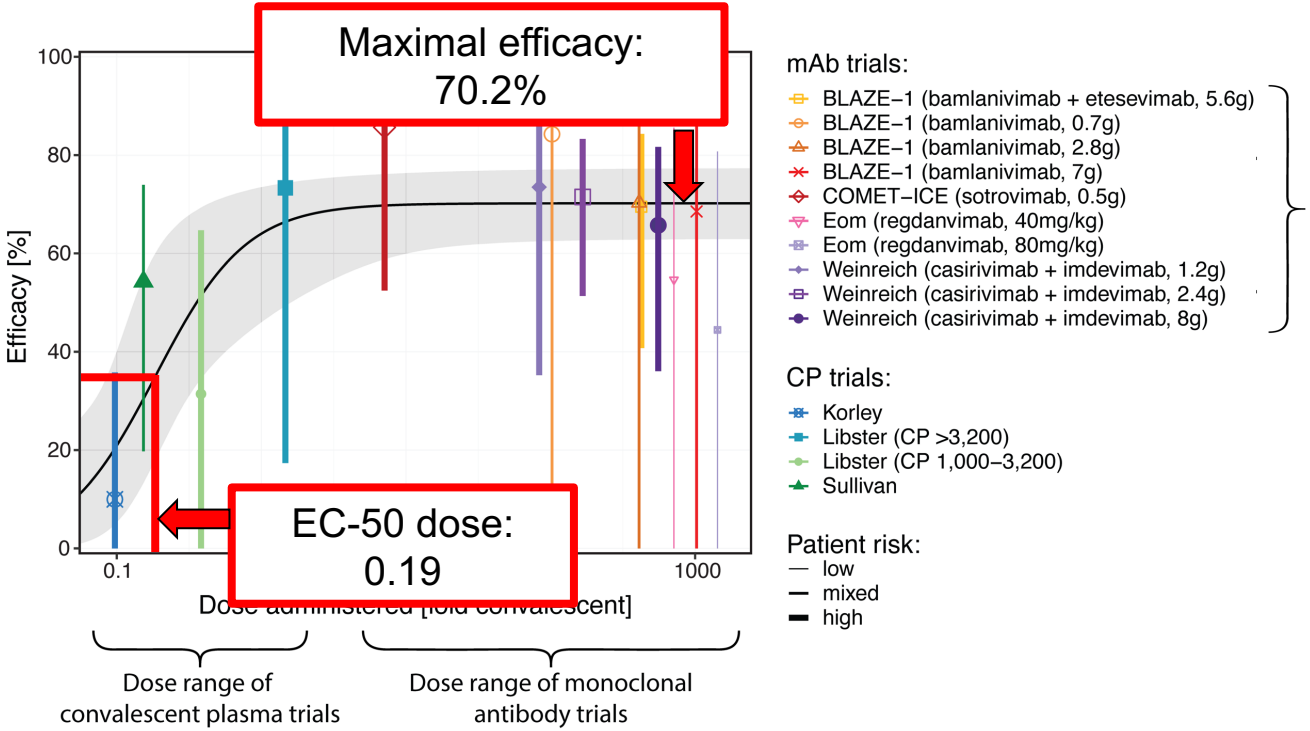


37 passive antibody RCT:

- 21 Convalescent plasma
- 4 HIVIG
- 12 mAb

Stadler MedRxiv 2022: https://www.medrxiv.org/content/10.1101/2022.03.21.22272672v1

