COVAX

Emerging Challenges to the Development of Covid-19 Vaccines

Clinical Development & Operations SWAT Team | Thursday January 28, 2021

CEPI

Gavi
The Vaccine Alliance

World Health Organization

Workshop Agenda

Time (CET)	Topic	Speaker(s)
15:00 – 15:10	Welcome & Meeting Objectives	Peter Dull
	PART 1: Path to approval of additional Covid-19 vaccines	
15:15 – 15:35	Status of EUA/Licensure and vaccine use globally and key updates from previous workshops, including correlates of protection	Peter Dull
15:35 – 15:45	The ethics of placebo-controlled COVID-19 efficacy studies when vaccines are available	Joseph Millum
15:45 – 16:05	Placebo-controlled efficacy studies: Possibilities and Challenges – Alternative trial designs based on clinical endpoints and non-inferiority assessment based on immunogenicity	Alan Fix & Dean Follmann
16:05 – 16:15	Phase 4 clinical studies: post authorization study designs to support accelerated or conditional approvals	Daniel Feikin
16:15 – 16:45	**PANEL DISCUSSION:** Practical paths to approval of vaccines still in development	Moderated by: Peter Dull
16:45 – 16:50	**Break**	

Workshop Agenda

continued

Time (CET)	Topic	Speaker(s)
PART 2: Clinical development gaps – optimizing vaccination schedules for currently available Covid-19 vaccines		
17:00 – 17:15	Post-infection and vaccine-induced immune responses against SARS-CoV-2: summary of impact of new variants	Shabir Madhi
17:15 – 17:30	Heterologous prime-boost & prolonged dosing interval: Immunologic considerations	Arnaud Didierlaurent
17:30 – 17:45	Comparing COVID-19 Vaccine Schedule Combinations (Com-COV)	Matthew Snape
17:45 – 18:15	**PANEL DISCUSSION:** Optimizing vaccine impact	Moderated by: Jakob Cramer
18:15 – 18:25	Expanding access to vaccine/filling-in clinical development gaps: CEPI new Call for Proposals (CFP) on clinical trials	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 MORE VACCINES AVAILABLE?

- Provide a forum to discuss developer needs and propose solutions to progress "Wave 2" vaccines toward EUA/licensure in the setting of the introduction and limited availability of new vaccines

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

- Review recently emerging data on SARS CoV-2 variants to better understand the potential relevance for existing vaccines
- Based on immunologic principles and previous vaccine experience, review research opportunities and data gaps to understand how to better use available vaccines

Part 1:

Path to approval of additional Covid-19 vaccines

Moderated By:

Peter Dull, MD

Deputy Director,

Integrated Clinical Vaccine Development,

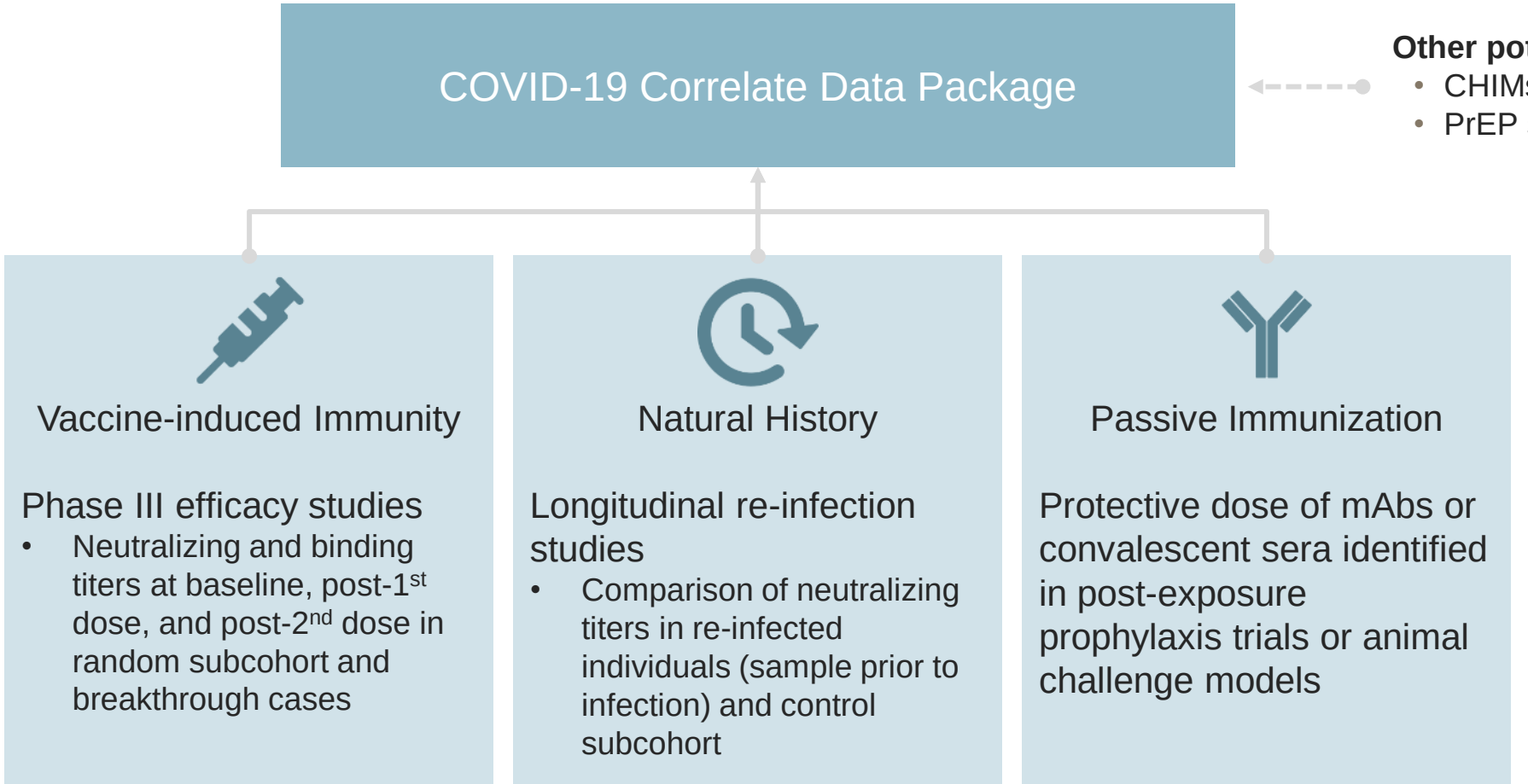
Bill & Melinda Gates Foundation (BMGF)

Status of EUA/Licensure and vaccine use globally and key updates from previous workshops, including correlates of protection

Peter Dull, MD

Deputy Director, Integrated Clinical Vaccine Development (BMGF)

Multiple sources of data will contribute to identification of a correlate – early evidence from these studies indicate a serological CoP exists



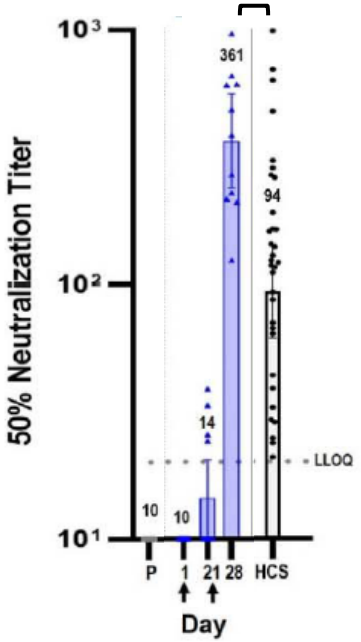
Early evidence in support of CoP:

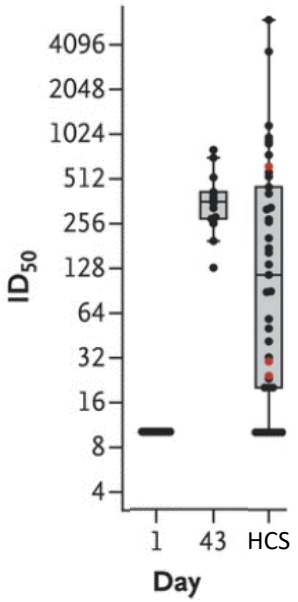
1. Ph I/II immunogenicity roughly correlates with Ph III efficacy
2. Case study: NAbs protect against infection in outbreak
3. Adoptive IgG transfer protects macaques from challenge

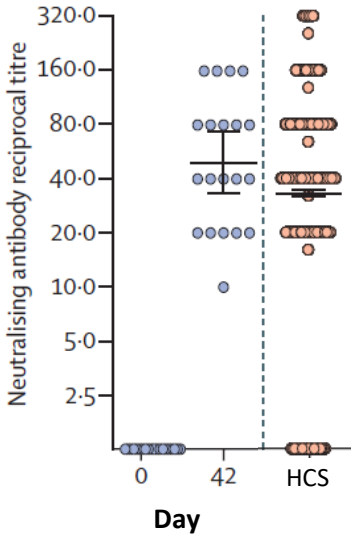
Neutralization titers from Phase I/II suggest correlation with efficacy, and a modest threshold of protection across platforms

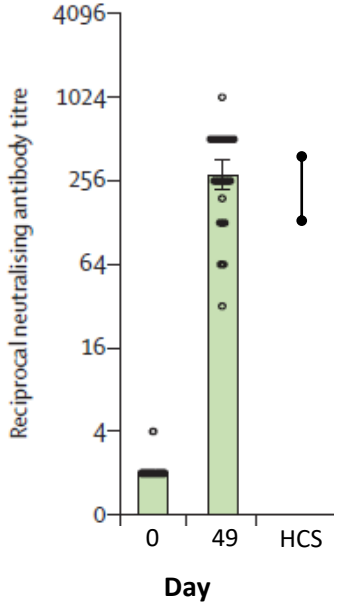
Note: Figures have been cropped / re-labeled as needed to enable comparison; Convalescent sera variably sourced from severe, moderate, mild disease and asymptomatic cases

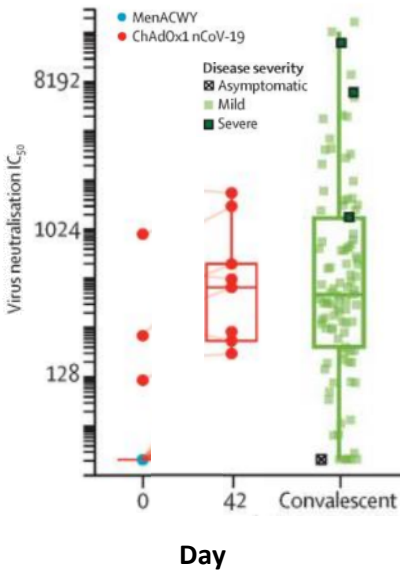
	BioNTech / Pfizer BNT162b2	**Moderna** mRNA-1273	**Gamaleya** Sputnik V	**Sinopharm** BBIP-CorV	**Oxford / AZ** ChAdOx1	**Sinovac** CoronaVac
Neuts relative to convalescents:	3.8-fold **higher**[1]	3.2-fold **higher**[2]	1.5-fold **higher**[3]	Comparable[4]	Comparable[5]	6-fold **lower**[6]
Efficacy:	**95%**[7]	**94.1%**[7]	**95%**[8]	**79.3%**[8]	**62.1% (up to 90%)**[8]	**50.4%**[7]

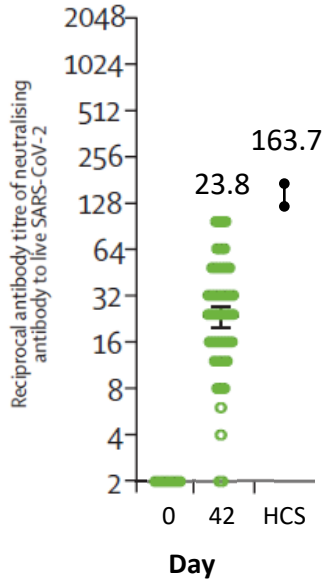












1. wt VNA titers (NT_{50}) in subjects aged 18-55, 7 days following 2nd 30µg dose; HCS: n=38, across full range of disease severity. 2. Lentivirus PsVNA titers (ID_{50}) in subjects aged 18-55, 14 days after 2nd 100µg dose; HCS: n=42, across full range of disease severity. 3. wt MNA titers in subjects aged 18-60, 21 days following rAd5-S boost; HCS: mild and moderate cases only. 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 VNA titers in subjects aged 18-59, 28 days following 2nd 3µg dose; HCS: n=117 symptomatic patients across full range of disease severity. 7. Primary analysis. 8. Interim analysis

Target: Compiled data package that a biomarker reasonably predicts protection against COVID-19, enabling EUA based on non-inferiority

Once additional understanding of SARS-CoV-2 immunology, and specifically ***vaccine immune responses that might be reasonably likely to predict protection against COVID-19***, is acquired, **accelerated approval of a COVID-19 vaccine…may be considered** if an applicant provides sufficient data and information to meet the applicable legal requirements.

