COVAX

Immune Correlates, SARS-CoV-2 variants and ‘mix and match’: How vaccine developer approaches might be impacted by emerging data

Clinical Development & Operations SWAT Team | Thursday February 25, 2020

CEPI

Gavi The Vaccine Alliance

World Health Organization

Workshop Agenda

Time (CET)	Topic	Speaker(s)
15:00 – 15:15	Welcome, meeting objectives, and immune correlates introduction	Peter Dull Donna Ambrosino
Part 1: Progress toward immune correlates for COVID-19 to enable accelerated vaccine development		
15:15 – 15:30	Overview: Establishing a correlate from imperfect evidence – a historical perspective	David Goldblatt
15:30 – 15:40	Evidence for a serological correlate of protection from animal models and planned future studies	Cristina Cassetti
15:40 – 15:55	Observed re-infections in longitudinal natural history studies and vaccine efficacy study placebo arms: impact of neutralizing titers, variant strains	Florian Krammer
15:55 – 16:15	Approaches for correlates analyses based on breakthrough cases from vaccine efficacy studies	Stephen Lockhart Daniel Stieh
16:15 – 16:30	Evidence of contribution of cell-mediated immunity to vaccine efficacy, and utility of T cell assays to correlates analyses	Julie McElrath
16:30 – 17:05	Panel Discussion	Moderated by: Peter Dull
17:05 – 17:10	Break	
Part 2: Investigating the impact of new SARS-CoV-2 variants: Assays and available vaccines		
17:10 – 17:20	International standard for SARS-CoV-2 immunoglobulins: Use of the existing International Standard to address new variants	Paul Kristiansen
17:20 – 17:30	Neutralizing antibody assays against new variants: Overview of current activities	William Dowling
17:30 – 17:40	‘Mix & Match’: Heterologous primary vaccination and heterologous boosting regimens	Jakob Cramer
17:40 – 18:25	Panel Discussion	Moderated by: Jakob Cramer
18:25 – 18:30	Wrap Up & Next Steps	Jakob Cramer

Welcome & Meeting Objectives

Peter Dull, MD

Deputy Director,

Integrated Clinical Vaccine Development,

Bill & Melinda Gates Foundation (BMGF)

Context for today's workshop

Overall objectives:

PART 1: HOW CAN WE MAKE ADDITIONAL APPROPRIATE AND IMPACTUFL VACCINES AVAILABLE?

- Review the accumulating evidence that a neutralizing antibody response provides the primary contribution to protection against COVID-19 and discuss alternative supportive mechanisms
- Discuss past approaches to advancing vaccine development despite imperfect evidence and lessons to mitigating the risks through confirmatory studies.

PART 2: HOW CAN WE USE THE AVAILABLE VACCINES IN A BETTER WAY?

- Review the available international standard in the context of new variants
- Provide an overview on the development of neutralising antibody assays against new variants
- Introduce and discuss a practical approach for the assessment of vaccine 'mix & match' strategies
  - ➢ Heterologous primary vaccination
  - ➢ Heterologous boosting regimens

Part 1:

Progress toward immune correlates for COVID-19 to enable accelerated vaccine development

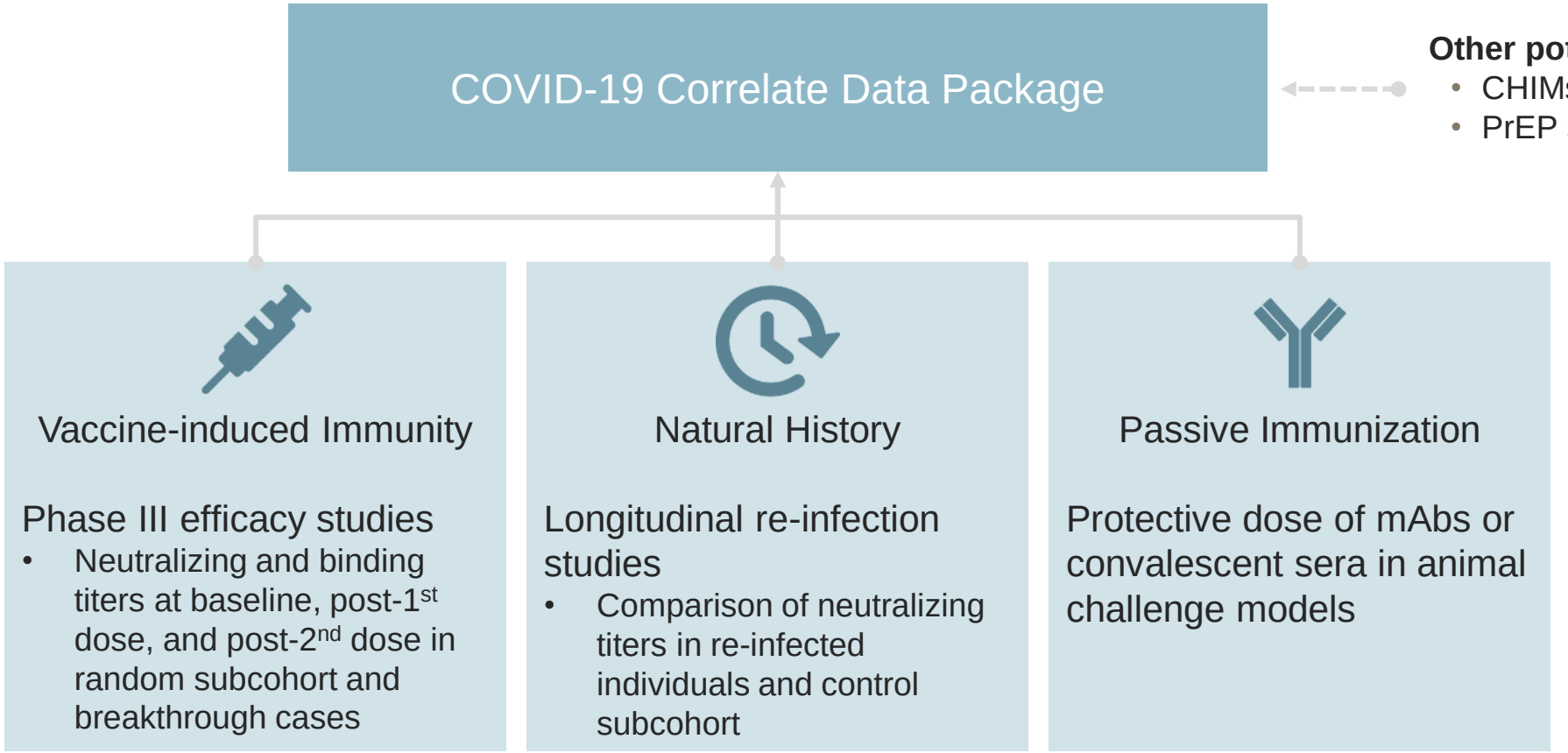
Peter Dull, MD

Deputy Director,

Integrated Clinical Vaccine Development,

Bill & Melinda Gates Foundation (BMGF)

Early evidence from multiple study types suggests a serological correlate of protection exists

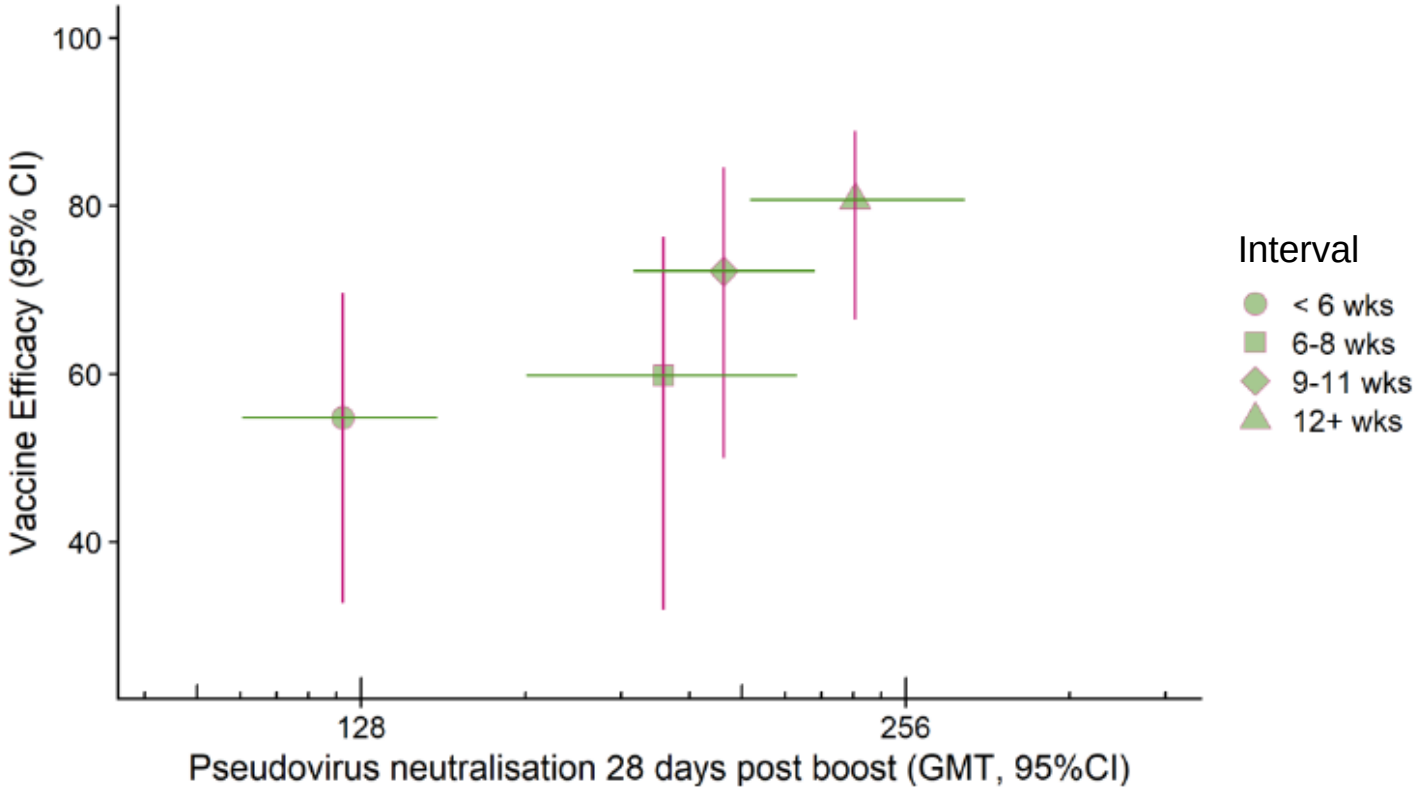


Early evidence in support of CoP:

1. Positive correlation between interval, nAbs, and efficacy
2. Cross-platform relationship between nAbs and efficacy
3. Case study: nAbs protect against infection in outbreak
4. Adoptive IgG transfer protects macaques from challenge

1 Neutralizing titers correlate with increased efficacy against symptomatic COVID-19 in the ChAdOx/AZ Phase III trial

Effect of interval between doses on immunogenicity and efficacy



As interval between doses **increases**:

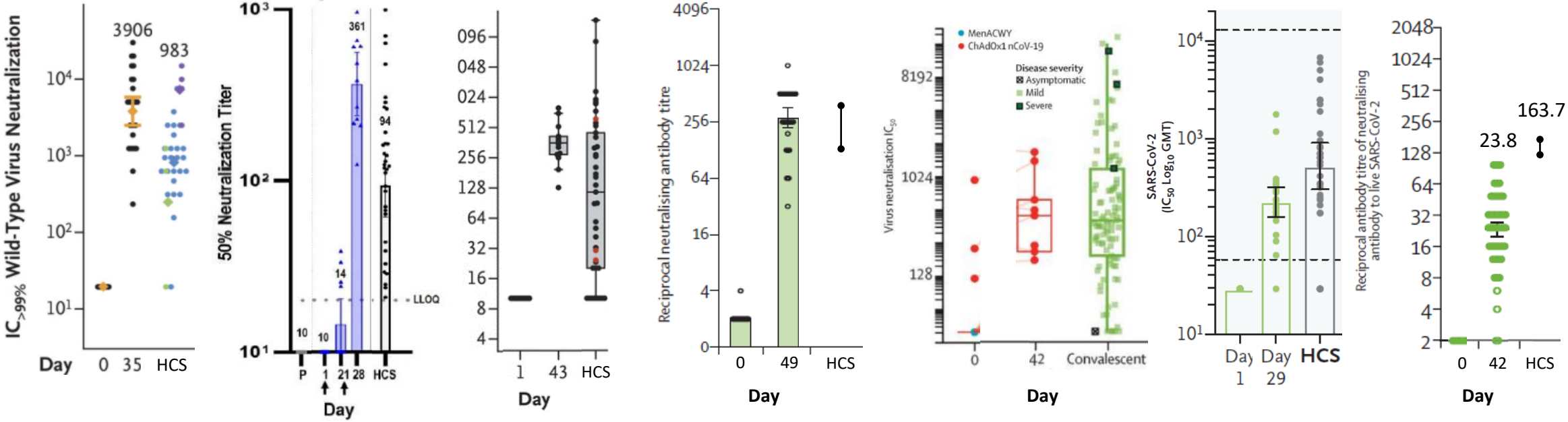
- Neutralizing titers **increase**
- Efficacy point estimates **increase**

Source: Voysey et al. 2021. Single dose administration, and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine. *Lancet* pre-print. doi: https://ssrn.com/abstract=3777268

2 Preliminary data suggest this relationship persists across platforms

Elevated neutralization titers in Ph I/II correlate with efficacy against ancestral SARS-CoV-2 strains

	Novavax Sub-unit	BioNTech / Pfizer mRNA	Moderna mRNA	Sinopharm Inactivated	Oxford / AZ Adenoviral vector	Janssen Adenoviral vector	Sinovac Inactivated
Neuts vs. HCS:	4.0-fold **higher**[1]	3.8-fold **higher**[2]	3.4-fold **higher**[3]	Comparable[4]	Comparable[5]	2.3-fold **lower**[6]	6-fold **lower**[7]
Efficacy:	**95.6%**[8]	**95%**[9]	**94.1%**[9]	**79.3%**[10]	**62.1%**[10]	**66-72%**[9]	**50.4%**[9]



1. wt MN titers in subjects aged 18-59, 14 days after 2nd 5µg dose; HCS: full range of disease severity. 2. wt VNA titers (NT_{50}) in subjects aged 18-55, 7 days following 2nd 30µg dose; HCS: n=38, across full range of disease severity. 3. Lentivirus PsVNA titers (ID_{50}) in subjects aged 18-55, 14 days after 2nd 100µg dose; HCS: n=42, across full range of disease severity. 4. wt VNA titers (50% CPE) in subjects aged 18-59, 28 days after 2nd 4µg dose; HCS range cited in supplement is plotted here for comparison, severity not specified. 5. Monogram lentivirus PsVNA titers in subjects aged 18-55, 14 days after 2nd $5x10^{10}$vp dose; HCS: n=146 hospitalized patients and 24 asymptomatic HCWs. 6. wt MN titers in subjects aged 18-55, 28 days following a single $5x10^{10}$ vp dose; HCS: n=32, mostly severe patients. 7. wt VNA titers in subjects aged 18-59, 28 days following 2nd 3µg dose; HCS: n=117 symptomatic patients across full range of disease severity. 8. Post hoc analysis. 9. Primary analysis. 10. Interim analysis

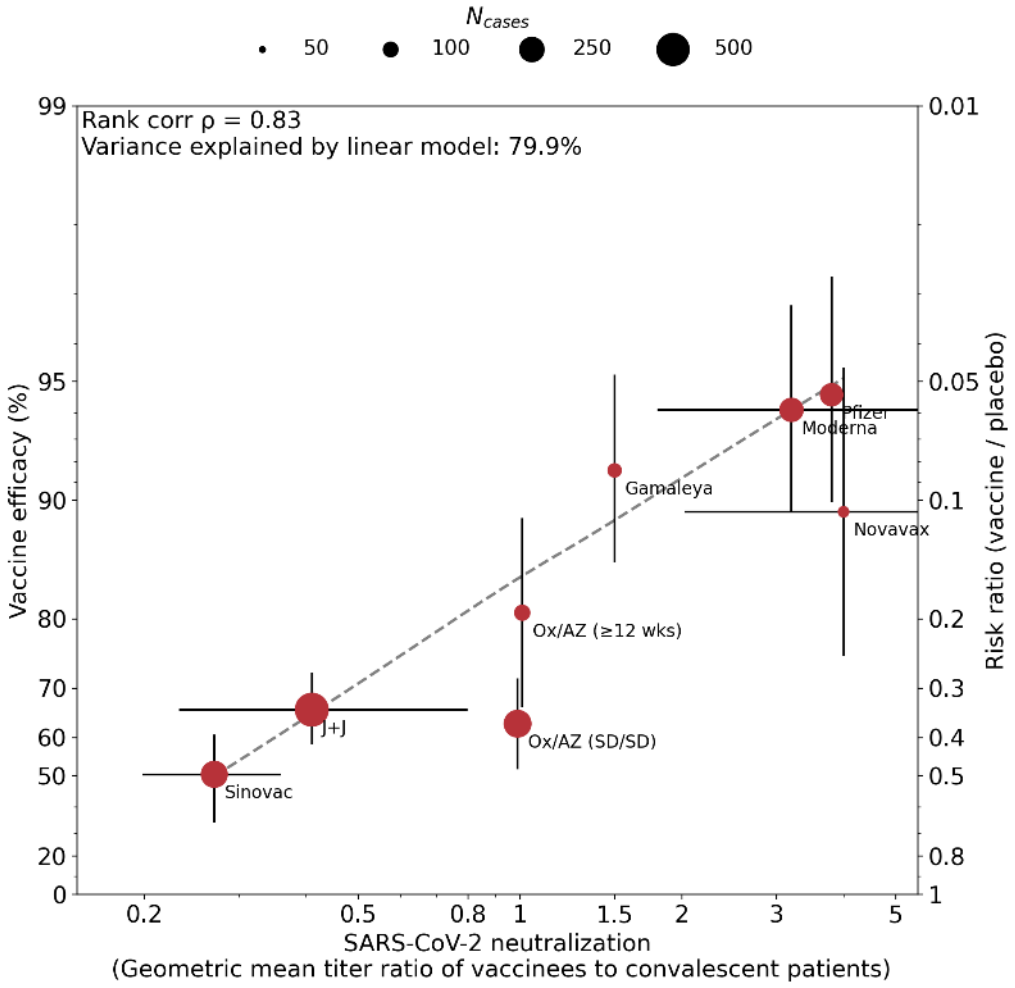
Analysis: Phase III efficacy highly correlated with Phase I/II neuts expressed relative to HCS panels

Strong correlation between Ph III efficacy and vaccinee / HCS GMT ratio (ρ = 0.83)

79.9% of variance in efficacy is explained by neut Abs

Methods / key:

- Includes all 7 vaccines for which Phase III efficacy and nAbs GMTs (run alongside HCS panels) are reported
- X-axis: Ratio of geometric mean neutralization titer (GMT, ND_{50}) at peak immunogenicity timepoint post-vaccination
- Error bars: 95% confidence interval, based on available data
- Marker size indicates number of cases underlying VE estimate
- Dashed line: non-parametric LOESS fit



Source: Analysis conducted by Donna Ambrosino, George Siber, Peter Gilbert and Andrew Fiore-Gartland

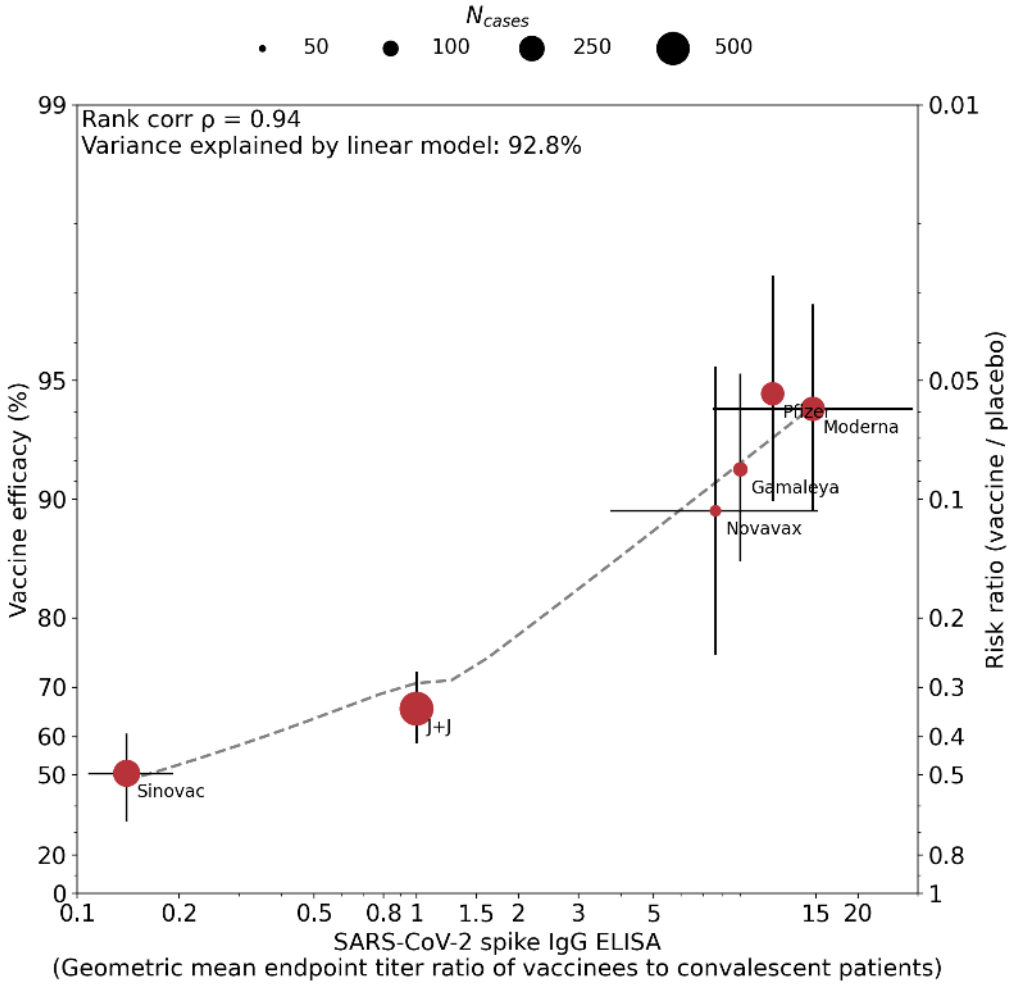
Analysis: Phase III efficacy highly correlated with Phase I/II ELISA GMEPTs expressed relative to HCS panels

Strong correlation between Ph III efficacy and vaccinee / HCS GMEPT ratio (ρ = 0.94)

92.8% of variance in efficacy is explained by binding Abs

Methods / key:

- Includes 6 vaccines for which Phase III efficacy and binding Ab GMEPTs (run alongside HCS panels) are reported
- X-axis: Ratio of geometric mean endpoint titer (GMEPT, ID_{50}) at peak immunogenicity timepoint post-vaccination
- Error bars: 95% confidence interval, based on available data
- Marker size indicates number of cases underlying VE estimate
- Dashed line: non-parametric LOESS fit



Source: Analysis conducted by Donna Ambrosino, George Siber, Peter Gilbert and Andrew Fiore-Gartland

Conclusions

Strong correlation between both neutralizing (ρ = 0.83) and binding (ρ = 0.94) antibody responses and efficacy

In absence of International Units to compare across studies, calibration to a human convalescent sera panel is necessary

- Relationship between efficacy and reported neutralizing / binding titers is weak (r^2 = 0.24, 0.21 respectively)

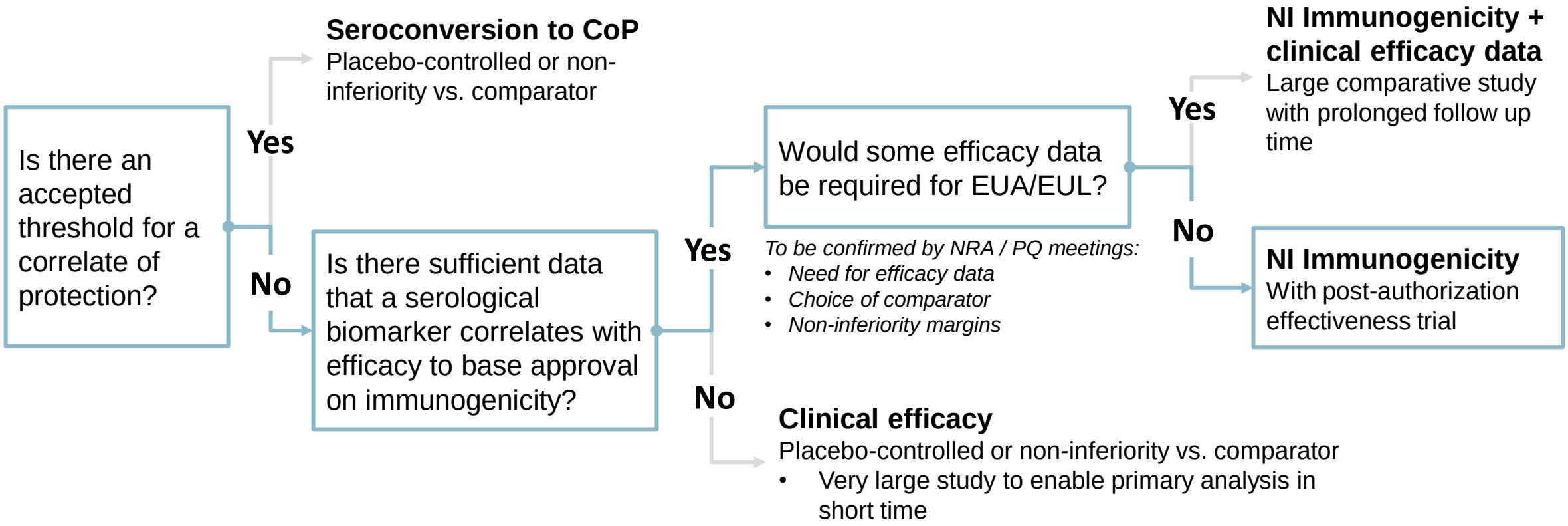
Calibration to WHO International Standard may improve correlation

Nearly all variance is explained by antibody responses, leaving little room for impact of T cells on correlation

Determination of a threshold value for a protective correlate will require individual antibody distributions (i.e., reverse cumulative distribution function curves)

We believe that there is adequate evidence to support a non-inferior immunogenicity approach for Wave 2 EUAs

Rationale for this approach:



Overview: Establishing a correlate from imperfect evidence – a historical perspective

David Goldblatt, PhD

Professor of Vaccinology and Immunology

University College London

February 2021

Overview: Taking action on a correlates despite imperfect evidence-a historical perspective

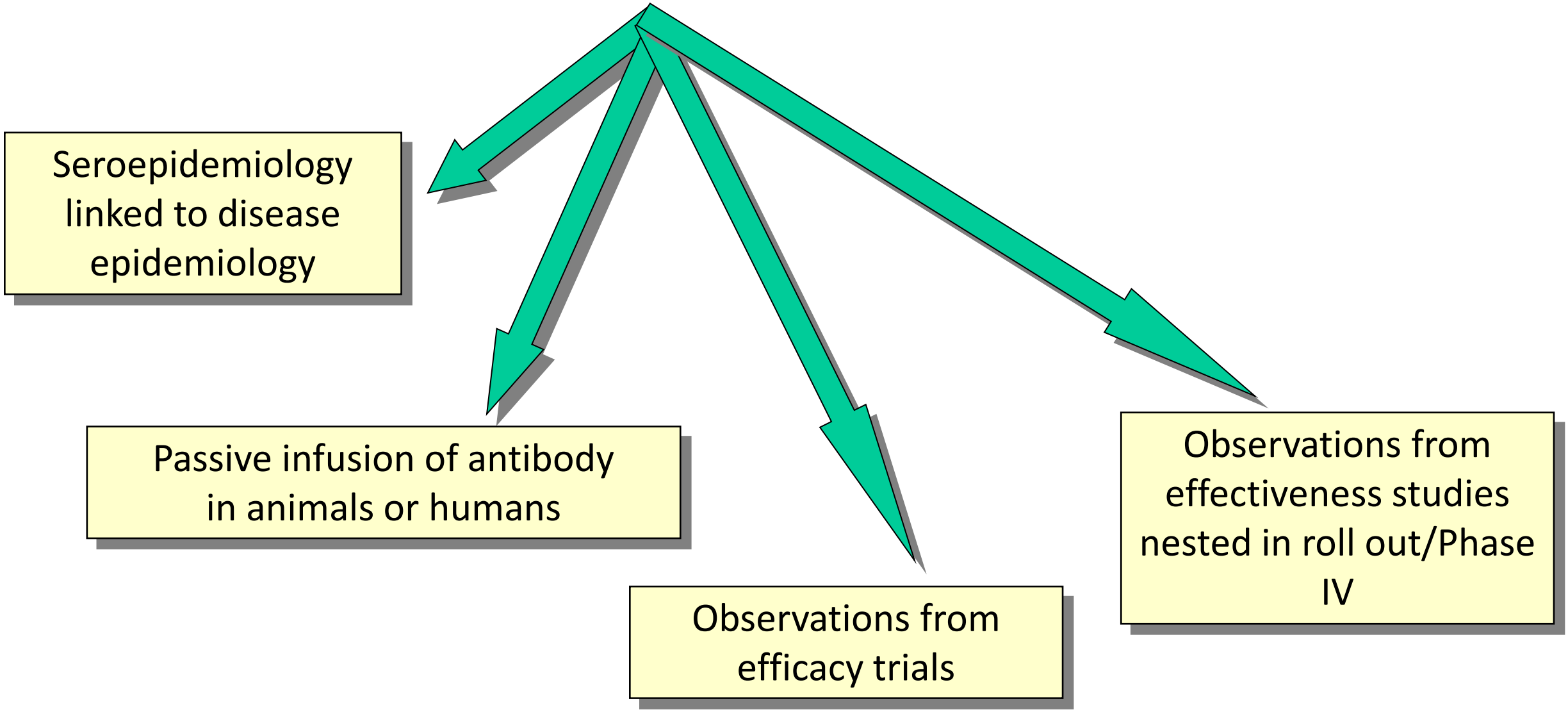
David Goldblatt

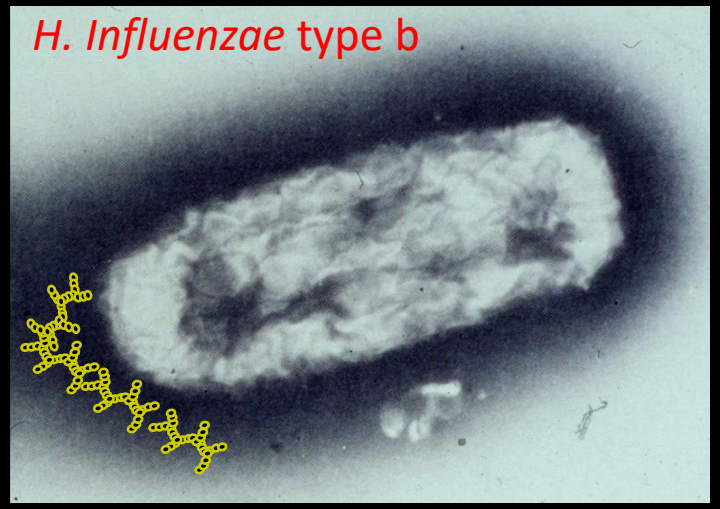
Professor of Vaccinology and Immunology

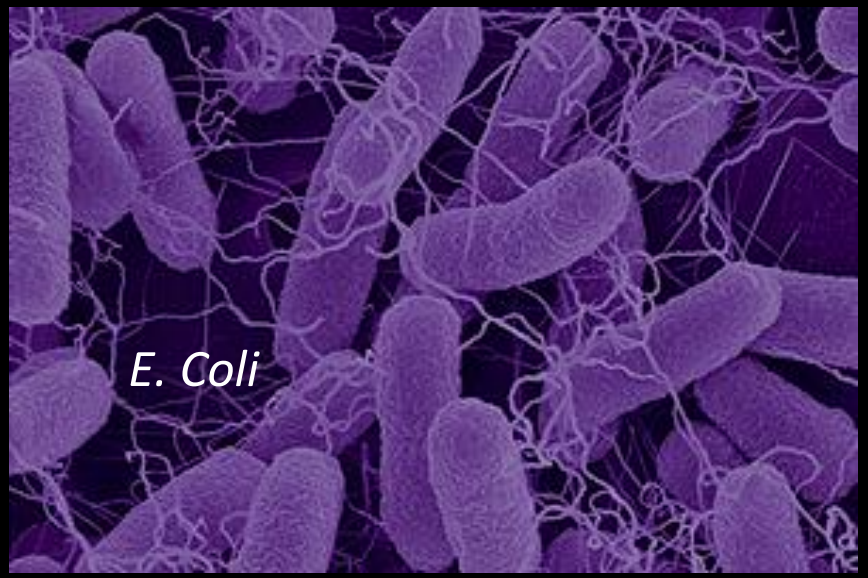
GREAT ORMOND STREET
INSTITUTE OF CHILD HEALTH
University College London

BILL & MELINDA GATES foundation

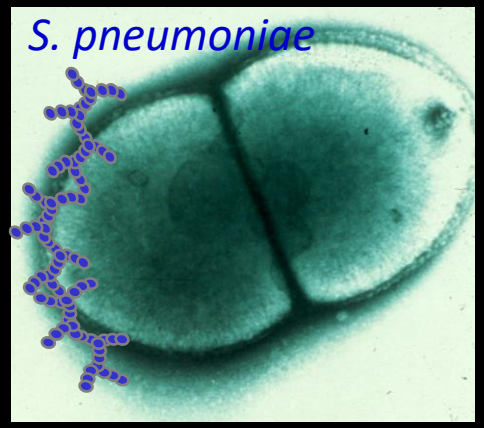
How to Define the Level of an immune marker that Is Protective?



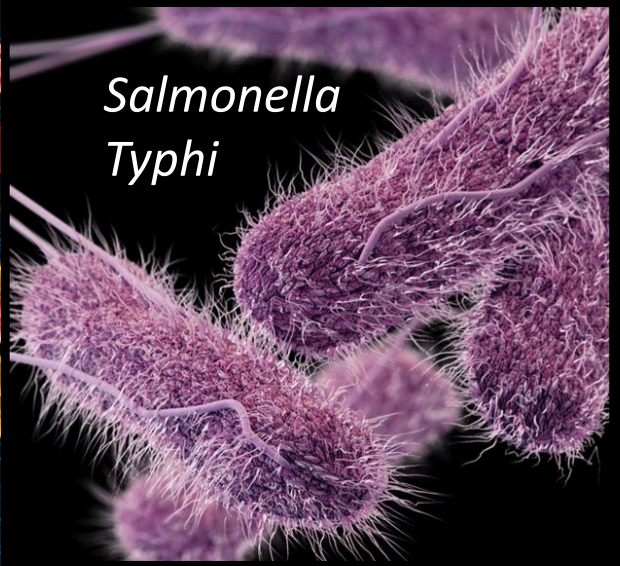

H. Influenzae type b


E. Coli

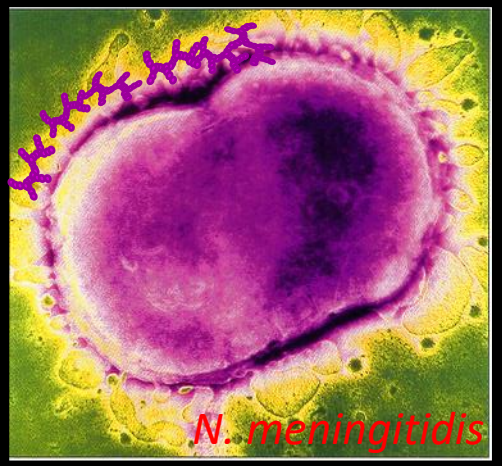

Group
B Strep


S. pneumoniae


Staphylococcus aureus

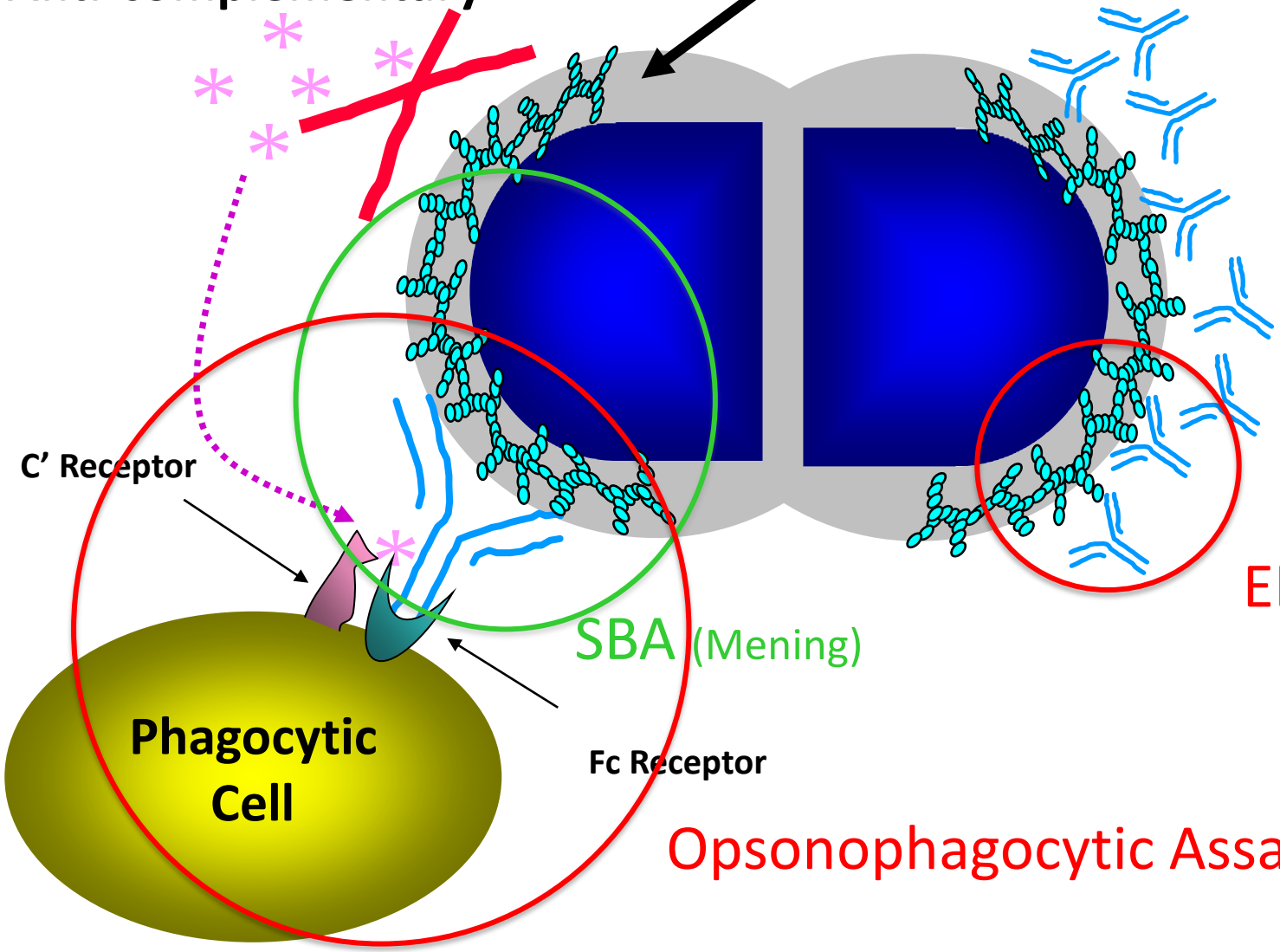

Salmonella
Typhi


Shigella


N. meningitidis

Capsule = Virulence Factor

Anti-complementary

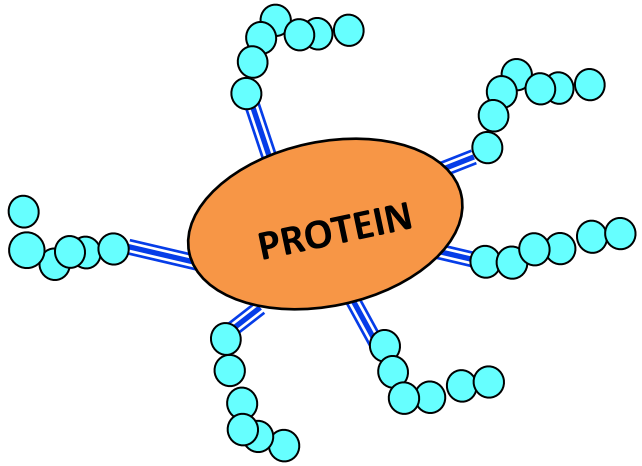


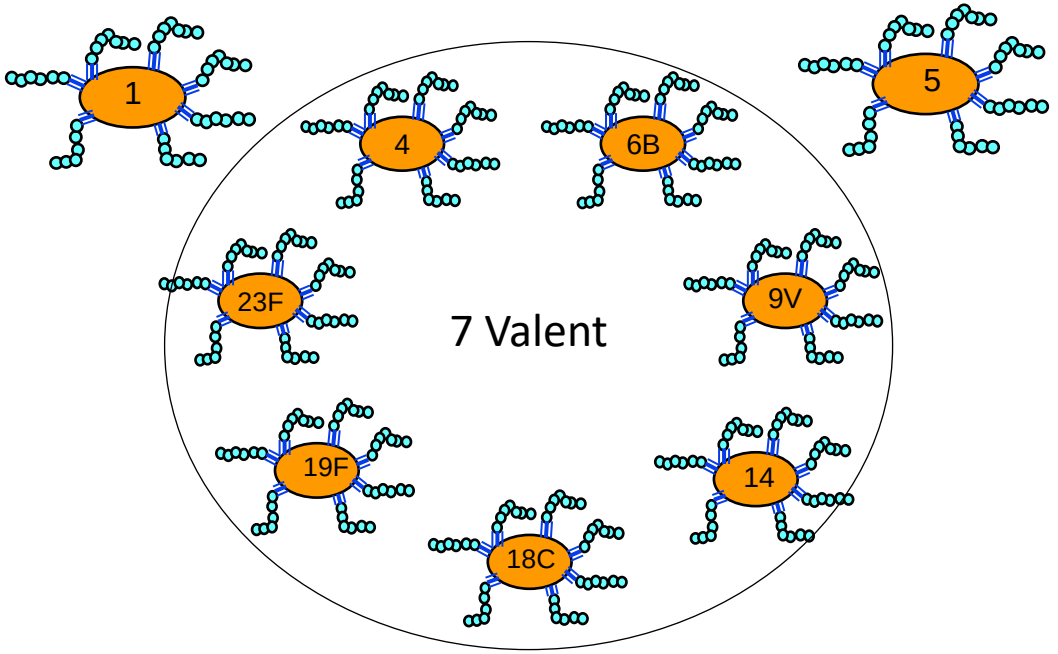
SBA (Mening)