Prevention of hospitalisations after treatment of symptomatic infections



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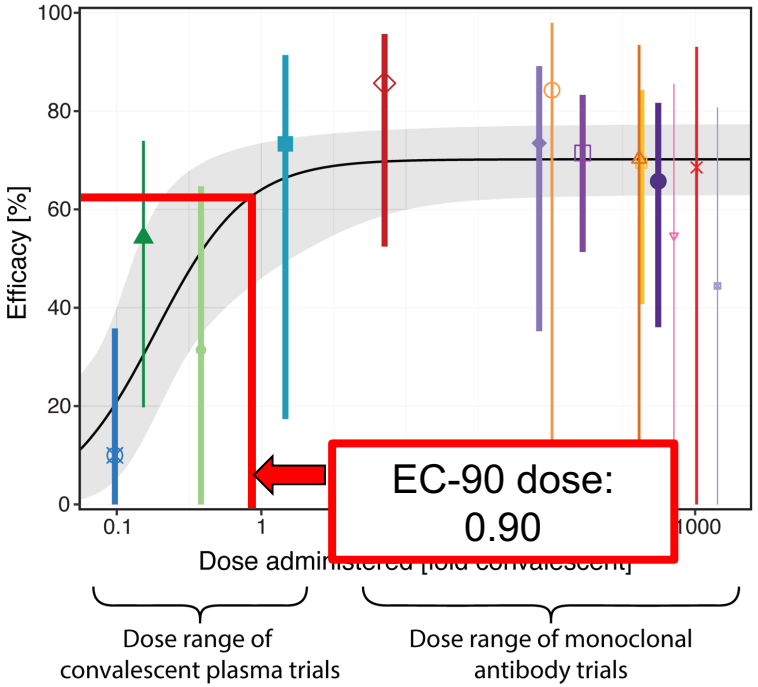


mAb trials:

- BLAZE–1 (bamlanivimab + etesevimab, 5.6g)
- BLAZE–1 (bamlanivimab, 0.7g)
- BLAZE–1 (bamlanivimab, 2.8g)
- BLAZE–1 (bamlanivimab, 7g)
- COMET–ICE (sotrovimab, 0.5g)
- Eom (regdanvimab, 40mg/kg)
- Eom (regdanvimab, 80mg/kg)
- Weinreich (casirivimab + imdevimab, 1.2g)
- Weinreich (casirivimab + imdevimab, 2.4g)
- Weinreich (casirivimab + imdevimab, 8g)

7- to >1000-fold of the EC-90 dose

CP trials:

- Korley
- Libster (CP >3,200)
- Libster (CP 1,000–3,200)
- Sullivan

Patient risk:

- low
- mixed
- high

EC-90 doses for mAbs:

- bamlanivimab: 6.2mg
- casirivimab: 6.5mg
- etesevimab: 5.96mg
- imdevimab: 21.4mg
- regdanvimab: 3.4mg
- sotrovimab: 63.3mg

Stadler MedRxiv 2022: https://www.medrxiv.org/content/10.1101/2022.03.21.22272672v1

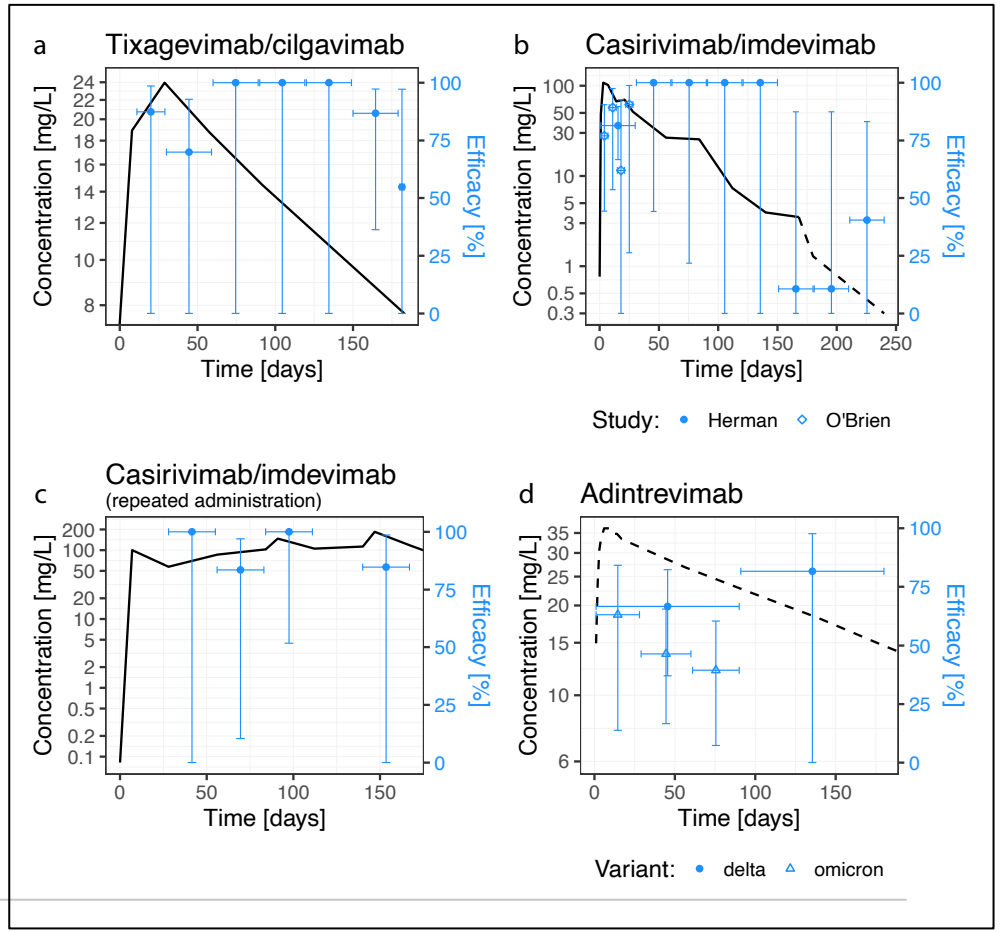
Outline:

- Vaccines - validating the relationship between neutralization and protection
- A dose response curve for therapeutic mAbs
- A dose response curve for prophylactic mAbs

Prophylactic mAbs:

- Range of mAb concentrations
- Waning antibodies levels (over time)

- Normalize concentrations relative to in vitro IC-50

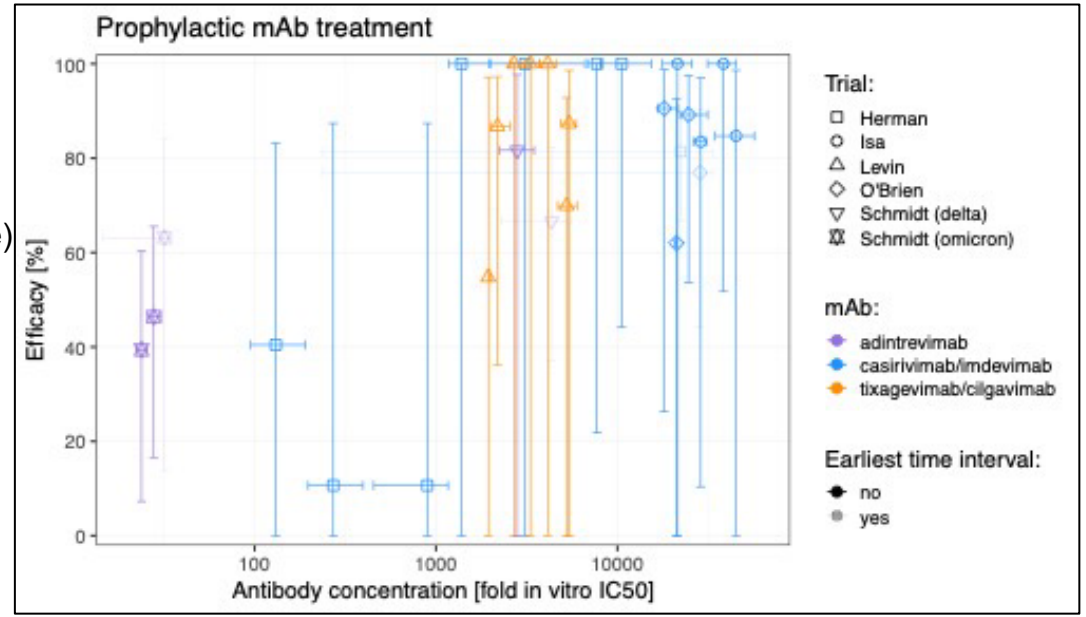


Stadler MedRxiv
https://www.medrxiv.org/content/10.1101/2022.11.22.22282199v2

Prophylactic mAbs:

- Range of mAb concentrations
- Waning antibodies levels (over time)

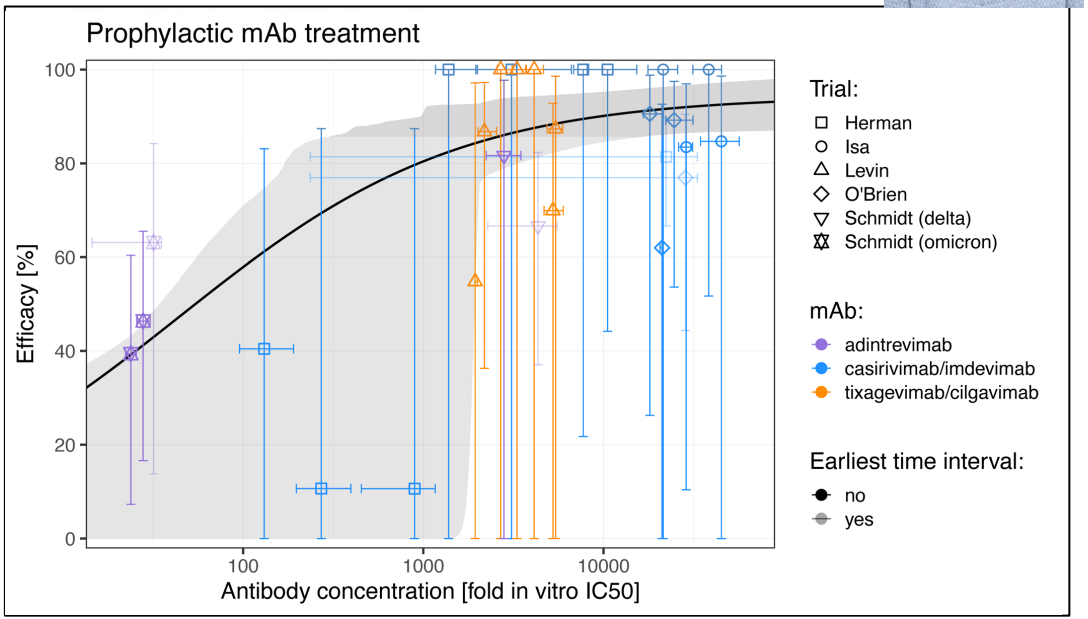
- Normalize concentrations relative to in vitro IC-50



Stadler MedRxiv (version 2.0)
https://www.medrxiv.org/content/10.1101/2022.11.22.22282199v2

Prophylactic mAbs:

- Range of mAb concentrations from waning antibodies levels (over time)
- Normalize concentrations relative to in vitro IC-50
- Normalize to convalescent titer