Source: "Development and Licensure of Vaccines to Prevent COVID-19," FDA Guidance Document

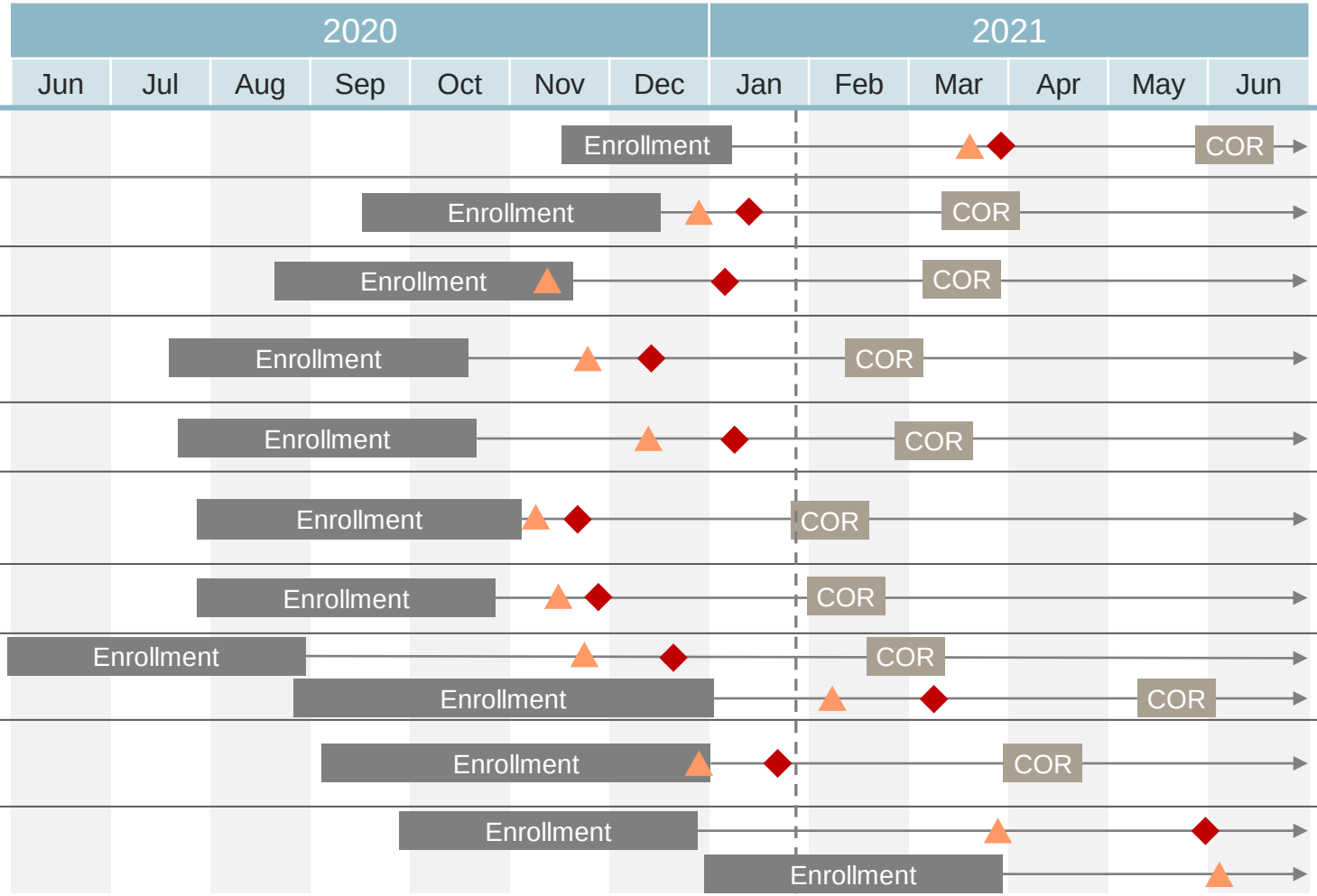
NB: "…companies are still required to conduct studies to confirm the anticipated clinical benefit"

To contribute data from a placebo-controlled efficacy trial to a CoP analysis, access a sample SAP at:
https://doi.org/10.6084/m9.figshare.13198595

Source: "Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry." FDA Guidance Document. Published 30 June 2020.

Pipeline of COVID19 vaccines is robust, with multiple products EUA'd[3] and contributing to correlates analyses

Key
- Interim analysis
- Primary analysis
- COR — Potential correlates analysis



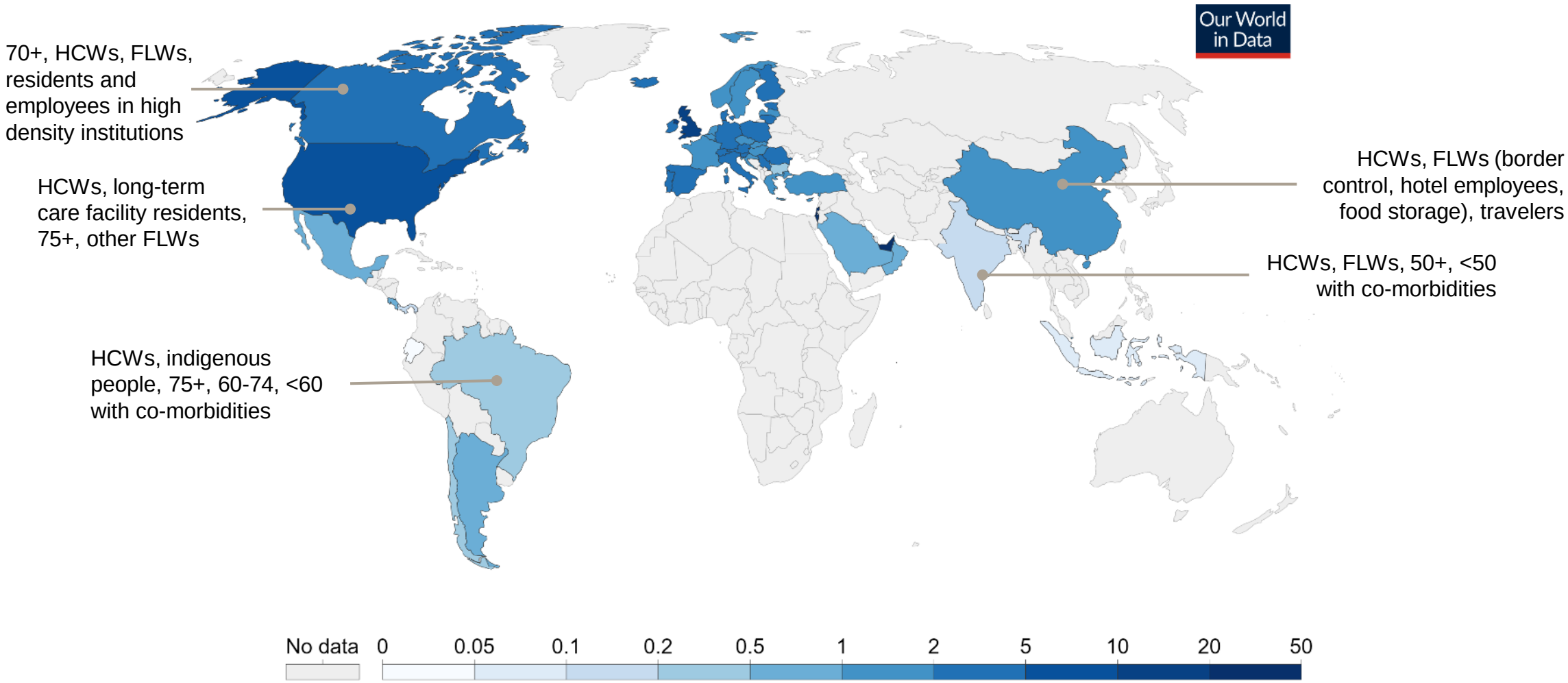
Developer	Ph III Sites[1]	EUA[3] / Licensed?
Bharat Biotech	IND	IND
CanSino	ARG, MEX, CHL, PAK, RUS	CHI
Gamaleya	RUS, BLR, UAE, VEN, IND	RUS, BLR, ARG, UAE, VEN, PAR[4]
Sinopharm	ARG, BHR, EGY, JOR, MOR, PER, UAE	CHI, UAE, BHR, EGY, JOR
Sinovac	**BRA**, CHI, CHL, IDN, TUR	CHI, IDN, TUR, BRA
Pfizer / BioNTech	**USA**, ARG, BRA, GER, RSA, TUR	UK, USA, EU, CAN, MEX, ARG[4]
Moderna	USA	USA, CAN, EU, ISR, UK, SWI
Oxford / AZ[2]	**BRA**, **UK**, PER, RSA **USA**	UK, ARG, IND, MEX, BRA, PAK[4]
Janssen	USA, ARG, BRA, CHL, COL, MEX, PER, RSA	
Novavax	**UK**, RSA (IIb) USA, MEX	

Assumptions:
- 6-month attack rate:
  - US, UK: 2%
  - Others: 5%
- VE: 50%
- Interim analysis: 75 cases
- Primary analysis: 150 cases
- Recruitment / vaccination: 3 mo
- Follow up for VE endpoint: 2 mo
- Data mgt & analysis before IA and PA: 1 mo.
- Preparation of correlates report: 2 mo.

1. Where multiple Phase III studies conducted, timeline represents site with predicted earliest readout (bolded), based on public sources (primarily clinicaltrials.gov) and modeled assumptions; 2. Top timeline for Oxford / AZ reflects pooled analysis of Brazil and UK sites, per Phase III interim analysis; 3. EUA (Emergency Use Authorization from FDA) used synonymously for national conditional / emergency use approval; 4. List not exhaustive.

Introductions have started, and countries are strategically rolling out approved products to high-risk populations

Cumulative COVID-19 vaccination doses administered per 100 people as of January 26, 2021



Sources: Official data collated by Our World in Data – last updated 26 January, 19:00 (London time); ACIP (USA); National Expert Group on Vaccine Administration for COVID-19 (India); NACI (Canada); NYTimes (China); Reuters (Brazil); .HCWs = Healthcare workers; FLWs = Frontline workers

As vaccine rollout advances, COVAX-supported clinical sites and dashboard provide resources for future Phase III site selection

COVAX-supported network includes 38 sites across countries with a wide range of incidence

Sites:

- Site ready, trial ongoing / planned
- Site ready, no trials planned yet
- Site readiness process underway

Incidence:

Cases / 100k people, 7-day average

- Less than 1
- 1-10
- 10-20
- 20-30
- 30-40
- 40+

Visit the COVAX EPI-Hub for:

- Dashboard of COVAX-supported sites with up-to-date site information
- Operational Preparedness Database with COVID-19 specific information on Regulatory and Ethics requirements by country
- Materials from previous workshops
- …and more!

Sources: COVAX EPI-Hub (epi.tghn.org/covax-overview/clinical); Google Maps

The Ethics of Placebo-Controlled COVID-19 Efficacy Studies When Vaccines Are Available

Joseph Millum, PhD

Bioethicist, Clinical Center
Department of Bioethics &
Fogarty International Center
NIH

The ethics of placebo-controlled COVID-19 efficacy studies when vaccines are available

Joseph Millum, Ph.D., M.Sc.

Clinical Center Department of Bioethics & Fogarty International Center

28 January 2021

The views expressed are my own and do not represent the views of the NIH, DHHS, or any other US government agency

The ethics of vaccine studies

- Many ethical considerations relevant to vaccine studies, including
  - Consent
  - Fair subject selection
  - Responsiveness to local health needs

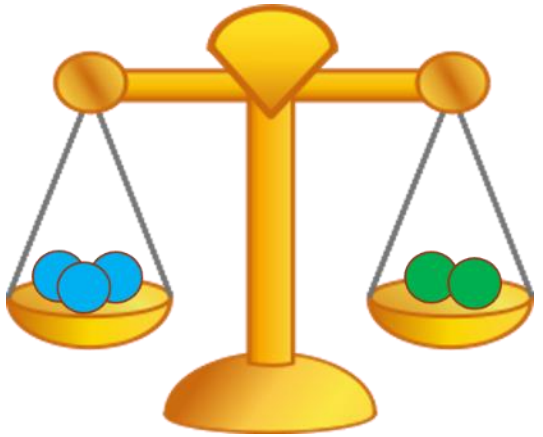
- My focus: risk assessment for placebo-controlled trials

Clinical research: A fundamental tension

- Clinical research places risks and burdens on participants in order to generate knowledge that will benefit others

Risk/benefit analysis

1. Minimize risks consistent with the goals of the research
2. Net risks should not be excessive
3. Risks to participants should be balanced by the benefits to participants and the social value of the knowledge gained

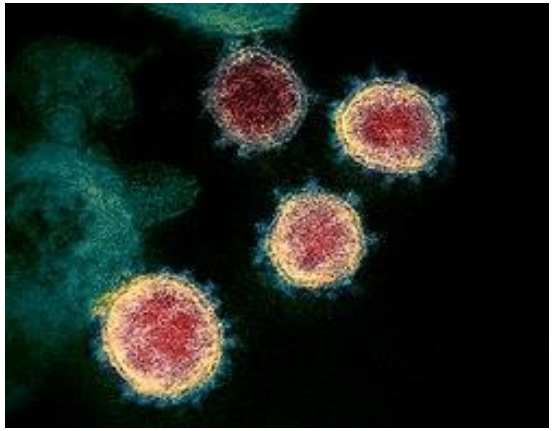


Risks in placebo-controlled trials of experimental vaccines

- Potential harms from experimental agent
- Potential harms from research tests and ancillary research activities
- Potential harms from foregoing an effective vaccine

Foregoing an effective vaccine

- Apparently safe and effective vaccines are authorized for use in multiple countries
- Typically, scarce supplies targeted to priority populations (e.g. health care workers, elderly)
- Clear benefit to trial participants from receiving effective vaccine

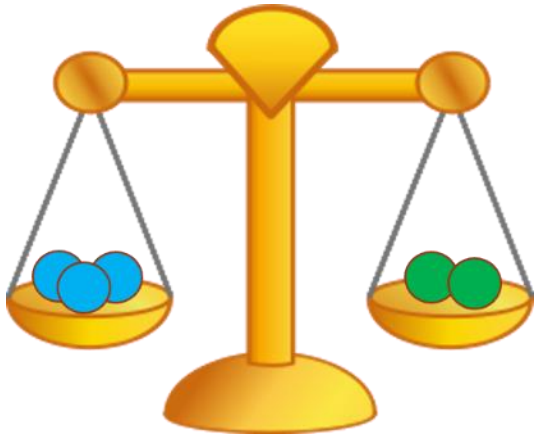


Does withholding effective vaccine impose a risk on participants?