Opsonophagocytic Assay

Target for Protective Antibody

ELISA





Serologic Correlate of Protection

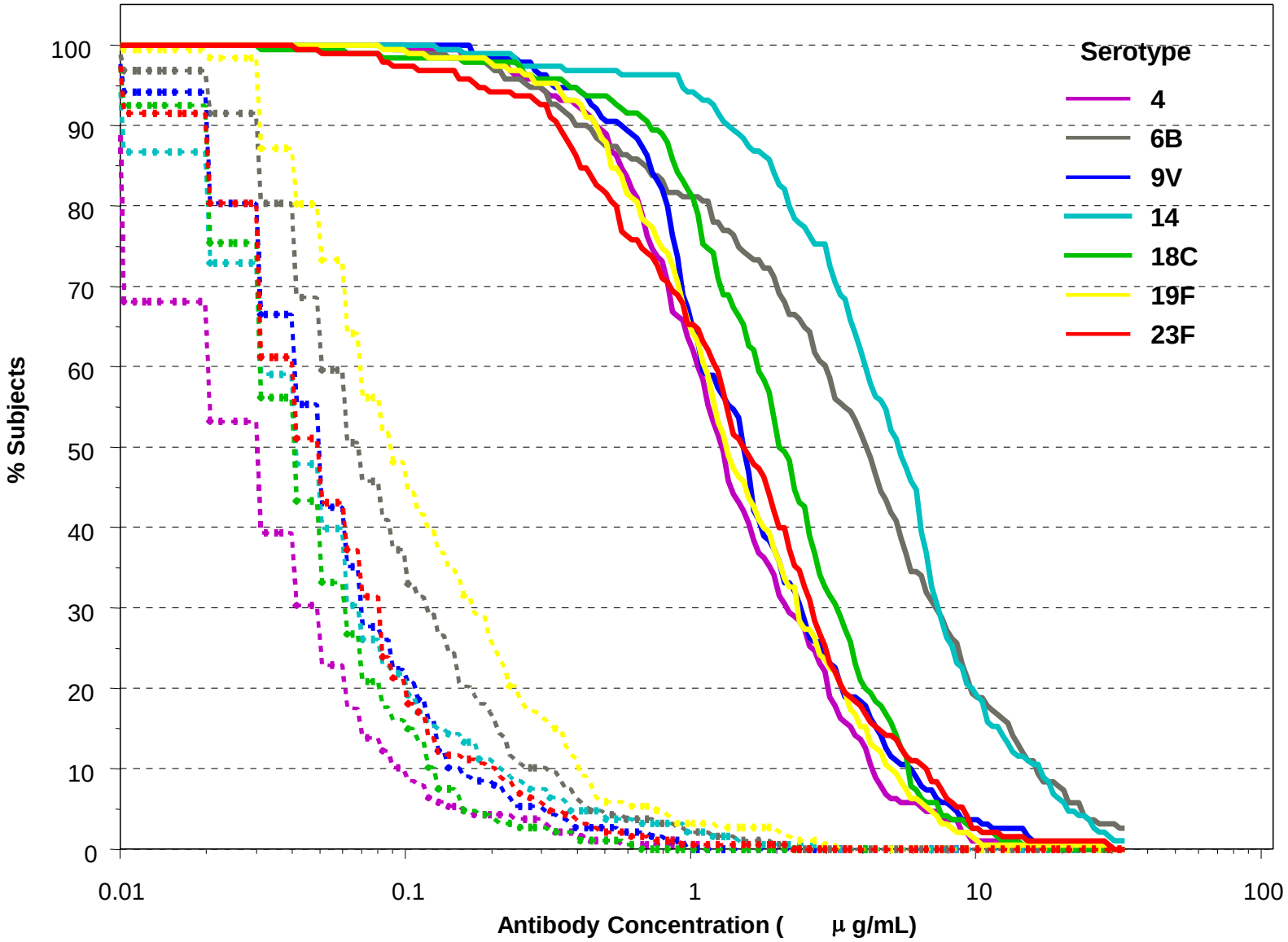
Vaccine efficacy for Invasive Pneumococcal Disease (% protected)

Serum Antibody Protective Threshold

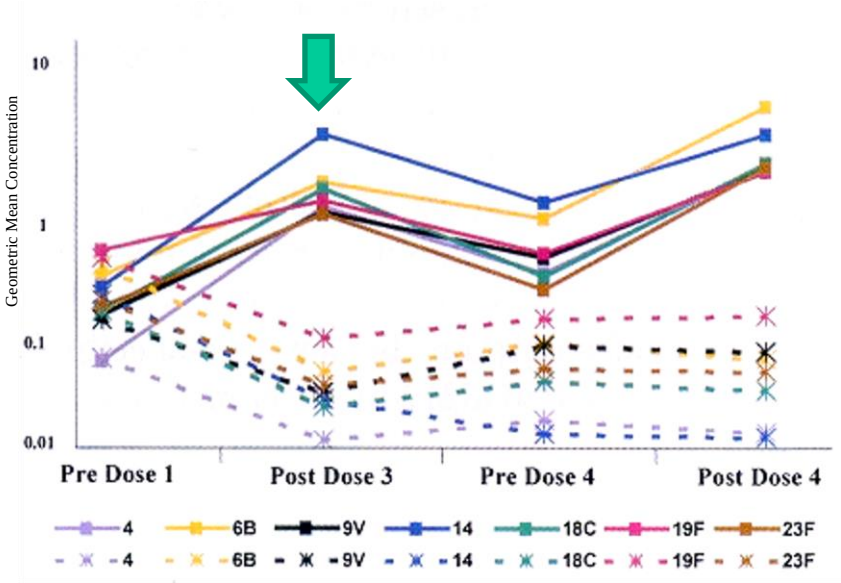
Distribution of serum antibody concentrations in vaccinated population

Siber GR, et al. *Vaccine*. 2007;25:3816-3826.

Reverse Cumulative Distribution Curves of Antibody Concentration: NCKP Trial



	No. of Cases		Per Protocol V_E (95% CI)
	Contr	PCV	
All types (PP)	39	1	97.4% (82.7, 99.9)



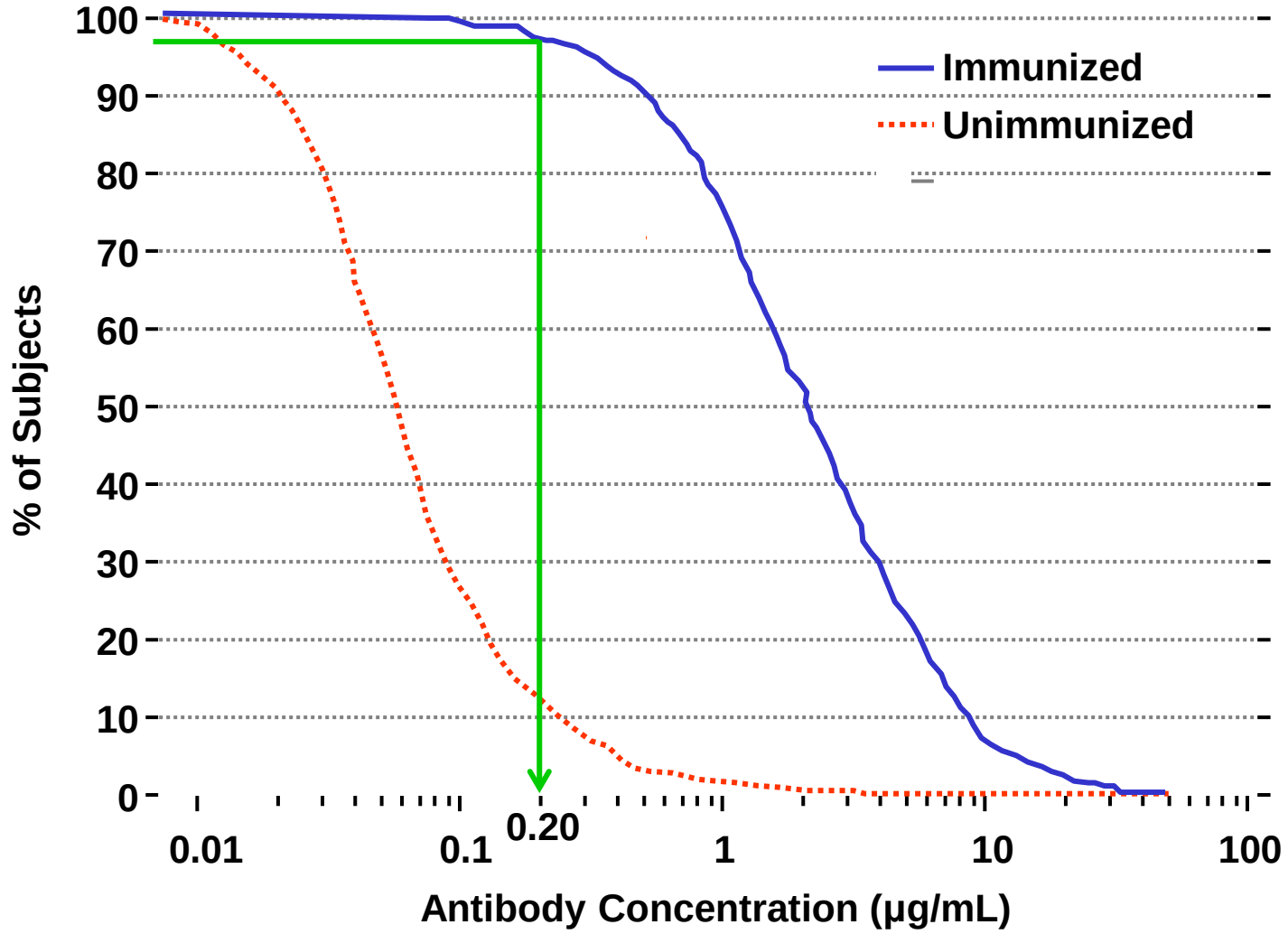
Black et al PIDJ 2000

Post Primary Concentrations

Black S, et al. *Pediatr Infect Dis J.* 2000;19:187-295.

Reverse Cumulative Distributions of Post-Dose 3 ELISA Antibody Concentrations in NCKP Population: 7 Serotype Aggregates

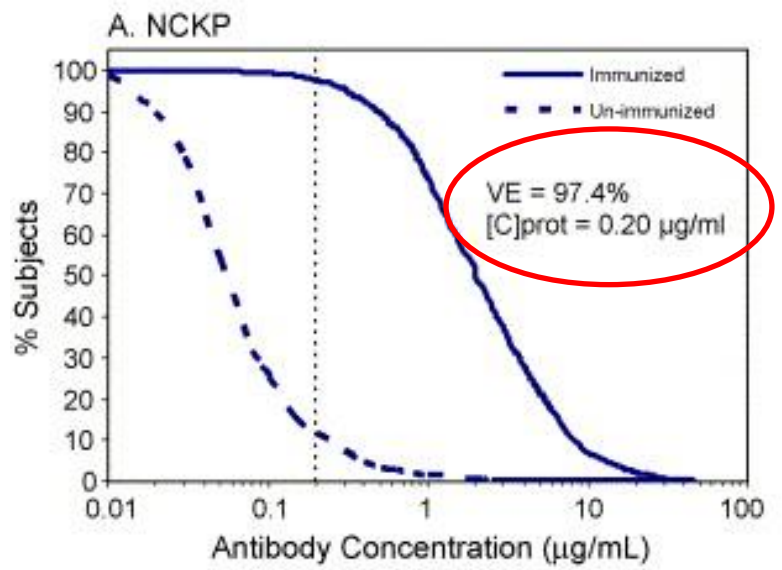
Per protocol VE: 97.4%

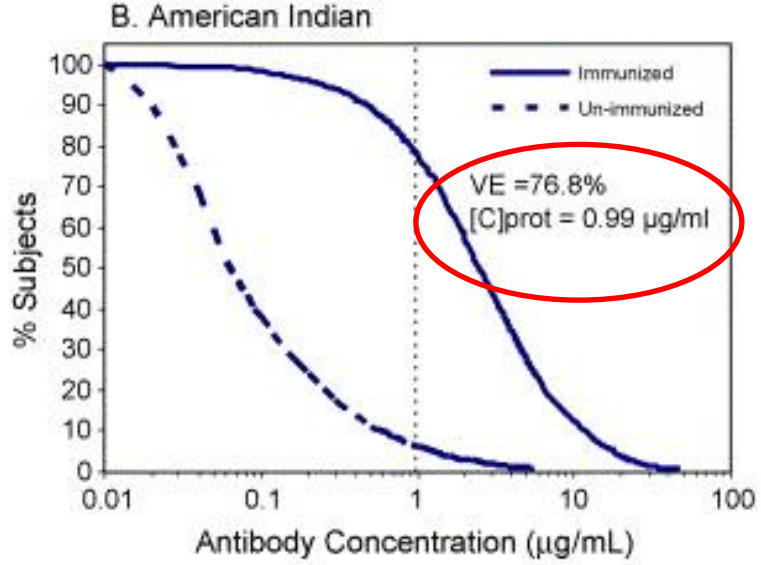


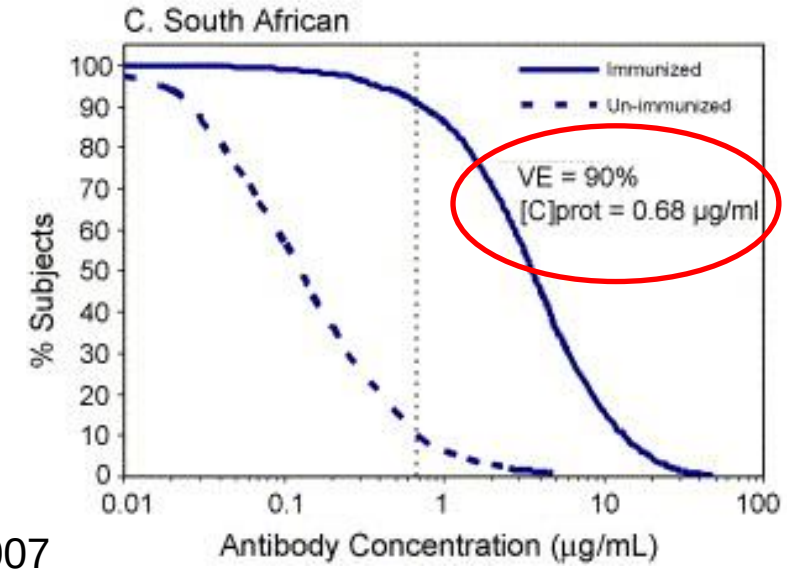
Predicted VE with 0.2µg/mL cut off: 97.3%

Black S, et al. *Pediatr Infect Dis J.* 2000;19:187-295. Jódar L, et al. *Vaccine*. 2003;21:3265-3272.

RCD's of IgG anti-pneumococcal capsular polysaccharide antibody concentrations **aggregated for the 7 vaccine types** in three controlled PnC efficacy studies and **the pooled studies** weighted for no. of study subjects.

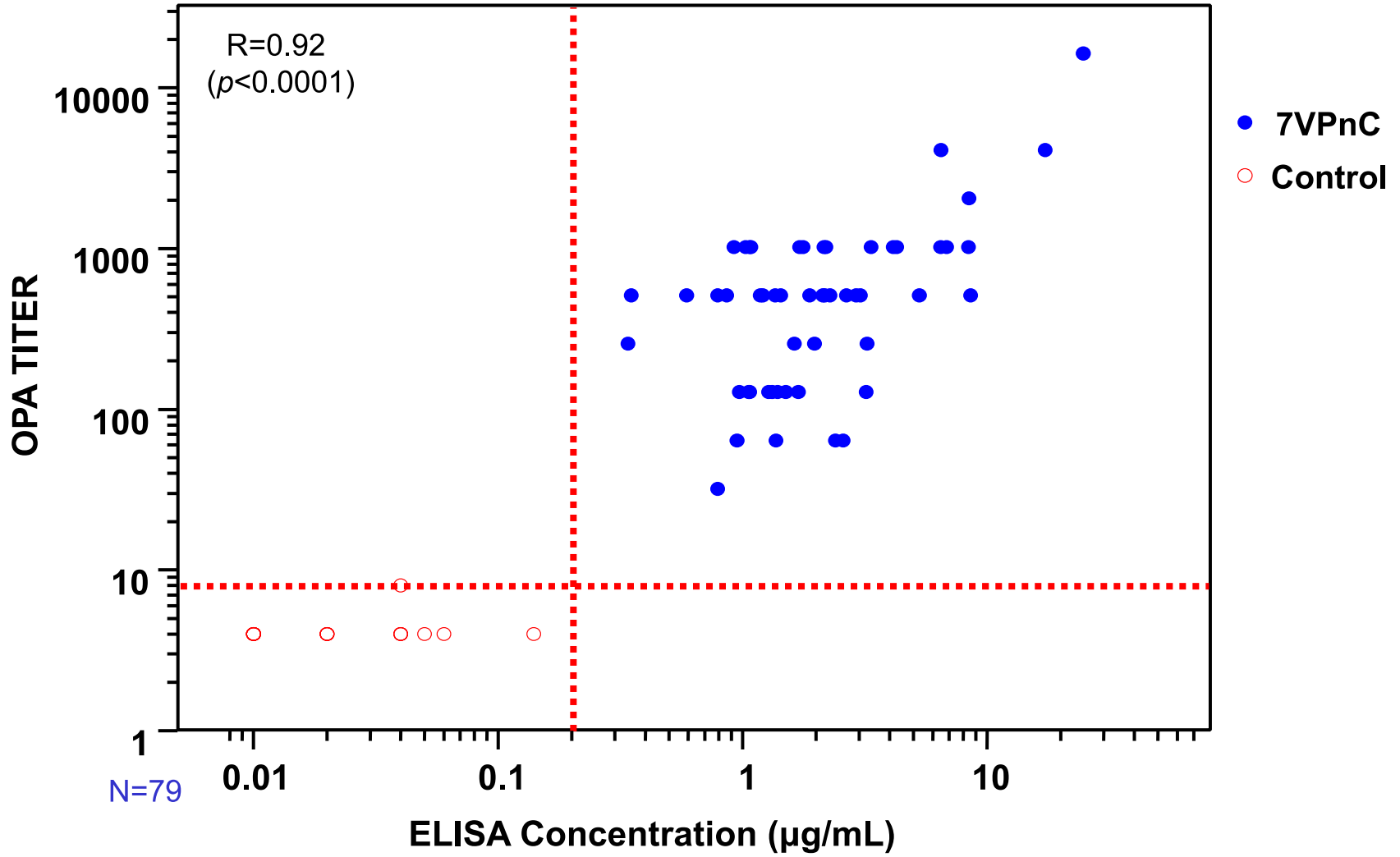






Siber et al. Vaccine 2007

Post-Dose 3 OPA Response: Type 4 (Types 6B, 9V, 14, 18C and 23F Are Similar)



ELISA titer of 0.20 ≈OPA titer of 1/8

Jódar L, et al. *Vaccine.* 2003;23:3265-3272.

Serological criteria for evaluation and licensure of new pneumococcal conjugate vaccine formulations for use in infants☆

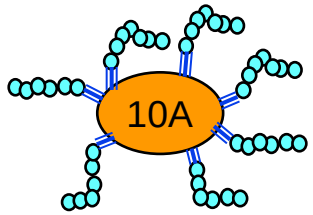
Luis Jódar[a,1], Jay Butler[b], George Carlone[c], Ron Dagan[d], David Goldblatt[e], Helena Käyhty[f], Keith Klugman[g], Brian Plikaytis[c], George Siber[h], Robert Kohberger[h], Ih Chang[h], Thomas Cherian[a,*]

WHO Technical Report Series, No. 927, 2005

Annex 2

Recommendations for the production and control of pneumococcal conjugate vaccines

Non-inferiority at the serological correlate of protection 0.35μg/ml



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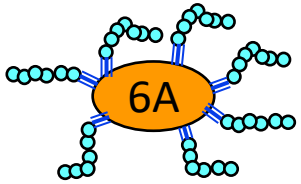

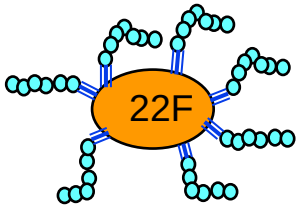

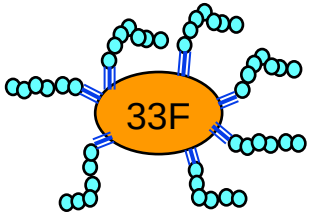

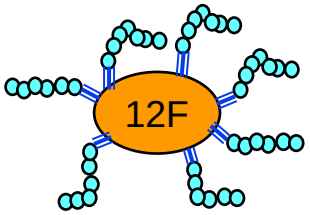

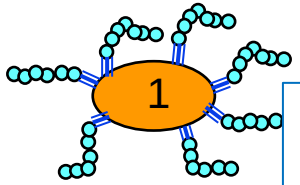

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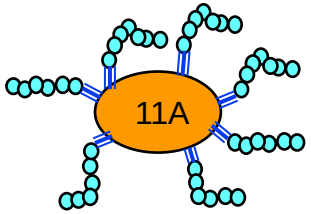
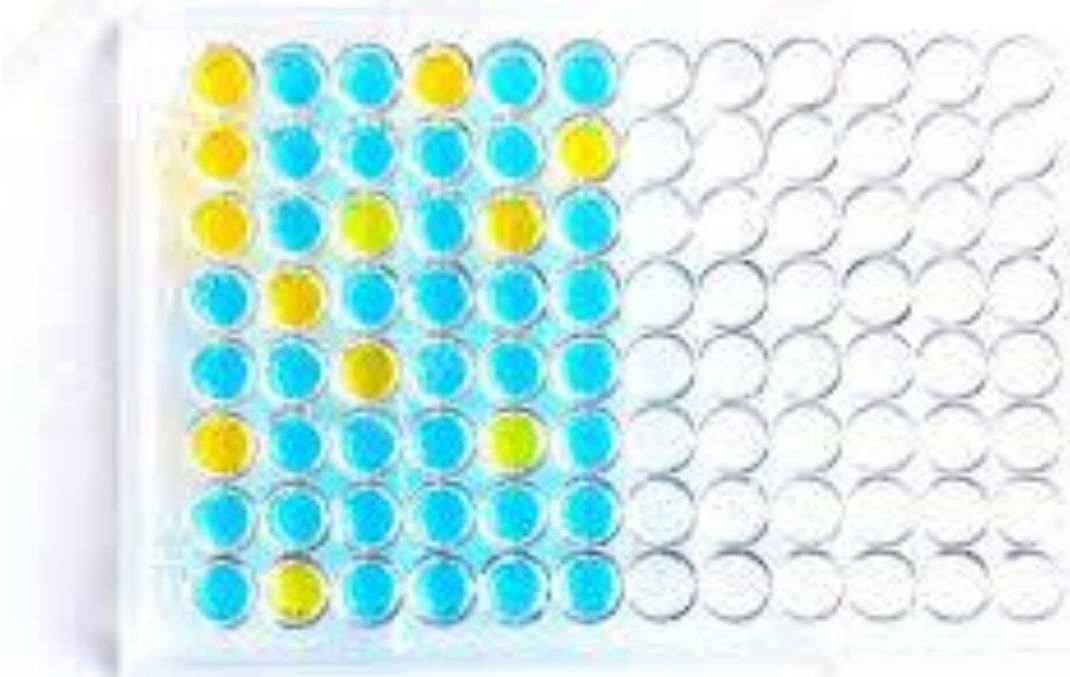
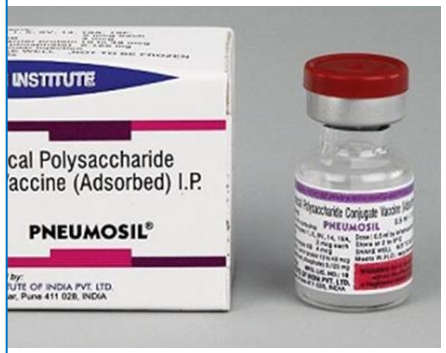


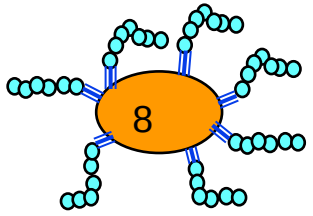
WHO Standards, QC Panels, Assay Standardisation

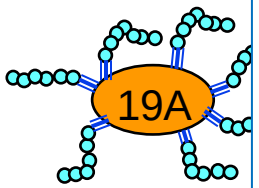


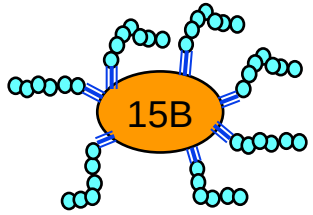
SINGLE SOURCE OF ANTIGENS



2020







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Synflorix™

10 Valent

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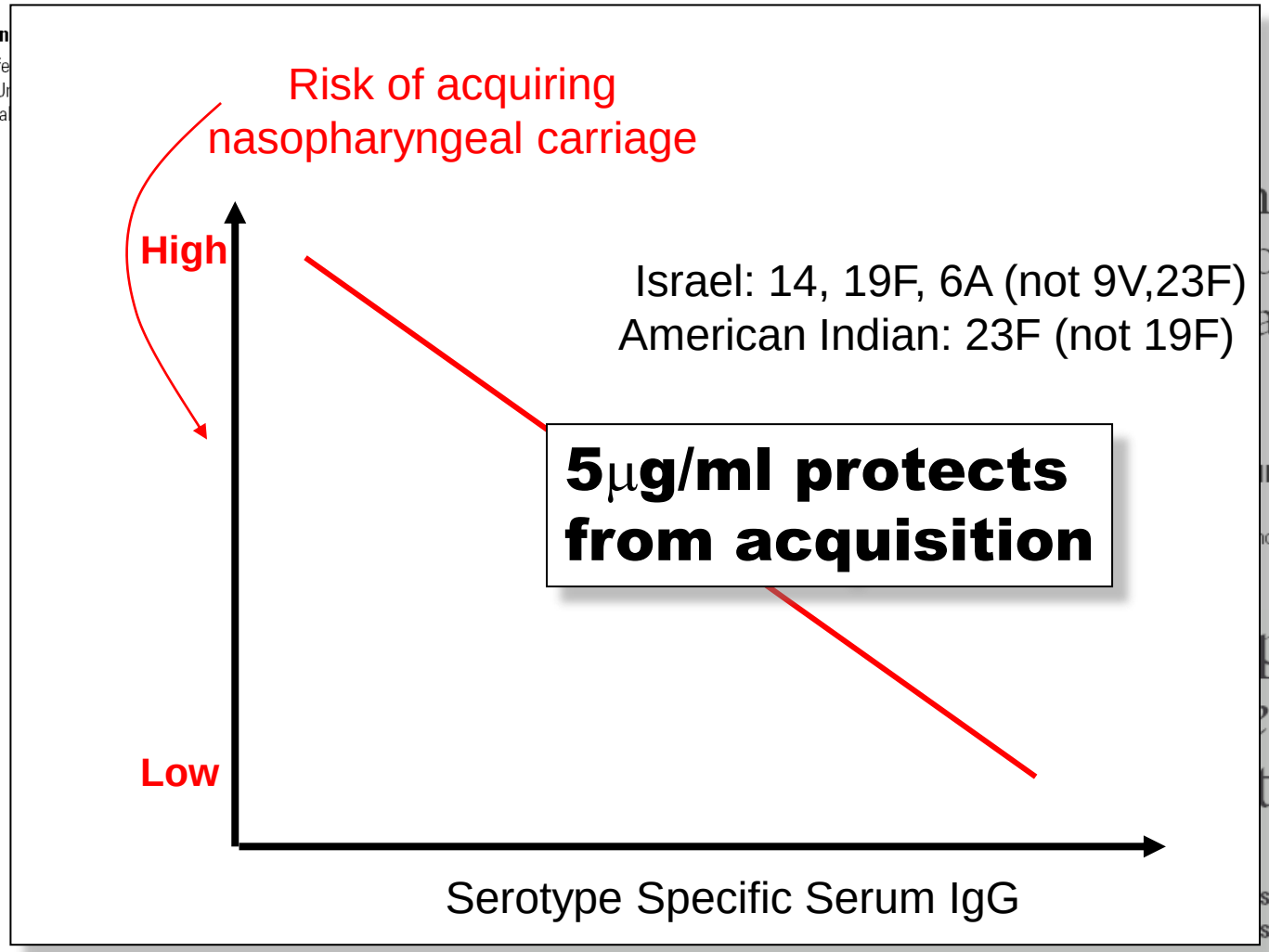
Are correlates developed with invasive disease endpoints relevant to mucosal carriage?

Serum Serotype-Specific Pneumococcal Anticapsular Immunoglobulin G Concentrations after Immunization with a 9-Valent Conjugate Pneumococcal Vaccine Correlate with Nasopharyngeal Acquisition of Pneumococcus

Ron Dagan
[1]Pediatric Infe
Ben-Gurion Ur
of Public Hea



CID 2007

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...l G. Hackell,[2] Raymond Reid,[1]

...ool of Public Health, Baltimore, Maryland;

...pharyngeal Carriage
... in Adults:
...tudy

...shton,[1] Camilla Virta,[3] Alessia Melegaro,[2]
...s,[2] Nigel Gay,[2] Helena Kayhty,[3] and Elizabeth Miller[2]

[1]Immunobiology Unit, Institute of Child Health, University College London, and [2]Health Protection Agency, London, United Kingdom;
[3]National Public Health Institute, Helsinki, Finland

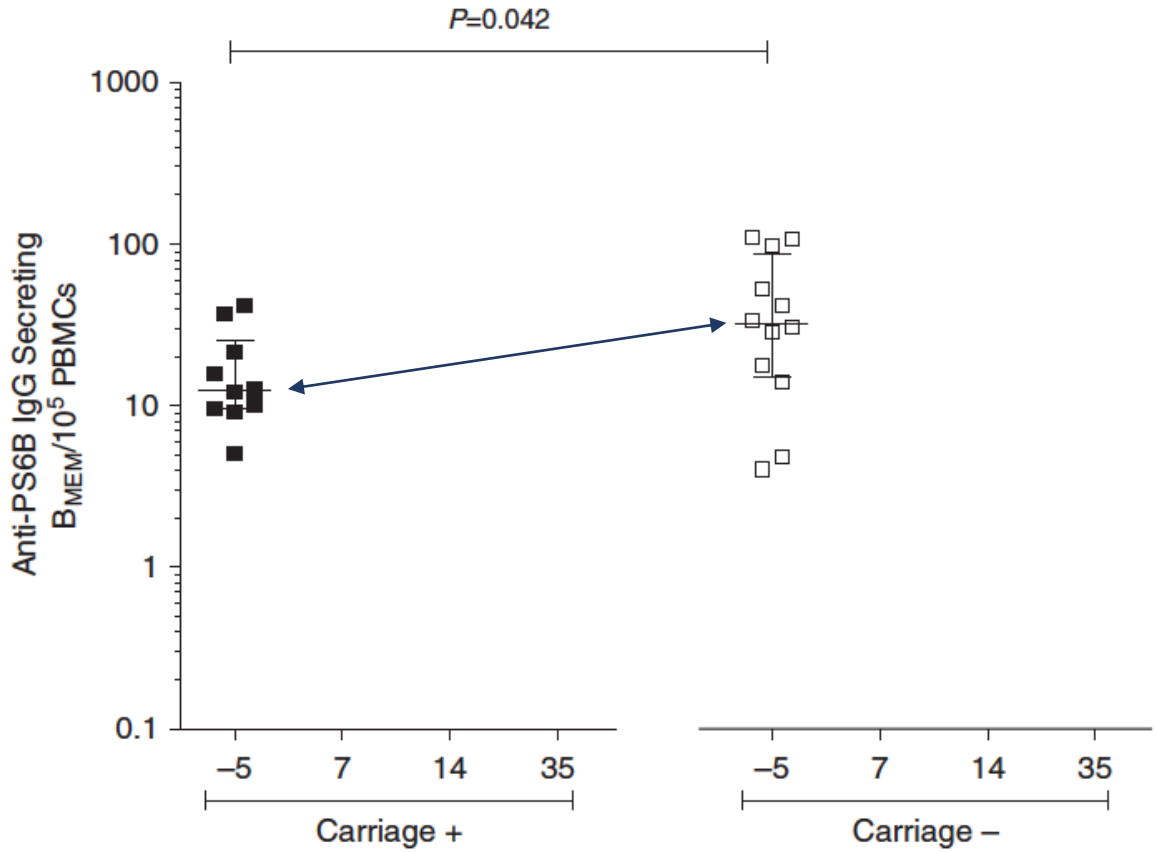
JID 2005

ORIGINAL ARTICLE

Polysaccharide-Specific Memory B Cells Predict Protection against Experimental Human Pneumococcal Carriage

Shaun H. Pennington[1,2], Sherin Pojar[1], Elena Mitsi[1], Jenna F. Gritzfeld[1], Elissavet Nikolaou[1], Carla Solórzano[1], Jessica T. Owugha[1], Qasim Masood[1], Melita A. Gordon[2,3], Angela D. Wright[1], Andrea M. Collins[1], Eliane N. Miyaji[4], Stephen B. Gordon[1,3*], and Daniela M. Ferreira[1*]

"circulating IgG at time of pneumococcal exposure did not protect against carriage"



Am J Resp Crit Care Med 2016

Is a single
aggregate
correlate (0.35)
valid for all serotypes?

Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study

Nick J Andrews, Pauline A Waight, Polly Burbidge, Emma Pearce, Lucy Roalfe, Marta Zancolli, Mary Slack, Shamez N Ladhani, Elizabeth Miller, David Goldblatt

Summary

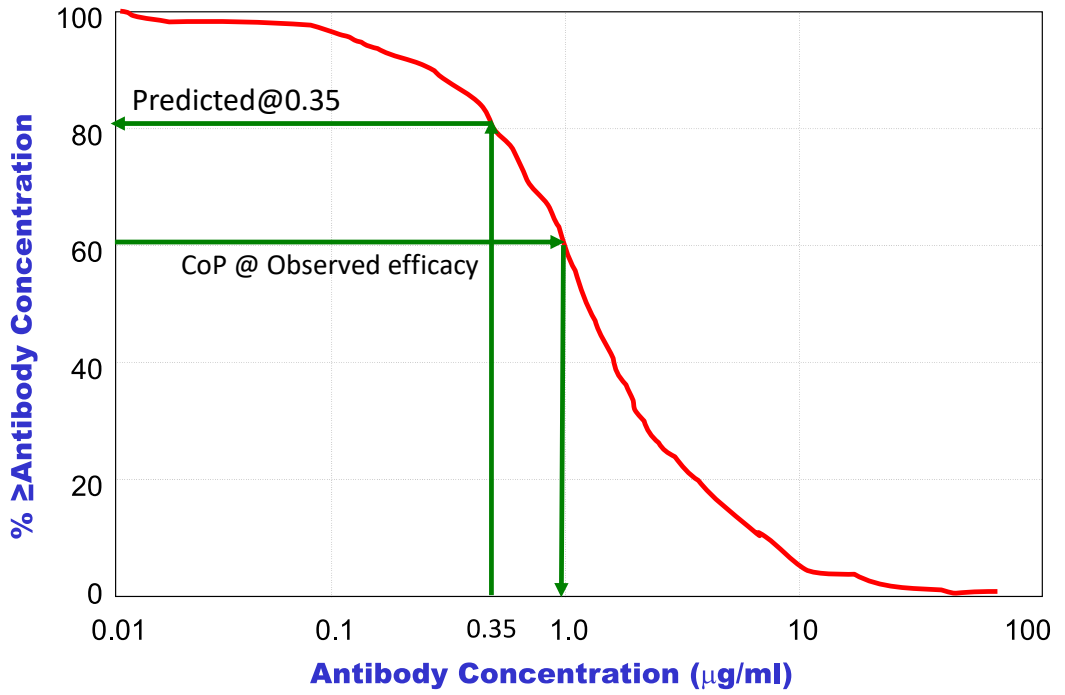
Background Efficacy of the 13-valent pneumococcal conjugate vaccine (PCV13) was inferred before licensure from an aggregate correlate of protection established for the seven-valent vaccine (PCV7). We did a postlicensure assessment of serotype-specific vaccine effectiveness and immunogenicity in England, Wales, and Northern Ireland to derive the correlates of protection for individual serotypes.

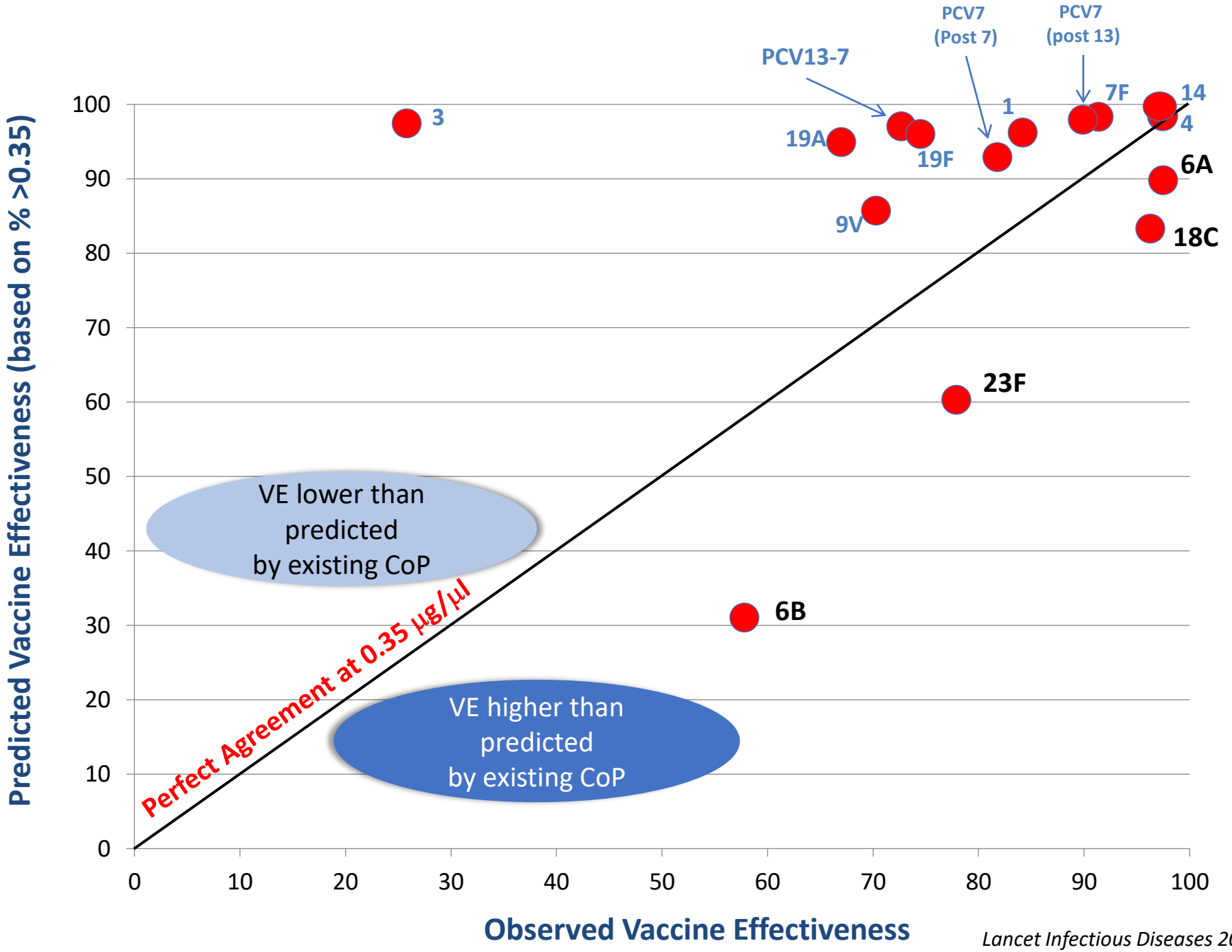
Lancet Infect Dis 2014
Published Online
July 18, 2014
http://dx.doi.org/10.1016/S1473-3099(14)70822-9

	Vaccine effectiveness (95% CI)	Predicted vaccine effectiveness at 0·35 µg/mL ELISA cutoff*	Calculated correlate of protection in µg/ml for ELISA* (95% CI)	Calculated correlate of protection in titres for opsonophagocytic antibody* (95% CI)
PCV13				
1	84% (54 to 95)			
3	26% (−69 to 68)			
6A†	98% (64 to 99·8)			
7F	91% (70 to 98)			
19A	67% (33 to 84)			
5	..			
Extra serotypes in PCV13 (plus 6C)	73% (55 to 84)			
Extra serotypes in PCV13 (plus 6C), excluding 3	80% (65 to 89)			
All PCV7 serotypes	90% (34 to 98)			
All PCV13 serotypes, (plus 6C)	75% (58 to 84)			
All PCV13 serotypes (plus 6C), excluding 3	82% (68 to 89)			
PCV7				
4	97% (65 to 99·8)			
6B	58% (3 to 82)			
9V	70% (−25 to 93)			
14	98% (88 to 99·5)			
18C	96% (81 to 99)			
19F	75% (37 to 90)			
23F	78% (23 to 94)			
All PCV7 serotypes	82% (72 to 89)			

Reverse Cumulative Distribution

Predicted Efficacy @ 0.35 µg/ml for each serotype?
Correlate of Protection @ Observed UK Vaccine Efficacy?