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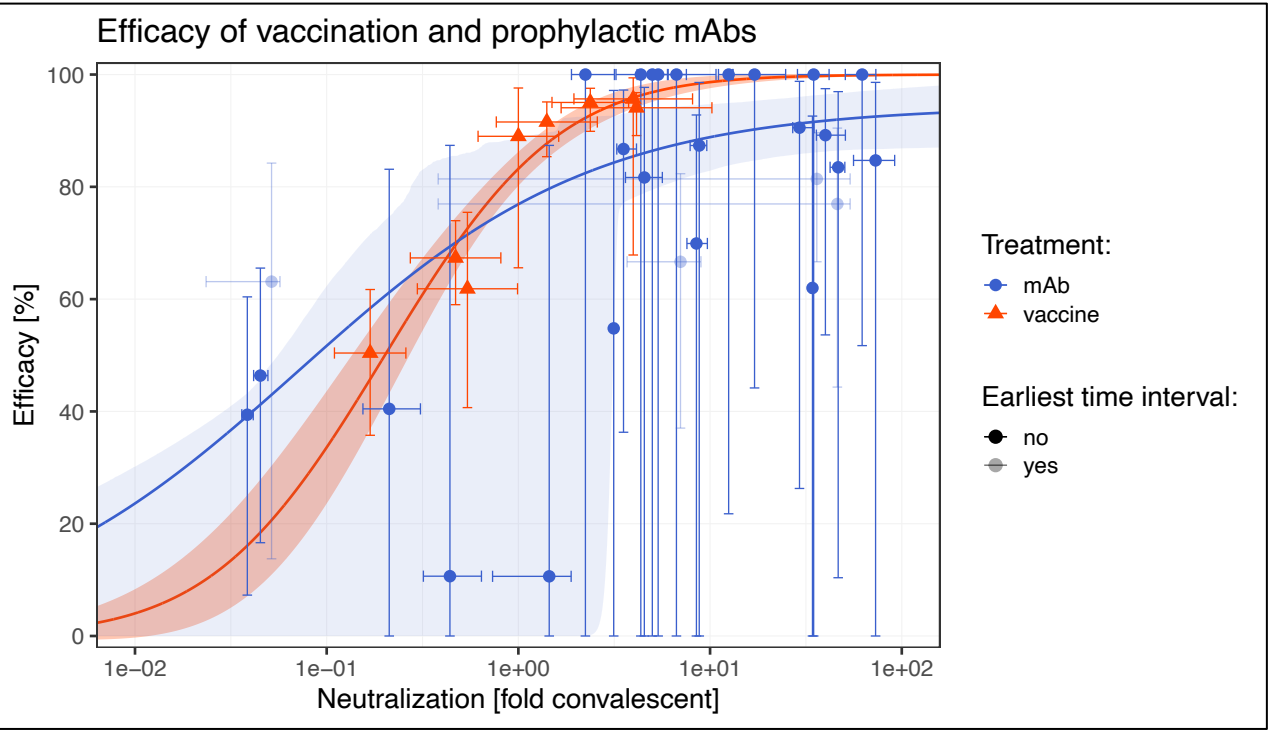
Prophylactic mAbs vs. vaccine:



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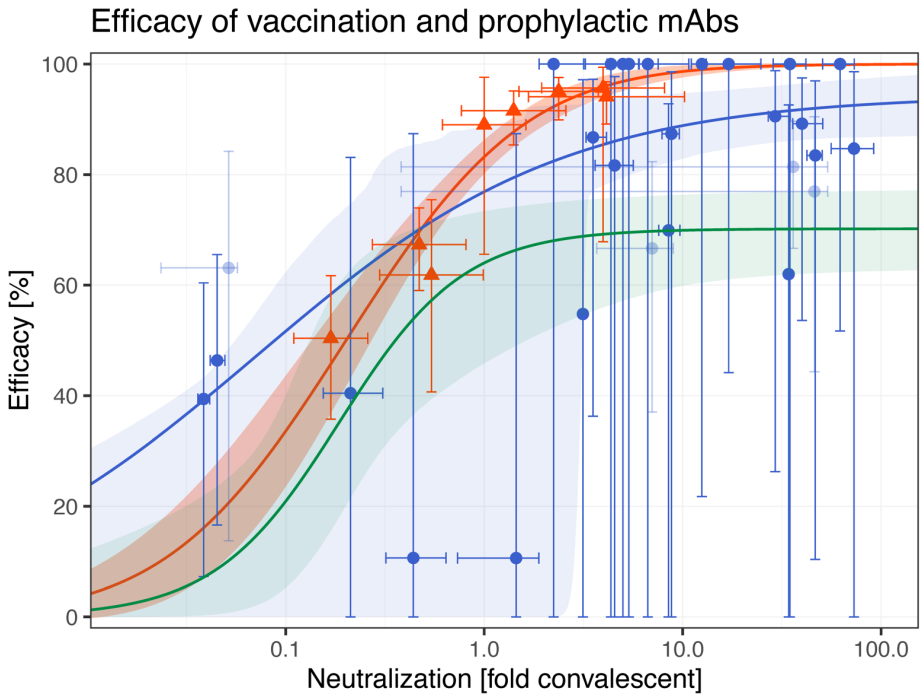
Prophylactic + therapeutic mAbs + vaccine:



Therapeutic mAbs max 70%

Treatment:
- mAb
- vaccine
- therapeutic mAbs

Earliest time interval:
- no
- yes

Stadler MedRxiv 2022
https://www.medrxiv.org/content/10.1101/2022.03.21.22272672v1