- If participants would be eligible for the vaccine, withholding vaccine is a research risk
- If participants would not be eligible, and the vaccine allocation plan is justifiable, not providing vaccine is not a research risk
- In other cases, it's an open question—err on side of caution

Risk/benefit analysis of placebo control

1. Minimize risks consistent with the goals of the research
2. Net risks should not be excessive
3. Risks to participants should be balanced by the benefits to participants and the social value of the knowledge gained



Risks and participant population choice

- Populations vary in their risk profiles and access to effective vaccines
- Minimize risks by selecting participants from populations at lowest risk *from research* consistent with *answering the socially valuable question*

Risks and alternative trial designs

- Alternative trial designs may pose lower risks to participants
- In general, where an effective intervention exists, use of placebo should be scientifically necessary to answer socially valuable question
- *Additional* risk should be justified by *additional* social value

Summary

- Placebo-controlled trials are sometimes ethical when an effective vaccine exists
- Providing placebo instead of effective vaccine as control requires justification
- Any risk imposed by withholding an effective vaccine must be:
  - Minimized
  - Not excessive
  - Justified by the social value of using placebo rather than an alternative

Placebo-controlled efficacy studies: Possibilities and Challenges – Alternative trial designs based on clinical endpoints and non-inferiority assessment based on immunogenicity

Alan Fix, MD
Deputy Director, Vaccine Clinical Team, Center for Vaccine Innovation and Access
PATH

Dean Follmann, PhD
Assistant Director of Biostatistics
NIAID at NIH

Path to approval of additional Covid-19 vaccines

Study Design Considerations for Advanced Development

Placebo-controlled efficacy studies: Possibilities & Challenges

Alternative trial designs based on clinical endpoints

Non-inferiority assessment based on immunogenicity

Alan Fix

Dean Follmann

COVAX Workshop, 28 January 2021

Study design options

A. Clinical endpoints

1. Placebo-controlled studies
    a. Inclusion of critical target groups
    b. Limited to those at lower risk of exposure and lower risk of morbidity
2. Active comparator studies
    a. Clinical superiority compared to partially effective vaccine
    b. Clinical non-inferiority compared to vaccine with “established” VE estimate

B. Immuno-bridging for EUA (+/-confirmatory efficacy or effectiveness study)

Placebo-controlled studies

- Inclusion of critical target groups (higher-risk of exposure and/or severe disease)
  - Pros
    - Clearest assessment of vaccine clinical impact/value
    - Provides important data for high-risk groups for both regulatory and policy considerations
    - Faster accumulation of requisite number of endpoints
    - More data for severe disease
  - Cons
    - Depending on when/where/what:
      - *Increasingly infeasible to enroll/retain higher-risk groups with rollout of other vaccines*
      - Potential ethical objections depending on context

- Inclusion limited to those not prioritized for vaccination (lower risk of exposure and lower risk of severe disease)
  - Pros
    - Greater feasibility for enrollment/retention
    - Greater acceptability
  - Cons
    - Larger/longer study due to lower attack rate
    - More limited data for prevention of severe disease (and none in critical target groups for severe disease)
    - No data for older populations

Licensure of New Vaccines Going Forward

Dean Follmann

National Institutes of Health

January 2021

- Multiple vaccines have demonstrated high efficacy with more expected.
- Placebo controlled vaccine trials may be difficult
- Vaccines will be increasingly rolled out
- SARS-CoV-2 infection rate will change in some way
  - Greatly reduced?
  - New steady state like seasonal coronaviruses/flu/dengue?
  - New variants?
- How to license additional vaccines?

Three Potential Paths

- Superiority vs a partially effective vaccine with disease endpoint
  - New vaccine anticipated to have high efficacy
  - Run trial in locations where partially effective vaccines the only option
- Non-inferiority trials with disease endpoint
  - Compare new vaccine to a licensed vaccine
  - Show new vaccine is not appreciably worse than licensed vaccine
- Immuno-bridging
  - Establish that an immune response (antibody) is reasonably likely to predict efficacy on a disease endpoint
  - Conduct an immunogenicity study to demonstrate sufficiently high immune response
  - Possibly link immuno-bridge to confirmatory efficacy or effectiveness study?

Path 1: Superiority vs Partially effective vaccine

- New vaccine anticipated to have very high efficacy
- Test in regions where partially effective vaccines are the only option

VE for Available Vaccine	VE for New Vaccine	# cases of disease	Sample size factor*
70%	90%	42	0.90
80%	90%	92	2.40

- Relative to 30,000 person placebo-controlled trial designed to achieve 150 events
  e.g. A factor of 2.4 results in a trial that requires that 72,000

Path 2: Non-inferiority Trials with Disease Endpoint

- Suppose licensed vaccine A has known 90% efficacy with median of 3 months follow-up conducted during winter 2020-21
- Want to show that new vaccine N is not much worse than vaccine A
- e.g. allow a doubling in cases with A compared to N

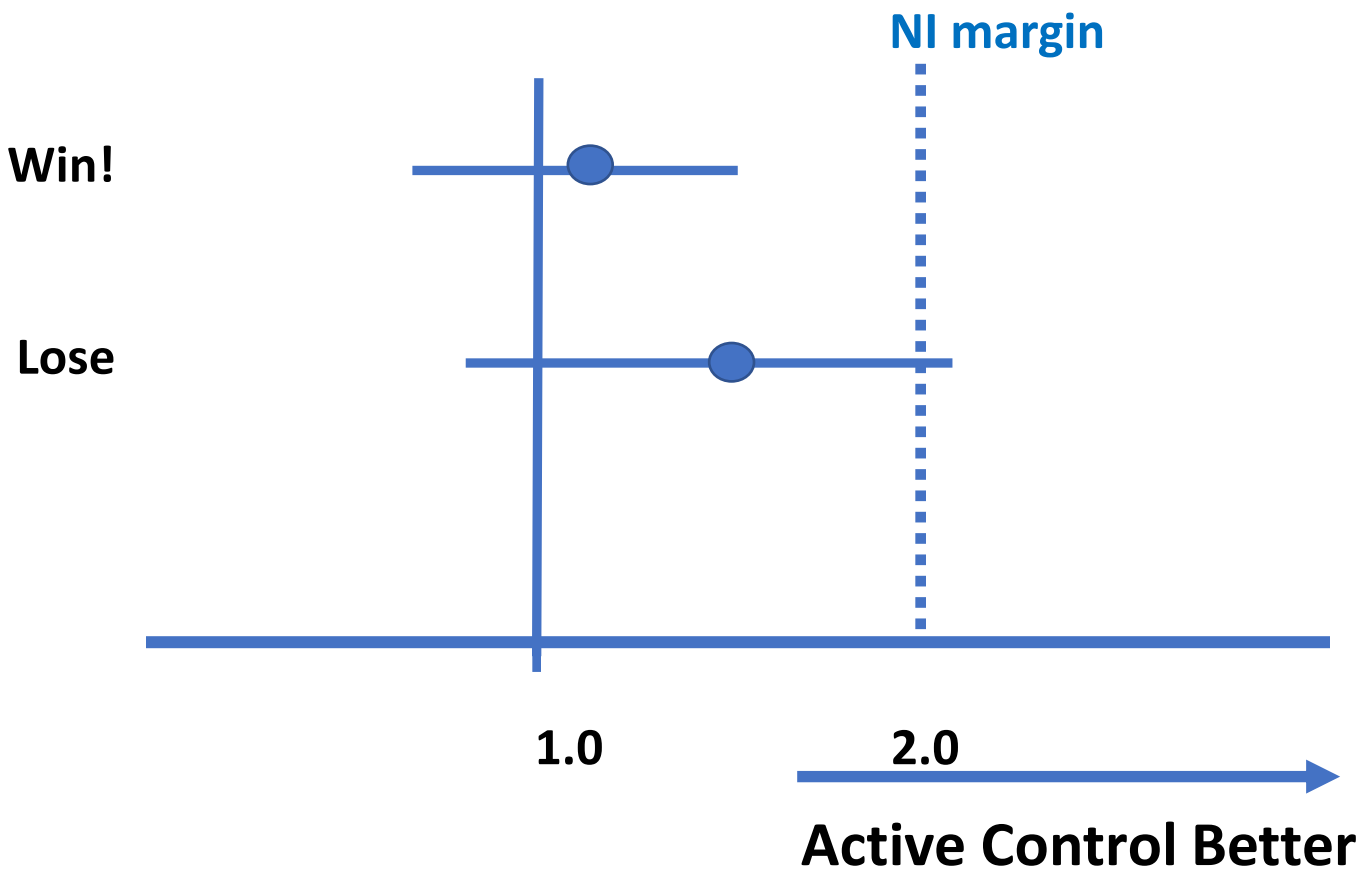
$$\frac{rate(New\ Vaccine\ \ N)}{rate(Licensed\ \ Vaccine\ A)} < 2.00\ = Margin$$

- Thus VE_N is at least = 1- {1-VE_A} 2.00 = 0.80; 80% efficacy is still very good!

Win or Lose with a non-inferiority trial

Ratio of Attack Rates (95% CI):
Vaccine N (new) vs. Vaccine A (Active Control)

Potential Outcomes



Adapted from Mauri and D'Agostino (NEJM, 2017)

Non-Inferiority (NI) trials with disease endpoint

Ratio Margin	Conservative VE Active Control (A)	'Allowable' VE New Vaccine (N)	# cases of disease	Sample size factor
2.00	90%	80%	94	3.42
2.00	80%	60%	94	1.87
4.00	90%	60%	26	0.95
4.00	80%	20%	*Oh No*	*Oh No*

- Constancy: 3-month VE of 90% for Vaccine A applies in summer/fall '21
  - VE for Vaccine 'A' might wane over 3-6 months
  - VE for Vaccine 'A' might be less against summer strains of SARS-CoV-2
  - Volunteers in NI trial might get less benefit from vaccine 'A'
- Need to be conservative in assumed VE for 'A' & Margin selection

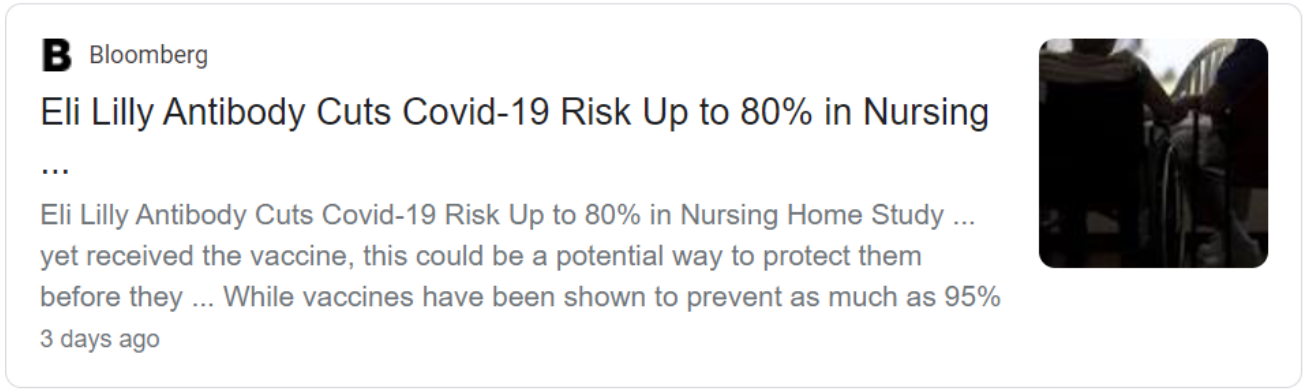
Path 3: Immuno-bridging of vaccine efficacy