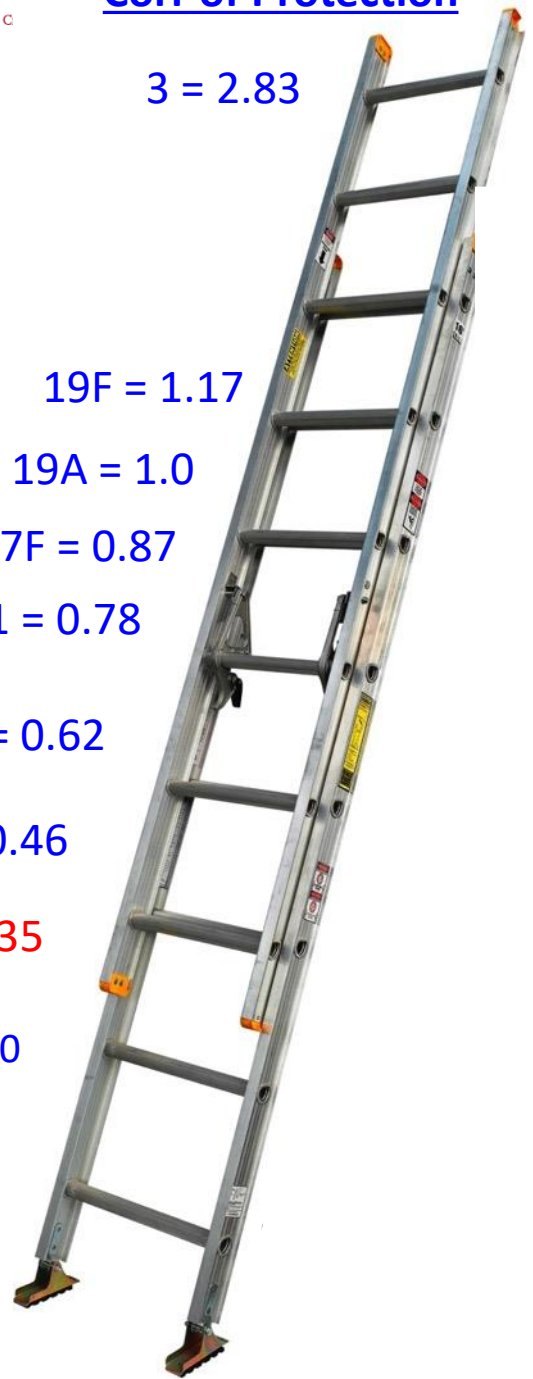


Lancet Infectious Diseases 2014

Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study

Nick J Andrews, Pauline A Waight, Polly Burbidge, Emma Pearce, Lucy Roalfe, Marta Zancolli, Mary Slack, Shamez N Ladhani, Elizabeth Miller, David Goldblatt

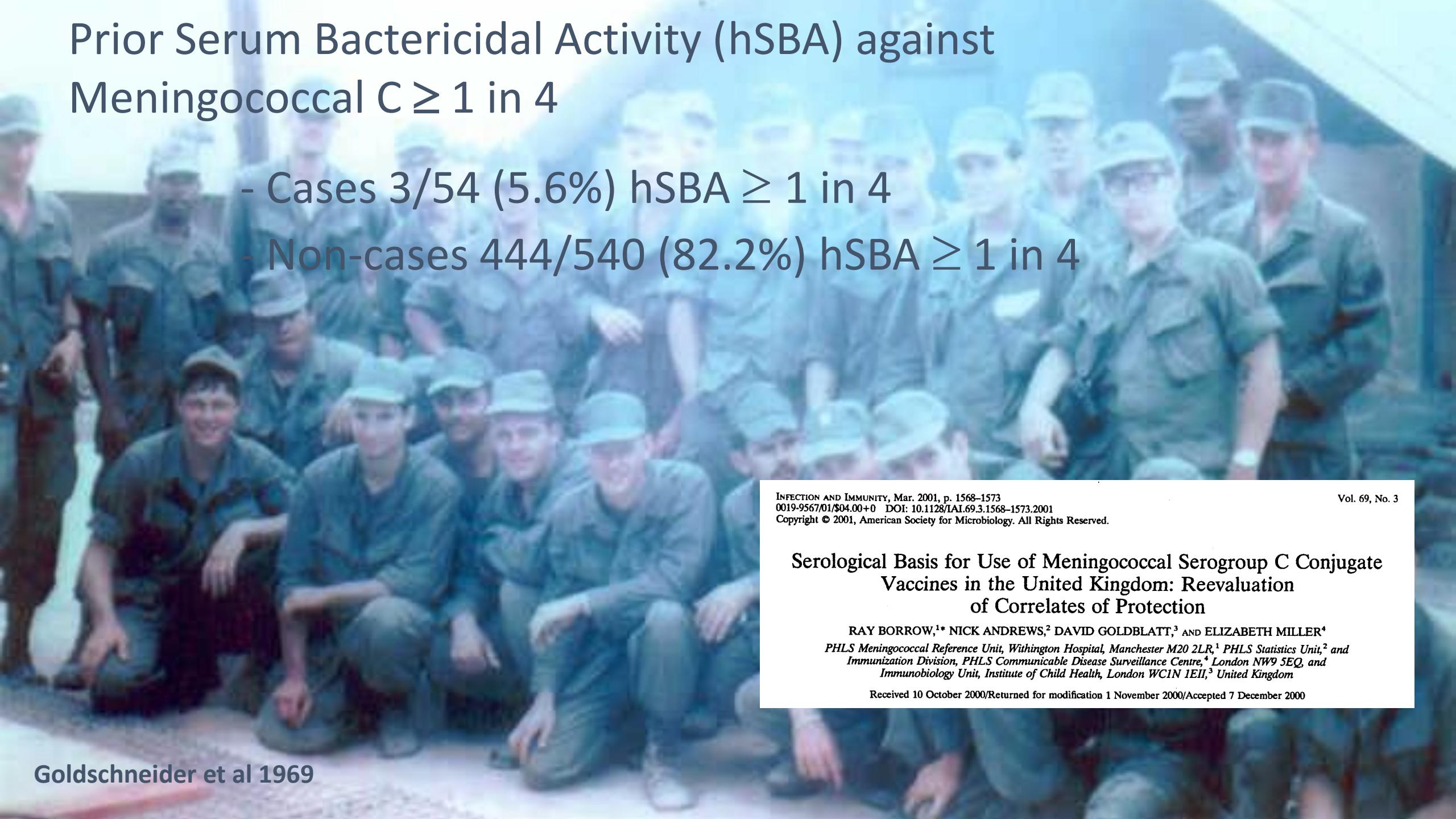
Corr of Protection



Lancet ID 2014

Prior Serum Bactericidal Activity (hSBA) against Meningococcal C ≥ 1 in 4

- Cases 3/54 (5.6%) hSBA ≥ 1 in 4
- Non-cases 444/540 (82.2%) hSBA ≥ 1 in 4



INFECTION AND IMMUNITY, Mar. 2001, p. 1568–1573 Vol. 69, No. 3
0019-9567/01/$04.00+0 DOI: 10.1128/IAI.69.3.1568–1573.2001

Serological Basis for Use of Meningococcal Serogroup C Conjugate Vaccines in the United Kingdom: Reevaluation of Correlates of Protection

RAY BORROW,[1]* NICK ANDREWS,[2] DAVID GOLDBLATT,[3] AND ELIZABETH MILLER[4]

PHLS Meningococcal Reference Unit, Withington Hospital, Manchester M20 2LR,[1] PHLS Statistics Unit,[2] and Immunization Division, PHLS Communicable Disease Surveillance Centre,[4] London NW9 5EQ, and Immunobiology Unit, Institute of Child Health, London WC1N 1EH,[3] United Kingdom

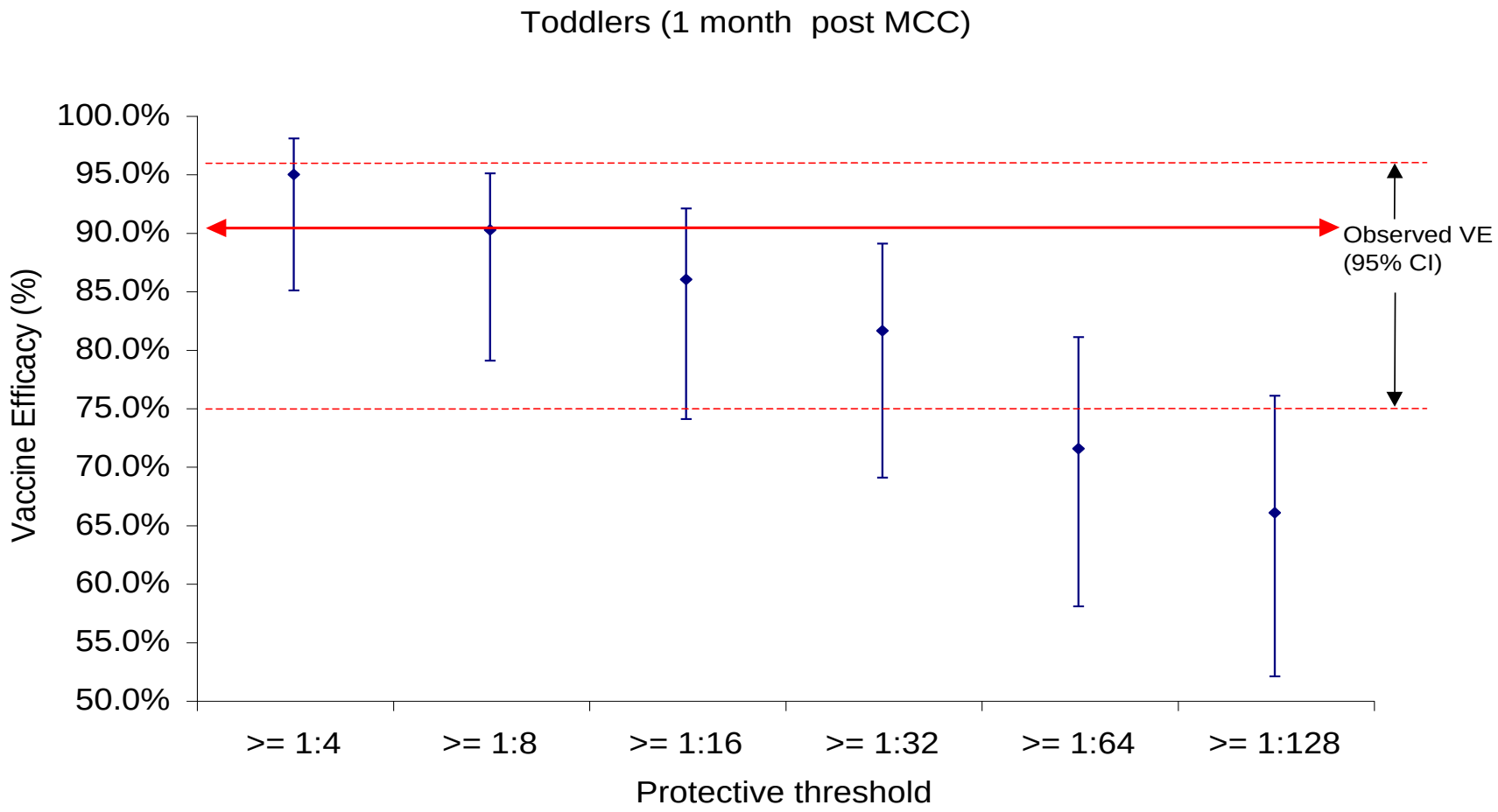
Received 10 October 2000/Returned for modification 1 November 2000/Accepted 7 December 2000

Goldschneider et al 1969


SBA using HUMAN complement
Polysaccharide immunogenicity
Adult responses
SBA using RABBIT complement
Conjugate immunogenicity
Infant and toddler responses

Validation of Serological Correlate of Protection for Meningococcal C Conjugate Vaccine by Using Efficacy Estimates from Postlicensure Surveillance in England

Nick Andrews,[1] Ray Borrow,[2] and Elizabeth Miller[1]*



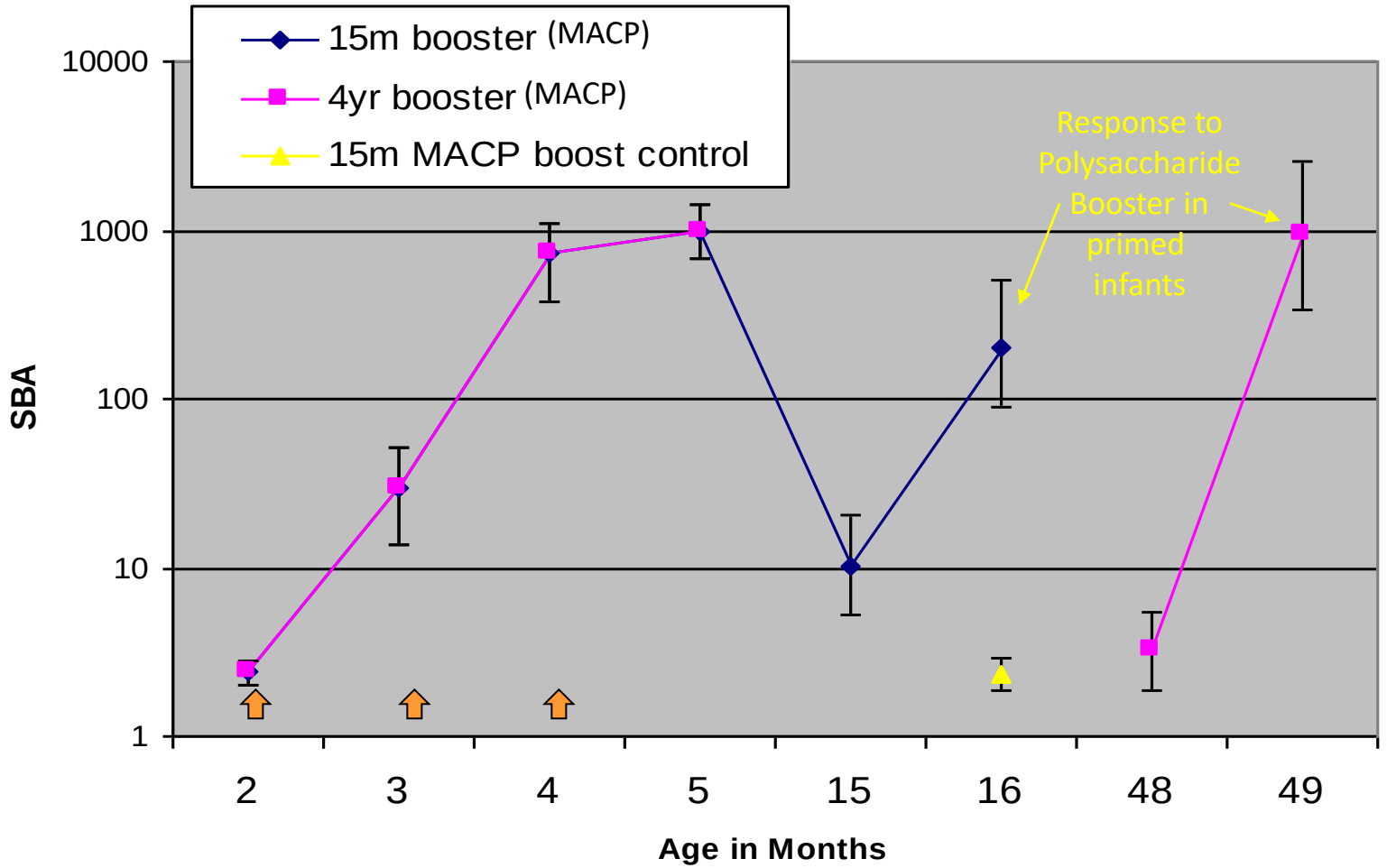
An rSBA titre ≥ 8 or 16 correlates closely with efficacy data.

CDLI 2003

Antibody Persistence and Immunological Memory at Age 4 Years after Meningococcal Group C Conjugate Vaccination in Children in the United Kingdom

Ray Borrow,[1] David Goldblatt,[2] Nick Andrews,[3] Jo Southern,[3] Lindsey Ashton,[2] Sarah Deane,[1] Rhonwen Morris,[4] Keith Cartwright,[4] and Elizabeth Miller[3]

[1]Public Health Laboratory Service Meningococcal Reference Unit, Withington Hospital, Manchester, [2]Immunobiology Unit, Institute of Child Health, and [3]Immunisation Division, Public Health Laboratory Service Communicable Disease Surveillance Centre, London, and [4]Public Health Laboratory, Gloucester Royal Hospital, Gloucester, United Kingdom



Prime with Conjugate Vaccine
Boost with Polysaccharide Vaccine

J Infect Dis 2002

Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction

Caroline L Trotter, Nick J Andrews, Edward B Kaczmarski, Elizabeth Miller, Mary E Ramsay

	Age at vaccination	Doses scheduled*	Period of observation, by quarter year	Overall		Within 1 year of scheduled vaccination†		More than 1 year after scheduled vaccination†	
				Cases (vaccinated)	Vaccine effectiveness (95% CI)	Cases (vaccinated)	Vaccine effectiveness (95% CI)	Cases (vaccinated)	Vaccine effectiveness (95% CI)
Cohort									
Routine	2–4 months	3	Q1 2000–Q1 2004	28 (21)	66% (6 to 86)	9 (3)	93% (67 to 99)	19 (18)	−81% (−7430 to 71)
Infant catch-up	5–11 months	2	Q3 2000–Q1 2004	13 (5)	85% (46 to 96)	6 (2)	87% (11 to 99)	7 (3)	82% (−8 to 97)
Toddlers catch-up	1–2 years	1	Q3 2000–Q1 2004	25 (10)	83% (60 to 93)	19 (6)	88% (65 to 96)	6 (4)	61% (−327 to 94)
Pre-school catch-up	3–4 years	1	Q3 2000–Q1 2004	37 (2)	98% (91 to 100)	45 (1)	98% (90 to 100)	19 (4)	93% (78 to 98)
Infant school catch-up	4–6 years	1	Q3 2000–Q1 2004	19 (0)	100% (71 to 100)				
Junior school catch-up	7–10 years	1	Q3 2000–Q1 2004	8 (3)	88% (38 to 98)				
Secondary school catch-up	11–16 years	1	Q2 2000–Q1 2004	40 (8)	96% (90 to 98)	45 (4)	96% (89 to 99)	39 (8)	90% (77 to 96)
Sixth form catch-up	17–18 years	1	Q1 2000–Q1 2004	44 (4)	93% (82 to 98)				
Total				214 (53)		124 (16)		90 (37)	

Q=quarter. *Vaccine effectiveness compares children eligible for complete vaccination who had received all scheduled doses versus no doses. Partly vaccinated children were excluded. †For the time change analysis, pre-school, infant, and junior cohorts were combined, as were the secondary school and sixth form cohorts.

Table: **MCC vaccine effectiveness in immunised cohorts to end of March, 2004**

Lancet 2004

Summary

- An aggregate threshold derived from aggregated efficacy data defined a CoP which led to the successful licensure of extended valency pneumococcal conjugate vaccines (n=3, soon n=5)
- All models are wrong but some are more useful than others
- Standardization of assays and reagents allowed multiple manufacturers to license using CoP and head to head non-inferiority trials
- There are lessons here for establishing correlates for the next generation of SARS CoV 2 vaccines

Evidence for serological correlate of protection from animal models and planned future studies

Cristina Cassetti, PhD

Deputy Director of NIAID’s Division of Microbiology and Infectious Diseases

NIAID at NIH

Immune correlates and SARS-CoV-2 variants: Mounting evidence for a serological CoP from animal models

Cristina Cassetti, Ph.D.
Deputy Director
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases, NIH
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NIH National Institute of Allergy and Infectious Diseases

Advantage of animal models to elucidate CoPs

- Dose down the vaccine (or serum from vaccinated animals/humans) to allow for breakthrough infections
- Intensive sample collection (esp. PBMCs for T-cell analysis)
- Select challenge timing and strain
- Compare different vaccines in the same study
- Use validated assays from Phase 3 trials- compare data from clinical trials

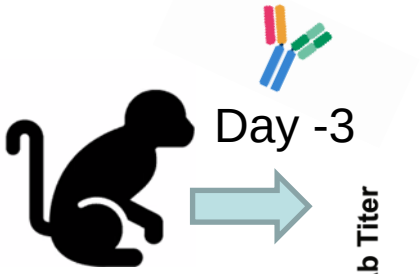
Outline

- Existing data in NHPs and hamsters
  - IgG passive transfer in NHPs/Dan Barouch
  - Novavax vaccine in NHPs/Galit Alter
  - Clover vaccine passive transfer in hamsters
  - Rockefeller U. mAbs in NHPs/ Michele Nussenzweig

- Ongoing study
  - BARDA/NIAID/Battelle 4 vaccine study

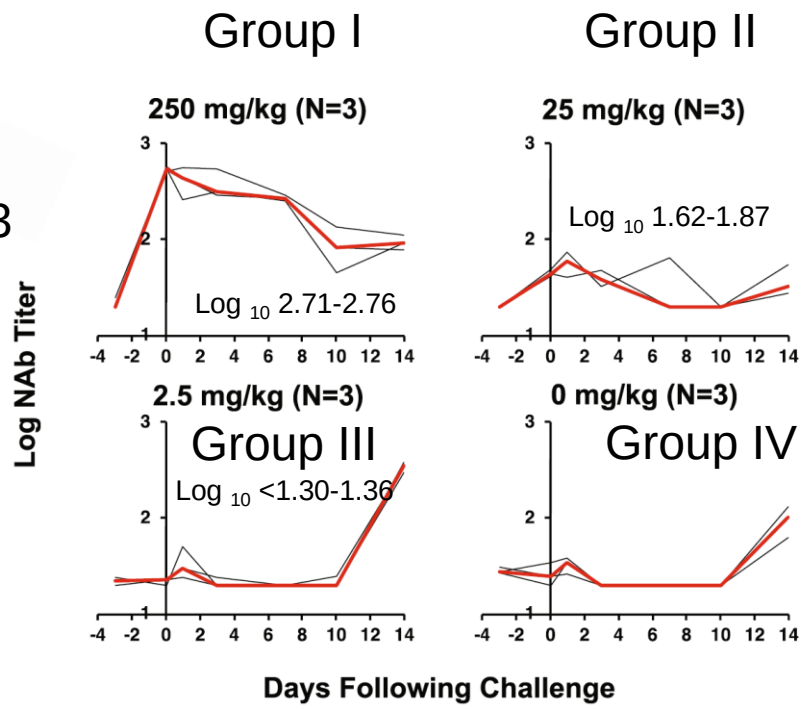
Purified IgG protects macaques against SARS-CoV-2 in a dose-dependent fashion

Pooled,
NAb = 1,581



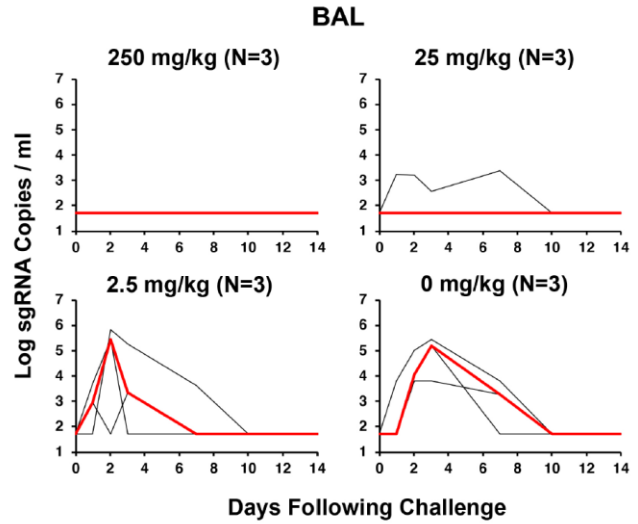
N = 12
Naïve

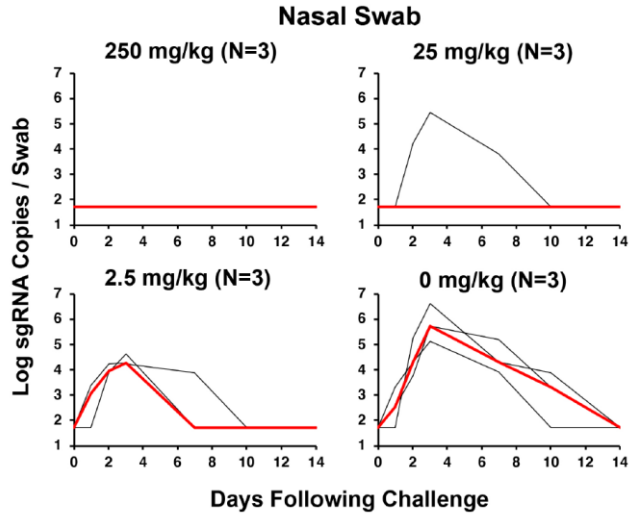
NAb Titers



Red lines depict median values

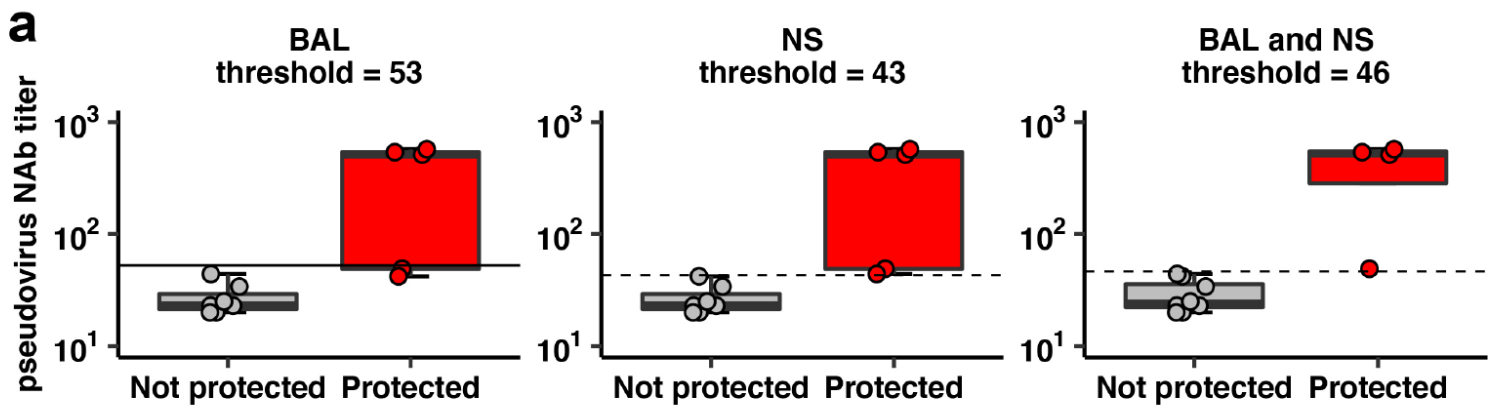
Viral Loads





Dan Barouch- https://www.nature.com/articles/s41586-020-03041-6

Logistical regression analysis defines Nab threshold titer of ~ 50 for protection

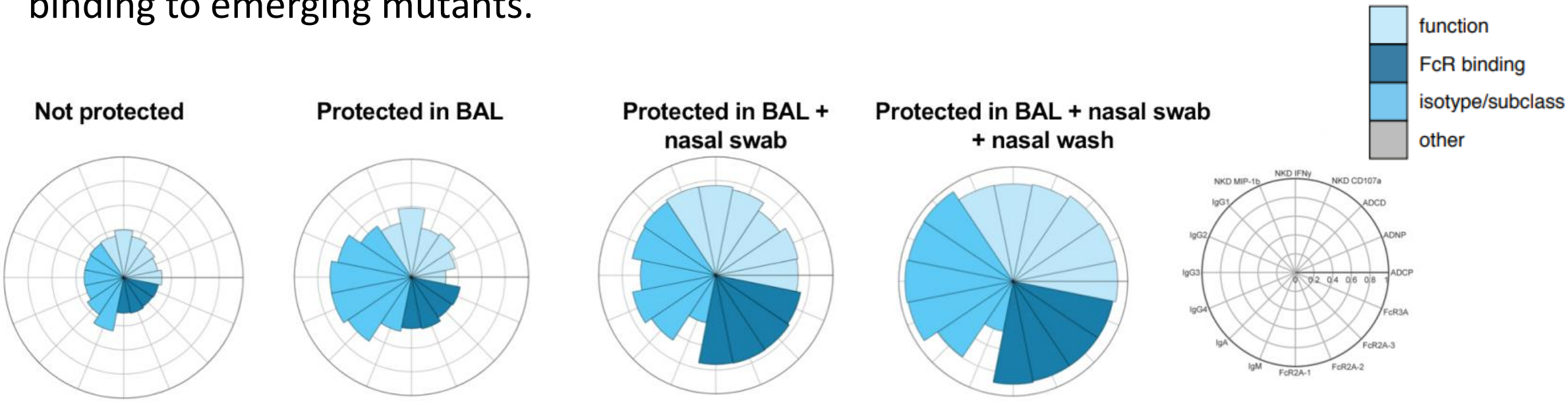


https://www.nature.com/articles/s41586-020-03041-6

National Institute of Allergy and Infectious Diseases

Novavax / Galit Alter-NHP and human CoP study

- System serology study of NHPs immunized with NVX-CoV2373
- Both neutralizing and Fc-effector functions contribute to protection, potentially through different mechanisms in the upper and lower respiratory tract
- Both macaque and human vaccine-induced antibodies exhibit altered Fc-receptor binding to emerging mutants.



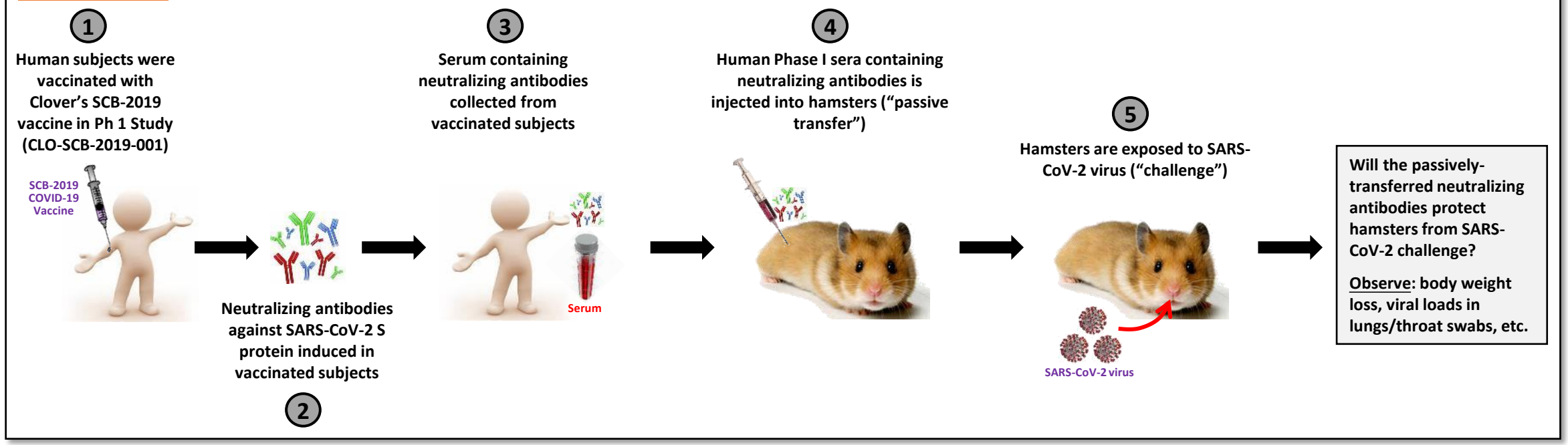
M.J. Gorman at al. - https://www.biorxiv.org/content/10.1101/2021.02.05.429759v1

Clover Vaccine: Passive Transfer (Human Ph 1 Sera) + Challenge Study (Hamster)

Key Question: Are neutralizing antibodies induced in humans by Clover's COVID-19 vaccine protective against exposure to SARS-CoV-2 virus?

- Are higher levels of neutralizing antibodies more protective?
- What level of neutralizing antibodies confers protection (correlate of protection)?

Study Concept:

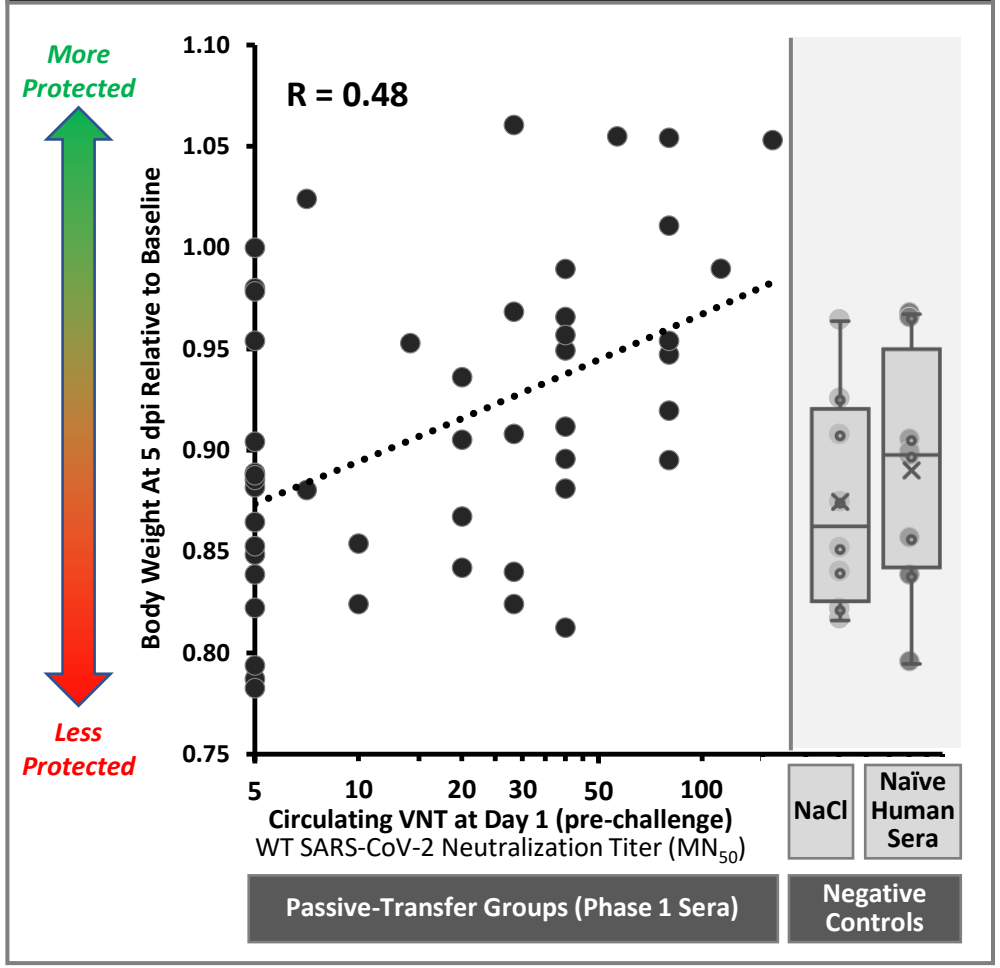


Note: dpi (days post-inoculation)

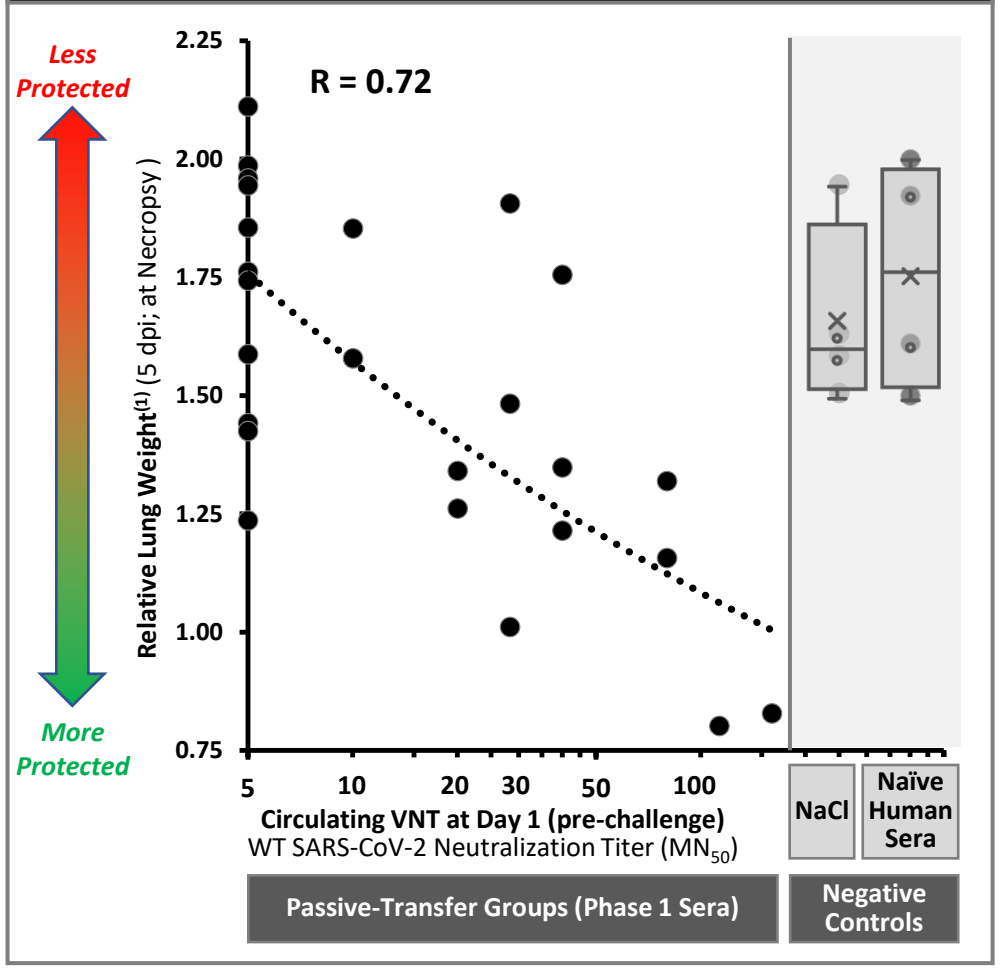
Thanks to Joshua Liang for unpublished results

Correlation Analyses: *Immune Protection vs. Baseline Circulating VNTs*

Change in Body Weight (5 dpi/Baseline)



Relative Lung Weight[1] (5 dpi; at necropsy)



Higher Circulating Neutralizing Antibodies (Day 1) Correlated with Better Protection from SARS-COV-2 Challenge

(Pending results for viral loads in throat swabs and lung tissue)

Note: Dpi (days post-inoculation). VNT (viral neutralization titer). Dots represent data for individual animals.
Represents data in 48 animals (body weight @ 5dpi) and 25 animals (relative lung weight @5dpi) passively transferred with pooled human sera from Phase 1 vaccinees (n=20) across three dilutions.
VNTs in negative control groups (NaCl and Naïve Human Sera) groups were all BLQ (below limit of quantification). Boxplot bars represent IQR, and whiskers represent min:max range.
(1) % of lung weight (g) in relation to body weight (g) upon necropsy.