Khoury et al, Nature Med 2021
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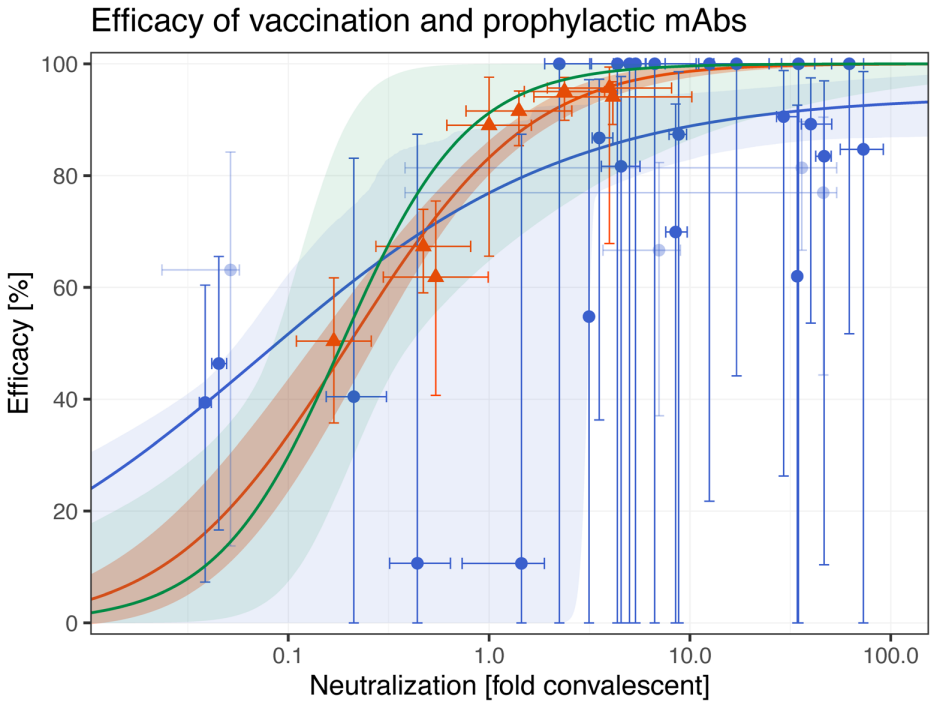


* Therapeutic scaled to 100%

Treatment:

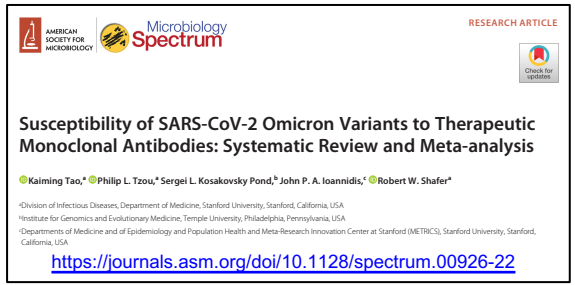
Measuring SAME THING

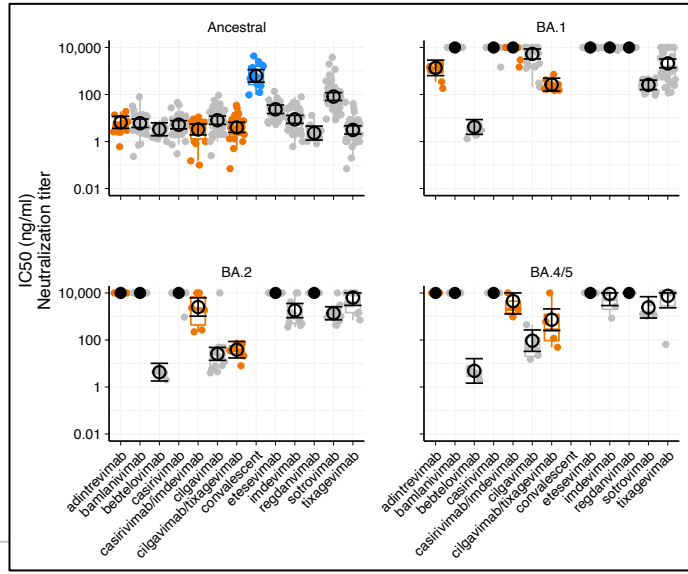
Using dose-response curve

Need:

- Dose response curve (therapeutic / prophylactic)
- Dose / route / PK (in vivo concentration)
- In vitro IC-50 of mAb against variant

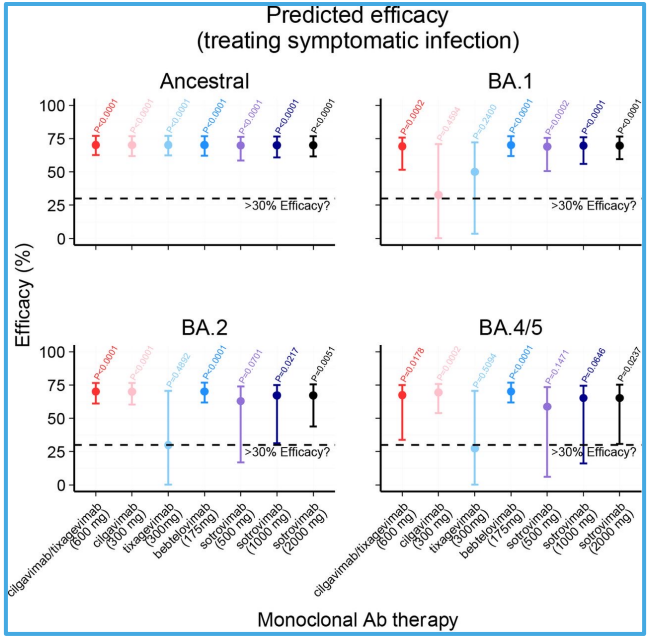
Average across multiple assays





Using dose response curve:

Therapeutic



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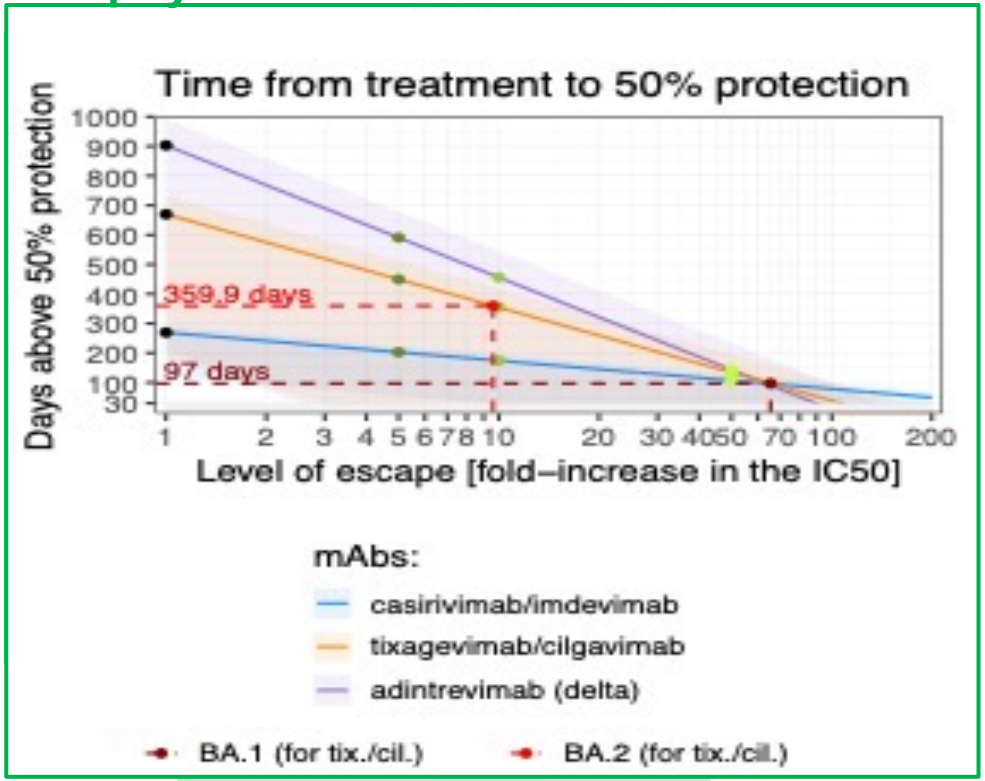
Prophylactic