- Argue that vaccine induced antibody from new vaccine is *reasonably likely to predict high Vaccine Efficacy*
- How?
  - Have mechanism of action similar to licensed vaccine
  - Possibly demonstrate protection and Ab/protection relationship in animal models
  - Cite other studies that demonstrate antibody's importance
  - Immunogenicity studies demonstrate antibody levels similar or greater than licensed vaccine with high efficacy

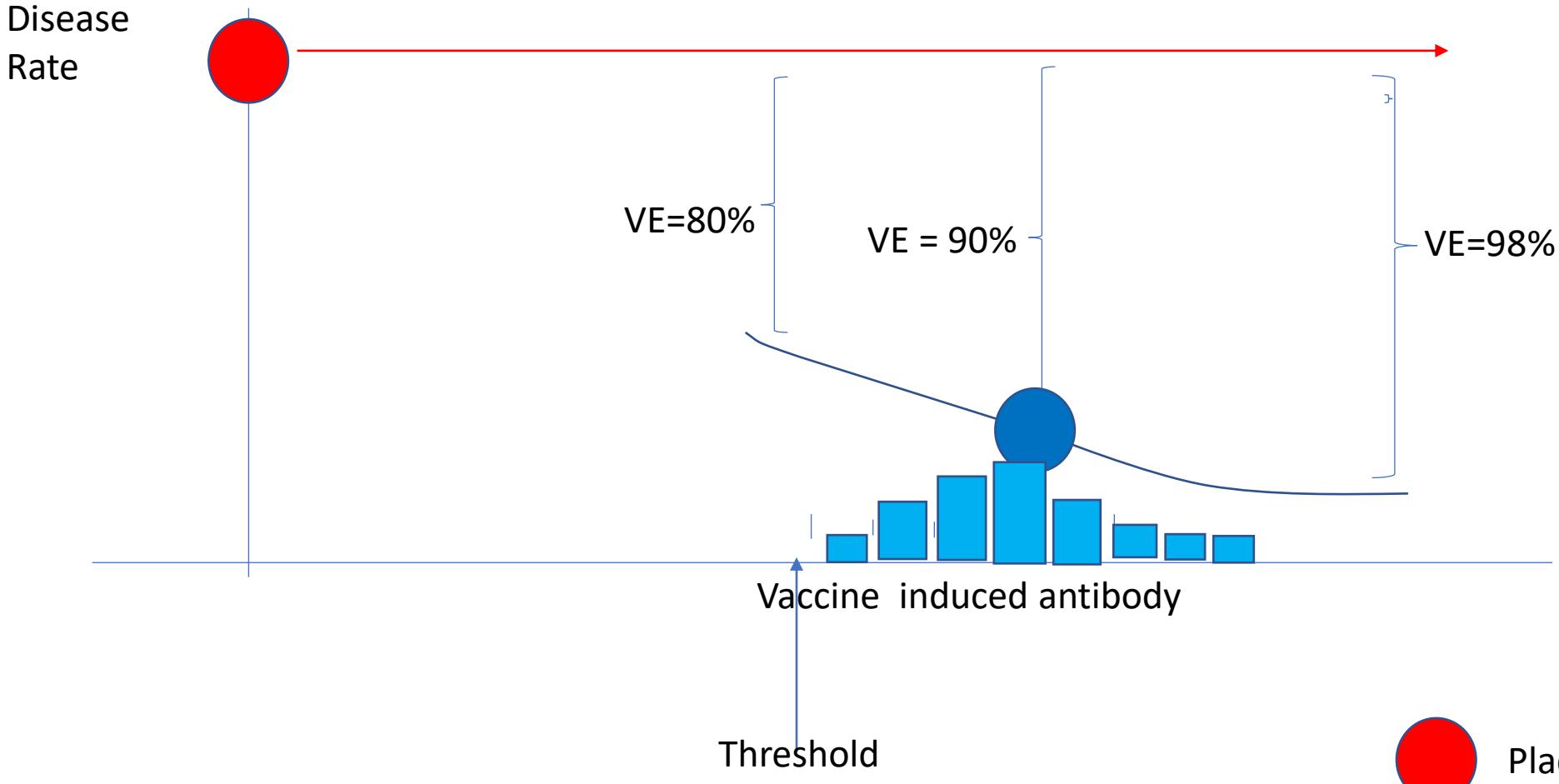
Antibody *reasonably likely to predict VE*

- Operation Warp Speed Key Tenets
  - SAMPLES FROM MULTIPLE TRIALS ARE INTENDED TO BE USED IN CORRELATES OR SURROGATES OF PROTECTION STUDIES AND DATA WILL BE SHARED WITH PARTIES AND PUBLISHED
  - Hope that analyses demonstrate antibody is a Correlate of Risk/Protection

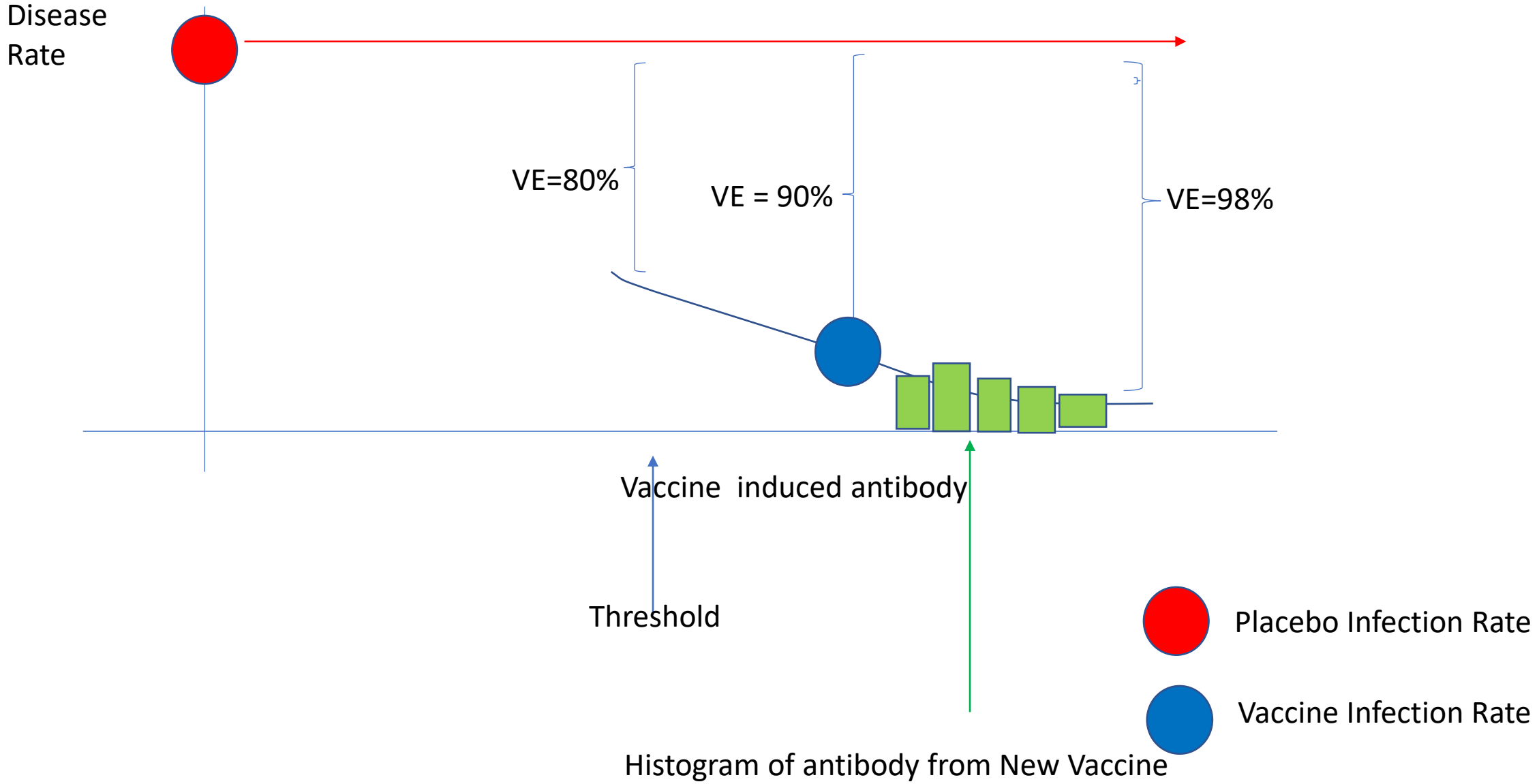
- Eli Lily's monoclonal antibody prevents acquisition of disease !



Illustrative Correlates Analysis



New Vaccine reasonably likely to achieve high VE



Show Similarity of Immune Response

- Demonstrate that the new vaccine is non-inferior to established vaccine in terms of immune response
- Possible endpoints
  - Geometric mean titer
  - Proportion who achieve antibody larger than a threshold
- Need to determine a margin that ensures a high predicted vaccine efficacy based on the correlates analyses
- Enroll a few hundred volunteers in relevant population, test for non-inferiority.
- Possibly coupled to an immuno-bridging study to a confirmatory efficacy or effectiveness study

Summary

- Various paths to licensure are still available
- Trials using clinical endpoints are more difficult without placebo groups
  - Case rates lower => longer, bigger trials
  - NI designs rely on applying an *estimated* VE for a comparator to a *new* setting
- Immuno-bridging based on vetted Correlate of Protection is appealing
  - Such analyses planned for OWS vaccine trials
  - Successful mAb prevention trial very encouraging!
  - Conduct animal studies with down-dosing to demonstrate Ab matters
  - Argue aggregated evidence supports use of Ab for licensure

Thanks

- Martha Nason

Phase 4 clinical studies: post authorization study designs to support accelerated or conditional approvals

Daniel Feikin, MD, MSPH
Department of Immunizations, Vaccines, and Biologics
WHO

Phase 4 clinical studies: post authorization study designs to support accelerated or conditional approvals

Daniel Feikin, MD

January 28, 2021

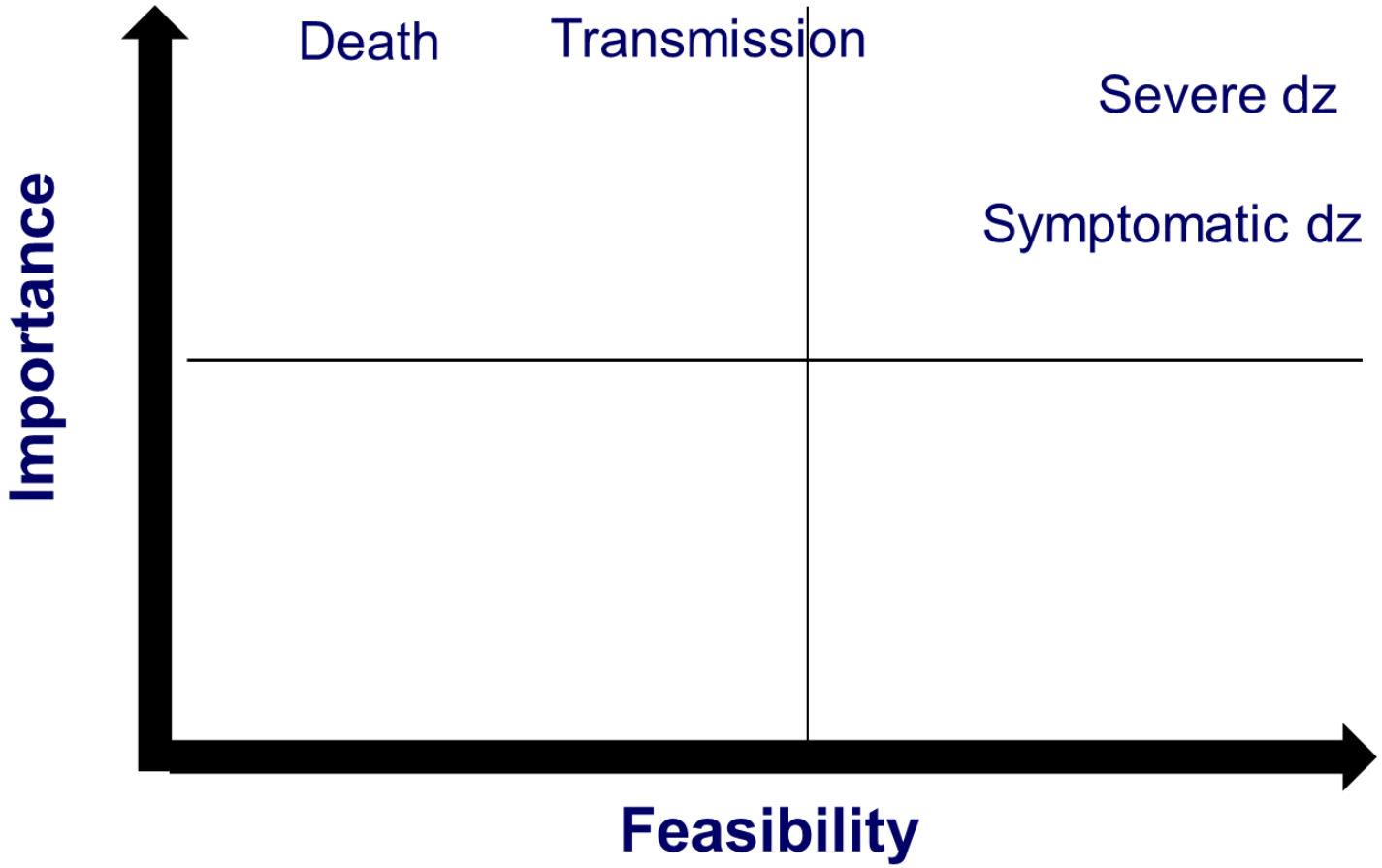
Why need for post-intro studies for Covid19 vaccines?