Passive Transfer of mAbs C144-LS + C135-LS into NHPs to Assess CoPs

N=4: 20 mg/kg
N=4: 6 mg/kg
N=4: 2mg/kg
N=2: control

IN + IT
1 x 10^6 $TCID_{50}$
SARS-CoV-2 WA1

- **Antibody titers**
- **viral RNA**
- **Pathology**
- **Clinical**

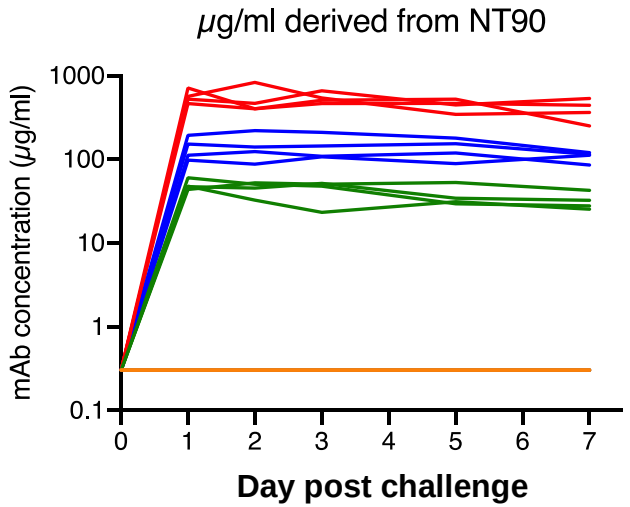
- In vitro IC_{50} of ~5ng/ml
- Neut epitopes on RBD
- long half life
- Ph I trial started Jan 21 (BMS)

N=14

Michel Nussenzweig, Rockefeller Univ, Chad Roy, TNPRC

NIH National Institute of Allergy and Infectious Diseases

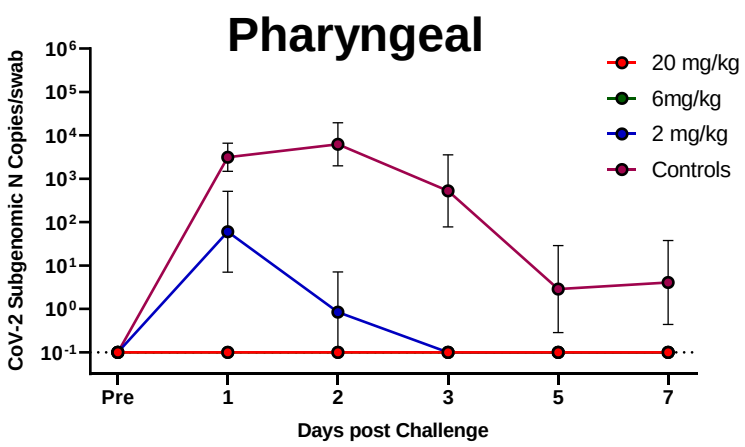
High mAb levels post challenge (pseudovirus neut. assay)

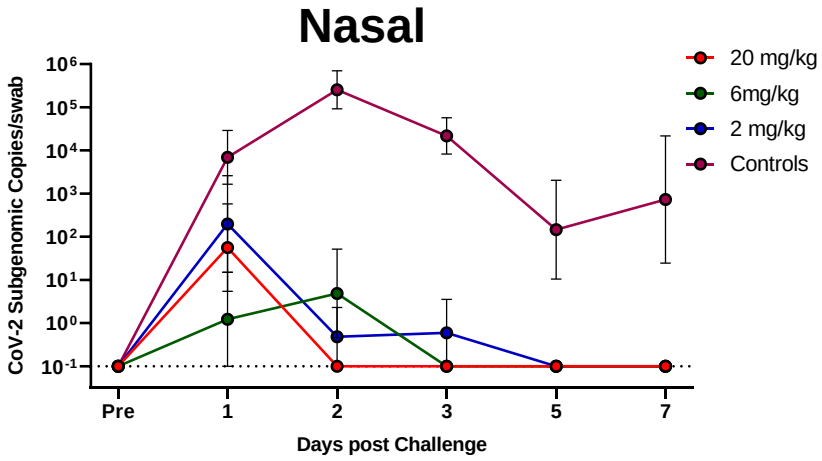


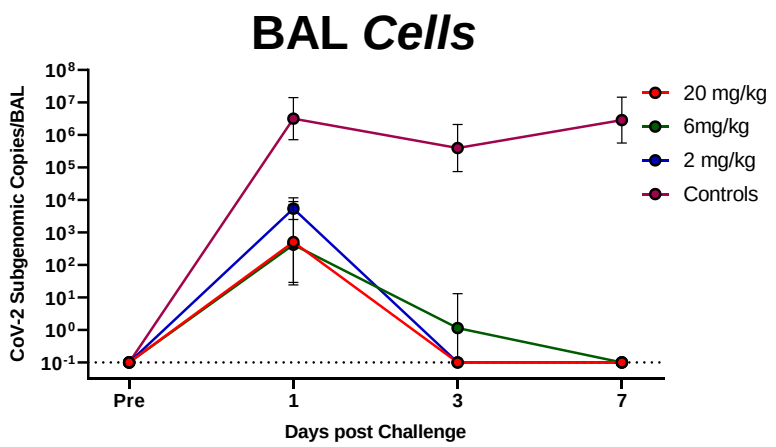
Day -3 Input Conc	Mean serum conc/NT90 titers
20mg/kg	550ug/ml ; 1:9000
6 mg/kg	140ug/ml ; 1:2300
2 mg/kg	50ug/ml ; 1:700

Ab half life = 47 days!

Prophylactic administration of 2 mAbs reduces viral shedding in URT and LRT







Unpublished results: Michel Nussenzweig, Rockefeller Univ, Chad Roy, TNPRC

One large, combined CoP NHP study sponsored by BARDA/NIAID

Vaccine products	• Janssen, Moderna, Novavax, Sanofi
USG provider	• Battelle
Study timeline	• Study initiated in **February 8** (1 large study)
Protocol harmonization	• Study protocol and Statistical Analysis plan agreed upon by product developers
Funding	• Provided by USG

National Institute of Allergy and Infectious Diseases

Study Design

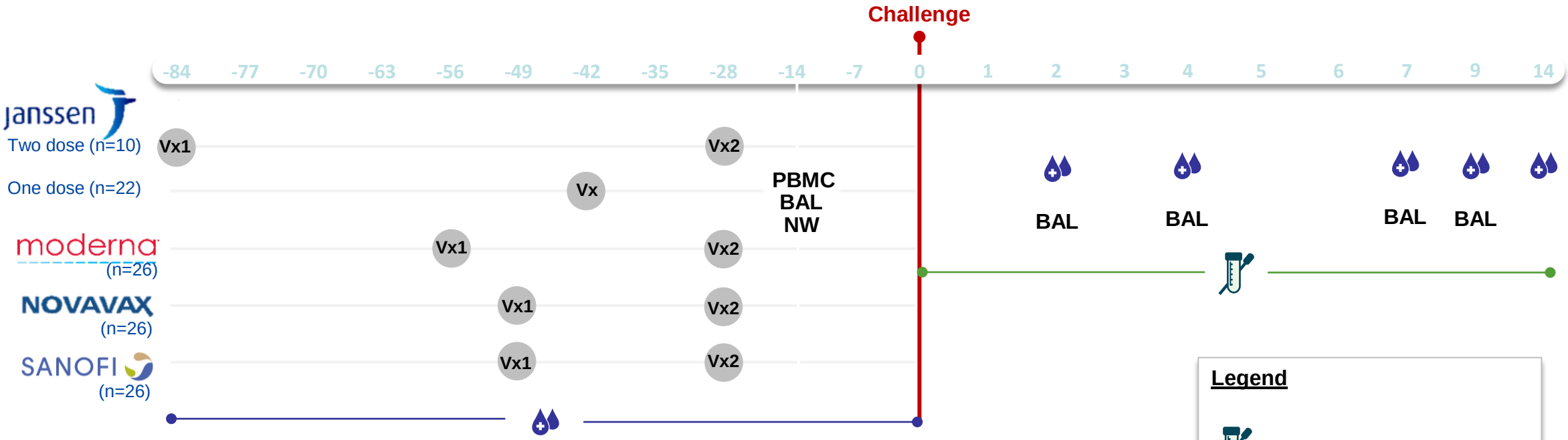
Test System: Rhesus macaque, Chinese origin, Naïve and specific pathogen free

Challenge Material: SARS-CoV-2, USA-WA1/2020, Lot TVP 23180, $1.6x10^4$ PFU/mL, passed characterization criteria

Readouts

Daily Clinical Evaluation
Viral load by sgPCR (BALF, swabs, and selected tissues)
Viral load by $TCID_{50}$ (swabs)
Lung histopathology

MNA
ELISA
PsVNA
Systems Serology
Cellular Immunity



This timeline is days relative to challenge, it does not reflect the actual chronology of the study activities as products are distributed across the 8 challenge days; Vx1 dates are staggered accordingly

Control animals (n=16) are vaccinated on days -56 and -28 relative to challenge

BAL, PBMC, and NW also collection prior to Vx1 for each candidate

Body Weights collected at least every 2 weeks

NIH National Institute of Allergy and Infectious Diseases

Summary

- Several pre-clinical studies suggest that neutralizing antibodies are sufficient to confer protection against SARS-CoV-2 infection
- Other immune responses (Fc-effector functions, CD8+) may contribute to protection, but their relative importance is still under investigation
- Ongoing study will compare CoPs in different vaccine platforms

Observed re-infections in longitudinal natural history studies and vaccine efficacy study placebo arms: impact of neutralizing titers, variant strains

Florian Krammer, PhD

Professor of Microbiology

Icahn School of Medicine at Mt. Sinai

Observed re-infections in longitudinal natural history studies and vaccine efficacy study placebo arms: impact of neutralizing titers, variant strains

Florian Krammer

Mount Sinai Professor in Vaccinology

Icahn School of Medicine at Mount Sinai

COVAX Workshop

February 25th, 2020

Mount Sinai

A glimpse of evidence for protection by neutralizing antibodies from a fishing vessel

- 122 individuals on the ship
- 3 had neutralizing antibodies before going to sea
- Outbreak with 82.5% attack rate occurred

Individuals with neutralizing antibodies were not infected

The New York Times

This Trawler's Haul: Evidence That Antibodies Block the Coronavirus

Three crew members aboard were spared when the virus spread through the boat. They were the only ones who had antibodies at the beginning of the trip.

nerican Dynasty, carrying 122 crew, returned to shore in May after 18 days at sea when a crew er became ill enough to need hospitalization. Michael Brunk/nwlens.com

By Apoorva Mandavilli

Aug. 19, 2020

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Virology

Neutralizing antibodies correlate with protection from SARS-CoV-2 in humans during a fishery vessel outbreak with high attack rate

Amin Addetia, Katharine H. D. Crawford, Adam Dingens, Haiying Zhu, Pavitra Roychoudhury, Meei-Li Huang, Keith R. Jerome, Jesse D. Bloom, Alexander L. Greninger

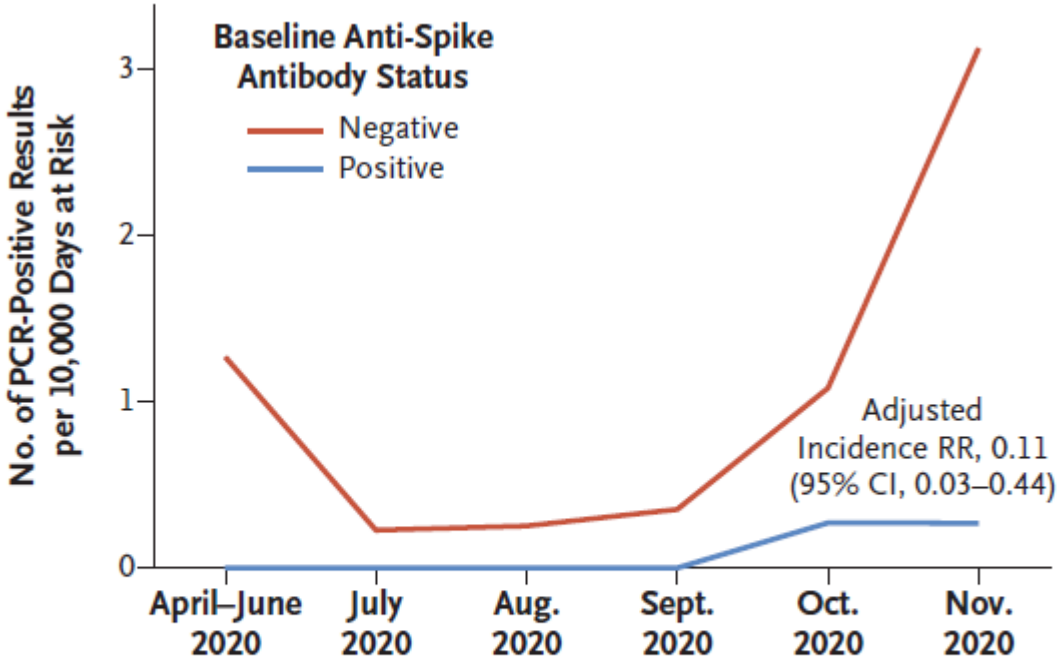
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers

S.F. Lumley, D. O'Donnell, N.E. Stoesser, P.C. Matthews, A. Howarth, S.B. Hatch, B.D. Marsden, S. Cox, T. James, F. Warren, L.J. Peck, T.G. Ritter, Z. de Toledo, L. Warren, D. Axten, R.J. Cornall, E.Y. Jones, D.I. Stuart, G. Screaton, D. Ebner, S. Hoosdally, M. Chand, D.W. Crook, A.-M. O'Donnell, C.P. Conlon, K.B. Pouwels, A.S. Walker, T.E.A. Peto, S. Hopkins, T.M. Walker, K. Jeffery, and D.W. Eyre, for the Oxford University Hospitals Staff Testing Group*

- **12 541 health care worker in the UK**
  - **11 346 serologically negative**
  - **1 265 serologically positive**
  - **Observation period 6 months**
  - **NAAT every two weeks**



Days at Risk						
Seronegative	456,963	307,508	316,141	312,027	332,704	329,469
Seropositive	316	19,474	31,601	34,011	36,824	37,098

- **223 of the negatives had a positive NAAT in observation period**
  - **1.09 per 10,000 days at risk**
- **2 of the spike serologically positives had a positive NAAT in observation period (asymptomatic)**
  - **0.13 per 10,000 days at risk, adjusted 0.11 per 10,000 days at risk**

Do antibody positive healthcare workers have lower SARS-CoV-2 infection rates than antibody negative healthcare workers? Large multi-centre prospective cohort study (the SIREN study), England: June to November 2020

AUTHORS:

Hall V[*∂1,2], Foulkes S[*1], Charlett A[1], Atti A[1], Monk EJM[1], Simmons R[1], Wellington E[1], Cole MJ[1], Saei A[1], Oguti B[1], Munro K[1], Wallace S[1], Kirwan PD[1], Shrotri M[1], Vusirikala A[1], Rokadiya S[1], Kall M[1], Zambon M[1], Ramsay M[1], Brooks T[1], SIREN Study Group, Brown CS[1], Chand MA[1], & Hopkins S[1,2].

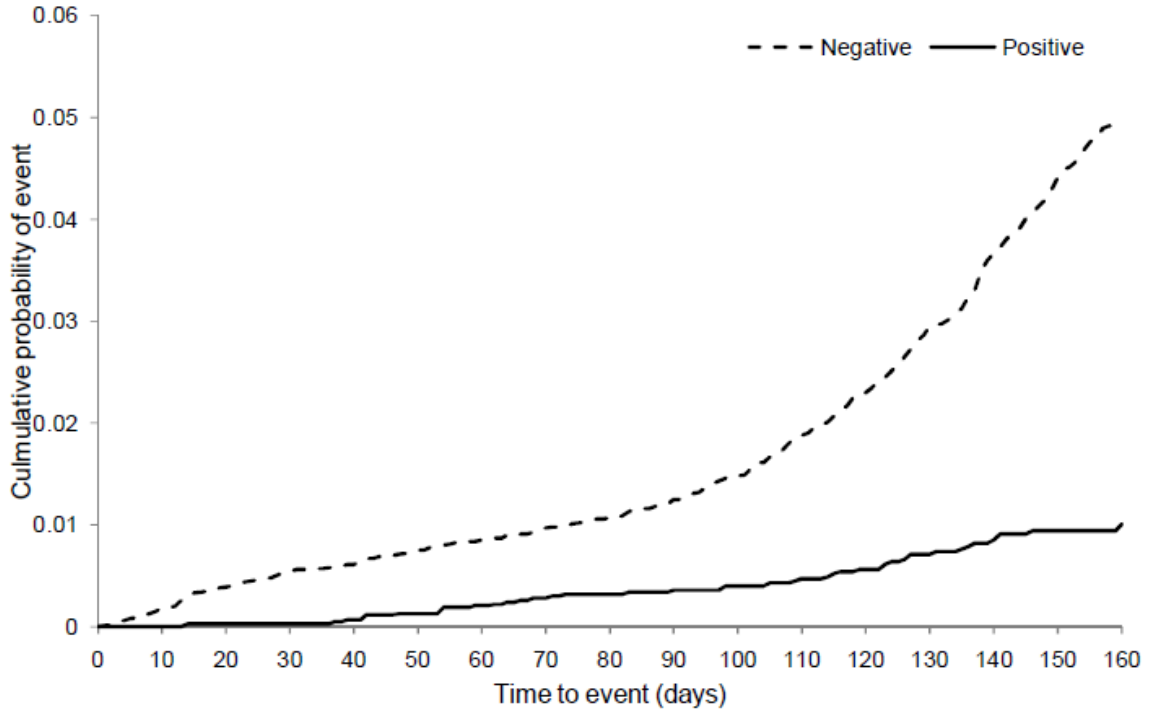
medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

Interpretation: A prior history of SARS-CoV-2 infection was associated with an 83% lower risk of infection, with median protective effect observed five months following primary infection. This is the minimum likely effect as seroconversions were not included.

- **Health care workers in the UK**
  - **14 173 serologically negative**
  - **6 614 serologically positive**
  - **Observation period June to November 2020**
  - **NAAT every 2 to 4 weeks**

- **318 of the negatives had a positive NAAT or in observation period (94 additional ones seroconverted)**
- **44 of the serologically positives had a positive NAAT or in observation period**

Figure 3: Time to PCR positive result by cohort in SIREN participants, detected up to 24 November 2020



JAMA Internal Medicine | Original Investigation

Association of SARS-CoV-2 Seropositive Antibody Test With Risk of Future Infection

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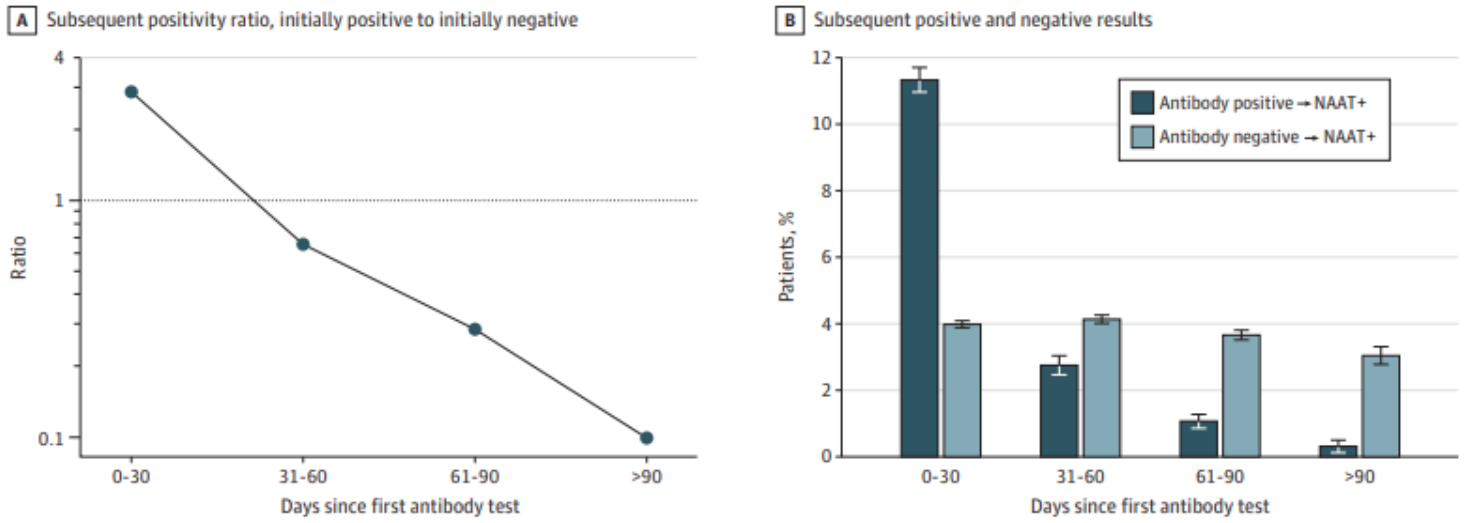
- **3.2 million individuals tested for antibodies**
- **2 876 773 were negative**
- **378 606 were positive**
- **PCR positives 90+ days after antibody test**
  - **3% of negatives**
  - **0.3% of positives**

Figure 2. Subsequent Diagnostic Nucleic Acid Amplification Test (NAAT) Results at 30-Day Intervals



This figure shows the results of diagnostic NAAT after initial antibody testing. A, The line shows the ratio of positive diagnostic tests among those who initially tested positive for antibodies vs those who initially tested negative. B, Over each time period, the dark blue bars show the percent of patients who tested positive for the diagnostic test among those who initially tested positive for antibodies with corresponding confidence intervals. The light blue bars show the percent of patients who tested positive for the diagnostic test among those who initially tested negative for antibodies with corresponding confidence intervals.

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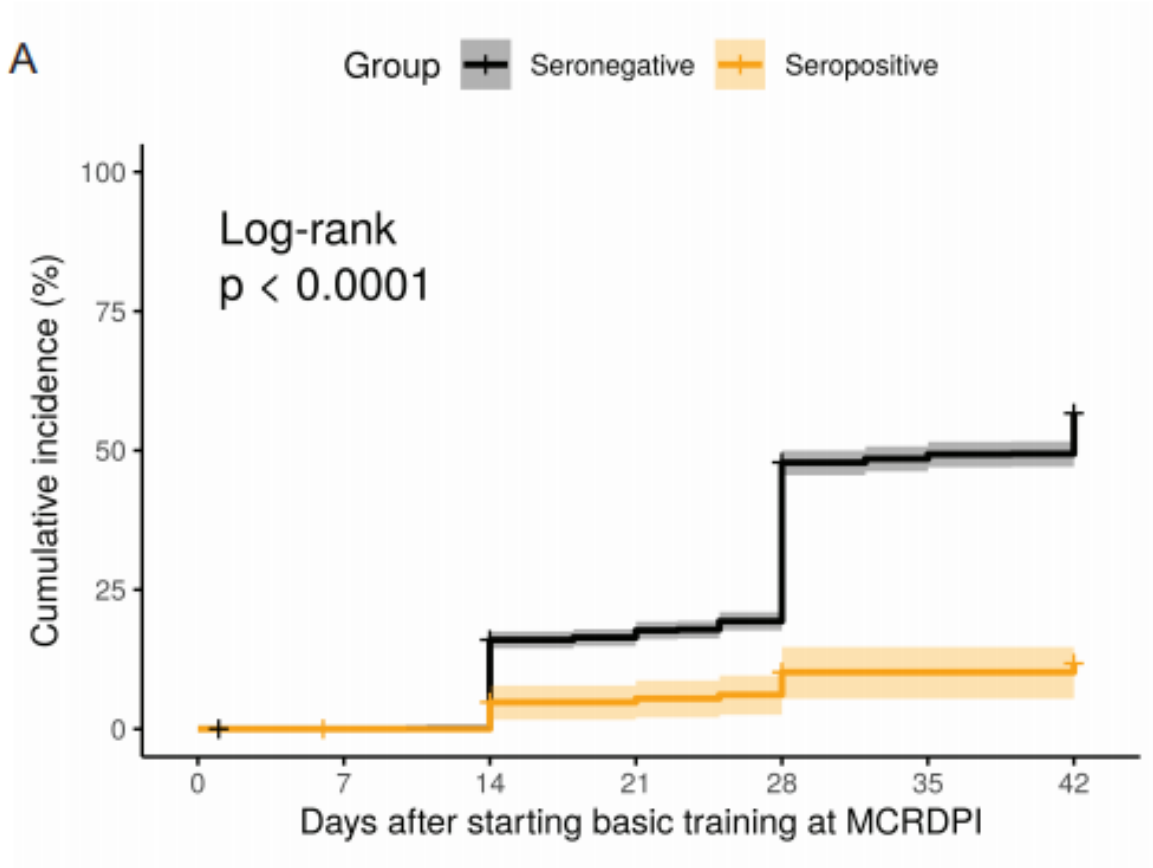
SARS-CoV-2 seropositivity and subsequent infection risk in healthy young adults: a prospective cohort study

Andrew G. Letizia*, Yongchao Ge*, Sindhu Vangeti*, Carl Goforth*, Dawn L Weir*, Natalia A. Kuzmina, Hua Wei Chen, Dan Ewing, Alessandra Soares-Schanoski, Mary-Catherine George, William D. Graham, Franca Jones, Preeti Bharaj, Rhonda A. Lizewski, Stephen A. Lizewski, Jan Marayag, Nada Marjanovic, Clare Miller, Sagie Mofsowitz, Venugopalan D. Nair, Edgar Nunez, Danielle M. Parent, Chad K. Porter, Ernesto Santa Ana, Megan Schilling, Daniel Stadlbauer, Victor Sugiharto, Michael Termini, Peifang Sun, Russell. P. Tracy, Florian Krammer, Alexander Bukreyev, Irene Ramos, Stuart C. Sealfon

- **3 249 eighteen to twenty year old marine recruits**
- **2 week quarantine**
- **RBD/spike titers assessed**

- **Tested 3x biweekly by PCRs post quarantine in training**

- **Among 189 seropositive participants, 19 (10.1%) had at least one positive PCR test**
- **1,079 (48.0%) of the 2,247 seronegative participants tested positive**



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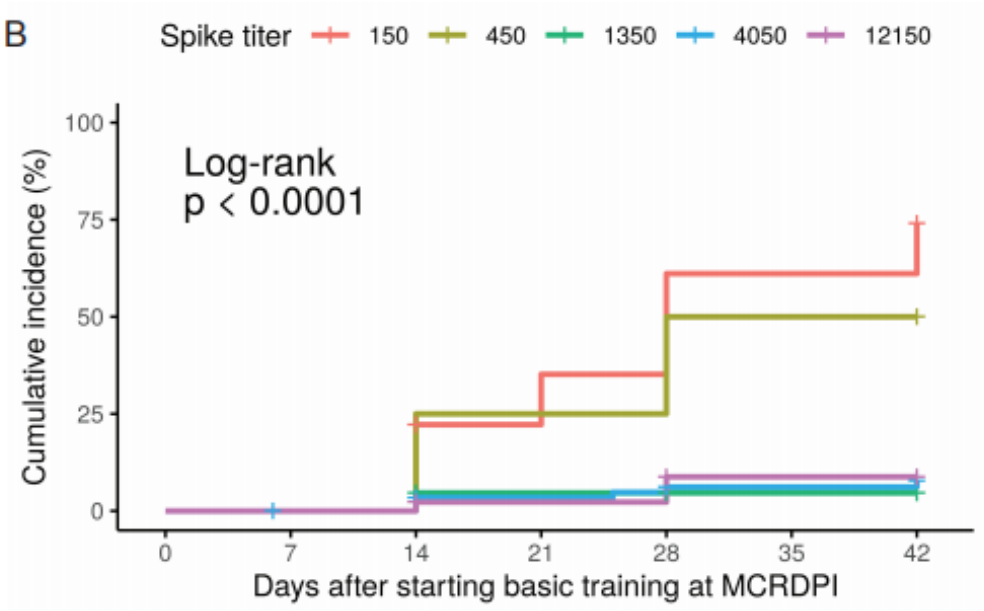
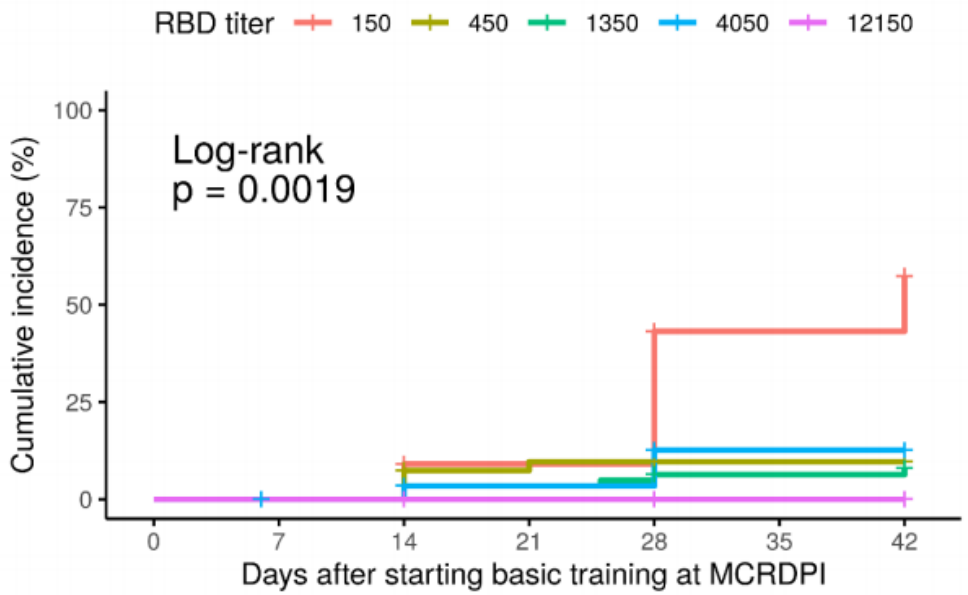




PARIS (SEM CIVIC)/SPARTA (CIVR)

Commonalities between all sites:

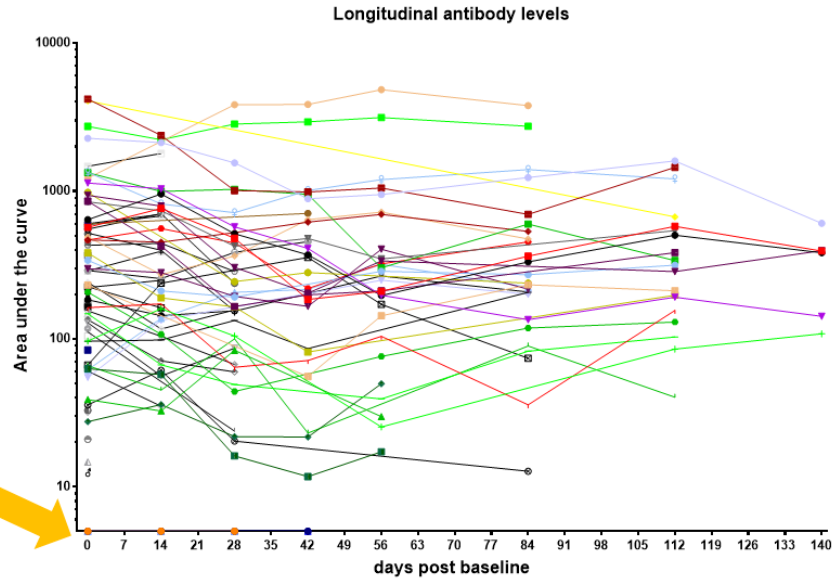
- Samples take every 2 months (most sites have shorter intervals)
  - Serum
  - Saliva
  - PBMCs (selected sites, but for several thousand subjects)
- Common serology (Mount Sinai ELISA)
- Nasal swap/nasopharyngeal sample take if somebody becomes symptomatic
  - SARS-CoV-2 PCR
  - Most sites also run a respiratory panel/Biofire
- Primary analysis at sites
- Secondary analysis: Sarah Cobey and Marc Lipsitch

PARIS

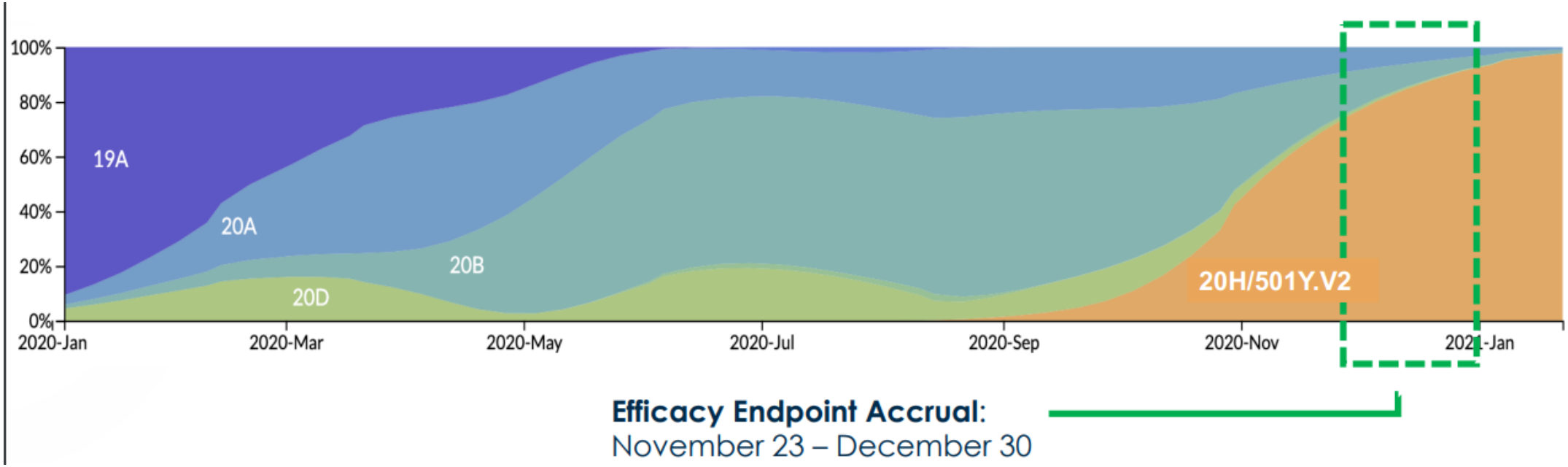
(**P**rotection **A**ssociated with **R**apid **I**mmunity to **S**ARS-CoV-2)

- **Approximately 400 individuals enrolled**
- **Since April 2020**
- **Approximately half antibody positive, half antibody negative**
- **So far 5 symptomatic SARS-CoV-2 infections in sero-negative group**
- **1 symptomatic infection in an individual that was sero-positive but sero-reverted**
- **Asymptomatic infections under investigation**

Day 0 is enrollment, not symptom onset, study started in the end of April, most people were likely already infected in March



Novavax Phase 2b in South Africa



- Placebo ITT population (7 days post-dose 1), symptomatic COVID
  - Seronegative: **3.9%** (58/1494; 2.961; 4.990): **2.3%** Mod/Severe (35/1494)
  - Seropositive : **3.9%** (26/674; 2.535; 5.601); **2.4%** Mod /Severe (16/674)

https://www.novavax.com/sites/default/files/2021-02/20210202-NYAS-Novavax-Final.pdf

Novavax Phase 2b in South Africa

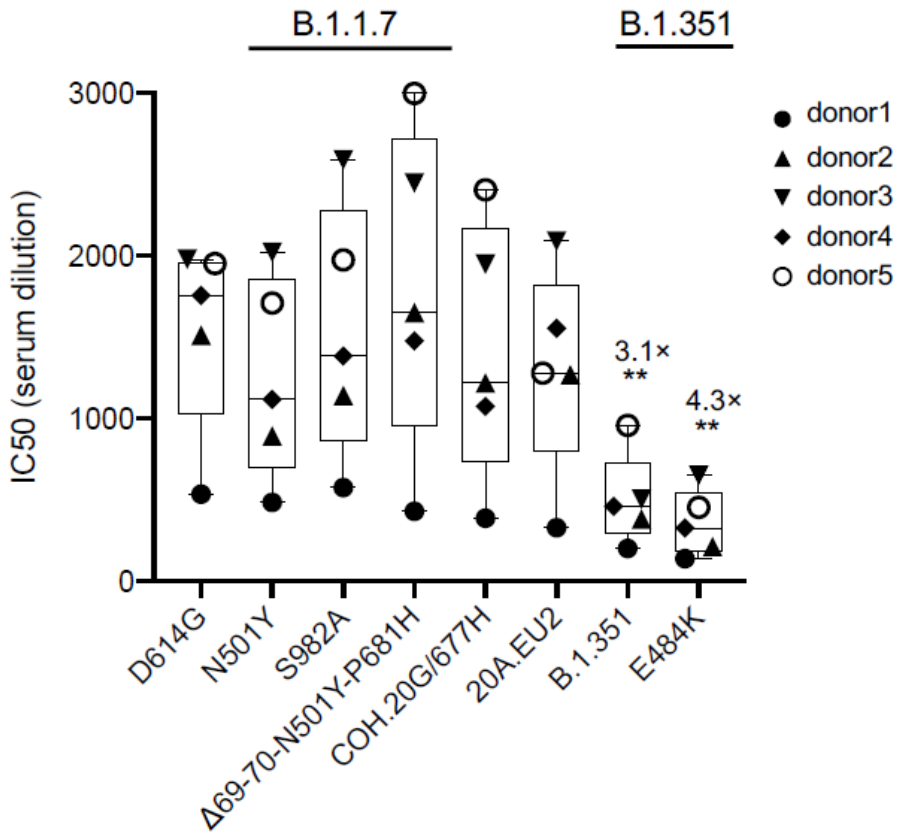
Serostatus	NVX-CoV2373 % (n/N)	Placebo % (n/N)	Efficacy (95% CI)
-	1.1% (15/1357)	2.2% (29/1327)	**49.4% (6.1, 72.8)**
+	1.2% (6/500)	2.5% (13/514)	**52.6% (-23.8, 81.8)**
+/-	1.1% (21/1857)	2.3% (42/1841)	**50.4% (16.6, 70.5)**

https://www.novavax.com/sites/default/files/2021-02/20210202-NYAS-Novavax-Final.pdf

Impact of variants on neutralization of convalescent and vaccine serum

Variant	Convalescent sera	Sera from vaccinated individuals
B.1.1.7	Little impact	Little impact (most studies) to up to 9-fold reduction after AZ vaccination
B.1.351	Strong reduction, loss in a proportion of individuals	Moderate impact (4 to 9-fold reduction), in some papers even higher
P.1	Likely similar to B.1.351	Likely similar to B.1.351

Impact of variants on neutralization of convalescent and vaccine serum

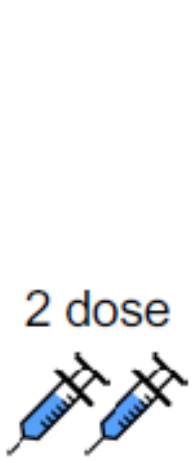


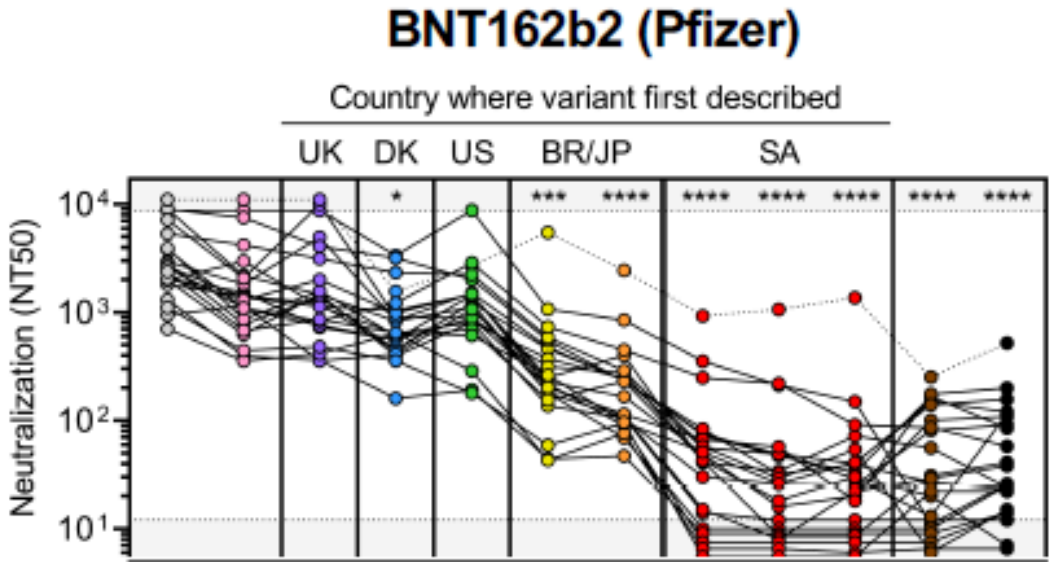
Tada *et al.*, bioRxiv, 2021

Figure 3

A

2 dose





Garcia-Beltran *et al.*, medRxiv, 2021

Efficacy of AZD1222 against B.1.1.7 and B.1.351

Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 VOC 202012/01 (B.1.1.7)

Katherine R. W. Emary[1]*, Tanya Golubchik[13]*, Parvinder K. Aley[1], Cristina V. Ariani[29], Brian Angus[2], Sagida Bibi[1], Beth Blane[29], David Bonsall[6], Paola Cicconi[2], Sue Charlton[3], Elizabeth A. Clutterbuck[1], Andrea M. Collins[7], Tony Cox[8], Thomas

Table 1 Vaccine efficacy against B.1.1.7 and non- B.1.1.7 strains. (SD/SD and LD/SD seronegative efficacy cohorts only)

	Variant	N (%)	ChAdOx1 nCoV-19	Control	VE 95%CI
Primary Symptomatic COVID-19					
	B.1.1.7	34 (14%)	7/4236	27/4270	74.6% (41.6%, 88.9%)
	Other variants	86 (34%)	12/4236	74/4270	84.1% (70.7%, 91.4%)
	No sequence result*	25 (10%)	5/4236	20/4270	75.4% (34.3%, 90.8%)
	Not sequenced**	105 (42%)	28/4236	77/4270	64.3% (44.9%, 76.8%)
	Total cases	250	52/4236	198/4270	74.2% (65.0%, 81.0%)
Asymptomatic/Unknown infections					
	B.1.1.7	14 (7%)	6/4236	8/4270	26.5% (-112.0%, 74.5%)
	Other variants	30 (14%)	6/4236	24/4270	75.4% (39.9%, 89.9%)
	No sequence result	37 (18%)	21/4236	16/4270	-28.7% (-146.6%, 32.8%)
	Not sequenced	127 (61%)	63/4236	64/4270	3.1% (-37.3%, 31.6%)
	Total cases	208	96/4236	112/4270	15.7% (-10.7%, 35.8%)
Any NAAT+ infection†					
	B.1.1.7	51 (10%)	13/4236	38/4270	66.5% (37.1%, 82.1%)
	Other variants	128 (26%)	21/4236	107/4270	80.7% (69.2%, 87.9%)
	No sequence result	69 (14%)	29/4236	40/4270	28.8% (-14.9%, 55.9%)
	Not sequenced	251 (50%)	101/4236	150/4270	33.8% (14.7%, 48.6%)

https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3779160

Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B.1.351 variant in South Africa

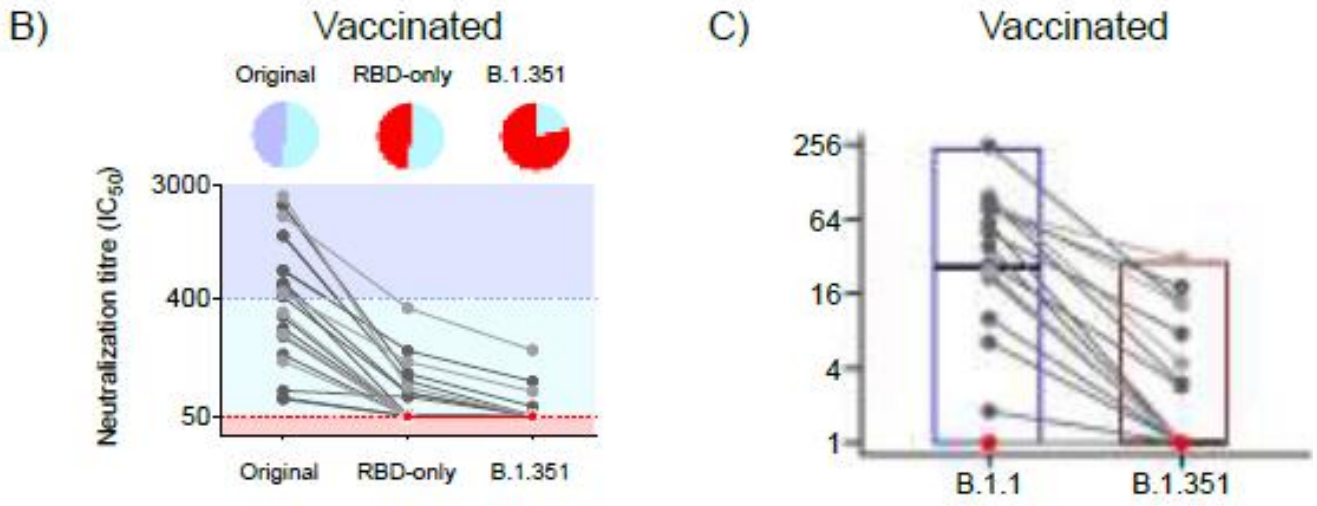
Shabir A. Madhi[1,2], Vicky Baillie[1,2#], Clare L. Cutland[3#], Merryn Voysey[4], Anthonet L. Koen[1,2*], Lee Fairlie[5*], Sherman D. Padayachee[6*], Keertan Dheda[7*], Shaun L. Barnabas[8*], Qasim Ebrahim Bhorat[9*], Carmen Briner[10*], Gaurav Kwatra[1,2], NGS-SA[11], Wits-VIDA COVID team[12], Khatija Ahmed[6], Parvinder Aley[4], Sutika Bhikha[1,2], Jinal N. Bhiman[15,16], As'ad Ebrahim Bhorat[9], Jeanine du Plessis[1], Aliasgar

Baseline serology[a]	Total number of cases	Placebo n/N (%)	IR[b] per 1000 person-years (person-days)	Vaccine n/N (%)	IR per 1000 person-years (person-days)	Vaccine efficacy (95%Confidence Interval)
Primary outcome: All severity COVID-19 illness >14 days post-boost						
Sero-negative	42[c]	23/717 (3.2)	93.6 (89714)	19/750 (2.5)	73.1 (94881)	21.9% (-49.9 to 59.8)
Secondary objective: All severity B1.135 variant COVID-19 illness >14 days post-boost						
Sero-negative	39	20/714 (2.8)	81.6 (89448)	19/750 (2.5)	73.1 (94881)	10.4% (-76.8; 54.8)
Secondary objective: All severity COVID-19 clinical disease >14 days post-boost						
Any	46	24/865 (2.8)	81.9 (106898)	22/884 (2.5)	73.2 (109[illegible]59)	10.6% (-66.4 to 52.2)
Post hoc: All severity Covid-19 disease (occurring >14 days after one dose until 31 October 2020 (proxy for non-B.1351 variant infection						
Overall	15	12/938 (1.3)	31.1 (140774)	3/944 (0.3)	7.6 (143140)	75.4% (8.9 to 95.5)

https://www.medrxiv.org/content/10.1101/2021.02.10.21251247v1.full.pdf

Impact of variants on neutralization of convalescent and vaccine serum

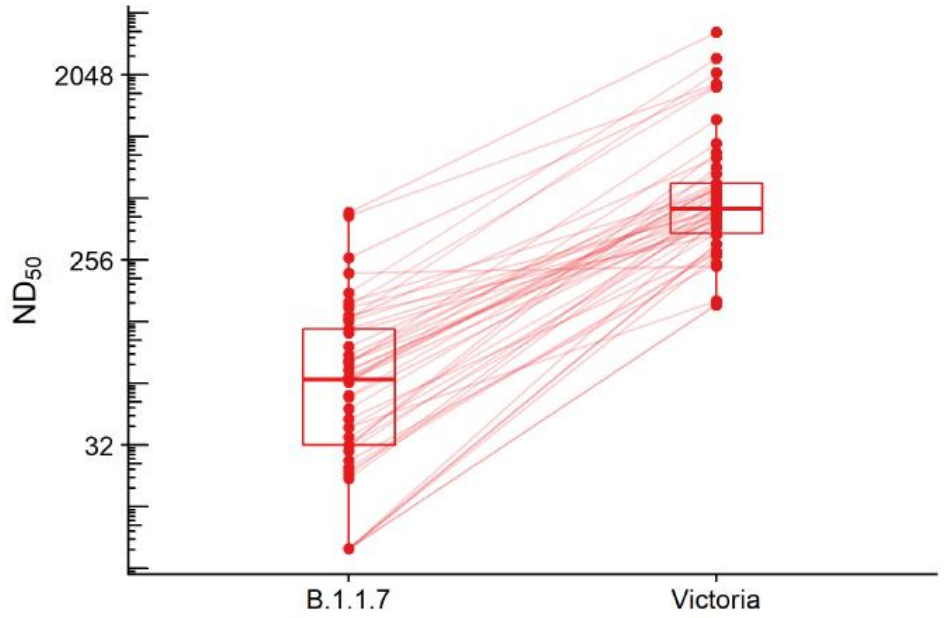
B.1.351



Madhi *et al.*, medRxiv, 2021

B.1.1.7

Figure 6. Live virus microneutralisation antibody titres of sera against B.1.1.7 and a canonical non-B.1.1.7 (Victoria) strain



	B.1.1.7	Victoria
GMT (95% CI)	58 (44, 77)	517 (424, 631)
GMR (B.1.1.7 vs Victoria) (95% CI)	8.9 (7.2, 11.0)	

Emary *et al.*, SSRN, 2021

Conclusions

Protection after natural infection is robust and as good or even better than after vaccination

Protection is correlated with antibody responses to spike

We urgently need studies that determine the impact of variants on neutralizing activity of post-vaccination sera side by side!