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Challenges

- **Meaningful reporting: Do regulators want**
  - *Best estimate of protection?*
  - *Level of confidence protection is above 50%?*

Challenges

- **Semi-immune populations**

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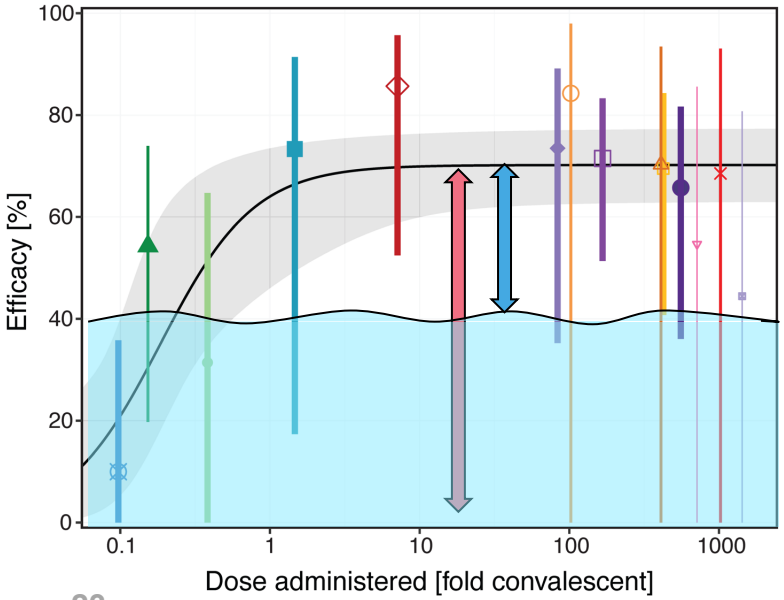

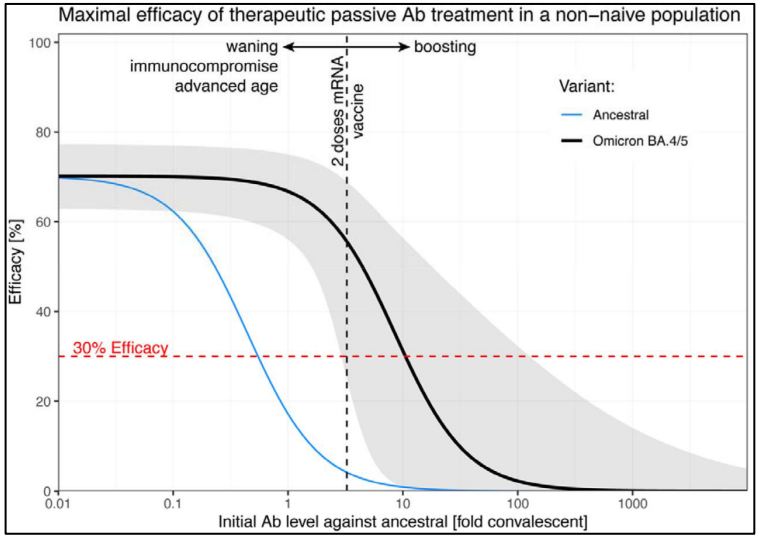

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Co-authors and funding

- Infection Analytics (UNSW)
- **David Khoury**
- **Deborah Cromer**
- **Eva Stadler**
- **Arnold Reynaldi**
- **Tim Schlub**

Sydney University

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University of Melbourne
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Jen Juno
Adam Wheatley

WHO Flu Centre (Melbourne)

Kanta Subbarao

Fred Hutch

Peter Gilbert

Monash University
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- Zoe McQuilten
- Erica Wood

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- Mark Polizotto

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- Nicole Skoetz

University of Oxford
- Lise Estcourt

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