- For all vaccines, Efficacy in RCTs differs from Effectiveness in the real world
- For Covid vaccines. Scenario 1. Vaccine gets EUL/EUA based on interim results, and vaccines are rolled out before all study outcomes are met
  - Risk groups, infection, severe disease, single dose, duration of protection
- For Covid vaccines Scenario 2. Vaccine approved conditionally on immunogenicity need post-introduction confirmation of effectiveness
  - Mening conjugate vaccine, JE vaccines, seasonal influenza vaccines

Why Covid-19 post-intro studies are challenging?

- **Rapid** changes in epidemiology
- **Rapid** rollout of vaccines in target populations
- **Rapid** results needed for policy and regulatory purposes
- Bias!

Outcomes of interest for studies



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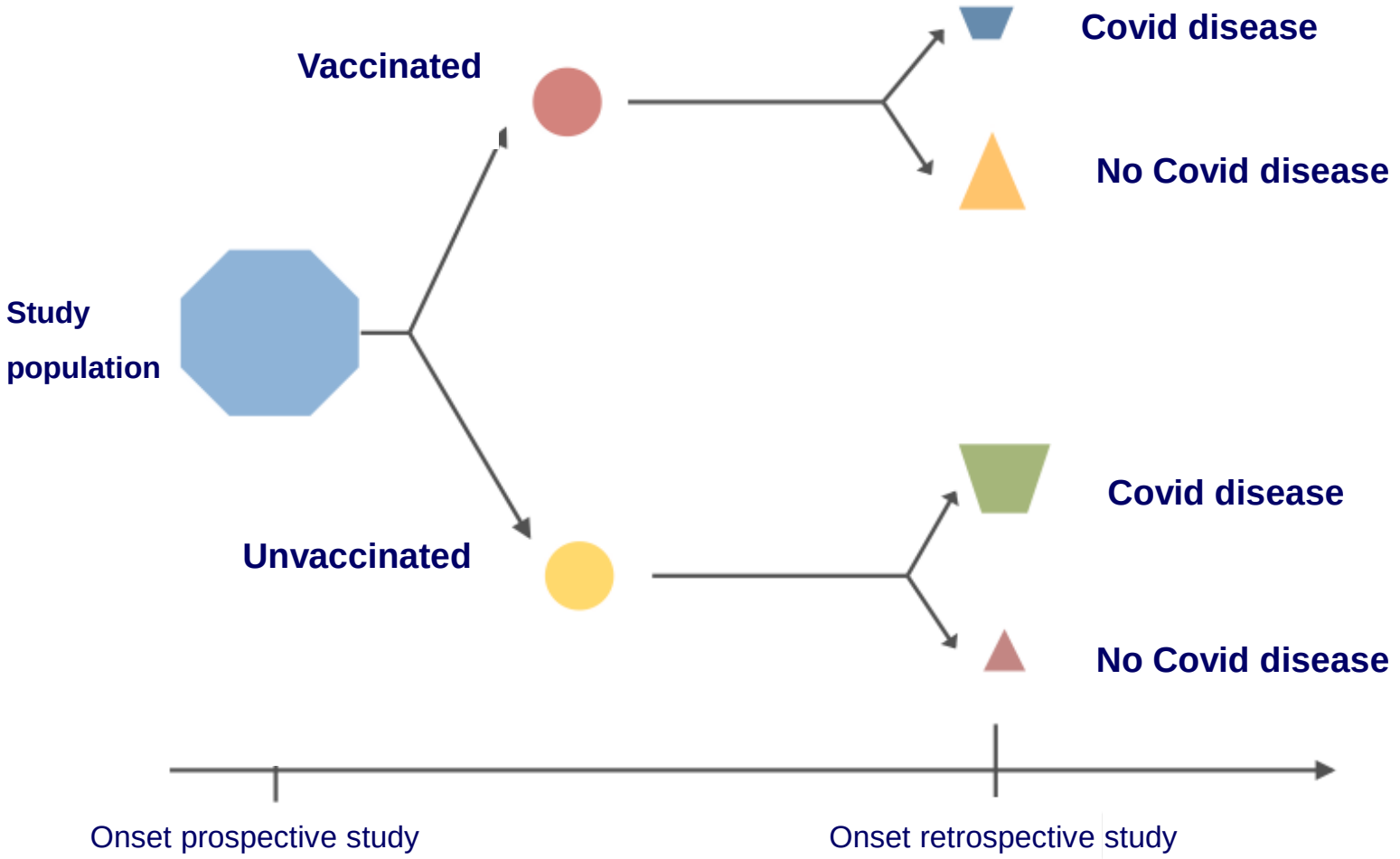
Cohort VE studies



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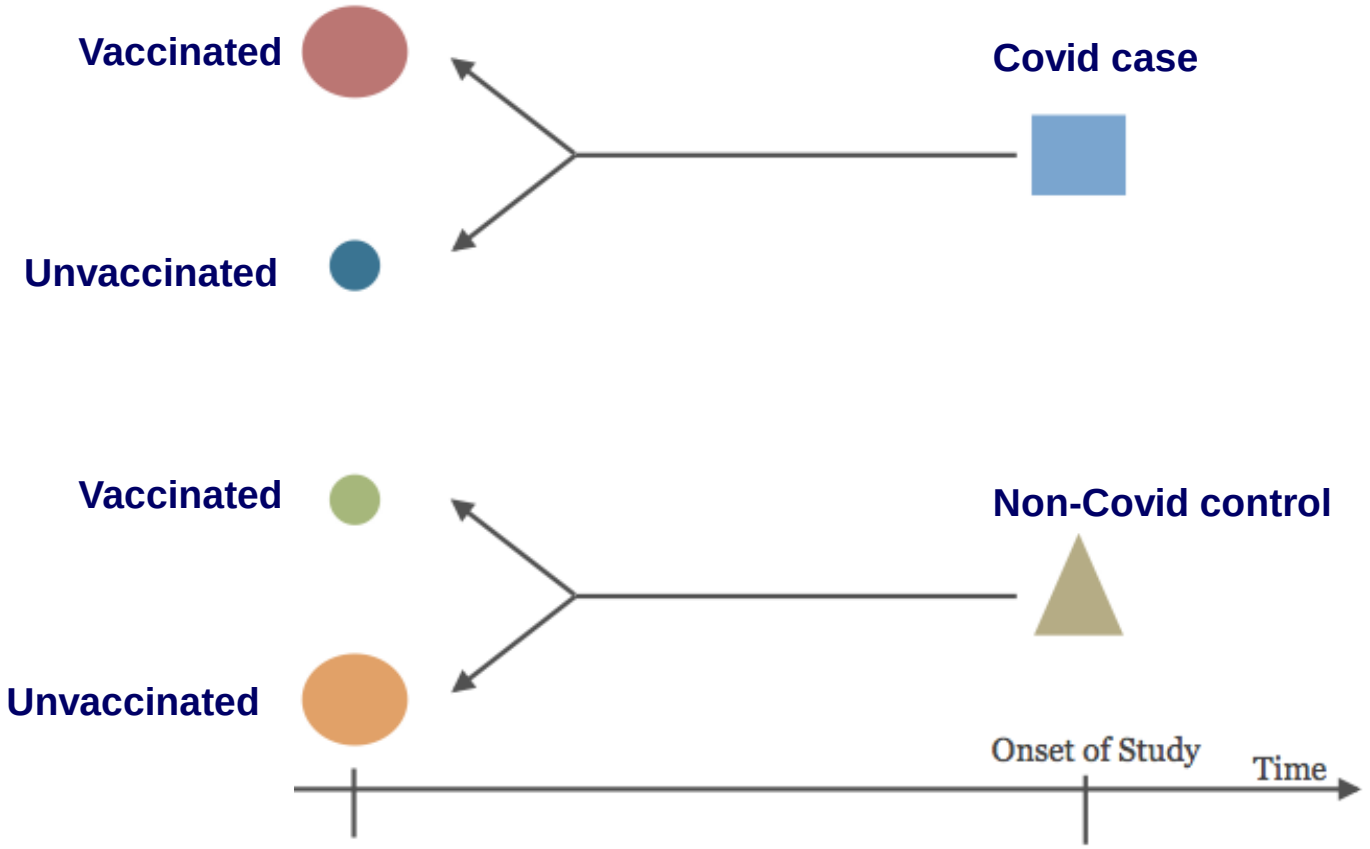
Cohort Studies

Method	• ADVANTAGE	DISADVANTAGE/CHALLENGE
Cohort Studies (prospective or retrospective)	• Can estimate risk reduction of vaccines • Can follow-up a well-defined vaccine cohort (e.g. HCWs) • Can more accurately define vaccine impact on asymptomatic infections	• Cohorts of vaccinees and non-vaccinees often different in many characteristics causing bias • Need large sample size and expensive • Possible ethical dilemma in following unvaccinated group

Case-control VE studies

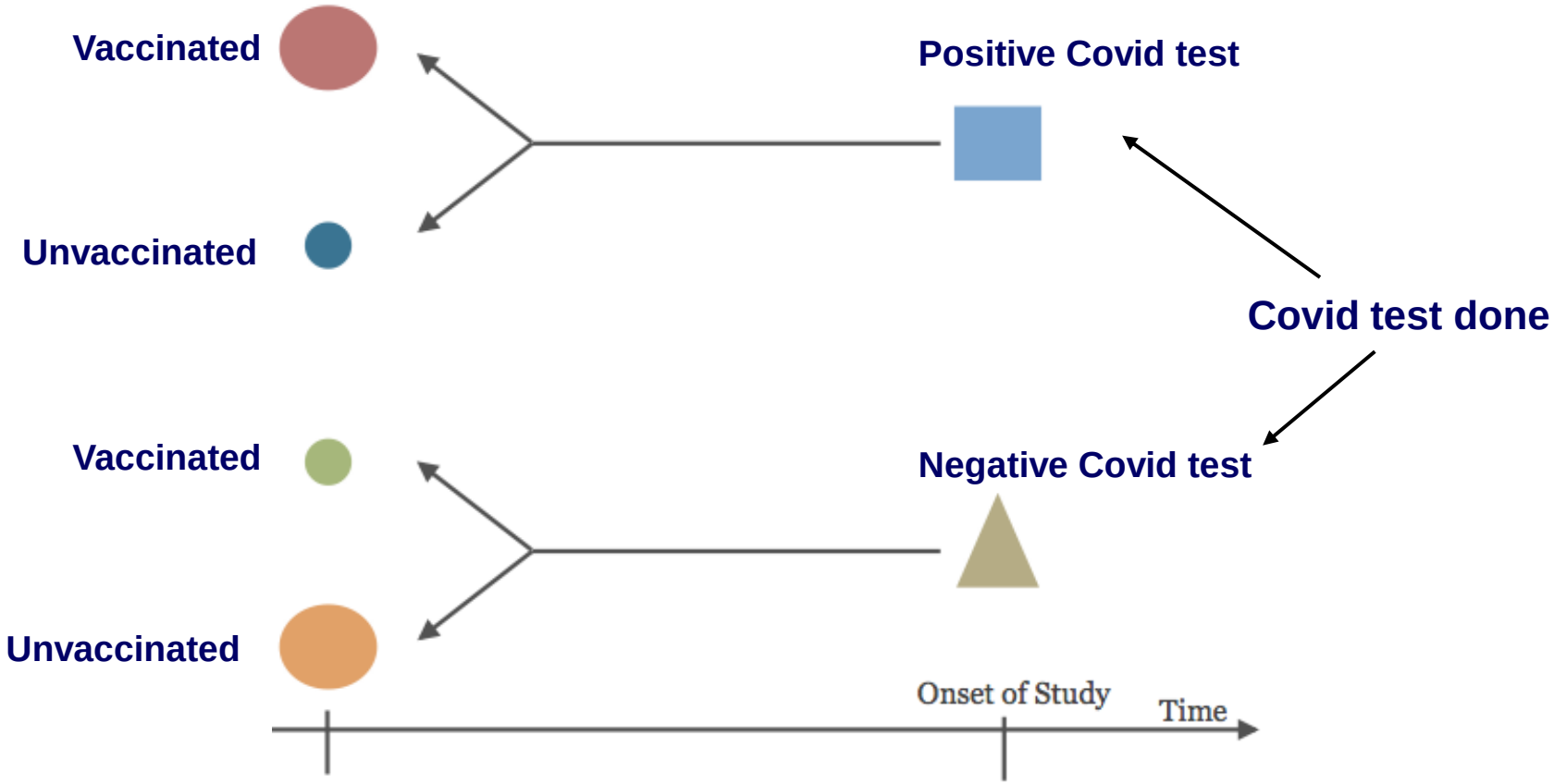


World Health Organization

Traditional Case-control studies

Method	• ADVANTAGE	DISADVANTAGE/CHALLENGE
Traditional Case-Control Studies	• Efficient as requires smaller sample size, less time, and thus less expensive	• Choosing control group comparable to cases in characteristics is difficult (i.e., biases occur) • Vaccinated persons more likely to seek care for Covid disease