Acknowledgements

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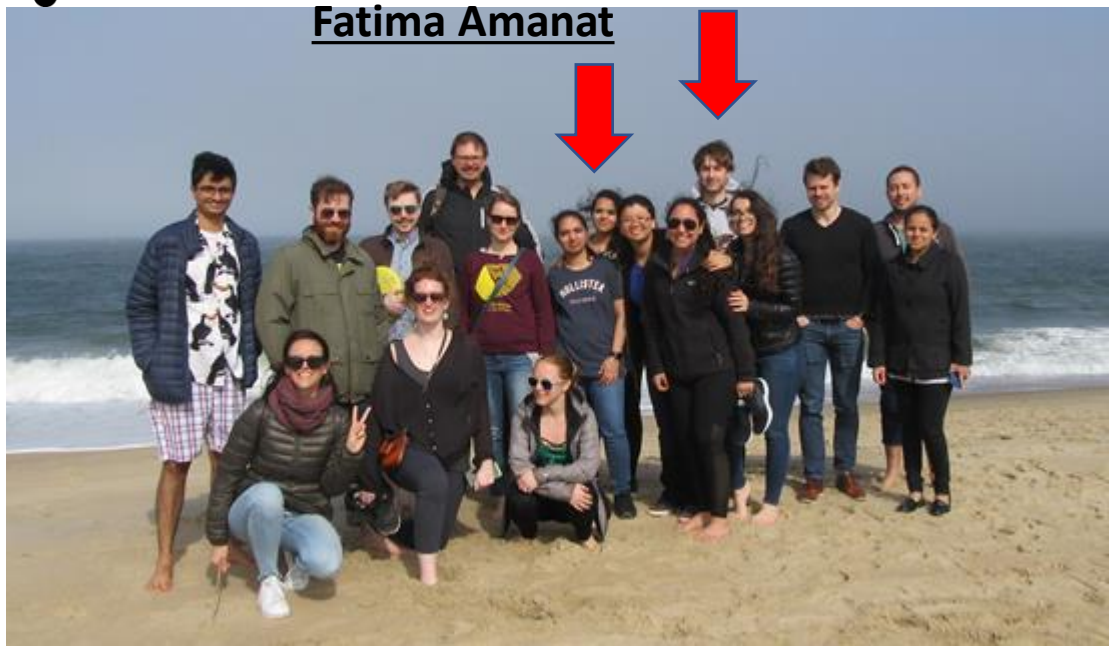
Daniel Stadlbauer

Fatima Amanat



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CIVICs
Collaborative Influenza Vaccine Innovation Centers

CEIRS
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Teresa Aydillo

Tom Moran

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Jussi Hepojoki (U Helsinki)
Olli Vapalahti (U Helsinki)

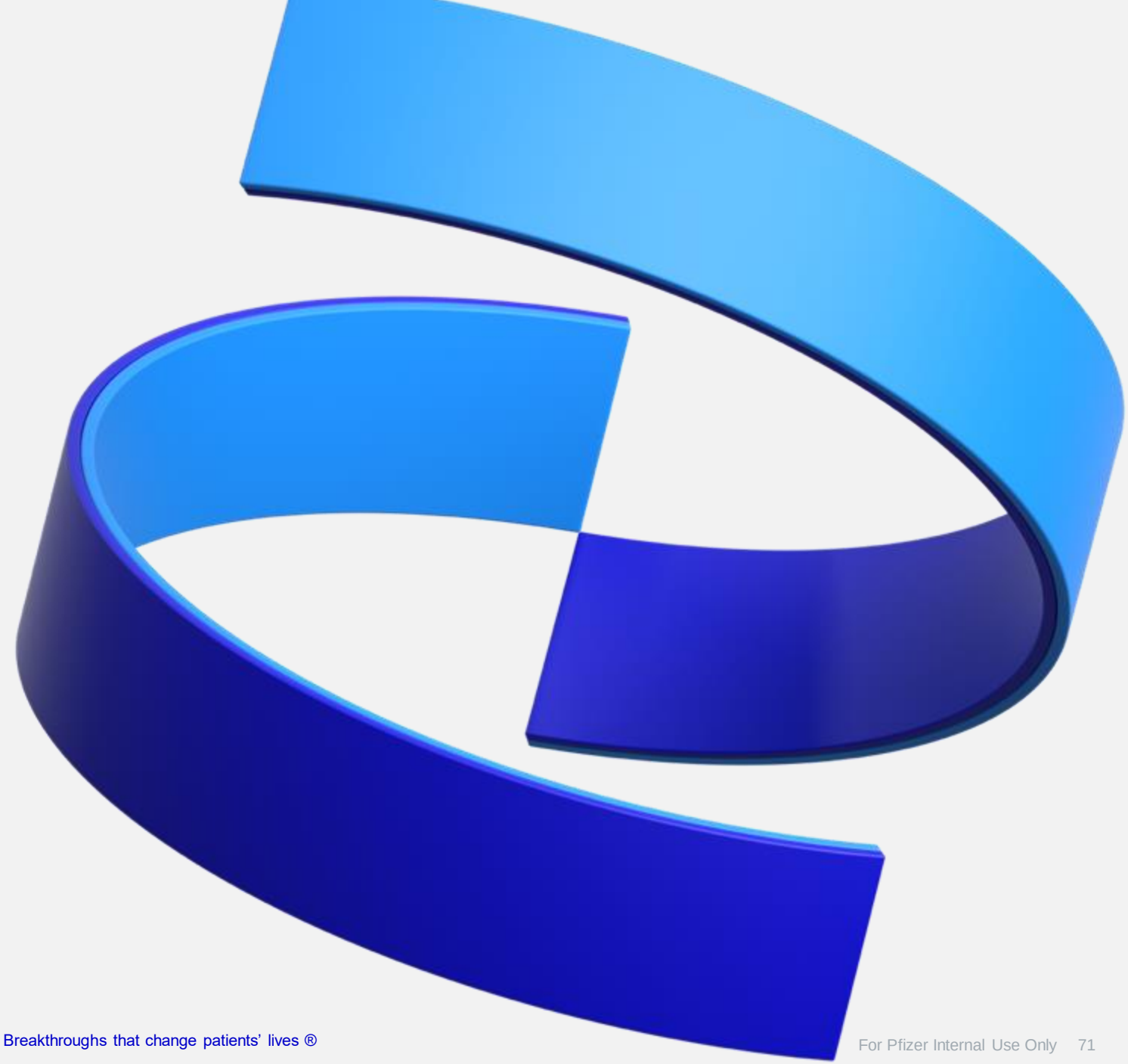
Approaches for correlates analyses based on breakthrough cases from vaccine efficacy studies (Part 1)

Stephen Lockhart, PhD

Vice President, Vaccine Clinical R&D Europe and Asia-Pacific Head

Pfizer

Thoughts on correlates



Stephen Lockhart

25 February 2021

Pfizer
Worldwide Research, Development and Medical
Vaccine Research and Development

Pilot work planned to assess cases in vaccine cohort

- 8 breakthrough cases without evidence of prior infection in November efficacy analysis for EUA[1]
  - More cases likely to be identified following subsequent unblinding.
- Post dose 2 sera retained in all subjects[2]
  - In process of assessing post dose 2 neutralization titers
- PMBC not collected on subjects so T cell analysis cannot be performed[2]

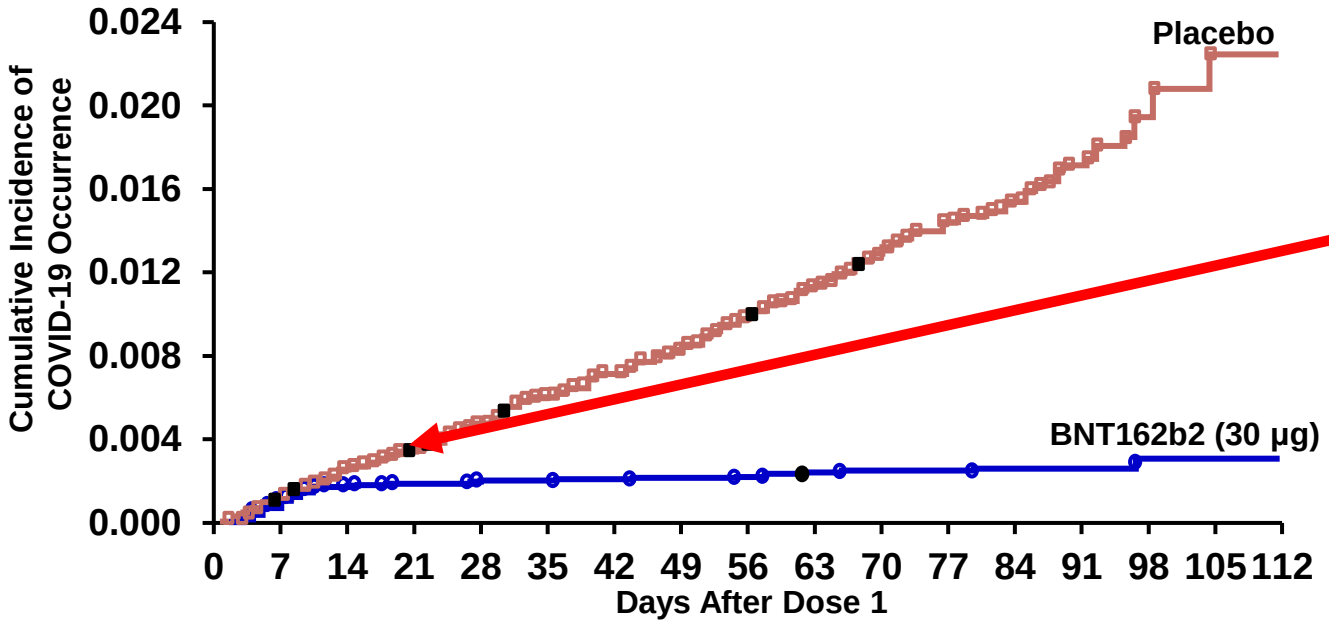
[1] Polack et al 2020

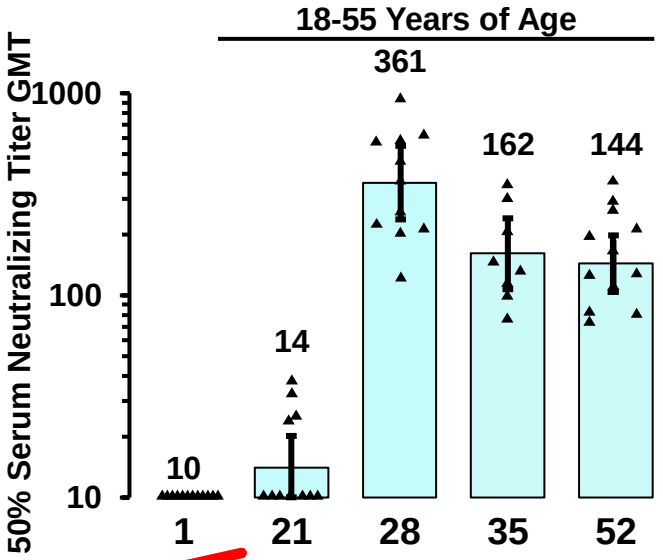
[2] https://pfe-pfizercom-d8-prod.s3.amazonaws.com/2020-11/C4591001_Clinical_Protocol_Nov2020.pdf

Hypotheses to consider

- Neutralising antibody as mechanism or correlate of protection, pilot work can test this
  - Absence of neutralising activity post dose 2?
  - Lower neutralising activity post dose 2?
  - No relationship post dose 2?
- T-cell responses as mechanism or correlate of protection
  - Large scale pre-infection assessment of CMI challenging
- Host factors: comorbidities, health, race
- Viral factors: mutations in spike protein

Onset of protection while neutralizing titers are low





Polack FP, et al. *N Engl J Med*. 2020

Walsh EE, et al. *N Engl J Med*. 2020

Approaches for correlates analyses based on breakthrough cases from vaccine efficacy studies (Part 2)

Daniel Stieh, PhD

Senior HIV Biomarker Lead

Janssen Pharmaceutical Companies of Johnson & Johnson

ENSEMBLE:
Immune Correlates Considerations & Planning

Daniel J Stieh, Sr. Biomarker Lead

25 February 2021

Janssen Infectious Diseases & Vaccines

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Janssen Investigational COVID-19 Vaccine Phase 3 Study: COV3001

A Study of Ad26.COV2.S for the Prevention of SARS-CoV-2-Mediated COVID-19 in Adults (ENSEMBLE)

- A multicenter, randomized, double-blind, placebo-controlled, phase 3 study evaluating the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19
- Locations: Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and United States
- Continuous, sequential monitoring for safety and efficacy
- Full protocol openly accessible at https://www.jnj.com/coronavirus/covid-19-phase-3-study-clinical-protocol

Healthy adults ≥18 years of age
(~20% aged 18 to 40 years, ~30% >60 years of age)
Total Enrollment >44,000

Single IM dose $5x10^{10}$ vp of Ad26.COV2.S
OR
Placebo

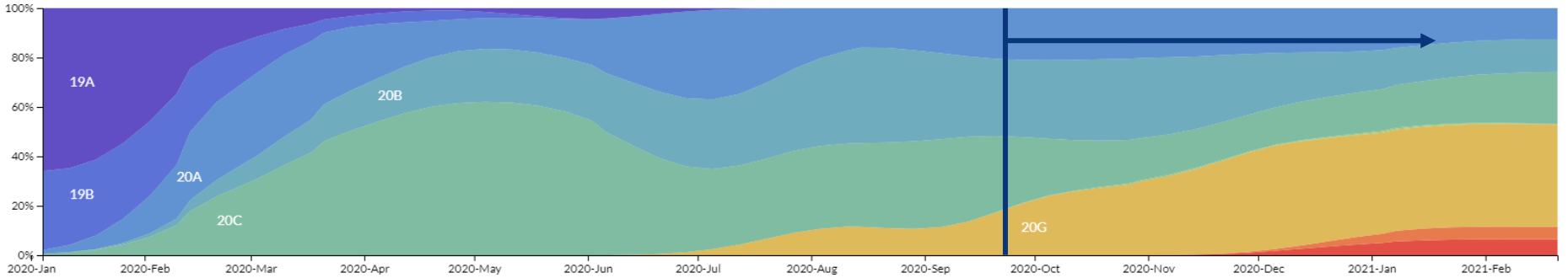
# of participants with first occurrence of molecularly confirmed moderate to severe/critical† COVID-19 w/seronegative status as of 14 days and 28 days after vaccination (planned follow up 2 years if feasible)

†Moderate defined as one sign and one symptom from a list of signs, such as heart rate >90 bpm and symptoms such as shortness of breath or cough or 2 symptoms from a list of symptoms or Severe COVID-19 defined in FDA guidance. *NLM Identifier: NCT04505722

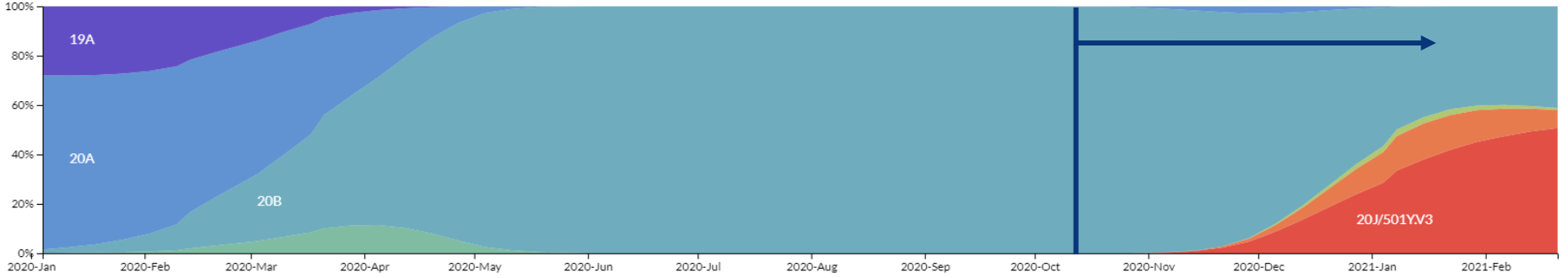
Variants assessed vary over time and by geography

Subset of countries participating in ENSEMBLE

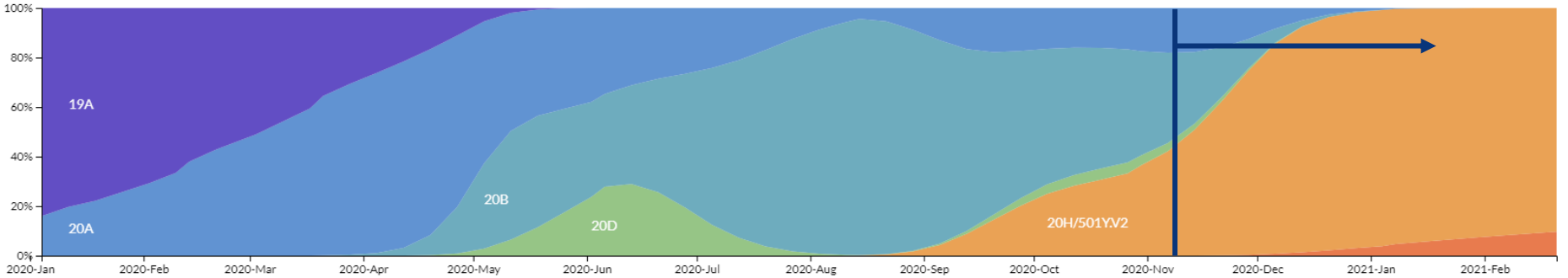
United States



Brazil



South Africa



Source: Nextstrain 20Feb2021

Overview of ENSEMBLE immune sampling plan

Based on ENSEMBLE protocol

Stage 1 – for primary analysis

2 timepoints at D1 and D29 for both random subcohort and infected cases

1. **Random subcohort**
2. Infected cases are from **vaccine group (baseline + and -) and placebo group (baseline + only)**

Stage 2 – for durability study / more correlates analysis

5 additional timepoints through month ~24 for random subcohort;
up to 7 timepoints total for additional infected cases

1. **Same random subcohort**
2. Additional infected cases from **vaccine group (baseline + and -) and placebo group (baseline + only)**

Randomly Sampled Sub-cohort:

Antibody Assessments of Immunogenicity and Immune Marker CoRs and CoPs

	Numbers of Participants Sampled Into 64 Strata of Study Participants (Total N=1616)																															
	Baseline SARS-CoV-2 Seronegative[b]																Baseline SARS-CoV-2 Seropositive[c]															
Baseline Demographic Covariate Strata[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Vaccine	58	58	58	58	58	58	58	58	58	58	58	58	58	58	58	58	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
Placebo	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18

[a]The 16 baseline demographic covariate strata are as follows: 1 = underrepresented minority (URM) in U.S., age >= 60, presence of comorbidities; 2 = URM in U.S., age >= 60, absence of comorbidities; 3 = URM in U.S., age 18-59, presence of comorbidities; 4 = URM in U.S., age 18-59, absence of comorbidities; 5 = non-URM in U.S., age >= 60, presence of comorbidities; 6 = non-URM in U.S., age >= 60, absence of comorbidities; 7 = Latin America, age >= 60, presence of comorbidities; 8 = South Africa., age >= 60, presence of comorbidities; 9 = Latin America, age >= 60, absence of comorbidities; 10 = South Africa, age >= 60, absence of comorbidities; 11 = non-URM in U.S., age 18-59, presence of comorbidities; 12 = non-URM in U.S., age 18-59, absence of comorbidities; 13 = Latin America, age 18-59, presence of comorbidities; 14 = South Africa, age 18-59, presence of comorbidities; 15 = Latin America, age 18-59, absence of comorbidities; 16 = South Africa, age 18-59, absence of comorbidities.

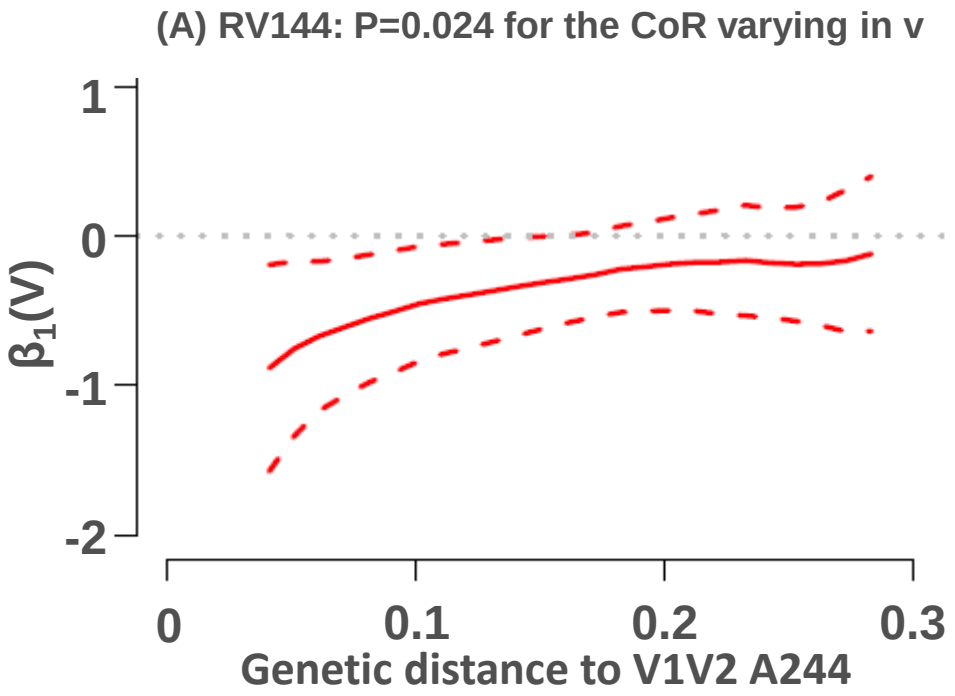
Current Correlates SAP Focuses on bAb / nAb to the Vaccine Strain and the Endpoint COVID with Any Strain

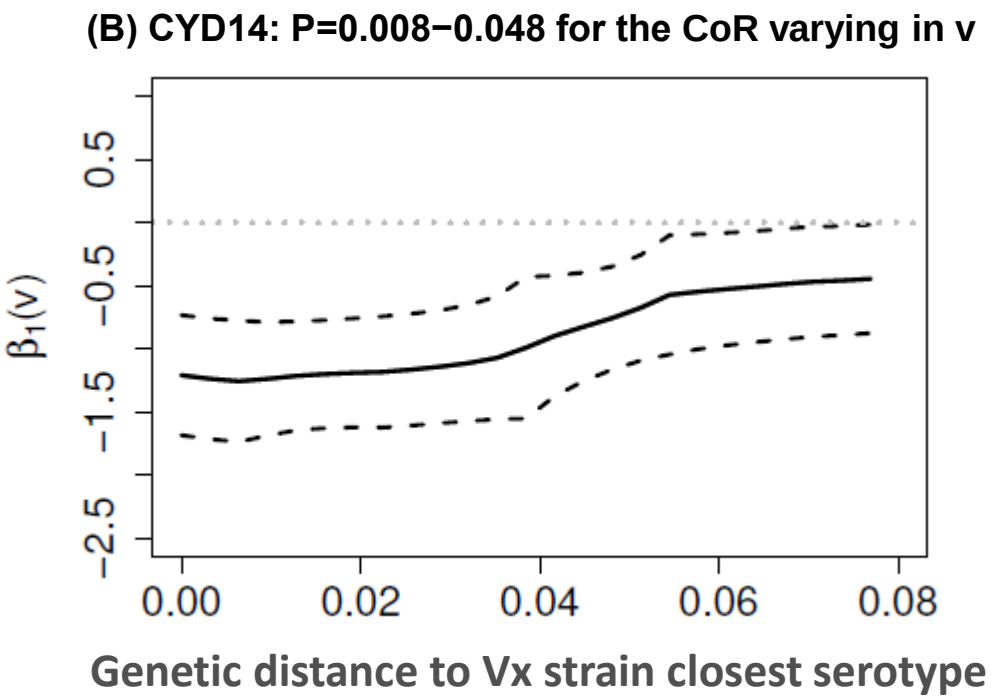
- Plan to conduct the correlates analysis by each region separately (U.S., Central/South America, South Africa)
- Because the South African variant 501Y.V2 dominates the cases occurring in South Africa, the analysis assesses bAb / nAb to the vaccine strain as a CoR/CoP against the South African variant
- Combined study analyses evaluate bAb / nAb as CoR/CoP for COVID of different sets of circulating strains
- Comparing correlates results by region may give insights about whether the correlate may differ by viral lineage
  - E.g., does the nAb titer threshold for low risk differ depending on the circulating virus population?

Assessment of bAb / nAb to the Vaccine Strain as CoRs of AA Sequence-Specific COVID

- Assess whether bAb/nAb to the vaccine strain is a weaker correlate of risk of COVID when the acquired virus is farther from the vaccine strain*
  - Farther defined by larger: (1) IC50; (2) AA-predicted IC50; AA-Hamming distance to vaccine strain

$\beta_1(v)$ = log relative risk of endpoint with a distance v virus per 10-fold increment in peak Ab immune response





Precedents (A) RV144: IgG and IgG3 to V1V2 of the A244 vaccine strain were less correlated with HIV-1 acquisition for viruses with greater V1V2 Hamming distance to the A244 vaccine strain (Yang et al., 2017, *Stat Biosc*; Sun et al., 2018, *Biometrical Journal*). (B) CYD14 dengue VE trial for $PRNT_{50}$ nAb titer and Hamming distance to vaccine insert.

Status report of correlates planning

- Sufficient vaccine breakthrough cases exist for correlates analyses, sample selection and distribution are in process
- Partnering with COVID-19 response team (formerly OWS) biostatistics for correlates analyses
- Binding Ab (Spike, RBD, N), wtVNA (MN50) are being considered for Day 1 and 29 samples
- Correlates analyses will be done as soon as the data set is available from one of the assays
  - E.g., may do correlates for bAb first: highest throughput assay
  - Accelerates time to some correlates results

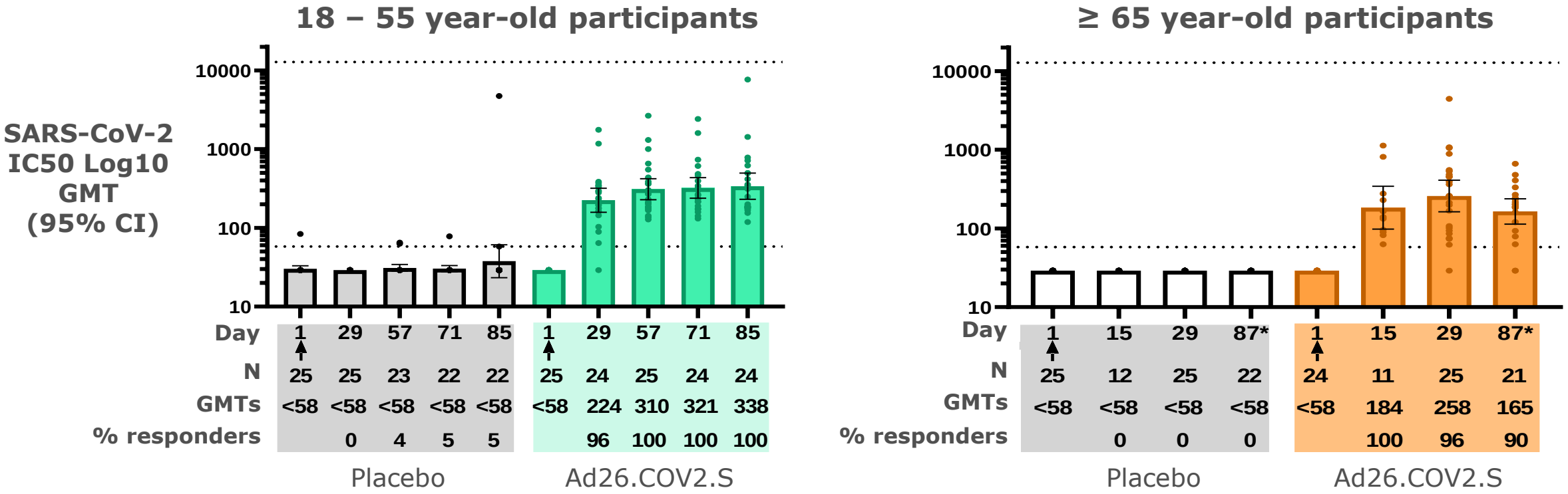
Can NAb titer be a CoP for ENSEMBLE?

- NAb response rate at Day 29 can be greater or less than the estimate of VE
- Potential explanations:
  1. nAb is sufficient for protection but not necessary (may be another mechanism)
  2. nAb is a 'perfect CoP' (necessary and sufficient for protection) but the assay was not sufficiently sensitive at the lower end
  3. nAb is sufficient for protection from exposing strain while cross protection may require sufficient breadth of nAb induction

  Note: If 1. were true, then the CoP could still be quite good – e.g., mediating 80% of vaccine efficacy, not 100%

Similar and Durable Humoral Immune Responses After Single Dose $5x10^{10}$ vp Ad26.COV2.S in Adults 18-55 and ≥ 65 Years

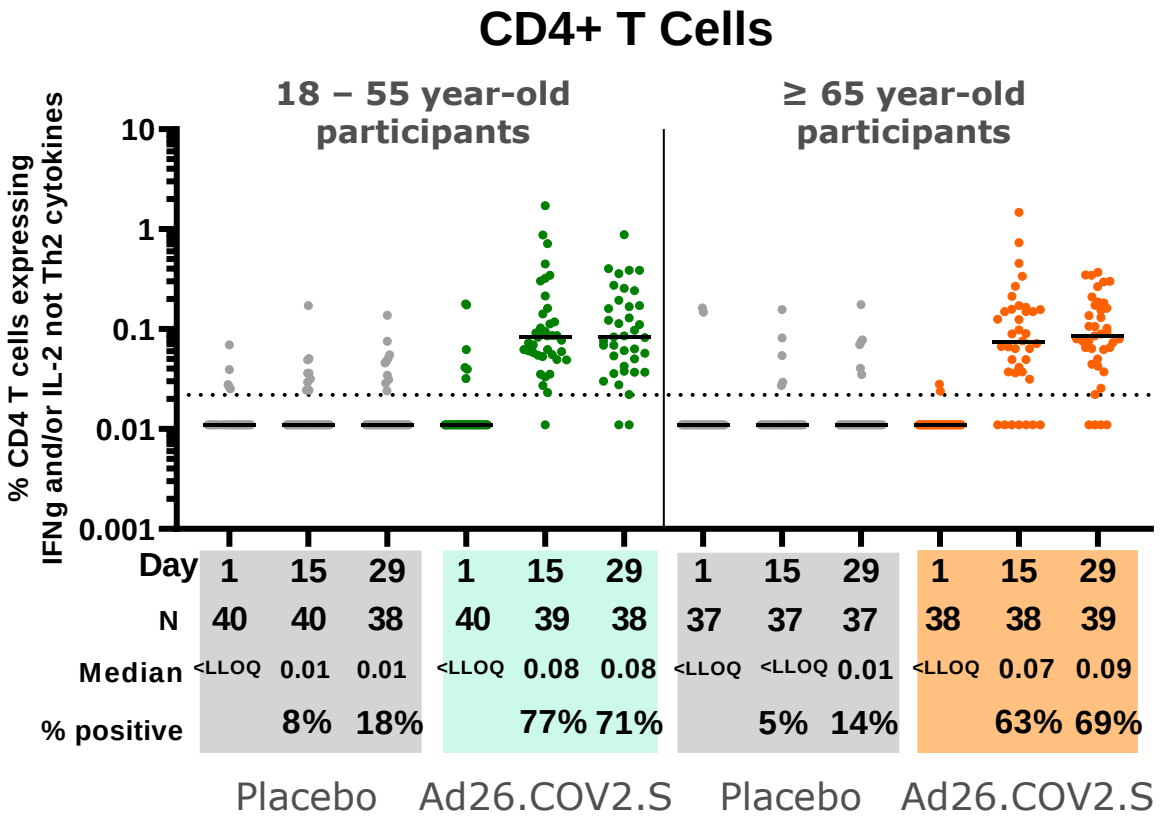
- Observed neutralizing antibody response: 96% of Ad26.COV2.S group (Day 29)
  - Response lasted ≥ 85 days in both age groups

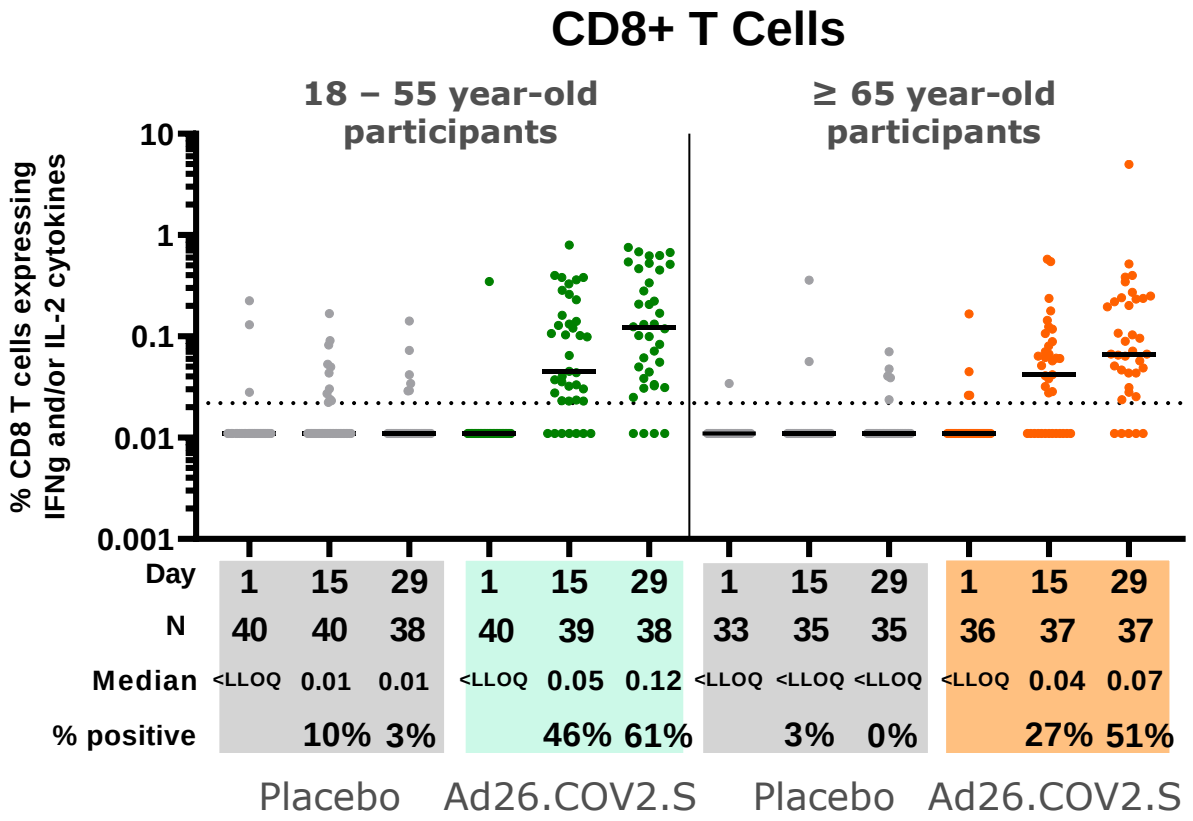


Adapted from Sadoff, Le Gars, et al NEJM, 2021

Ad26.COV2.S Elicits CD4+ and CD8+ T Cell Responses

Th1:Th2 ratio well above 1 in all vaccine responders





% Positive responder defined by one-sided Fisher's exact test comparing non-stimulated versus S-peptide stimulated cells

Later Add 'By Variant' CoR and CoP Analysis

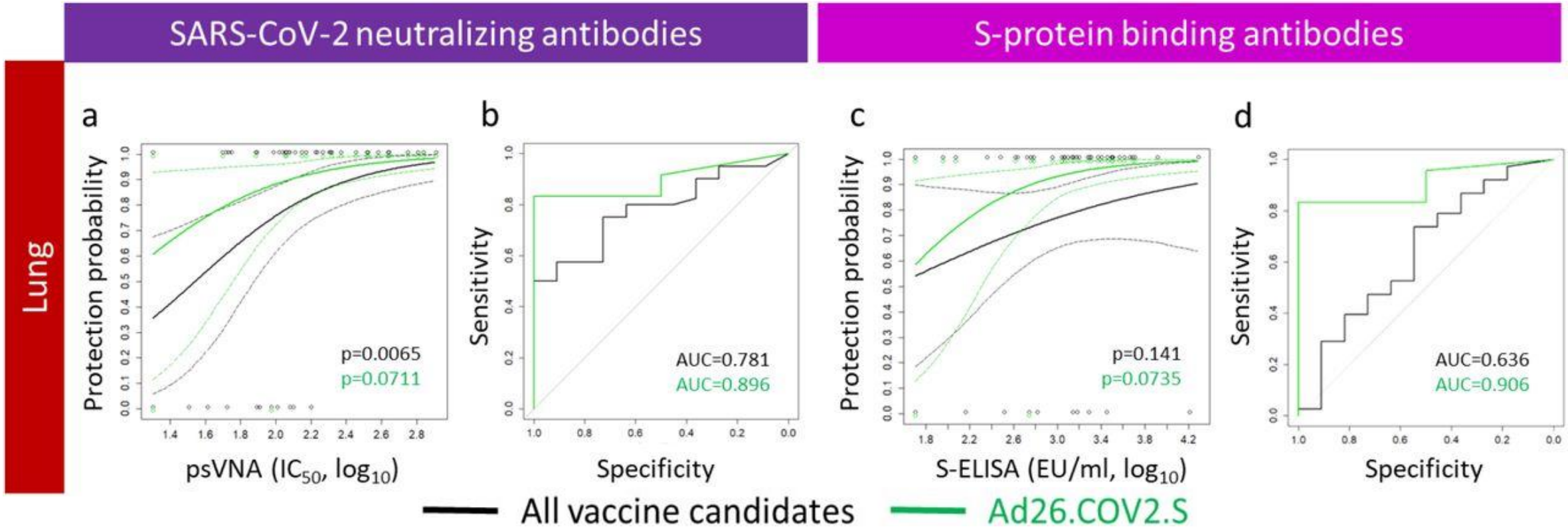
- Sequential correlates analyses will add data on bAb / nAb to panels of viral variants
- Assess bAb / nAb to a specific variant as a CoR / CoP against disease with the same variant
  - E.g., assess bAb / nAb against South African variant as CoR / CoP against South African variant COVID in the South Africa region
- May also study bAb / nAb against a specific variant as CoR/CoP against a vaccine-mismatched variant, to document weakening of the correlate

Challenge: Lack of the Same Set of Major Variants in the Same Region/Trial

- Currently, the B.1.351 variant can only be studied in the South Africa region (95% of South African cases with variant; few such cases outside of South Africa)
  - Thus, cannot infer whether different VE within South Africa is caused by the variant or by other regional factors
  - Baseline determinants of immunogenicity as well as mapping the presumed variant giving rise to baseline seropositivity on the observed efficacy may be able to disentangle these effects

Learning from NHP SARS-CoV-2 CoP analyses

- bAb and nAb are highly correlated, with both responses predicting protection in NHP for both Ad26.COV2.S and a range of Ad26-based vaccines
  - Similar responses induced in humans



Evidence of contribution of cell-mediated immunity to vaccine efficacy, and utility of T cell assays to correlates analyses

Julie McElrath, MD

Senior Vice President and Director
Vaccine and Infectious Disease Division

Fred Hutch Cancer Research

Contribution of cell-mediated immunity to vaccine efficacy

HVTN Laboratory Center
Fred Hutchinson Cancer Research Center

Julie McElrath, Kristen Cohen, Steve De Rosa
February 25, 2021

FRED HUTCH
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Wide array of T cell immune assays for SARS-CoV-2 vaccine trials

Assay	Advantages	Disadvantages
1. IFN-γ ELISpot	• High sensitivity for IFN-γ • Relatively low cell requirements • **Validated**	• Limited ability to multiplex cytokines • Unknown sensitivity for Th2-type cytokines (e.g., IL-4) • Validated assay does not distinguish CD4+ vs CD8+ T cells
2. Activation-induced marker (AIM)	• Multiplexed phenotypic, functional markers • High sensitivity	• Inability to distinguish Th1/Th2 • Concern for lower specificity in comparison to other T cell assays
3. CyTOF	• Highly multiplexed for cytokines, tetramers, phenotyping	• Low throughput • Low cell recovery
4. Antigen-stimulated PBMC or whole blood cytokine secretion assay	• High sensitivity (depending on cytokine) • Multiplex capability • **Qualified** (PBMC)	• Bulk assay does not provide cell type (e.g., CD4 or CD8) and does not provide frequency of responding cells
5. Intracellular cytokine staining (ICS)	• Multiplexed phenotypic, functional markers • High sensitivity for some key cytokines • **Validated** for Th1 CD4+ and CD8+ T cells, standardized for Th2	• Requires multiparameter flow cytometer instruments

Minimal 12-color ICS panel for high-throughput and/or tech transfer

Antigen	Role
Viability	**Live/Dead**
CD14	Monocytes
CD19	B cells
CD16	NK cells (FcgR)
CD56	NK cells
CD3	**T cells**
CD4	
CD8	
CD45RA	**Memory T cells**
CCR7	
CD25	Tregs
FoxP3	

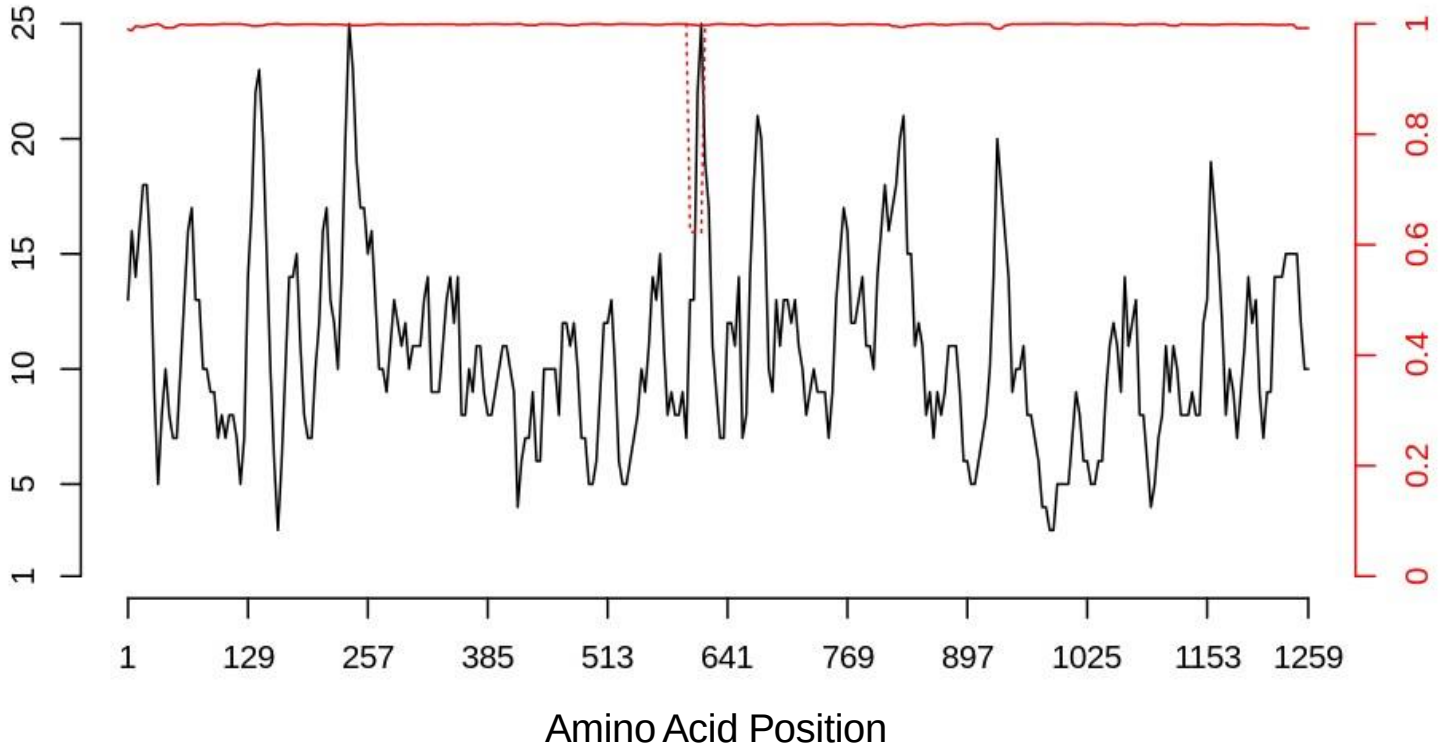
Antigen	Role
IFN-γ	**Th1**
IL-2	
TNF-α	
IL-17a	**Th17**
IL-4	**Th2**
IL-5/IL-13	
CD154	**CD4 response**
CRTh2	Th2 (surface)

Antigen	Role
Granzyme B	Cytotoxicity
Perforin	
CD32	FcgR
CD64	
CXCR3	Th subsets
CCR6	
Ki67	Activation

Design of consensus spike SARS-CoV-2 peptides

Diversity

# of unique 15mers
(out of 17,811 sequences)

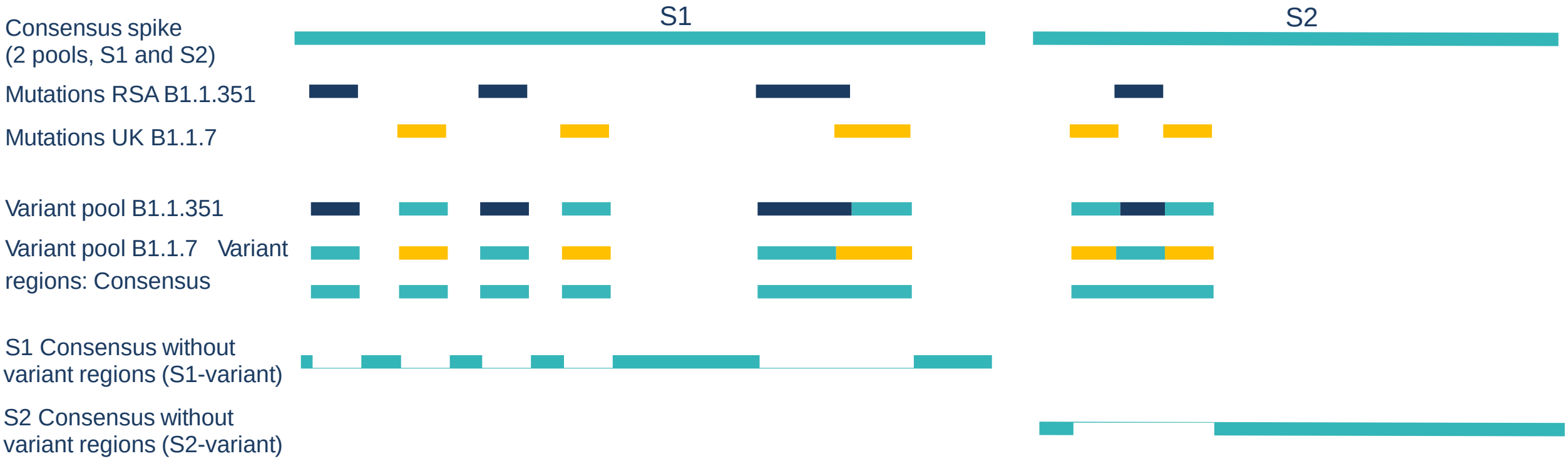


Coverage

Proportion of sequences matched to consensus

- Generated consensus sequence from alignment of available SARS-CoV-2 spike global sequences (n= 17,811) from GISAID database in May 2020
- The consensus was a **perfect a.a. match** to the Wu-Han strain except for 614
- Designed variants to cover the diversity at position 614 (D/G variants) to bring overall coverage to >99%

Peptide pools for spike for variant regions



Peptide pools to use for stimulation:

1. S1 Consensus without variant regions
2. S2 Consensus without variant regions
3. Variant regions: Consensus
4. B1.1.351 variant pool
5. Optional: B.1.1.7 variant pool

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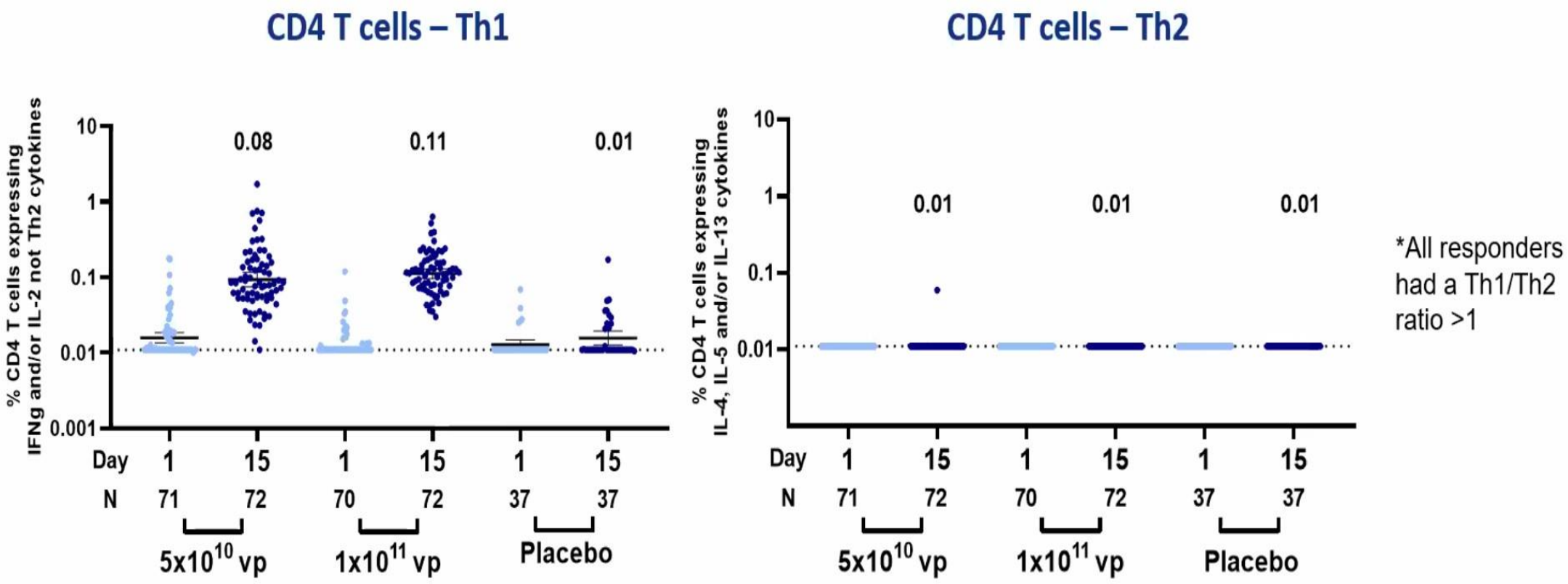
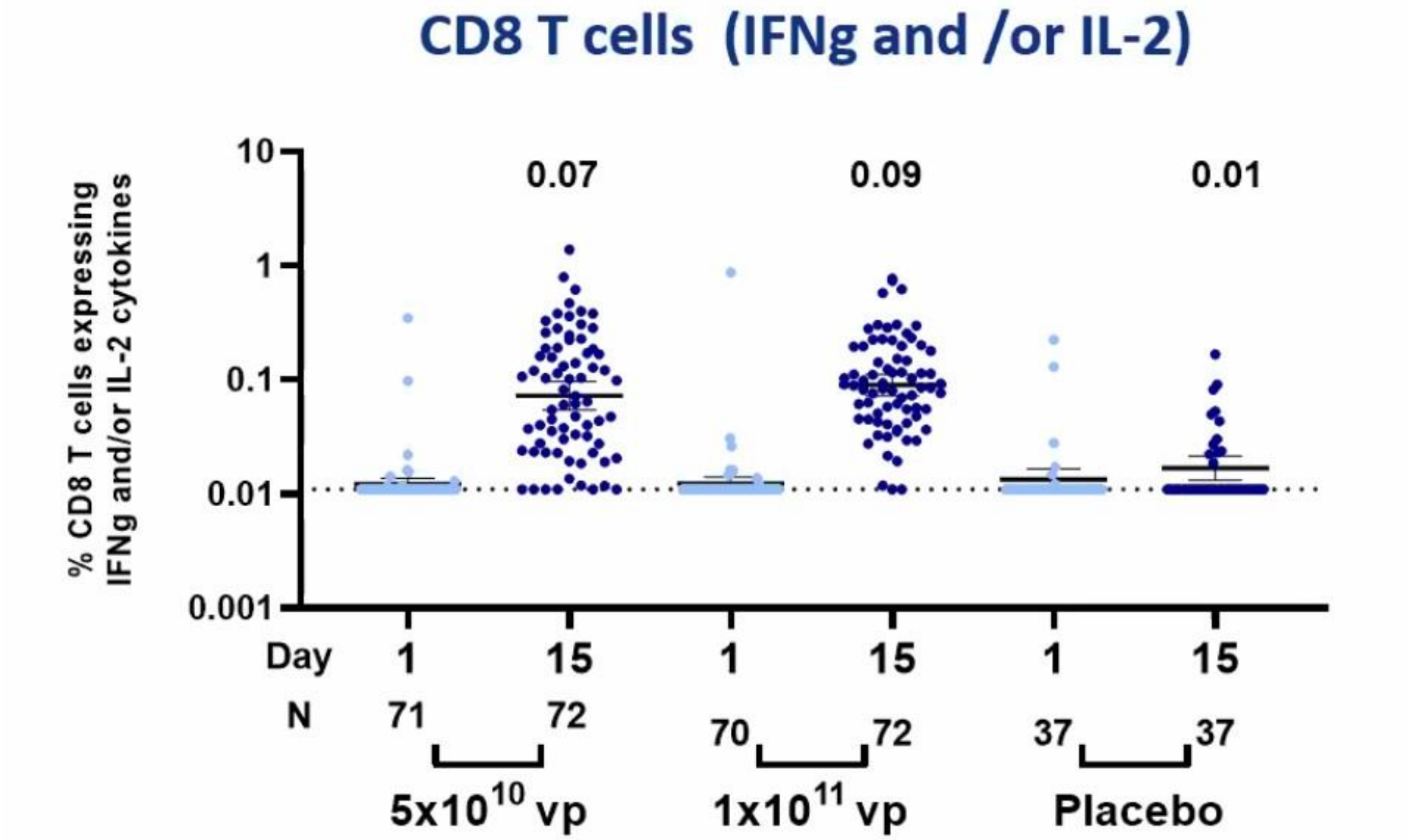
Janssen Ad26.CVO2.S Phase 1/2a Study



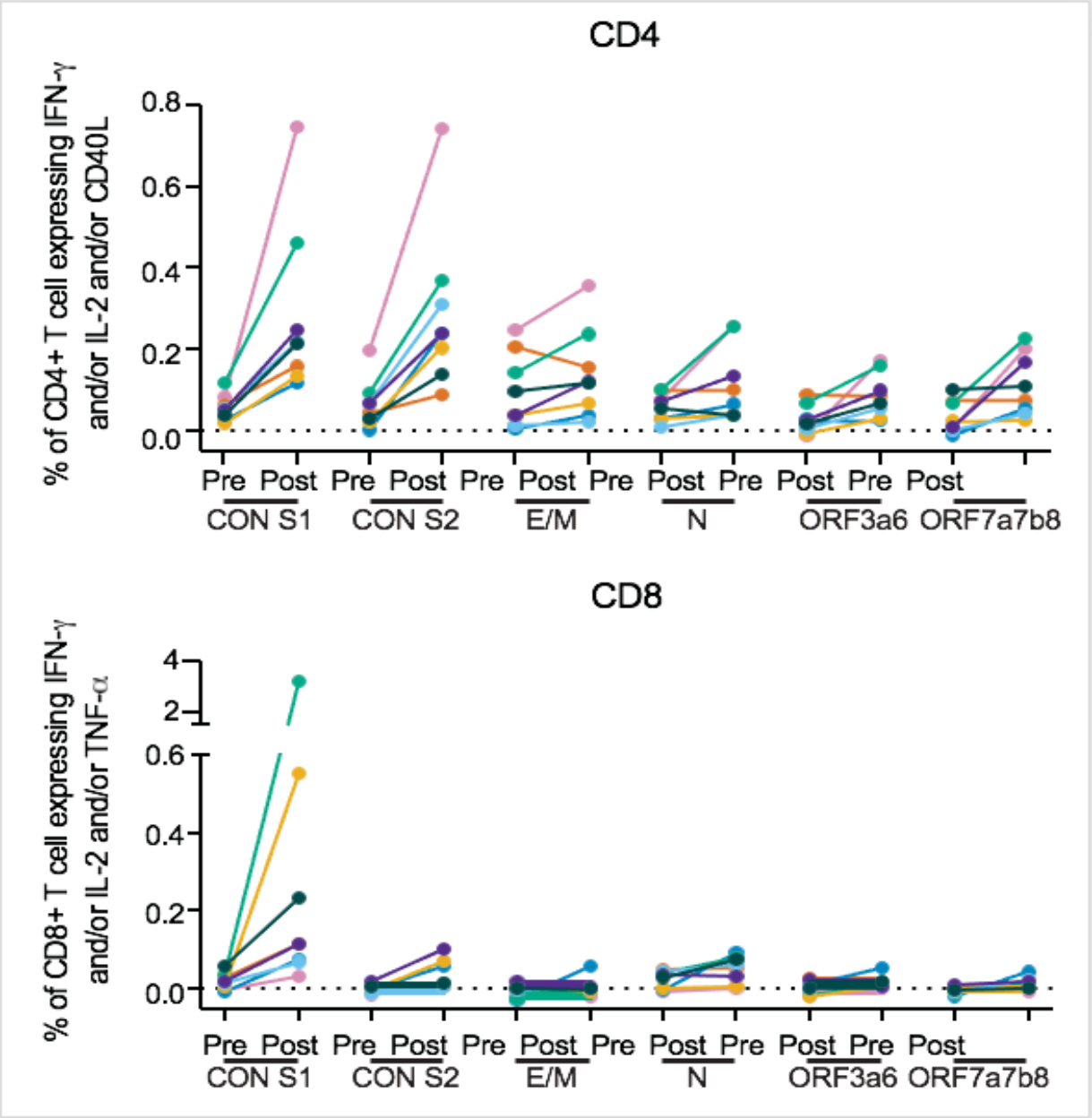
Sadoff et al, NEJM Jan 2021

Janssen Ad26.CVO2.S Phase 1/2a Study



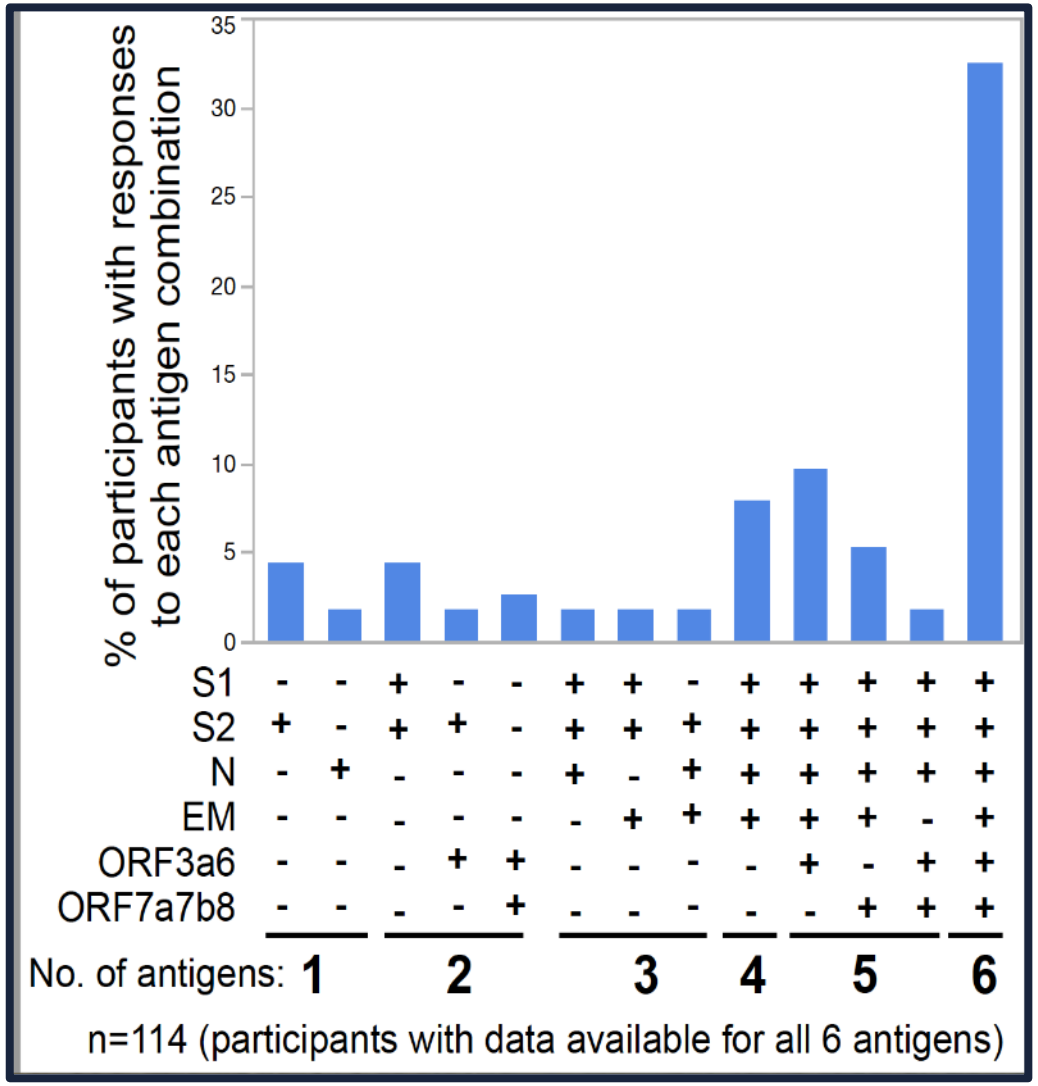
Sadoff et al, NEJM Jan 2021

T cell responses in SARS-CoV-2 infection post-mRNA vaccination

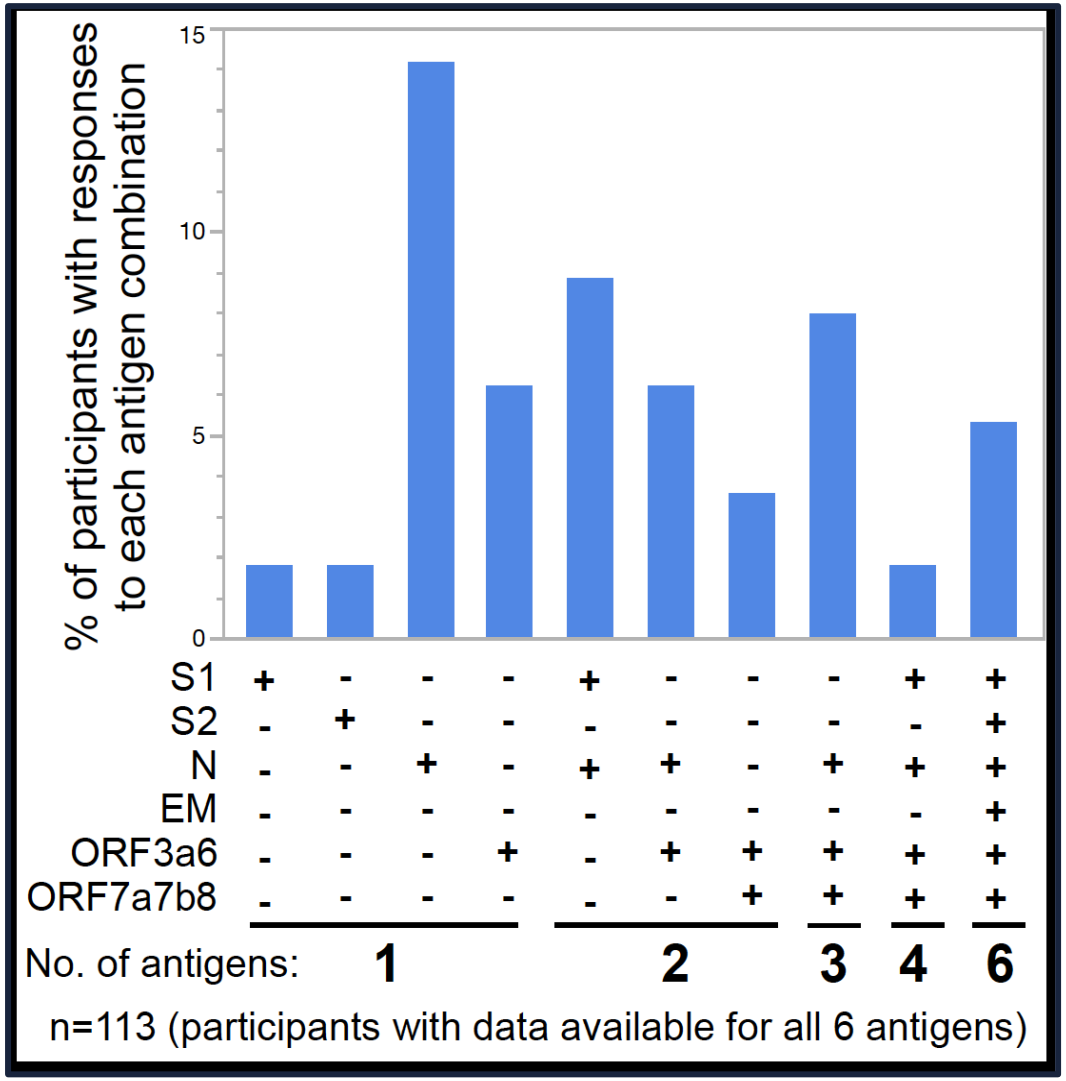


T cell specificities: % of COVID-19 patients recognizing SARS-CoV-2 antigens

CD4+ T Cells



CD8+ T Cells



Conclusions

1. A wide array of T cell-based assays are being deployed in COVID-19 vaccine trials, which will illuminate differences in immune responses to various vaccine platforms
2. IFNɣ ELISpot and ICS are most widely used, but their correlation with efficacy is currently unknown
3. Lack of validated SARS-CoV-2-specific assays across the trials, and difficult sample collection remain challenges for the utility of T cell assay-based biomarkers in large scale trials
4. Requirement for T cell durability to be determined

Panel Discussion

Moderated By:

Peter Dull, MD

Deputy Director,

Integrated Clinical Vaccine Development,

Bill & Melinda Gates Foundation (BMGF)

Discussion Panel Members and Example Questions

Panel Members

- **George Siber,** Co-founder and Member of Board at Affinivax, Inc., United States
- **Andy Pollard**, University of Oxford, United Kingdom
- **David Goldblatt,** University College London, United Kingdom
- **William Dowling,** CEPI, United States
- **Florian Krammer,** Icahn School of Medicine at Mt. Sinai, United States
- **Stephen Lockhart,** Pfizer, United Kingdom
- **Daniel Stieh,** J&J, Netherlands
- **Julie McElrath,** Fred Hutch Cancer Research Center, United States

Potential Discussion Questions

1. Where are we on the “road to a correlate” as we think about others that are currently licensed based on a biomarker? HPV? Polio? Pneumococcus? MenB?

2. Neutralizing antibody and binding antibody responses seem to correlate well across most vaccines studied. Why not focus on binding antibodies as a more robust and scalable assay readout?

3. What are the product development implications if there is a different biomarker associated with infection or with disease?

4. How can we support vaccine licensure where efficacy is no longer possible but the mechanism of protection is via mucosal antigen delivery with modest humoral immunity?

5. What is the status of the tools for reliably and consistently measuring T-cell biomarkers without the isolation of PBMCs

Break

Part 2:

Investigating the impact of new SARS-CoV-2 variants: Assays and available vaccines

Moderated By:

Jakob Cramer

Head of Clinical Development

Coalition for Epidemic Preparedness Innovations (CEPI)

International Standard for SARS-CoV-2 immunoglobulins: Use of the existing International Standard to address new variants

Paul Kristiansen, PhD

Head of Standards and Assays, Preclinical and Immunology

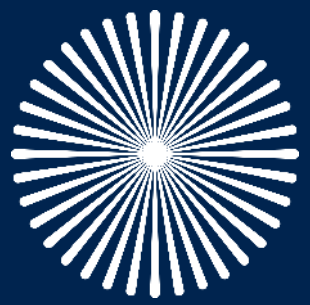
CEPI

International Standard for SARS-CoV-2 immunoglobulins: Use of the existing International Standard to address new variants

Paul Kristiansen

Enabling Sciences SWAT Team co-lead

CEPI - Head Biological Standards and Assays, Preclinical and Immunology



February 2021

SARS-CoV-2 WHO International Antibody Standard

- Development of SARS-CoV-2 antibody reference material:
  - Convalescent serum as **Research Reagent** and **reference panel** available from April 2020
  - **International antibody standard** adopted by WHO ECBS in December 2020.

To acquire the reference material:
https://www.nibsc.org/science_and_research/virology/centre_for_aids_reagents/covid-19_reagents.aspx

International Standard available at NIBSC

First WHO International Standard for anti-SARS-CoV-2 immunoglobulin, human (NIBSC code: 20/136)

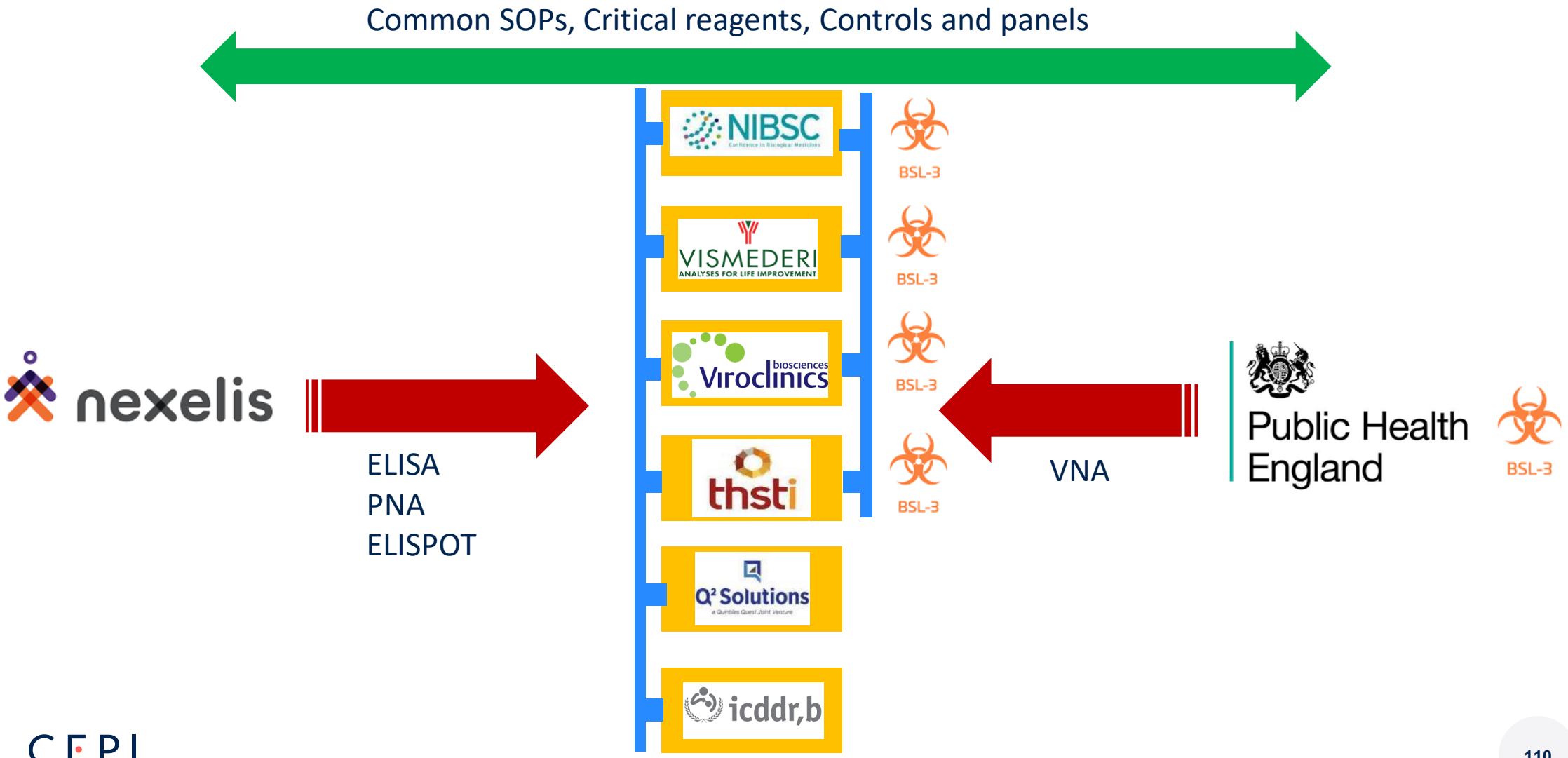
Material: Antibody, human, convalescent plasma, WHO IS
Intended use: Primary calibrant for serological assays
Description: Pool of convalescent plasma from recovered COVID-19 patients, containing high titre antibodies against SARS-CoV-2. Plasma has been solvent detergent treated to minimise the risk of presence of enveloped viruses.
Enquiries: standards@nibsc.org

First WHO International Reference Panel for anti-SARS-CoV-2 immunoglobulin, human (NIBSC code: 20/268)

Material: Antibody, human, convalescent plasma, WHO reference panel
Intended use: Serological assay development and evaluation, Vaccine evaluation, Research,
Description: comprises of 5 panel members; four pools of convalescent plasma from recovered COVID-19 patients, containing high, medium, low anti-S but relatively high anti-N, low antibodies against SARS-CoV-2, and a negative control, pool of plasma from healthy donors collected before 2019.
Enquiries: standards@nibsc.org

CEPI Centralized Laboratory Network

Assay harmonization and tech transfer



CEPI

CEPI Centralized Laboratory Network

2020 achievements in numbers

Laboratories worldwide

Nexelis (Canada), Q2 Solutions (US), PHE Porton Down (UK), NIBSC (UK), VisMederi Srl (Italy), Viroclinics (The Netherlands), icddr,b (Bangladesh),THSTI (India)

Samples requested for analysis

From Preclinical, Clinical Phase I and Clinical Phase II studies

Available assays

S,RBD,N ELISA assay
Pseudo virus neutralization assay
Wild type virus neutralization assay
IFNy, IL-5 ELISPOT assay

Covid-19 Vaccine developers engaged

In 4 continents among CEPI-funded and non CEPI-funded developers

USD invested

Of the 16M USD total budget allocated to the program

Concluding remarks

1. **We have a tool for harmonizing the assessment of immunresponses to COVID-19 vaccine and to assess the impact of variants - use it!**

2. **Upcoming events:**
   - **Workshop on the Centralized Laboratory Network: 12. March**
   - **WHO Assays Working group on how to implement the International Standard: by end of March**

CEPI

Neutralising Antibody assays against new variants: Overview of current activities

William Dowling, PhD

Non-Clinical Vaccine Development Leader

CEPI

Neutralizing Antibody assays against new variants: Overview of current activities

William Dowling, CEPI

CEPI

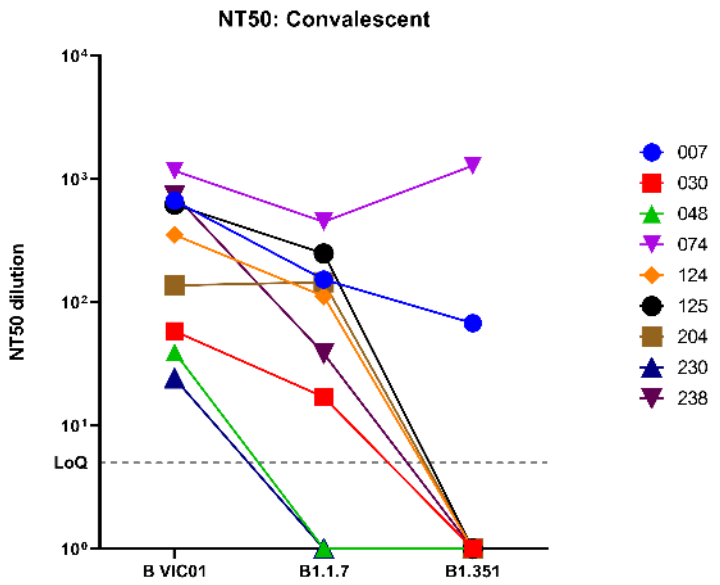
25 February 2021

Live virus neutralization Assays

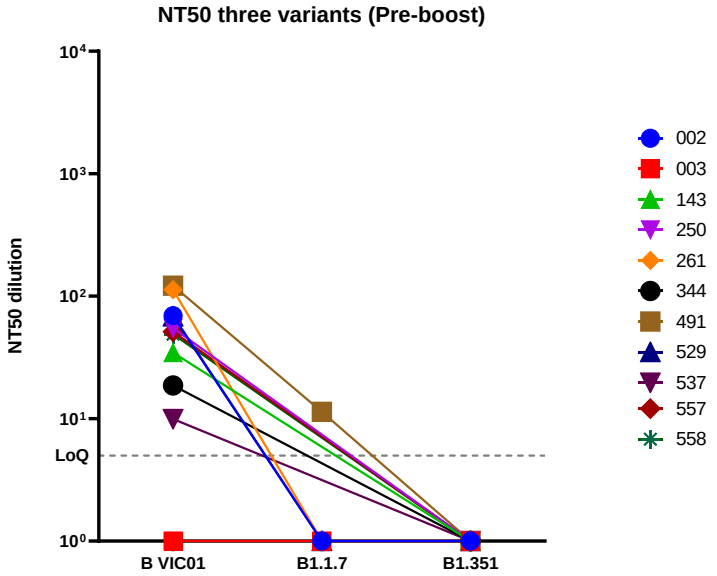
Assay	Virus	Institution	Reference
Microneutralizaion assay (MNA)	B.1.351: 501Y.V2.HV001 501Y.V2.HVdF002	African Health Research Institute (AHRI)	Cele et al 2021 Madhi et al 2021
Cytopathic effect (CPE) assay	B.1.351: GDPCC strain	Chinese Academy of Sciences (CAS)	Huang et al 2021
Plaque reduction neutralization test (PRNT)	B.1.1.7: hCoV-19/India/20203522	National Institute of Virology, India (NIV)	Sapkal et al 2021
S-Fuse assay	B.1.1.7: Tours isolate B.1.351: CNR 202100078	Insitiut Pasteur (IP)	Planas et al 2021
Microneutralizaion assay (MNA)	B.1.17:201/501Y.V1.HMPP1 B.1.351: 501Y.V2HV001	Oxford University and Public Health England (Oxford/PHE)	Skelly et al 2021 Emary et al 2021
Focus Reduction Neutralization test (FRDT) Plaque reduction neutralization test (PRNT)	B.1.1.7: US CDC isolate Recombinant WA-1 with 69-70 del, E484K, N501Y or all B.1351 changes	University of Texas Medical Branch (UTMB)	Edara et al 2021 Xie et al 2021 Liu et al 2021