Test-negative design case-control VE studies



World Health Organization

TND case-control studies

Method	• ADVANTAGE	DISADVANTAGE
Test-Negative Case-Control Studies	• Minimize bias of differences in healthcare seeking behavior/access on vaccine status • All cases and controls from same community • Logistics easier, uses existing platforms	• Controls still may be different from cases • Misclassification of case status, particularly if presenting late in course (severe>nonsevere)

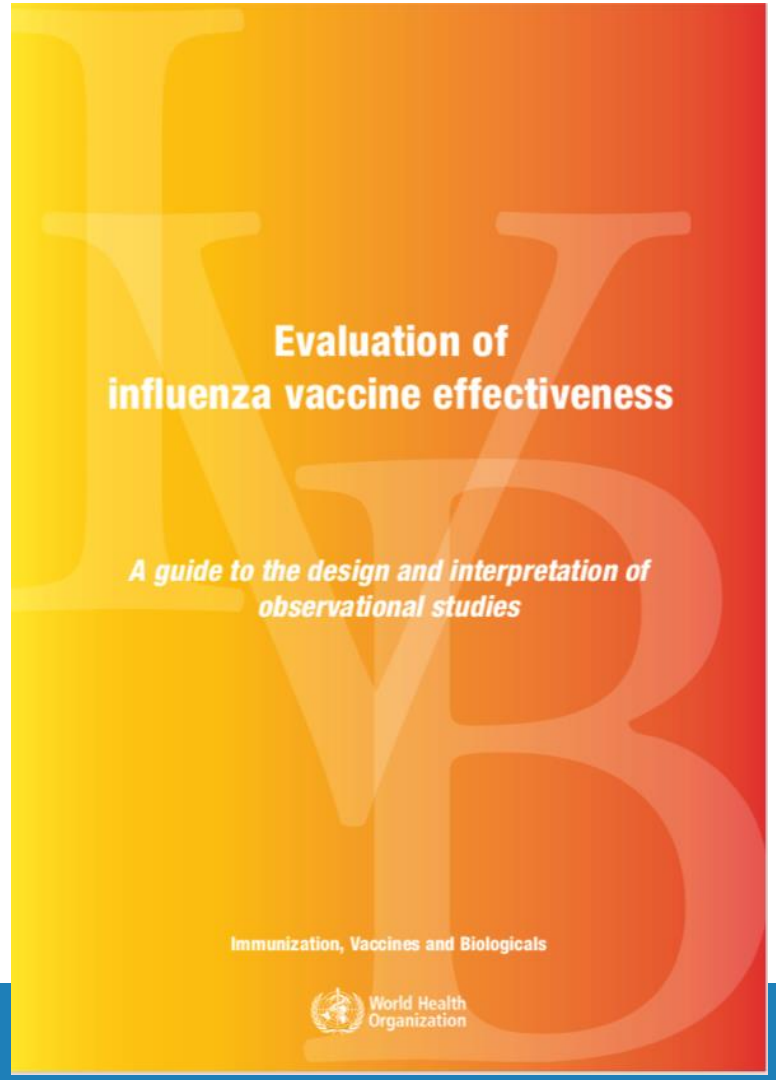
Other methods for post-intro studies

- Screening method
  - % of cases vaccinated vs vaccine coverage in population
  - But coverage estimates will be difficult for COVID-19 vaccines, esp. early on
- Regression Discontinuity Design
  - Quasi-experimental, strict cut-off for vaccine deployment (e.g., 65 years of age)
  - Compare disease in people just above and below cut-off
- ”Randomized” introductions
  - Phased introduction (e.g., step-wedge)
  - Can look at impact in population (e.g., transmission)

Biases and confounding of VE studies

- Health-care seeking and access correlated with vaccination
- Misclassification of disease status (esp. for TND)
- Confounding – vaccination related to Covid risk (e.g., HCWs, adherence to NPI)
- Spurious waning of VE – depletion of susceptibles faster among unvaccinated than vaccinated persons
- Prior Covid-19 infection
  - Both known infection (confounder) and unknown infection (non-confounder)

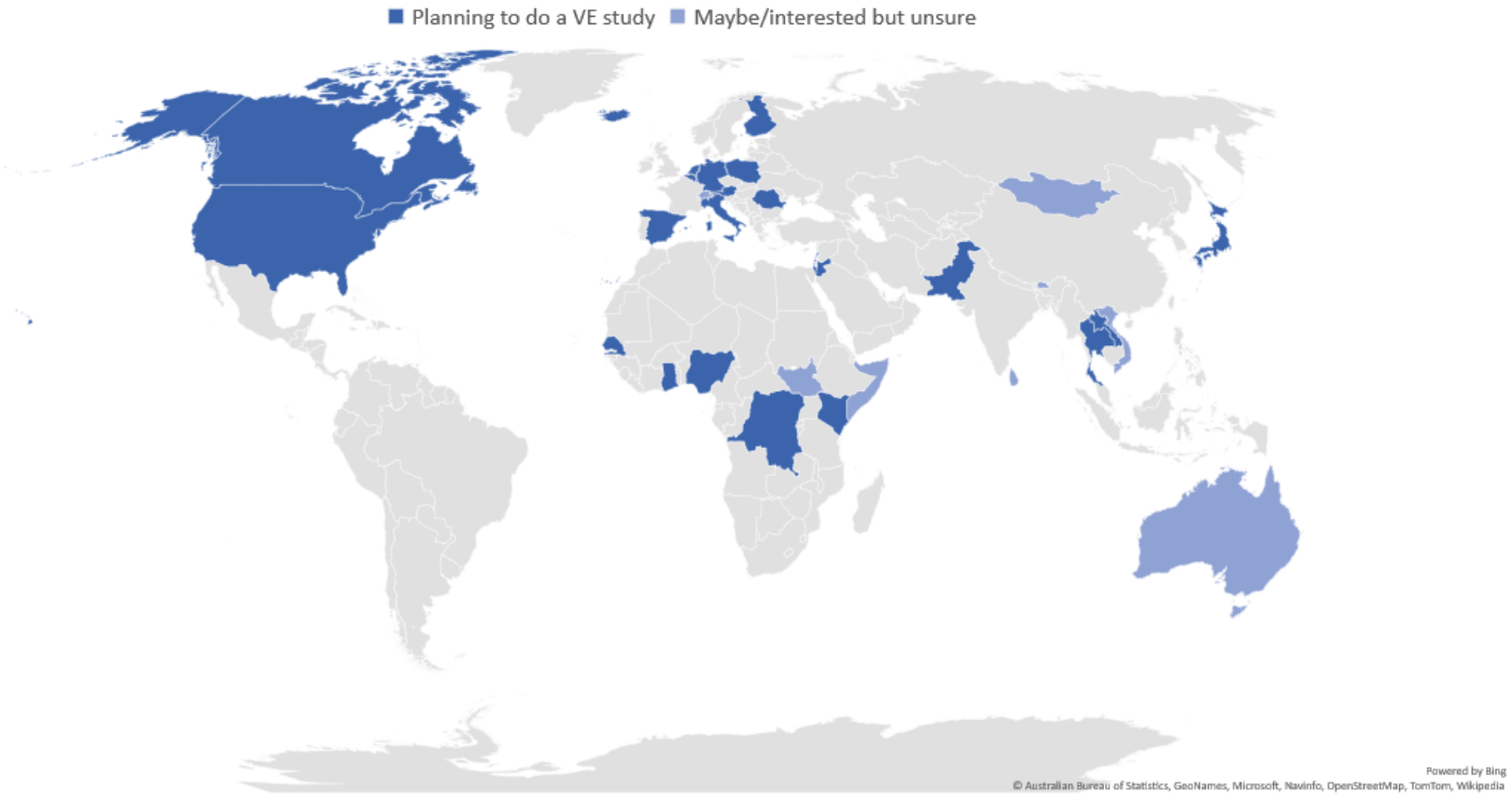
Covid VE guidance doc



World Health Organization

Global Landscape of VE studies

Results from Landscaping Survey: Countries with Plans or Interested to do a Vaccine Effectiveness Study
(n=33 studies planned+other regional studies without country specified (e.g. LAC/PAHO)



***if you are planning a VE study, we'll put you on the map patelm@who.int, feikind@who.int**

R&DBlueprint

Powering research
to prevent epidemics

Overarching research priorities for 2021

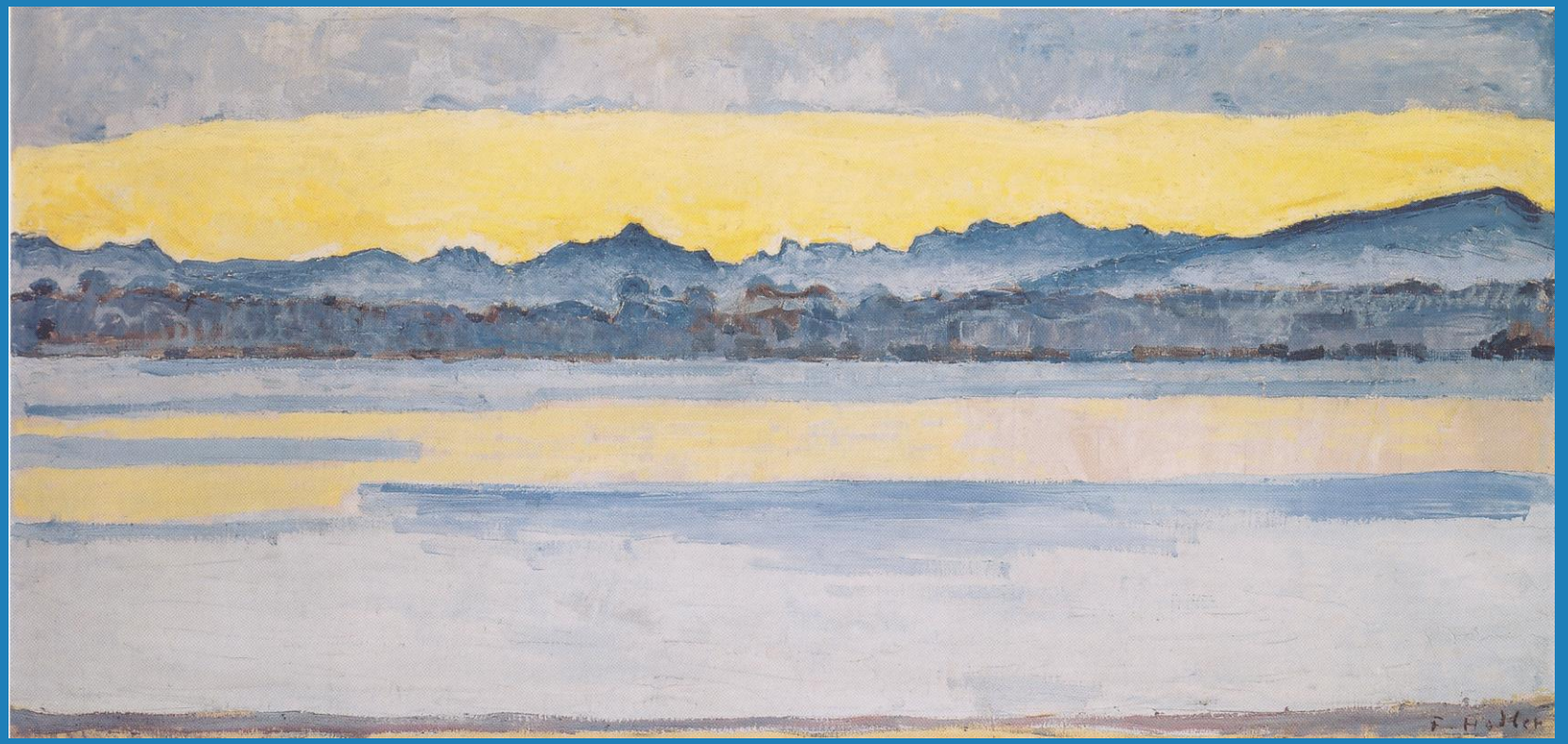
1. **Address the knowledge gaps** for vaccines in Phase 3 or being deployed

2. Monitor and assess the impact of **new COVID-19 variants** on vaccine efficacy

3. **Speed up the search** for additional effective vaccines for all countries.