Neutralization of B.1.1.7 and B.1.351 by Convalescent and Pfizer vaccine sera

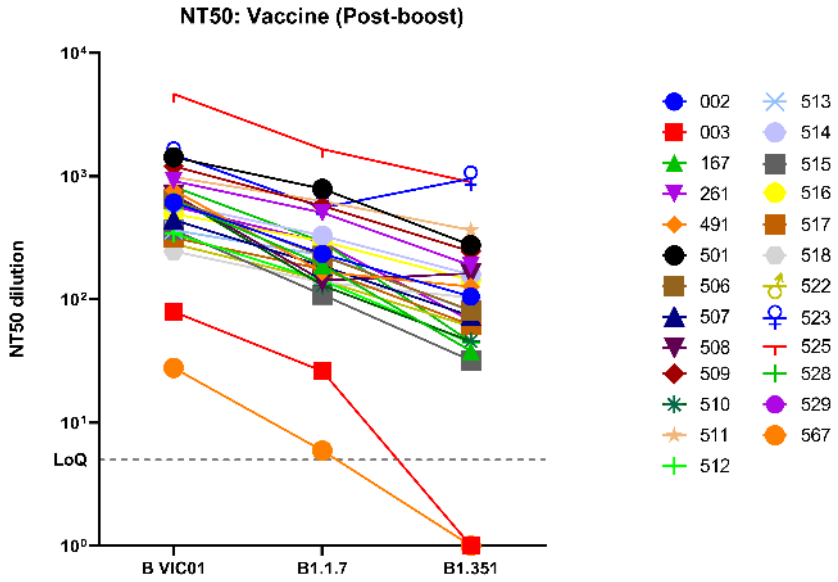
Convalescent



Pre-boost (V1+28) Pfizer vaccine

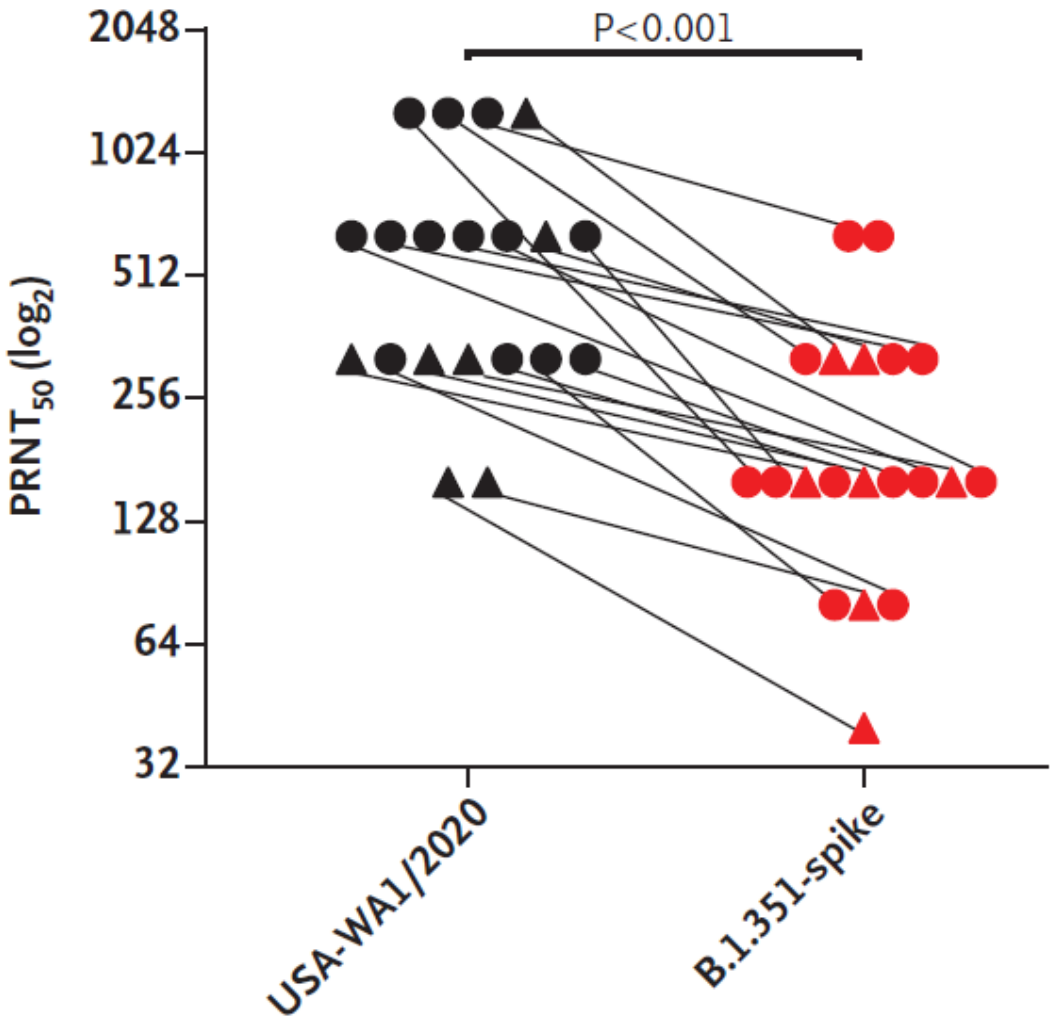


Post boost (V2+7) Pfizer vaccine



Skelly et al 2021

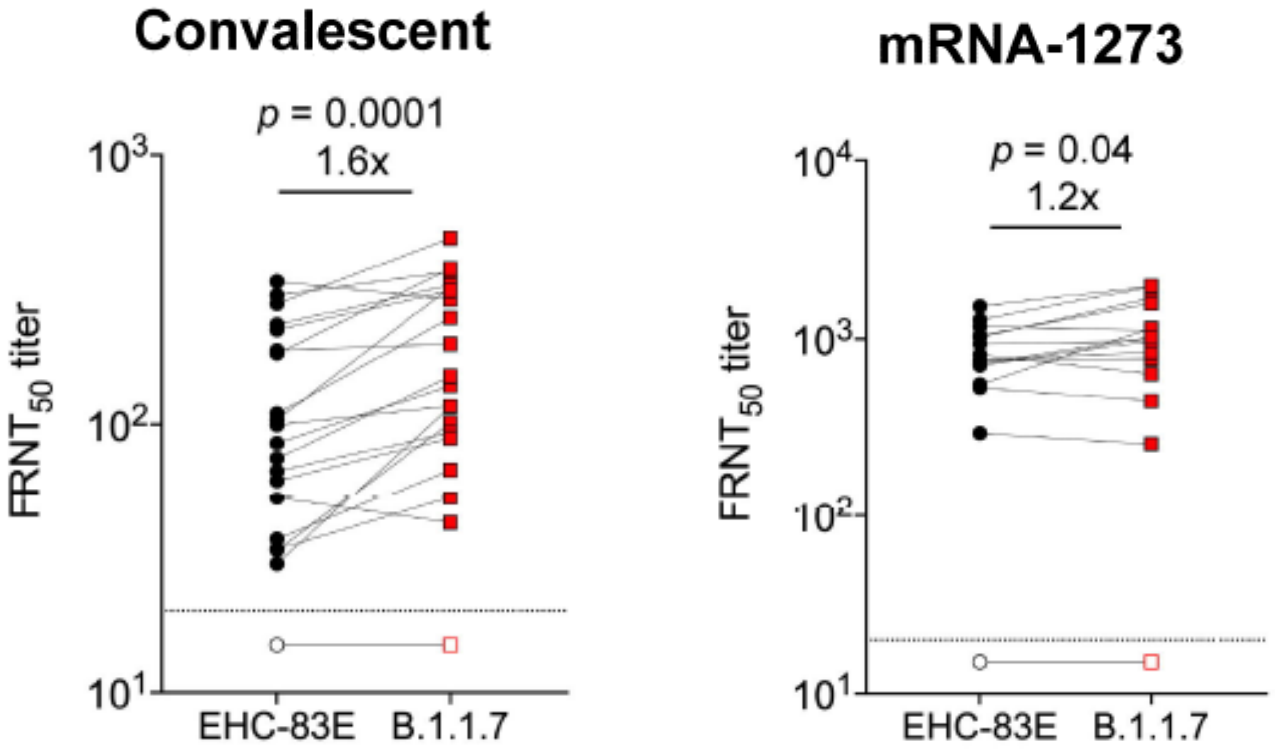
Neutralization of recombinant WA-1/B.1.351 Spike by Pfizer vaccine sera



Liu et al 2021

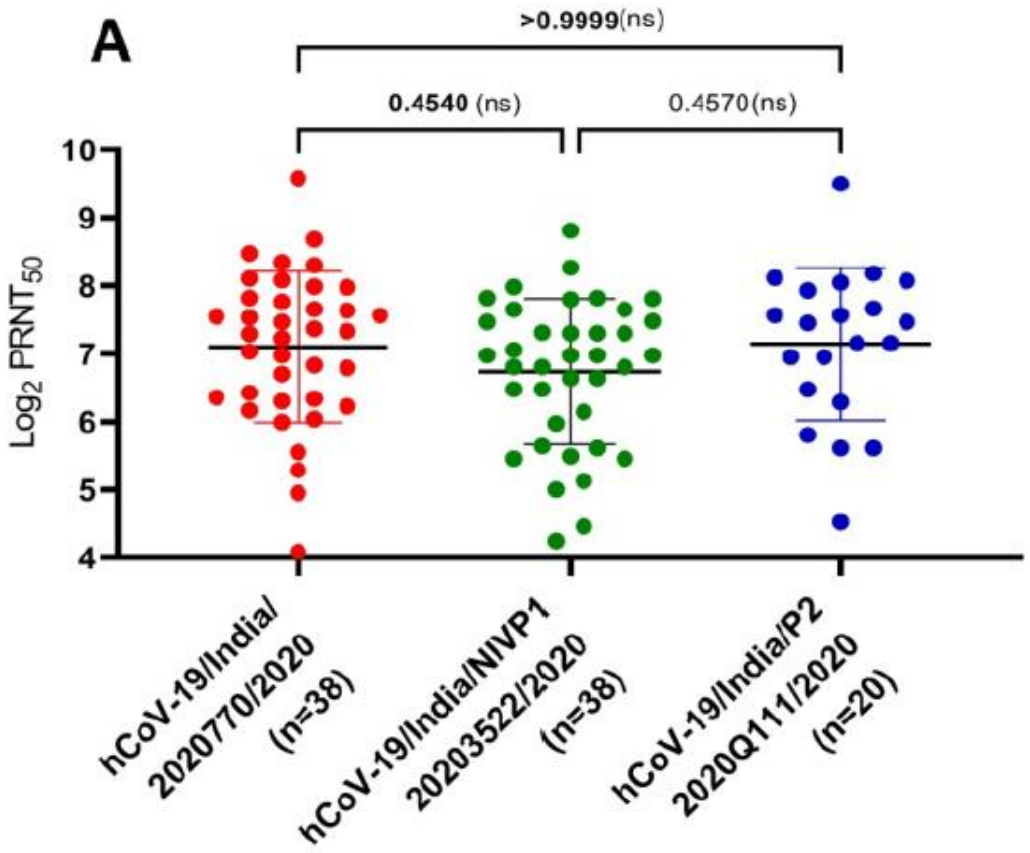
CEPI

Neutralization of B.1.1.7 by Convalescent and Moderna Vaccine sera



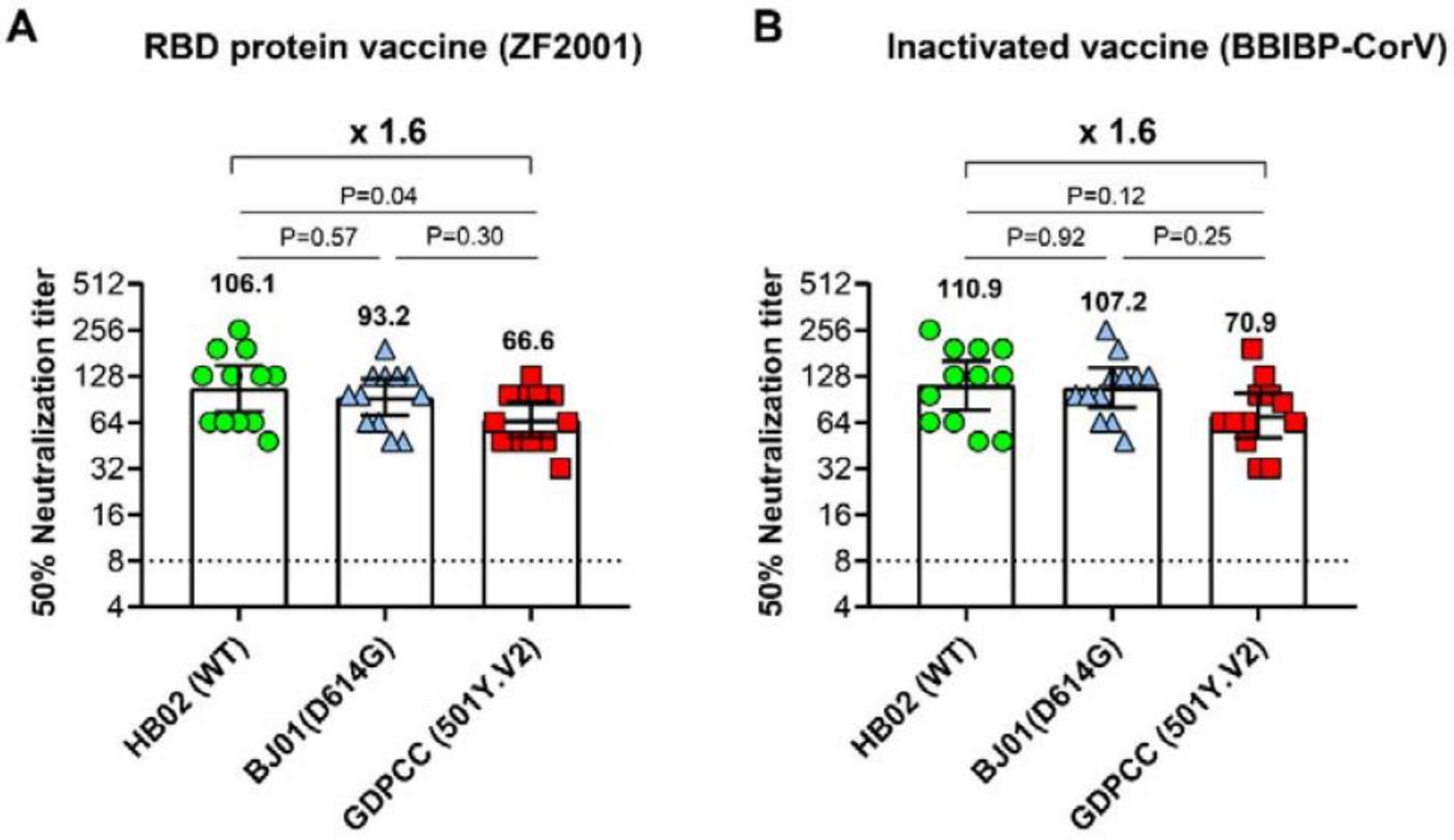
Edara et al 2021

Bharat Biotech vaccine sera efficiently neutralized B.1.17



Sapkal et al 2021

BBIBP-CorV and RBD ZF2001 vaccine sera both neutralized B.1.351



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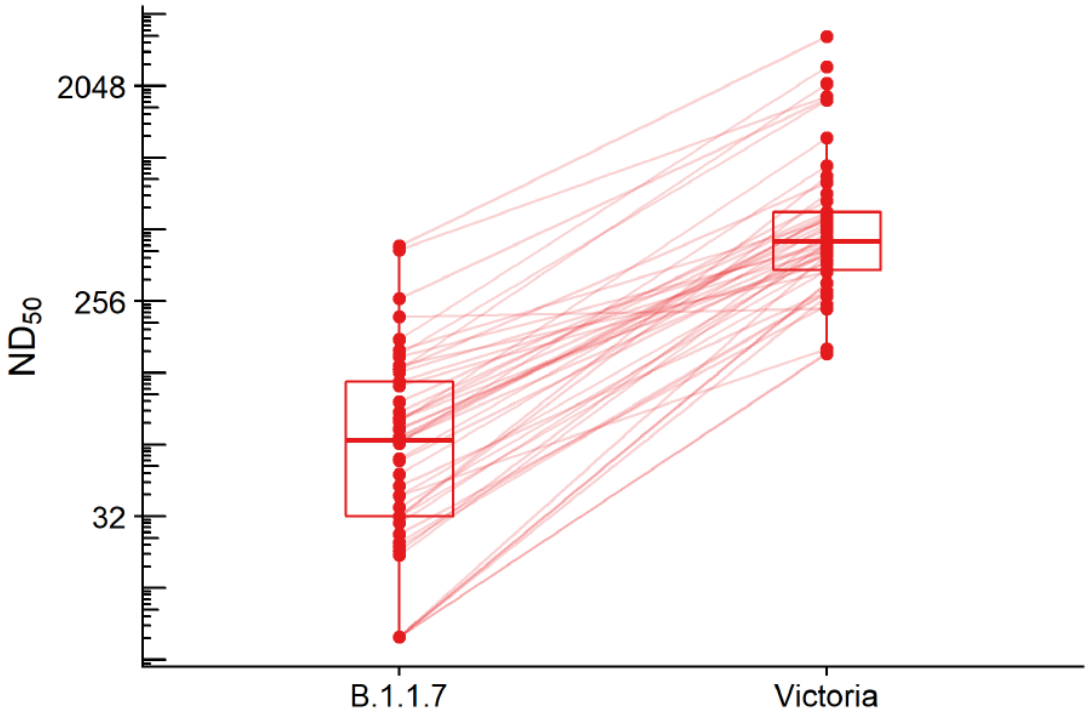
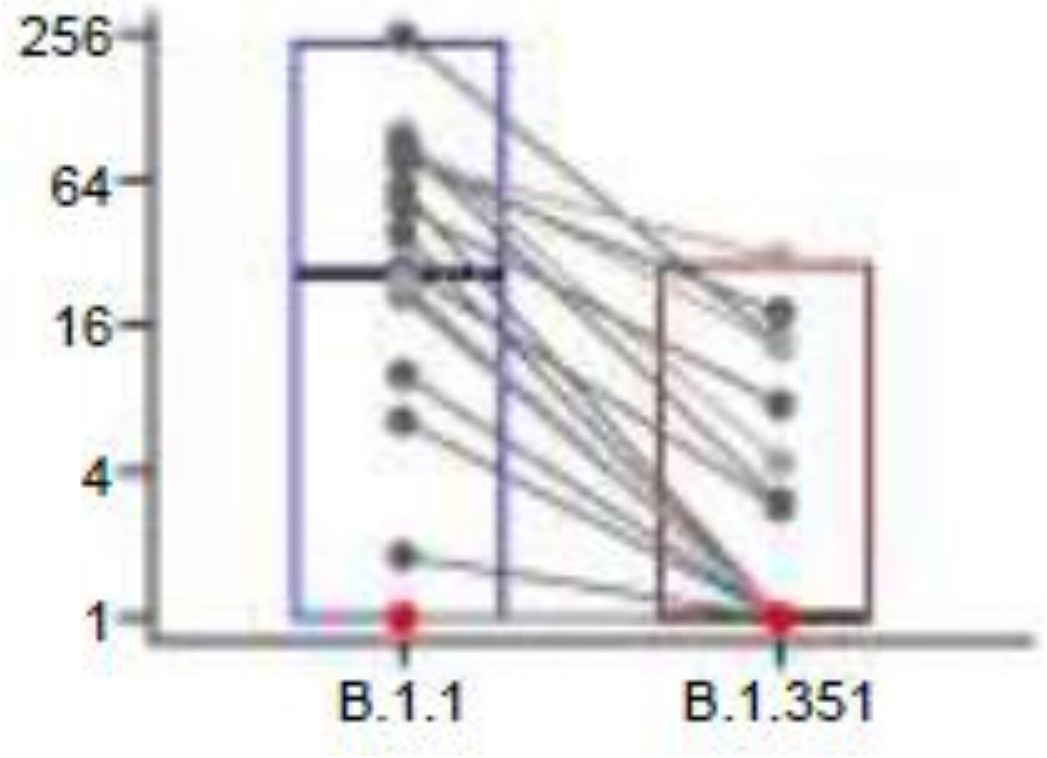
Huang et al 2020

Oxford/AstraZeneca vaccine neutralization affected by both variants

Figure 6. Live virus microneutralisation antibody titres of sera against B.1.1.7 and a canonical non-B.1.1.7 (Victoria) strain

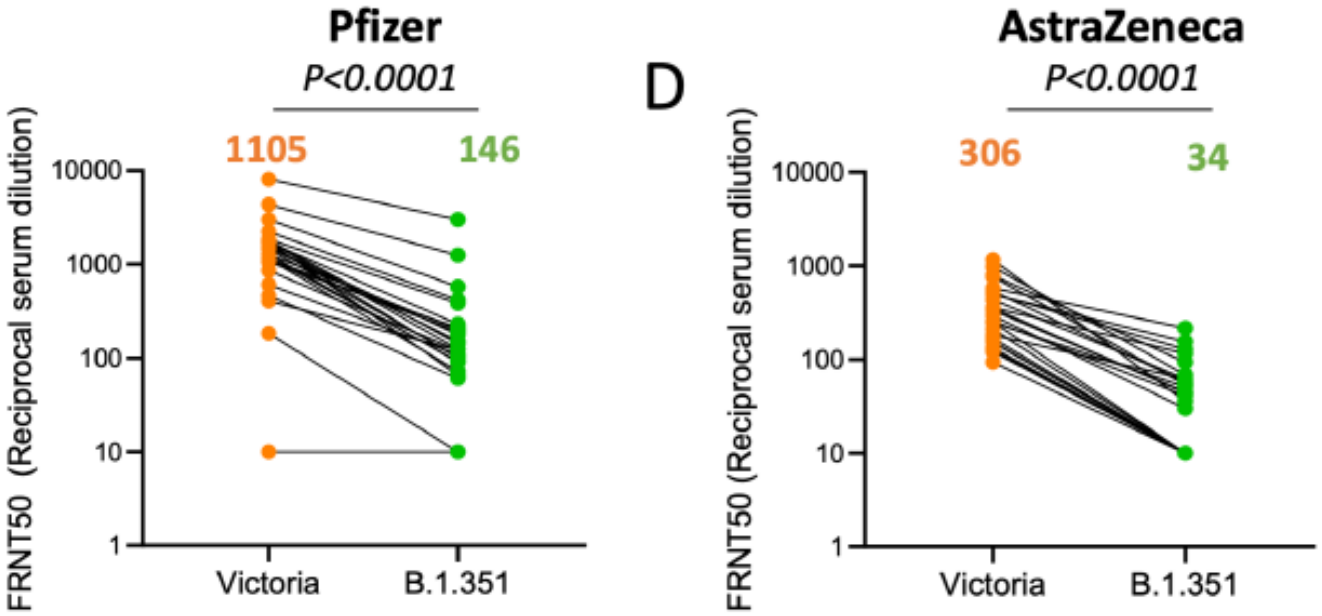


Emary et al 2021



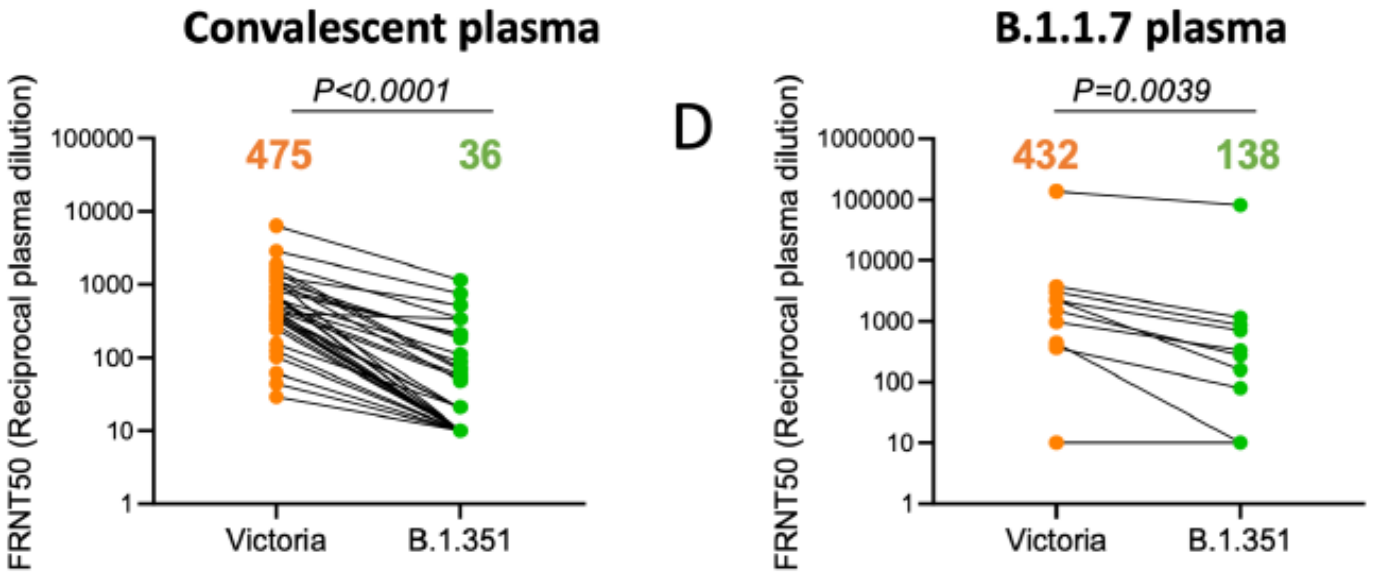
Mahdi et al 2021

Oxford/AstraZenca and Pfizer vaccine sera neutralization



Zhou et al 2021

Convalescent plasma from B.1.1.7 patients neutralizes B.1.351 more efficiently than pre-B.1.1.7 plasma



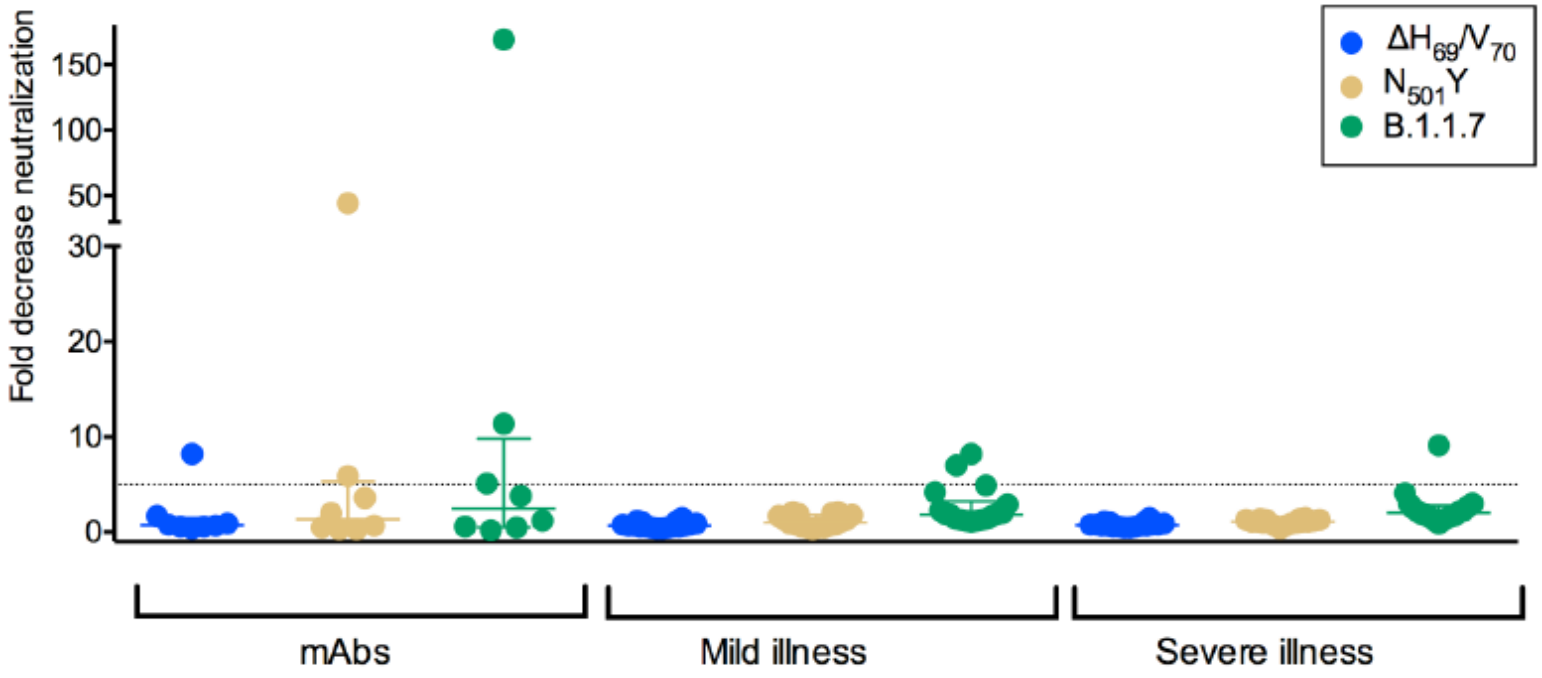
Zhou et al 2021

Pseudovirus neutralization

CEPI

Neutralization with Variant B.1.1.7 pseudoviruses

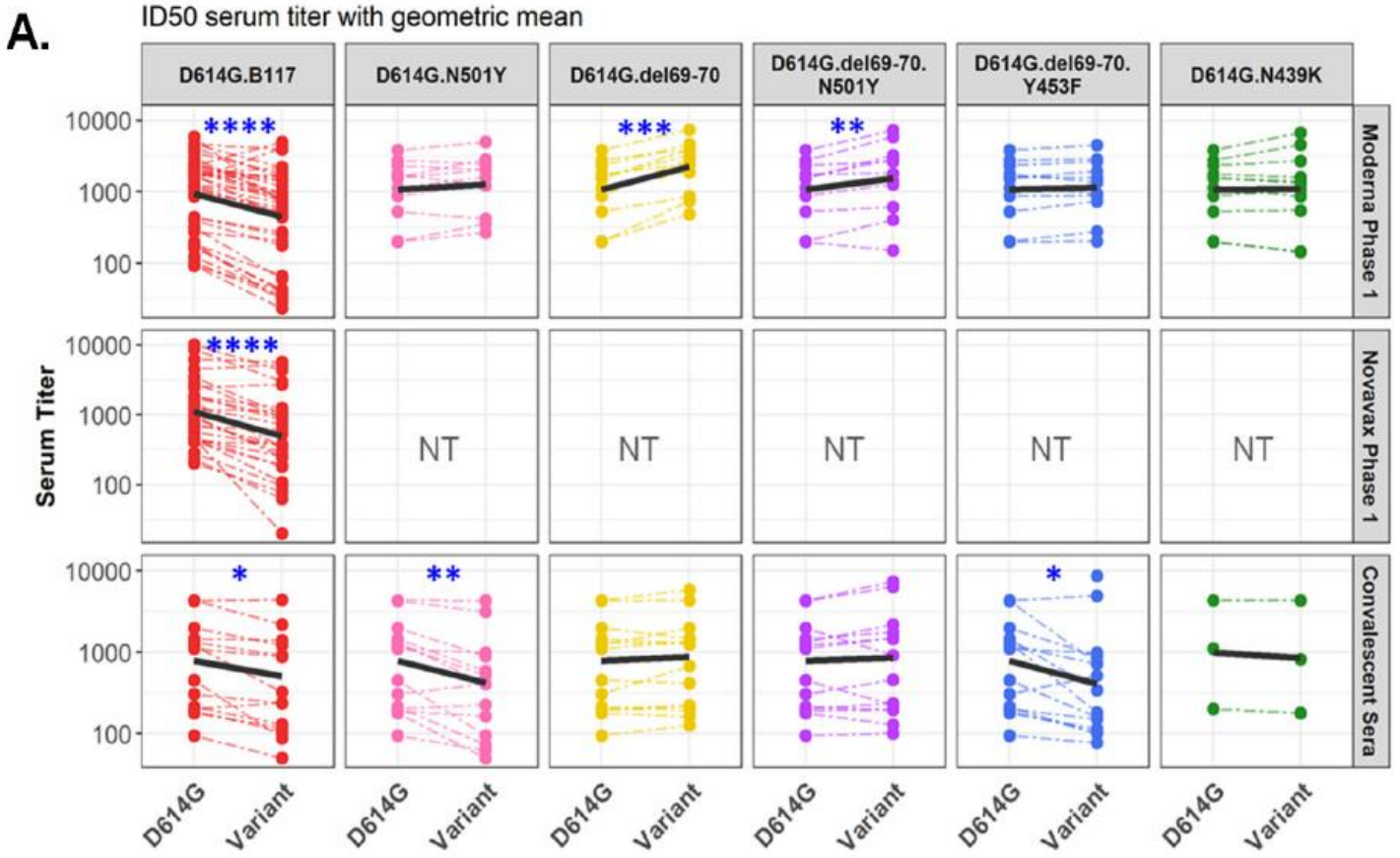
Full set of B.1.1.7 Spike mutations – little effect on convalescent sera; some effects on mAbs



Rees-Spear et al 2021

Convalescent sera, Moderna and Novavax vaccine Phase I sera

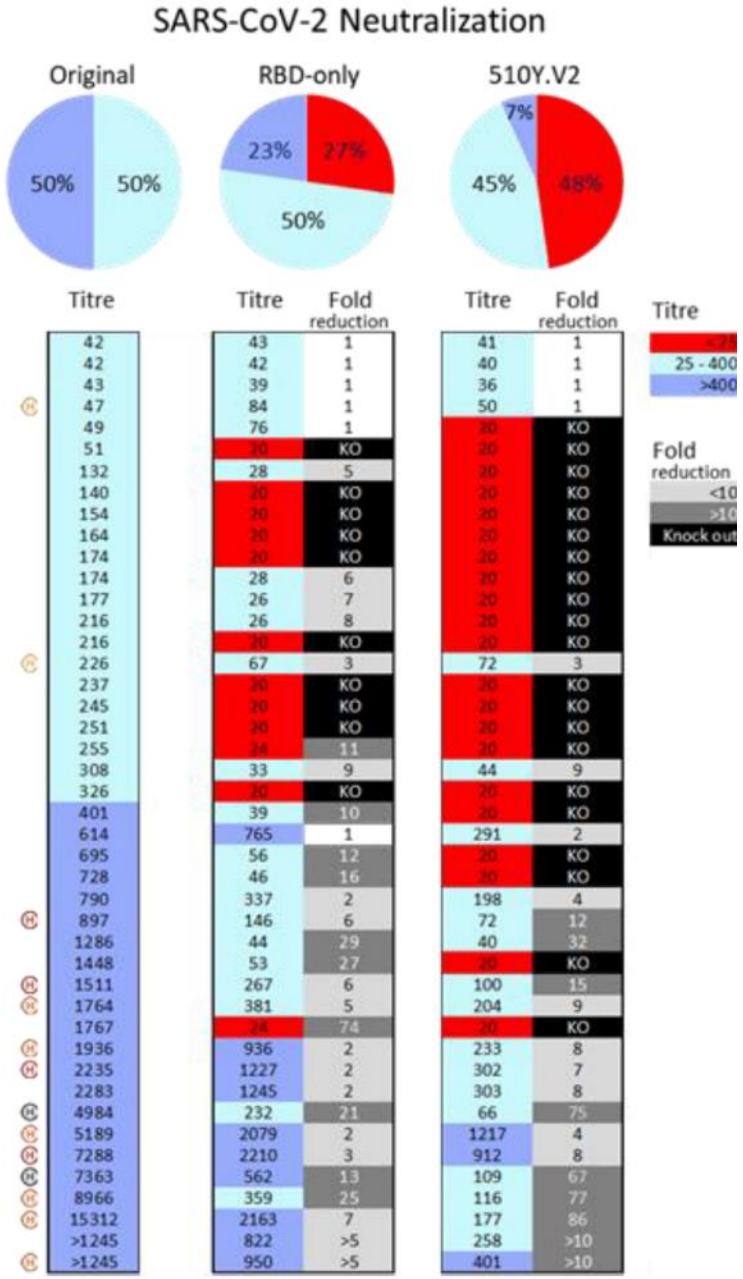
- Pseudovirus neutralization from Montefiori lab
- B.1.1.7 – all mutations or individual
- Convalescent, Moderna and Novavax sera
- Modest effect on neutralization, 2 fold reduction



Shen et al 2021

Convalescent sera poorly neutralize Variant B1.351 pseudovirus

- **Key mutation in RBD or all Spike mutations**
- **Significant decrease in neutralization by convalescent sera**
- **Neutralization escape for class 1 and class 2 mAbs**

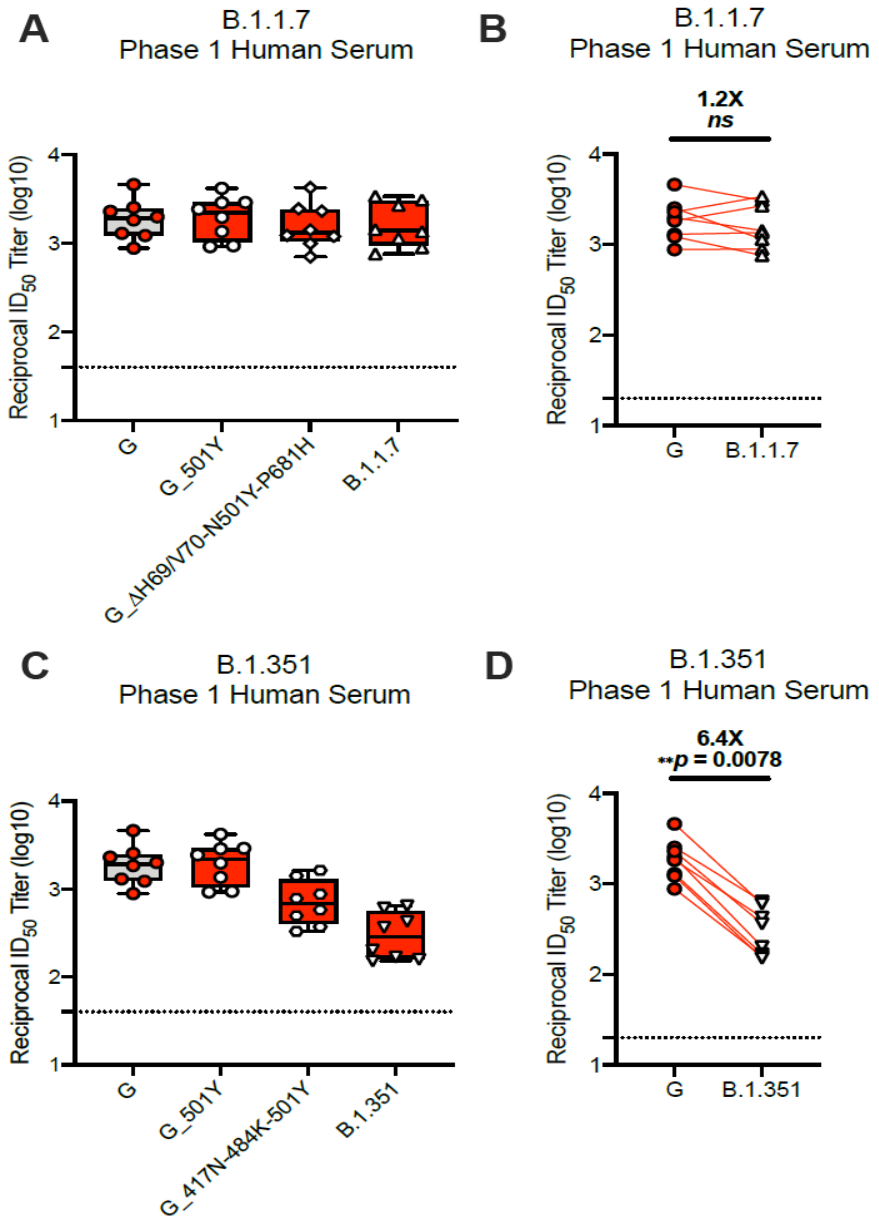


Wibmer et al 2021

Moderna vaccine Phase I sera

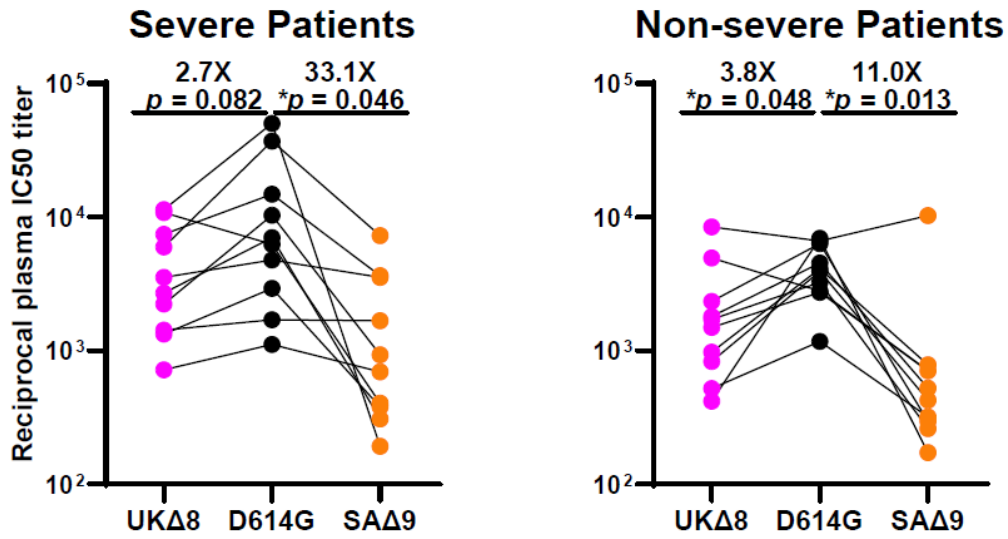
Neutralization with pseudoviruses: Wu et al 2021

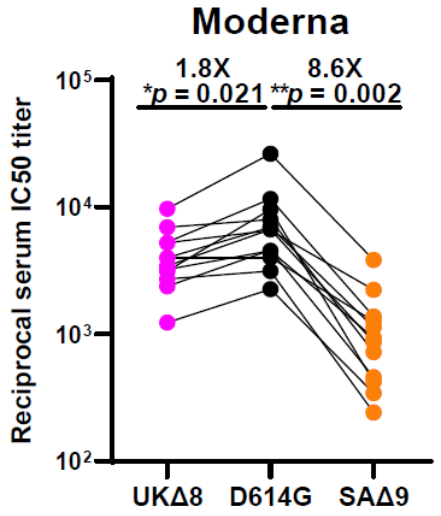
- **No significant reduction neut by B.1.1.7**
- **Reduction in neut by B.1.351 6 fold**

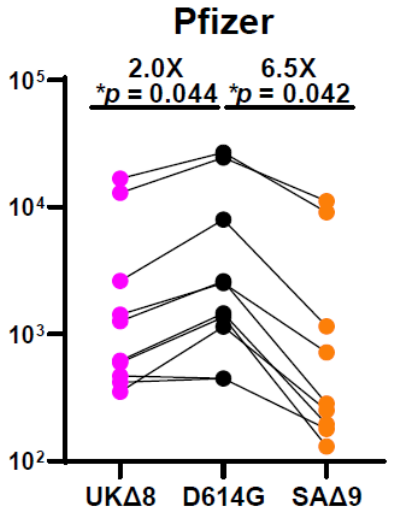


Wu et al 2021

Convalescent sera, Moderna and Pfizer vaccines







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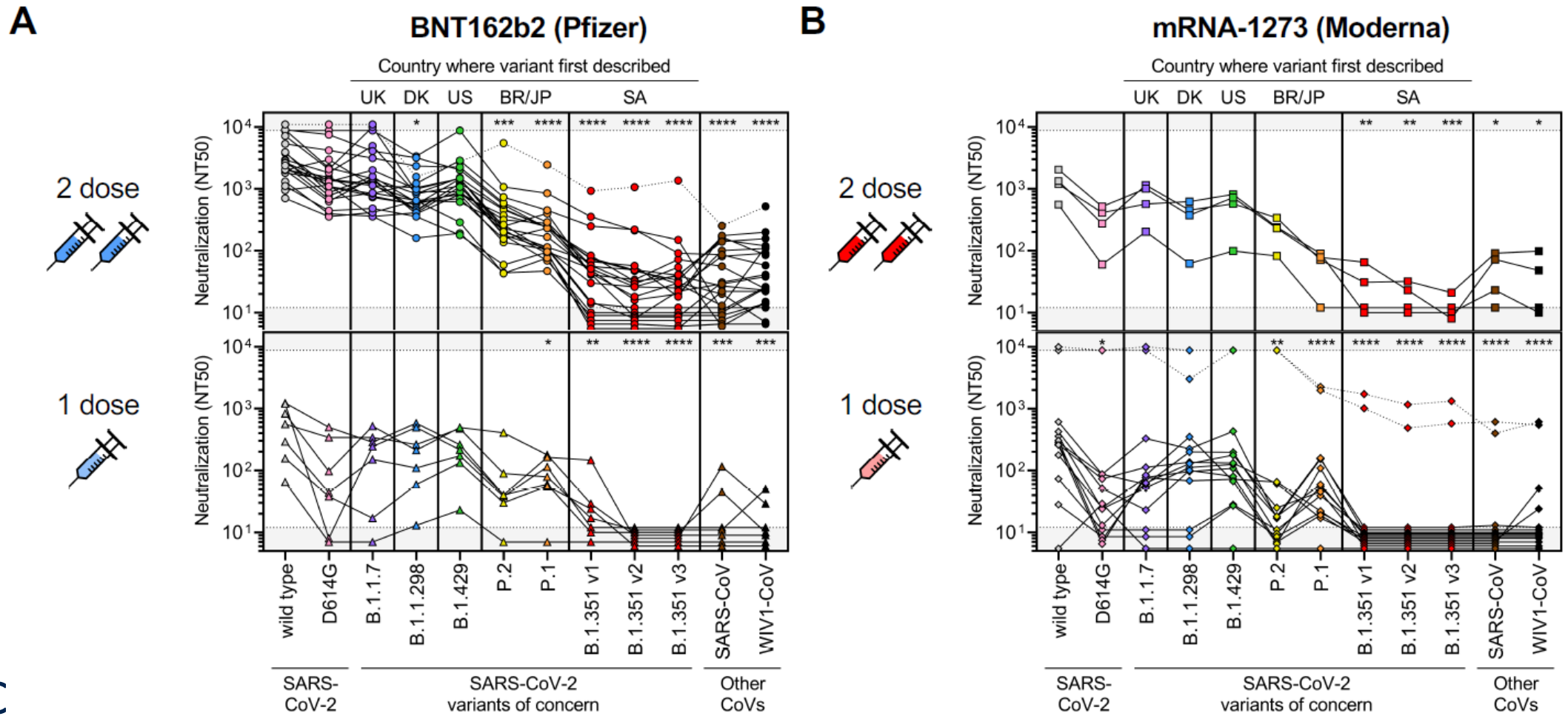
Wang et al 2021

Moderna and Pfizer vaccine sera tested against a panel of pseudoviruses



C

Garcia-Beltran et al 2021

Summary

- Studies from different labs involving new variants have used distinct viral isolates or pseudoviruses and diverse assay formats, which makes direct comparison of the data difficult; use of the WHO International standard could be useful in this regard
- In general , there is a slight reduction in neutralization of convalescent or vaccine sera observed with VOC B.1.1.7 and more significant reductions in neutralization observed with VOC B.1.351. This was seen in both live virus and pseudovirus assays.
- VOC P.1 and P.2 have recently been used in pseudovirus assays and neutralizing titers fell between B.1.1.7 and B.1.351
- Neutralization of variants after a single dose is low versus post-second dose
- Convalescent plasma from B.1.1.7 patients neutralizes B.1.351 more efficiently than pre-B.1.1.7 plasma

Heterologous Prime:Boost SARS-Co-2 vaccines

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Pre-clinical studies

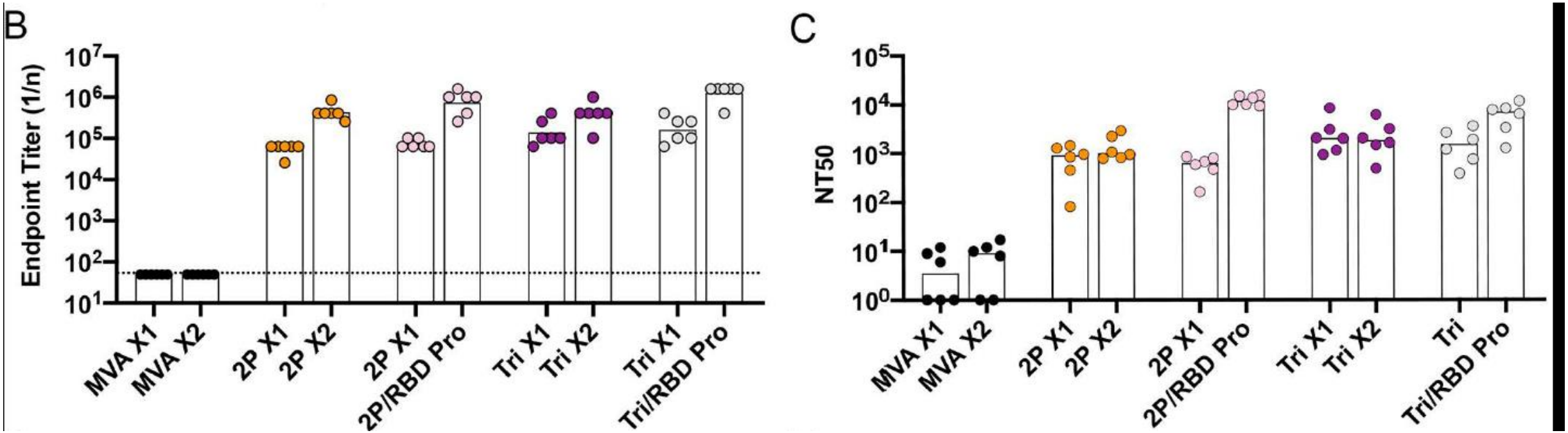
25 February 2021

- Heterologous prime: boost approaches:
  - Vaccinate with two different vectors or delivery system expressing the same antigen
  - Vaccinate with different antigens using the same delivery system (e.g boost with a new variant)

- Example of licensed ERVEBO Ebola vaccine – Ad26 prime, MVA boost

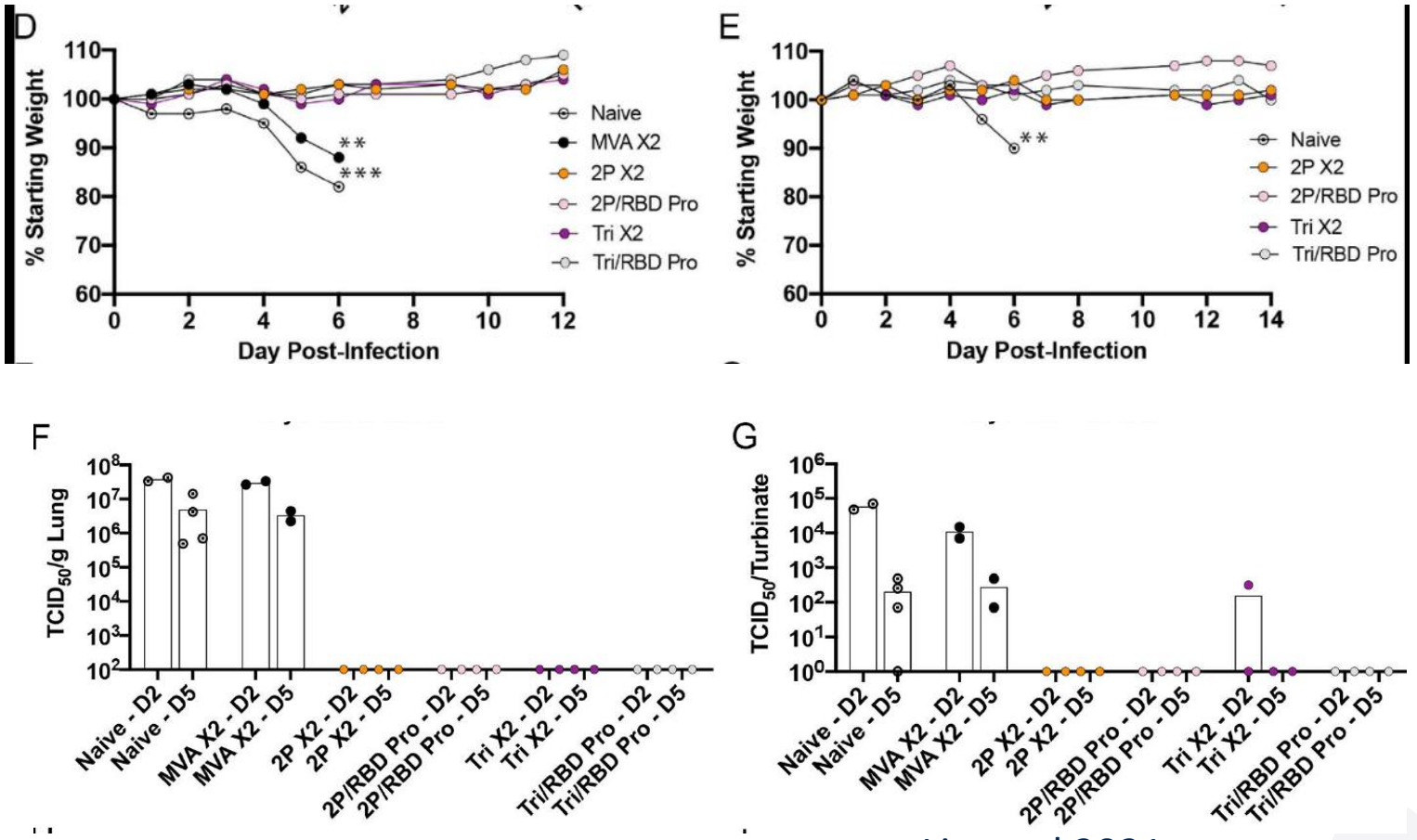
- For COVID-19, the Gam-COVID-Vac vaccine, consists of an Ad26 prime with an Ad5 boost, both expressing the full Spike protein. This vaccine is approved for Emergency use in several countries. Pre-clinical data on this vaccine, however, are not available.

MVA prime and RBD protein boost produce higher ELISA and neutralizing Ab titers than a homologous boost



Liu et al 2021

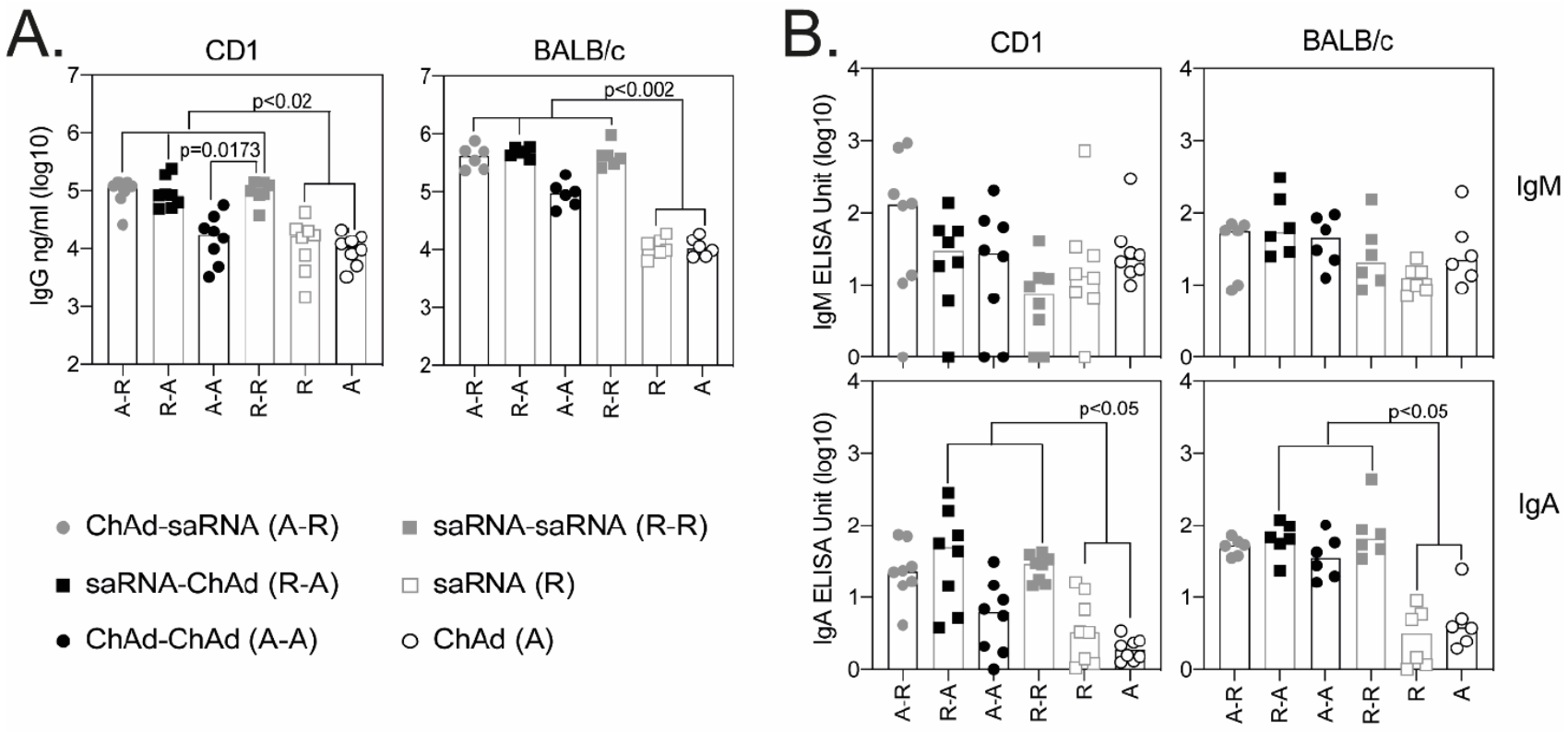
MVA prime with RBD boost protects K18:hACE2 mice from SARS-CoV-2 challenge



Liu et al 2021

saRNA and ChadOx1 prime:boost

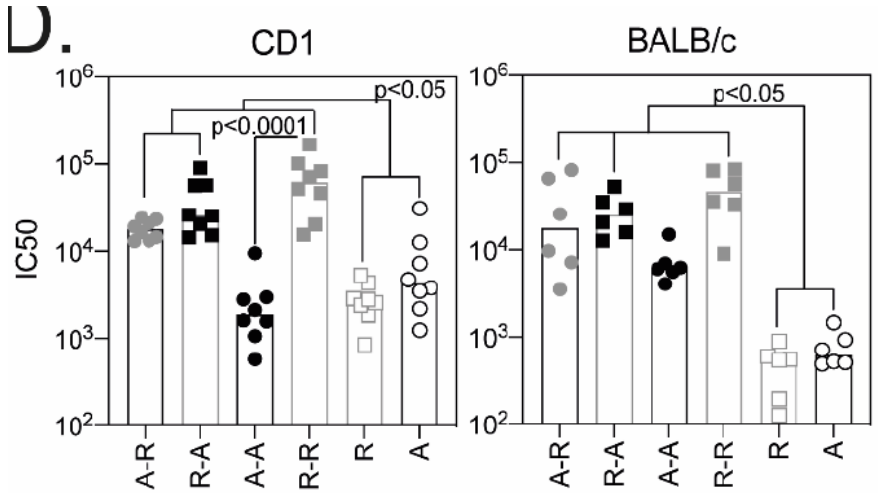
- Heterologous prime:boost produces higher IgG titers than prime alone or ChAd homologous boost

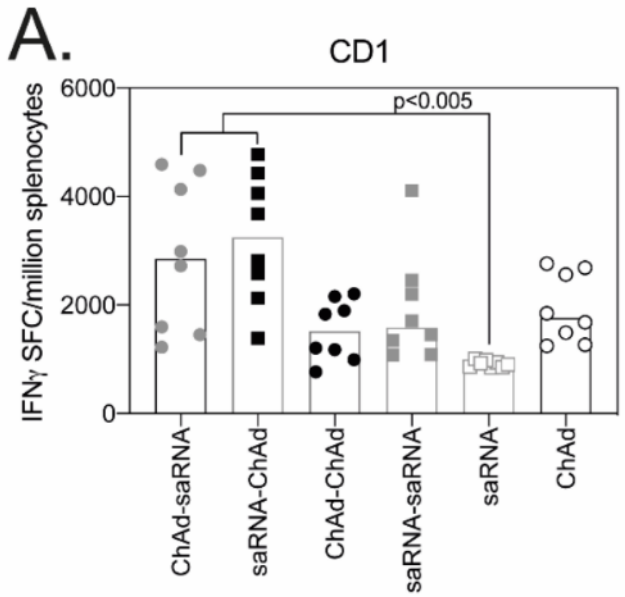


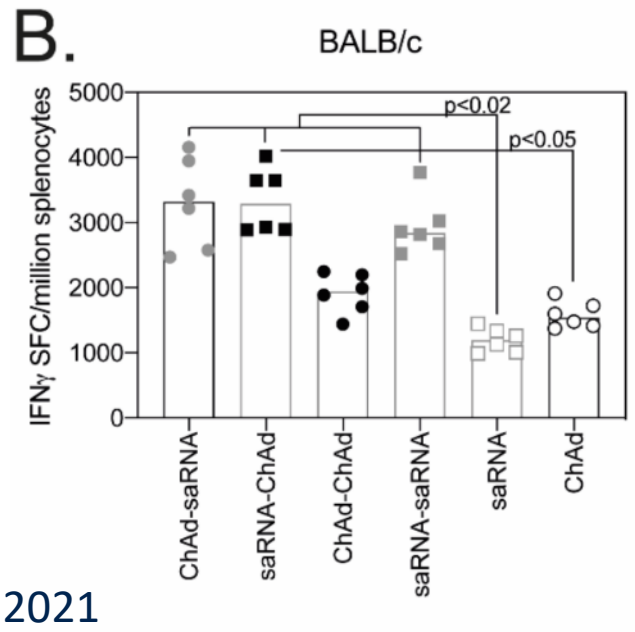
Spencer et al 2021

saRNA and ChadOx1

- Heterolgous prime:boost produces higher neutralizing titers than prime alone or ChAd homologous boost and higher T cell responses than prime alone, RNA prime:boost or rAd prime:boost



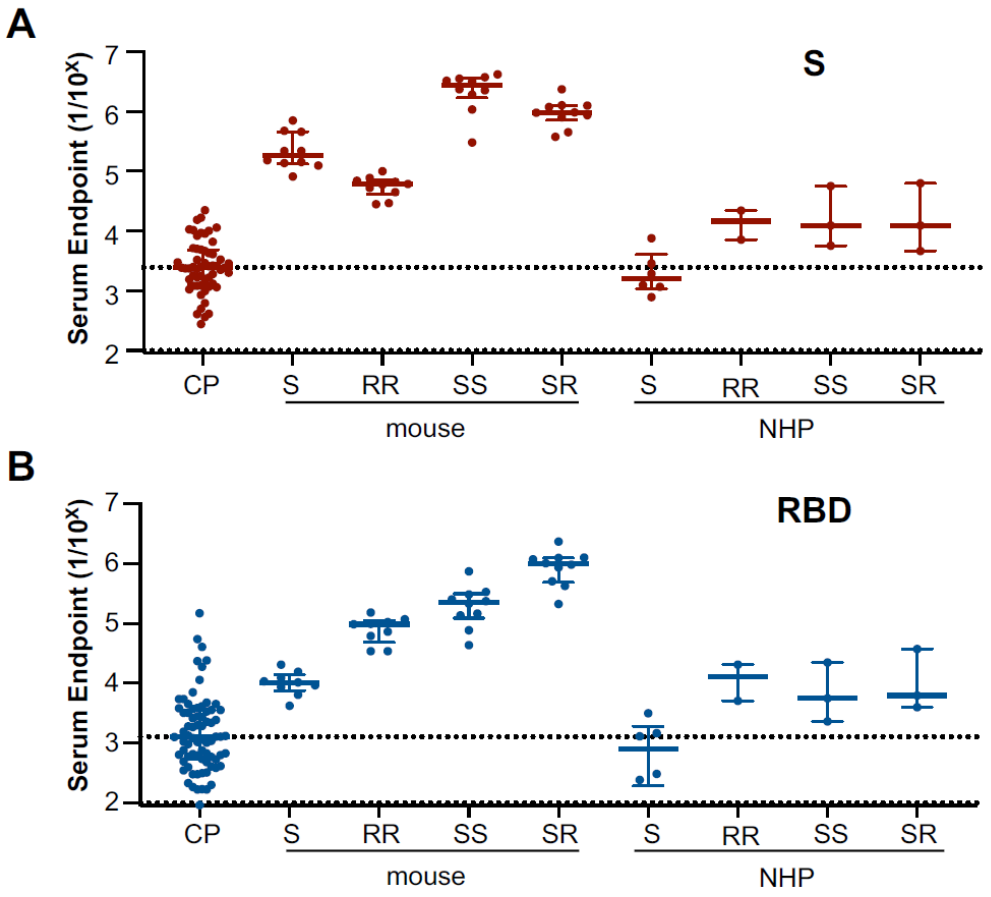


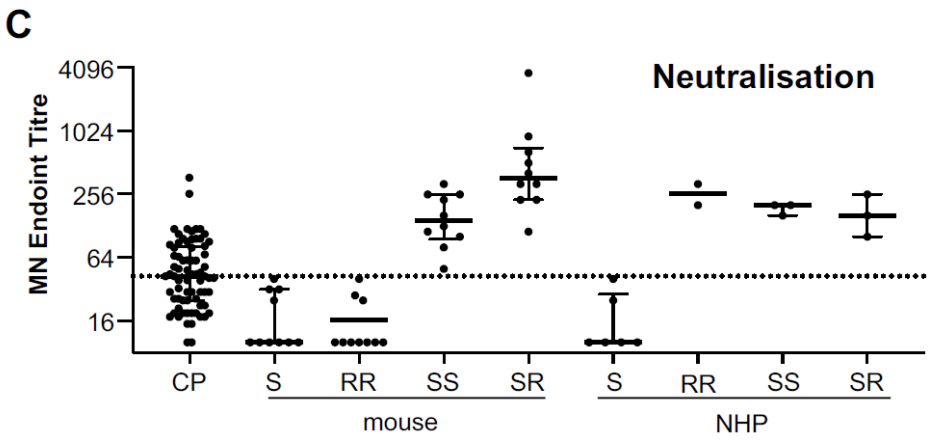


Spencer et al 2021

Spike and RBD proteins prime:boost

- In mice, Spike protein prime with RBD boost leads to high S titers, highest RBD titers and highest Neutralising titers, when compared to homolgous prime boosts (S-S or R-R)
- However, in NHPs, there is no advantage to the heterologous prime :boost.





Tan et al 2021

Summary

- Heterologous prime:boost is an approach that has been successful in other contexts, including the Gamalaya Gam-COVID-Vac vaccine.
- Heterologous prime:boost approaches for COVID-19 vaccines may lead to strengthening and broadening of immune responses
  - Binding and neutralizing Ab responses in mice were highest for MVA vectors with RBD protein boosts rather than MVA boosts
  - Heterologous prime boost with saRNA and ChadOx1 led to stronger T cell responses than homologous boosts with either ChAD or RNA and higher antibody responses than ChAd prime:boost.
  - Heterologous prime:boost of S and RBD proteins led to higher neutralizing Ab titers in mice; however, there was no advantage over homologous boost in NHPs

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‘Mix & Match’: Heterologous primary vaccination and heterologous boosting regimens

Jakob Cramer

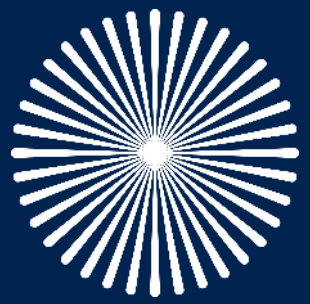
Head of Clinical Development

Coalition for Epidemic Preparedness Innovations (CEPI

‘Mix & Match’: Heterologous Primary Vaccination and Heterologous Boosting Regimens

Jakob Cramer, MD

February 25th, 2021



COVID-19 Vaccines Against New Strains: Options

1. Address new variants with **currently approved vaccines**

2. **Vaccine adaptation against new variants**
   a) Based on approved ‘prototype’ vaccines (against original strain)
   b) Licensure of new vaccines against new strains without approved ‘prototype’ / without availability of evidence supporting vaccine efficacy of the ‘prototype’

3. Monovalent versus **bi-/multivalent vaccines**

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COVID-19 Vaccines Against New Strains: Options

1. Address new variants with **currently approved vaccines → ‘Mix & Match’**

2. **Vaccine adaptation against new variants**
   a) Based on approved ‘prototype’ vaccines (against original strain)
   b) Licensure of new vaccines against new strains without approved ‘prototype’ / without availability of evidence supporting vaccine efficacy of the ‘prototype’

3. Monovalent versus **bi-/multivalent vaccines**

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I. Available COVID-19 Vaccines: "Mix & Match"

Concepts:

- **Heterologous primary vaccination*:** A – B
- **Heterologous boosting:** A – A

Aim:

- **Improve immune response***
  a) Breadth of IR
  b) Duration
- **Address practical / operational aspects** ('interchangeability' of vaccines)
- **Adjuvant- / antigen-saving** strategy?
- **Anti-vector immunity**?
- Improve **tolerability** (of the 2nd dose)?

→ **Several trials** covering **different regions / populations, vaccine combinations, circulating SARS-CoV-2 variants**

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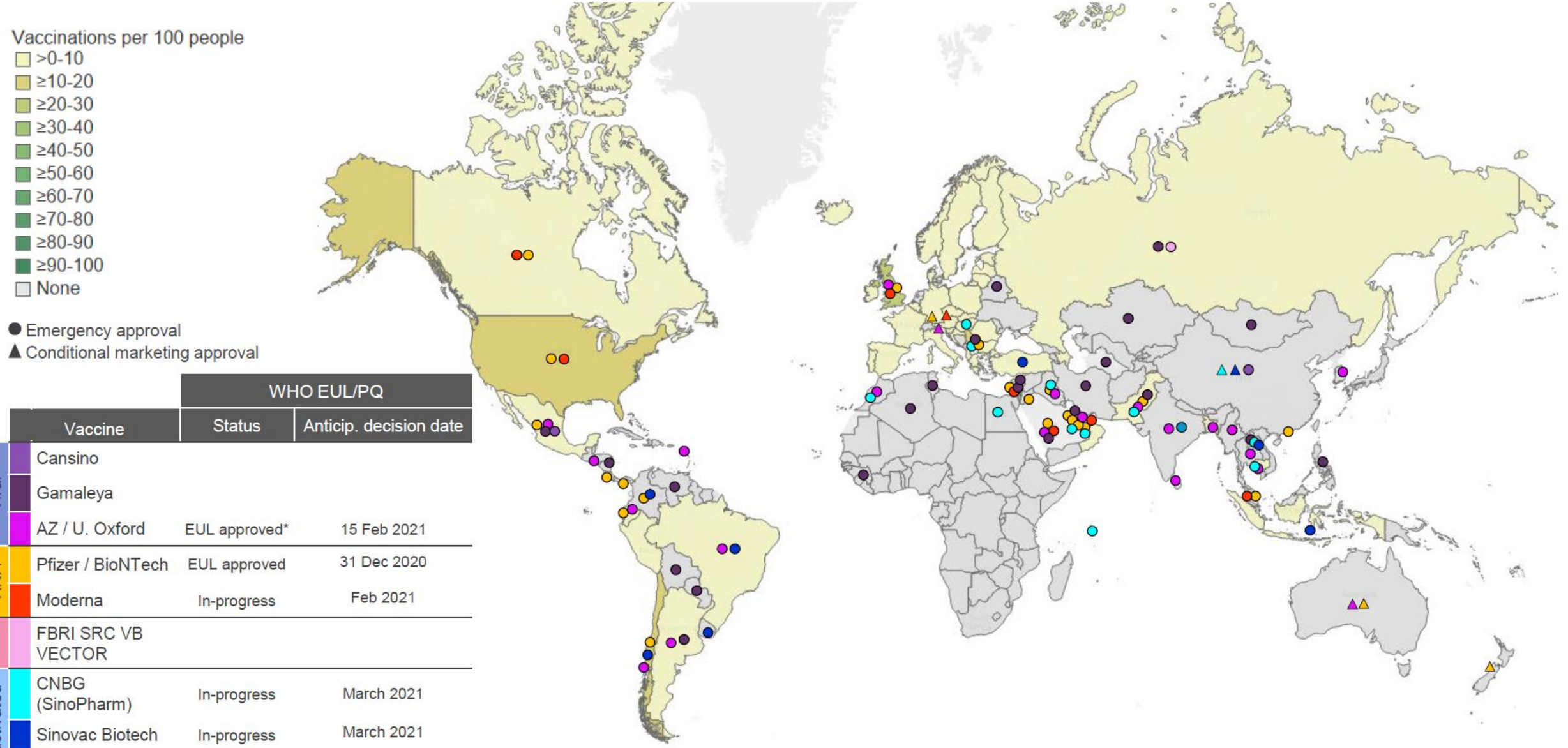
*) dosing interval important as well: priming evolves over months

Current COVID-19 Vaccine Approval Status



	Vaccine	WHO EUL/PQ Status	WHO EUL/PQ Anticip. decision date
Viral	Cansino		
Viral	Gamaleya		
Viral	AZ / U. Oxford	EUL approved*	15 Feb 2021
RNA	Pfizer / BioNTech	EUL approved	31 Dec 2020
RNA	Moderna	In-progress	Feb 2021
Protein	FBRI SRC VB VECTOR		
Inactivated	CNBG (SinoPharm)	In-progress	March 2021
Inactivated	Sinovac Biotech	In-progress	March 2021
Inactivated	Bharat Biotech		

*Data for COVAX expected in March 2021

Regulatory sources:
Regulatory Affairs Professionals Society, Covid 19 Tracker
WHO guidance document: Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process

Incomplete list – for discussion

Potential "M&M" Options – Heterologous Priming

Two different vaccines given as 1st and 2nd dose for primary vaccination (e.g. 4-12 weeks apart)

Platform	1st dose	2nd dose	Considerations
VV - mRNA	• AZ/Oxford [ChadOx-1]; • JnJ [Ad26]; • CanSino [Ad5]; • Gamaleya [Ad5, Ad26]	• Pfizer/BNT; • Moderna; • CureVac	• Enhance both CD4 and CD8 response, prolonged antigen presentation ?
VV – VV	• AZ/Oxford [ChadOx-1]	• JnJ [Ad26]; • CanSino [Ad5];	• Avoid anti-vector immunity ?
	• JnJ [Ad26]; • Gamaleya [Ad26]	• AZ/Oxford [ChadOx-1] • Gamaleya [Ad5]	• Avoid anti-vector immunity ?
VV – protein	• AZ/Oxford [ChadOx-1]; • JnJ [Ad26]; • CanSino [Ad5]; • Gamaleya [Ad5, Ad26]	• NVX (+ Matrix M); • Clover (+ Al/CpG)	• Tfh induction → more focused effect on B-cell differentiation and breadth of binding / neutralising antibody response ?
WIV – protein	• Sinovac; • Sinopharm	• NVX (+ Matrix M); • Clover (+ Al/CpG)	• Tfh induction
mRNA – Protein	• Pfizer/BNT; • Moderna; • CureVac	• NVX (+ Matrix M); • Clover (+ Al/CpG)	• Strong Tfh priming ?
Protein - VV	• NVX (+ Matrix M); • Clover (+ Al/CpG)	• AZ/Oxford [ChadOx-1]; • JnJ [Ad26]; • CanSino [Ad5]; • Gamaleya [Ad5, Ad26]	• Strong Tfh priming ?
mRNA - VV	• Pfizer/BNT; • Moderna; • CureVac	• AZ/Oxford [ChadOx-1]; • JnJ [Ad26]; • CanSino [Ad5]; • Gamaleya [Ad5, Ad26]	• Strong Tfh priming ?

VV = viral vector; WIV = whole inactivated virus; Tfh = T follicular helper cells

Incomplete list – for discussion

Potential "M&M" Options – Heterologous Boosting

Different vaccine given e.g. 6-12 months after homologous primary vaccination

Platform	Priming	Single booster dose
VV → mRNA	• AZ/Oxford [ChadOx-1]; • JnJ [Ad26] – single dose; • CanSino [Ad5] – single dose; • Gamaleya [Ad26, Ad5]	• Pfizer/BNT; • Moderna; • CureVac
VV → VV	• AZ/Oxford [ChadOx-1]	• JnJ [Ad26]; • CanSino [Ad5]; • Gamaleya [Ad26, Ad5]
	• JnJ [Ad26] – single dose	• AZ/Oxford [ChadOx-1]; • CanSino [Ad5]; • Gamaleya [Ad5]
	• CanSino [Ad5] – single dose	• AZ/Oxford [ChadOx-1]; • JnJ [Ad26]; • Gamaleya [Ad26]
VV → protein	• AZ/Oxford [ChadOx-1]; • JnJ [Ad26] – single dose; • CanSino [Ad5] – single dose; • Gamaleya [Ad5, Ad26]	• NVX (+ Matrix M); • Clover (+ Al/CpG)
WIV → protein	• Sinovac; • Sinopharm	• NVX (+ Matrix M); • Clover (+ Al/CpG)
mRNA → protein	• Pfizer/BNT; • Moderna; • CureVac	• NVX (+ Matrix M); • Clover (+ Al/CpG)
…	…	…

VV = viral vector; WIV = whole inactivated virus

Potential Strategies to Investigate 'M&M'

- Plan **prospective clinical trials**
  - Partnership between 2 different developers
  - Recruit subjects that have received a 1st dose / full primary immunization and provide heterologous 2nd dose (heterologous priming) or booster dose (heterologous boosting)
- **Speed**: Flexibility necessary to allow timely start of a series of trials and release of IA data
- **Core elements**:
  - Align on **overall trial design aspects / endpoints** to allow comparability: Uo Oxford COM-CoV (protocol available here: https://comcovstudy.org.uk/study-protocol)
  - Use of **WHO international reference standards** in serologic assays (www.nibsc.org)
  - Consider plans to integrate immunological testing (of a comprehensive subset of samples) which would utilize CEPI's available **Centralised Laboratory network** (email: centralizedlab@cepi.net)
  - **Site readiness initiative**: BMGF / CEPI preparing operational readiness of trial sites in LMICs (https://epi.tghn.org/covax-overview/clinical-science/clinical/#ref1)
  - **DSMB support** offered as part of the Safety Platform for Emergency vACcines (SPEAC) project (https://brightoncollaboration.us/speac/)

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COVID-19 Clinical Development Call for Proposals

- CfP CCT launched by CEPI on 28 January 2021
- **Aim:** Rapidly expand access to and confidence in COVID-19 vaccines by
  - i) generating clinical evidence in **special / sub-populations / age groups** or
  - ii) addressing **clinical development gaps**.
- Clinical trials which expand access and capacity **in LMICs are particularly encouraged**
- Call open through **28 May 2021**
- Applications will be reviewed on a **rolling basis** as received
- **US $140 million** funding available
- CEPI prepared to respond quickly

https://cepi.net/get_involved/cfps/

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Panel Discussion

Moderated By:

Jakob Cramer

Head of Clinical Development

Coalition for Epidemic Preparedness Innovations (CEPI)

Discussion Panel Members and Example Questions (1 of 2)

Panel Members

- **Helen Rees**, University of the Witwatersrand, South Africa
- **Farah Qamar,** The Aga Khan University, Pakistan
- **Matthew Snape**, Oxford Vaccine Group, United Kingdom
- **Arnaud Didierlaurent**, University of Geneva, Switzerland
- **Adam Hacker**, CEPI, United Kingdom
- **William Dowling**, CEPI, United States
- **Paul Kristiansen**, CEPI, Norway

Potential Discussion Questions

1. If 2 developers decide to partner to establish evidence on ‘M&M’, what data would likely be required for a **label claim**?
2. For most vaccines, it is unlikely that respective label claims will be sought. What would be a minimum data package that would allow NITAGs to allow a recommendation on **vaccine ‘interchangeability’**?
3. From a country perspective (rolling out vaccines), what are options and **challenges to implement respective ‘M&M’ trials** (using deployed vaccines, respecting existing recommendations in populations at risk)?
4. It has been observed that different vaccine (platforms) have been perceived differently in the population. Could this impact **acceptability of heterologous vaccination regimens** and what has to be taken into account?
5. Different vaccines (platforms) are associated with different **logistical challenges and contraindications**. How will this increased complexity have to be balanced against potential benefits?

Discussion Panel Members and Example Questions (2 of 2)

Panel Members

- **Helen Rees**, University of the Witwatersrand, South Africa
- **Farah Qamar,** The Aga Khan University, Pakistan
- **Matthew Snape**, Oxford Vaccine Group, United Kingdom
- **Arnaud Didierlaurent**, University of Geneva, Switzerland
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- **William Dowling**, CEPI, United States
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Potential Discussion Questions

6. Given the diversity of vaccine platforms being used, there is in theory numerous possible vaccine combinations. What are some key **immunologic considerations** that need to be taken into account re priming / boosting (strong priming effect, antigenic sin, Th1 bias re VMED, …)?

7. For heterologous primary vaccination, what additional aspects need to be considered for **selecting the appropriate 1st vaccine** (relevant vaccine efficacy post 1st (single) dose, improve reactogenicity of the 2nd dose, …)?

8. For heterologous boosting, **vaccines adapted to new SARS-CoV-2 strains** might be available in 6-9 months from now. For primed individuals, a single dose of an adapted vaccine may suffice. What are considerations re vaccines used for primary vaccinations as well as single booster?

Wrap Up & Next Steps

Jakob Cramer

Head of Clinical Development

Coalition for Epidemic Preparedness Innovations (CEPI)

Closing remarks

- Thank you all for your participation and engagement today
- Workshop report distributed shortly to summarize today's conversation
- We will continue to share resources at the website here: https://epi.tghn.org/covax-overview/clinical-science/
- The COVAX Clinical SWAT Team plans to continue sharing learnings across developers as we pursue our common goal – a global supply of safe and effective vaccines

Clinical Development & Operations SWAT Team