Thank you.

Acknowledgments to WHOs Covid VE Advisory Group



World Health Organization

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

- **Ralf Clemens, MD, PhD**
  Principal and Founder
  GRID Consulting

- **Adam Hacker, PhD**
  Head of Global Regulatory Affiars
  CEPI

- **Anh Wartel, MD**
  Associate Director
  General, Epidemiology, Public Health, Impact, and Clinical Development
  International Vaccine Institute (IVI)

- *+ Presenters from Parts 1*

Potential Discussion Questions

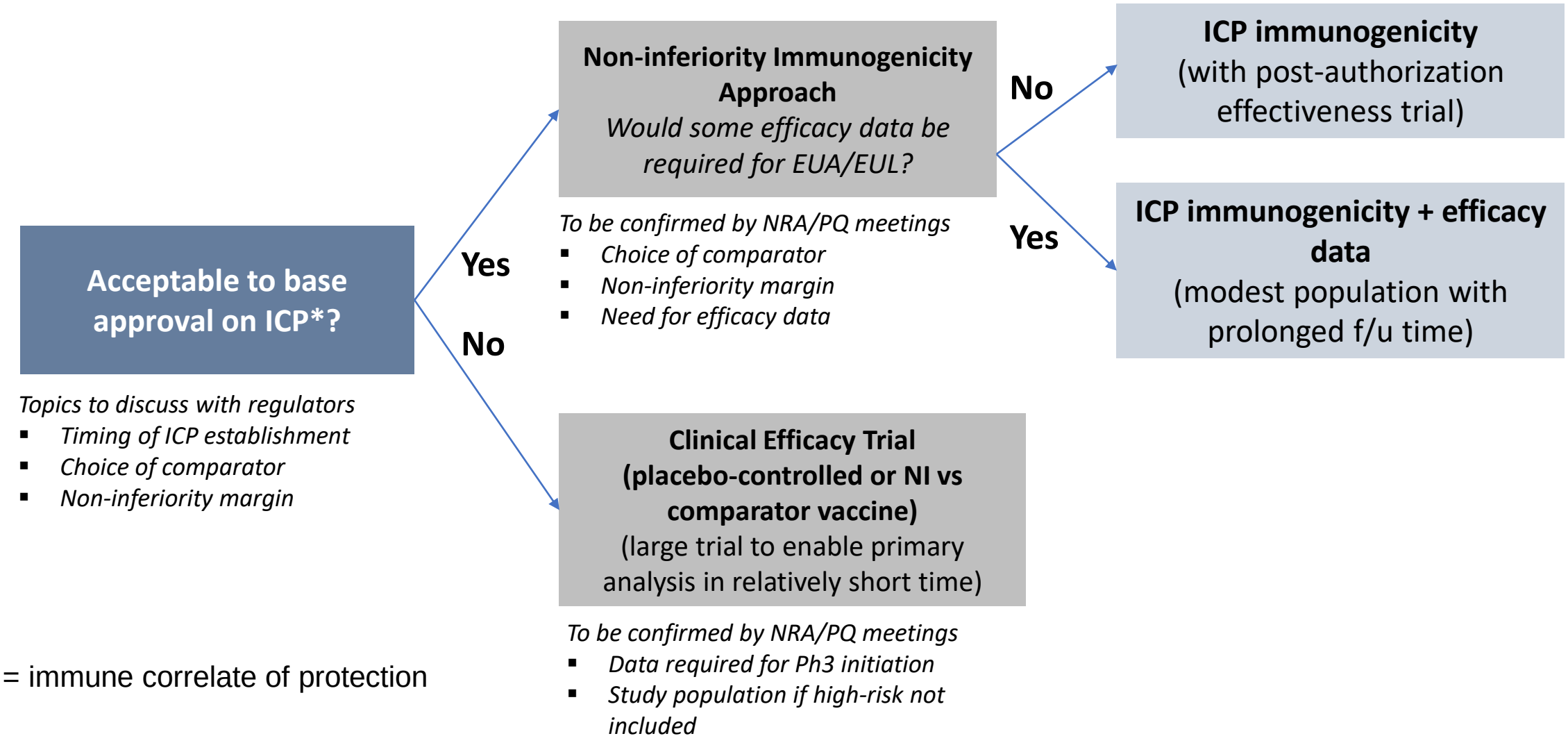
1. How can we accelerate access to data and supportive analyses to inform progress toward an immune correlate of protection

2. What are the practical barriers to enrolling and maintaining subjects in a placebo-controlled studies based on experiences to date?

3. If comparator vaccines are required, what mechanisms are available to facilitate developer access so important new vaccines can be studied?

4. If immunological non-inferiority based on neutralizing or binding antibodies is acceptable for accelerated/conditional approval, what cell-mediated immunity evaluations should accompany the application?

Immunogenicity-based Efficacy Pathway



*ICP = immune correlate of protection

5-minute break

Part 2:

Clinical development gaps

Moderated By:

Jakob Cramer, MD

Head of Clinical Development

Coalition for Epidemic Preparedness Innovations (CEPI)

COVID-19 Vaccine WHO Target Product Profile

Vaccine Characteristic	WHO TPP – Preferred	WHO TPP – Critical	Clinical evidence of vaccines with EUA*
Indication for use	LT: Immunization of at-risk persons to prevent COVID-19	LT: Immunization of at-risk persons to prevent COVID-19	Available with all licensed vaccines. *However, further data in risk populations e.g. older age groups / persons with chronic diseases necessary.*
Contraindication	None	Few (e.g immunocompromised) may be acceptable	Contraindication in persons allergic to vaccine or its component.
Target population	All ages. (including pregnant & lactating women)	Adults including elderly	*EUAs exclude pregnant and lactating women and pediatric population. No trials ongoing among pregnant/lactating women.*
Safety / Reactogenicity	Highly favourable benefit/risk profile in the context of observed VE; with only mild, transient AEs and no SAEs	Outbreak: whereby vaccine benefits outweigh safety risks LT: Highly favourable benefit/risk profile in the context of observed VE; No related SAEs	Available with all licensed vaccines. *Long terms safety lacking.*
Protective efficacy	70% against disease, severe disease, and/or shedding/transmission. Outbreak: 2 week onset	50% against disease, severe disease, and/or shedding/transmission.	>50% efficacy with licensed vaccines against disease / any severity. Promising data against severe disease (however: low number of severe cases) *No data on shedding or transmission available. Evidence related to new variants?*
Dosing regimen	Outbreak: Single-dose primary series LT: Lower frequency (Yearly or less) of booster doses is preferred	Outbreak: No more than two dose regimen LT: Booster doses permitted	*No single dose vaccines licensed; a few under development.* *Limited data post single dose available* *No information on booster dosing, few trials are ongoing.*

** - These include Pfizer/BioNTech, Moderna and Oxford/AZ that have made public detailed and peer reviewed data that formed the basis of Emergency Use Authorisation (EUA)*

COVID-19 Vaccine WHO Target Product Profile

Vaccine Characteristic	WHO TPP – Preferred	WHO TPP – Critical	Clinical evidence of vaccines with EUA*
Durability of protection	Confers protection for at least 1 year	Confers protection for at least 6 months	*Trials ongoing to assess this.* *No data presently on duration of protection.* *Further data will accrue over time.*
Route of administration	Outbreak: Non-parenteral due to ease administration & logistical issues. LT: any route of administration is acceptable	Any route of administration is acceptable, if vaccine is safe and effective	All licensed vaccines (and most in development) are injectable. *No oral or intranasal vaccines in Phase 3 clinical trials presently.*
Co-administration	Outbreak: stand-alone product LT: potential for coadministration with other vaccines that are typically administered in campaigns preferred	Stand-alone product	*No evidence on co-administration of COVID vaccines with other routine vaccines.* *No clinical trials ongoing – evidence may become more important in future?.*
WHO registration and PQ	Outbreak: WHO prequalified and/or made available under EUA/WHO EUL LT: WHO pre-qualified	Outbreak: Meets criteria for EUA/ WHO EUAL LT: WHO pre-qualified	*WHO EUL: One vaccine*

** - These include Pfizer/BioNTech, Moderna and Oxford/AZ that have made public detailed and peer reviewed data that formed the basis of Emergency Use Authorisation (EUA)*

Part 2

Clinical development gaps: Optimizing vaccination schedules of currently available Covid-19 vaccines to

1) address delivery barriers

2) optimize durability of protection

3) improve breadth of protection against new variants

Call for Proposals: Support clinical trials / trial amendments

- Expand access to COVID-19 vaccines
- Fill in clinical development gaps

Post-infection and vaccine-induced immune responses against SARS-CoV2: Summary of impact of new variants

Shabir Madhi, PhD

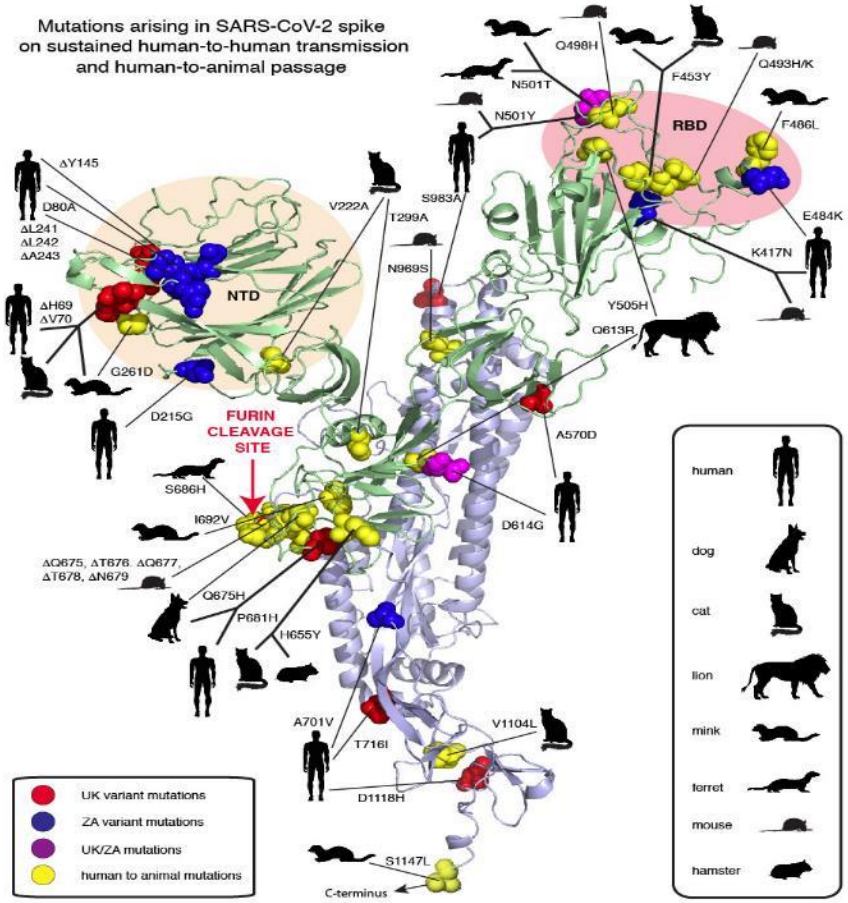
Professor of Vaccinology
School of Pathology
University of Witwatersrand

SHABIR A MADHI,

Post-infection and vaccine-induced immune responses against SARS-CoV-2: summary of impact of new variants

SARS-COV-2 SPIKE MUTATIONS ARE OCCURRING IN HUMANS AND ANIMALS

Mutations in SAR-CoV2 have been constantly occurring as would be expected for a RNA virus..



….but the emerging variants in the UK, South Africa and Brazil have multiple mutations and are of concern

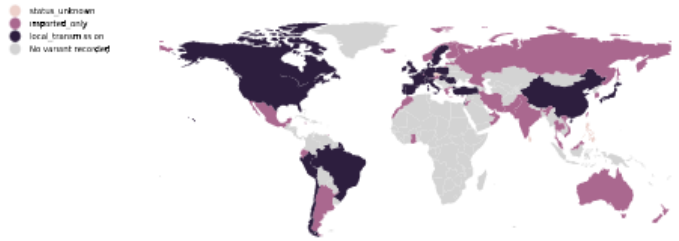
- Epidemiology
- Impact on natural immunity and reinfection risk
- Impact on vaccines
- Impact on monoclonal antibody therapies
- Diagnostics
- Plans for Vx roll out

Robert Garry - virological.org

VARIANTS OF CONCERN ARISE AND SPREAD GLOBALLY

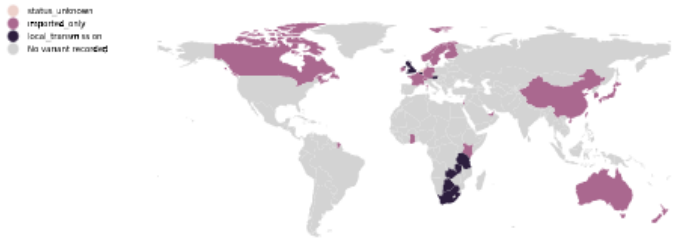
Colors indicate reports of imported cases (pink) or of local transmission (darker purple) as of Jan 24th, 2021

Global Report Investigating Novel Coronavirus Haplotypes



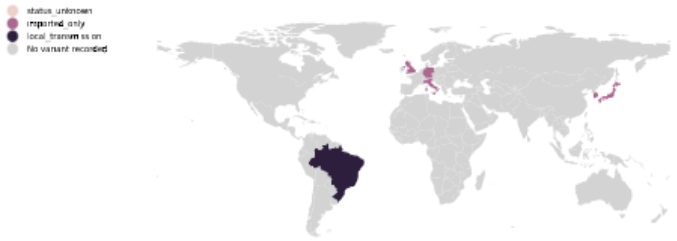
B.1.1.7 report **V501Y.V1**

Daily global report for lineage B.1.1.7



B.1.351 report **V501Y.V2**

Daily global report for lineage B.1.351

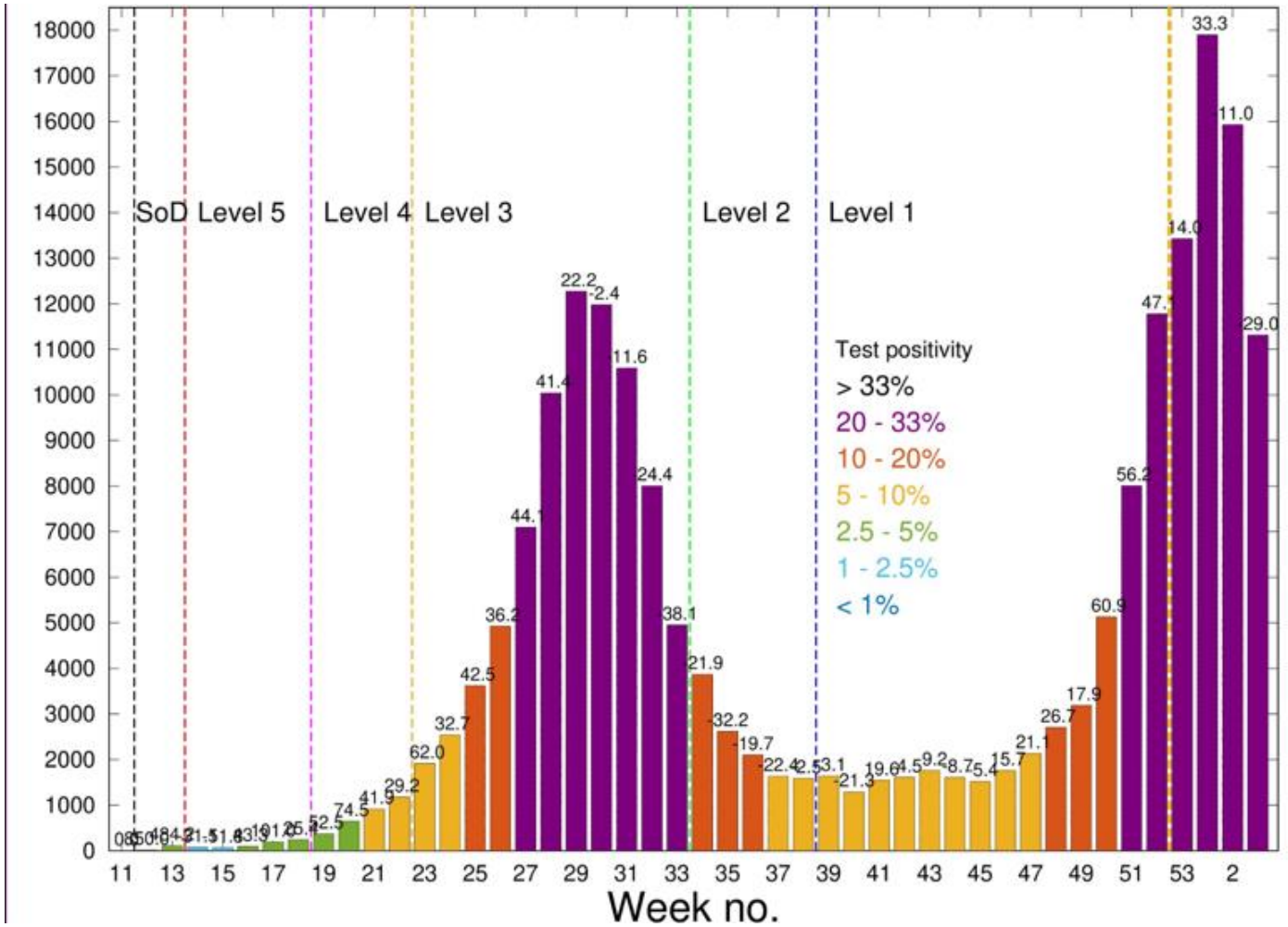


P.1 report **V501Y.V3**

Daily global report for lineage P.1

https://cov-lineages.org/global_report.html

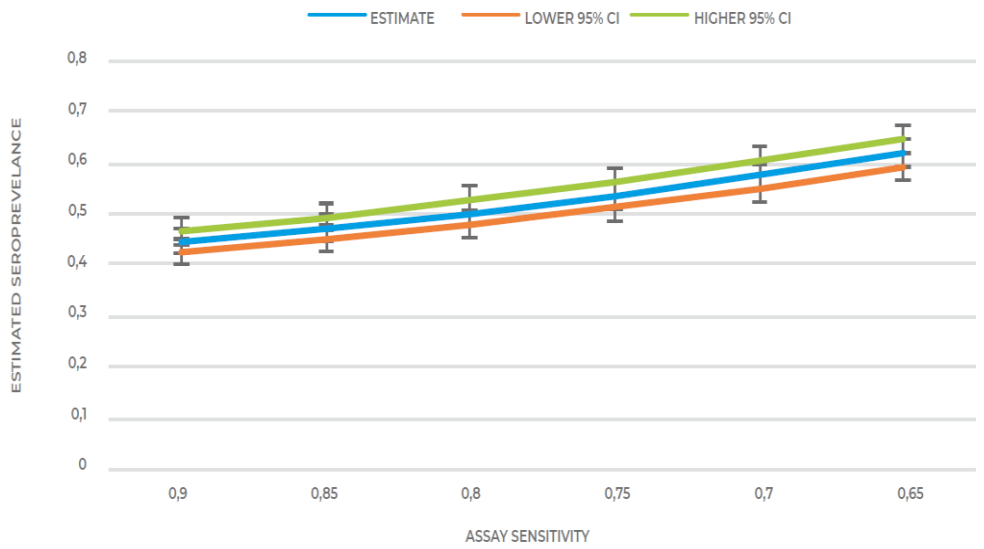
AVERAGE DAILY COVID-19 CASES AND POSITIVITY RATES PER WEEK IN SOUTH AFRICA



Courtesy Ridwaan Suliman

IMPACT OF ASSAY SENSITIVITY REDUCTION ON ESTIMATED SARS-COV-2 SEROPREVALENCE IN CAPE TOWN METRO, SOUTH AFRICA

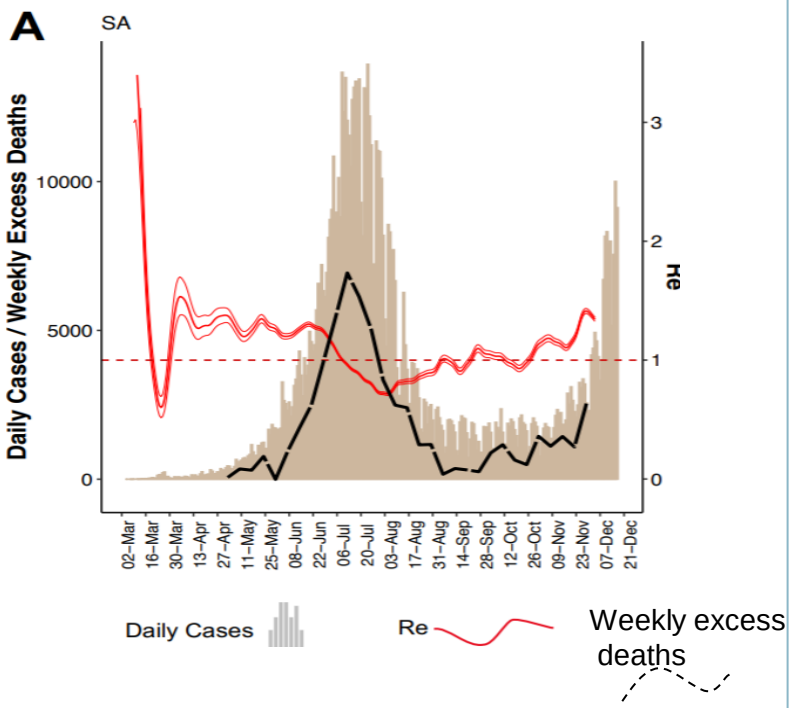
- Test using Roche Elecsys anti-SARS-CoV-2 assay.
- Residual sample of pregnant women (blood grouping) and HIV (viral load testing)
- Sampling 15 July to 7 August (downward trajectory of 1st wave)
- 40% sero-positivity in pregnant women and people living with HIV.
- Sero-prevalence range from 31- 46% in sub-districts.



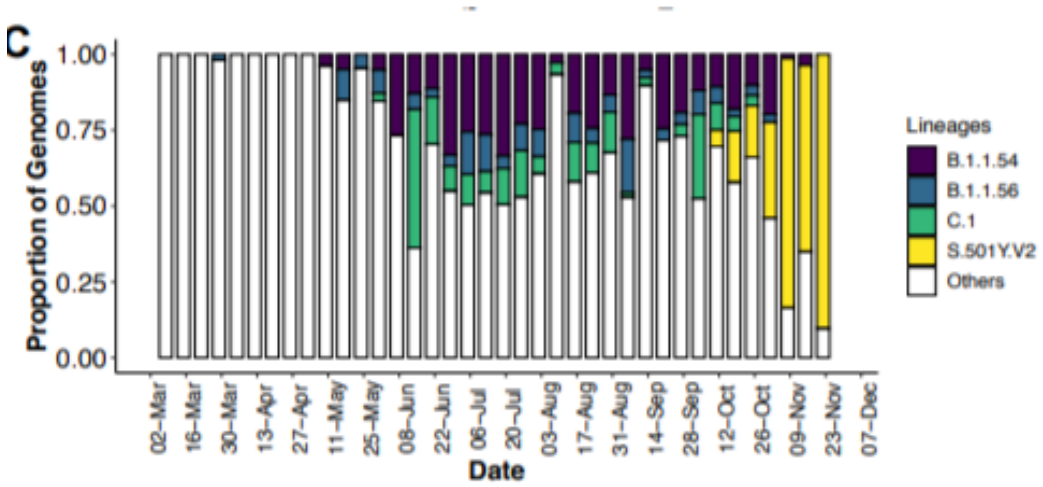
Hsiao M et al. NICD Surveillance Bulletin; 2020; 18 (5): 1-5

EMERGENCE AND RAPID SPREAD OF **501Y.V2** LINEAGE WITH MULTIPLE SPIKE MUTATIONS IN SOUTH AFRICA

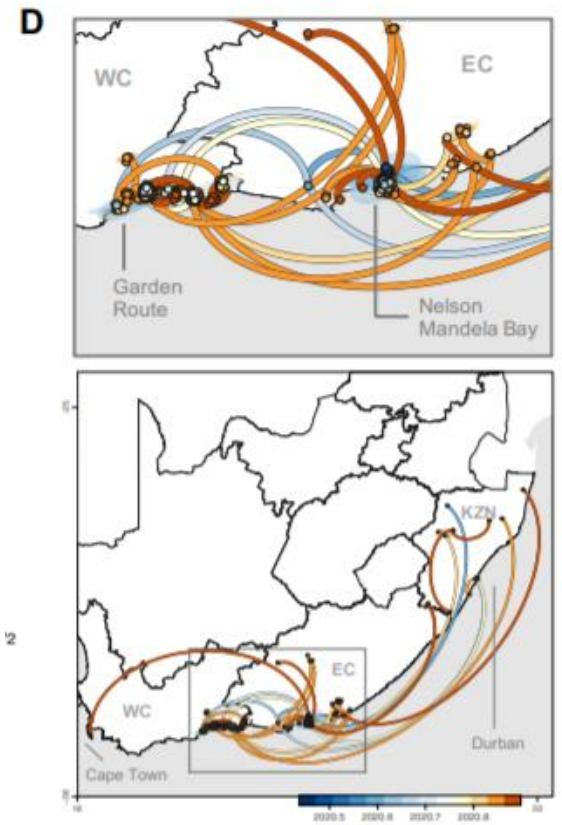
Early and rapid resurgence prompted intensified genomic surveillance in October. Positivity rates >30% in many areas and increasing Re….



…..by mid December 501Y.V2 had replaced the precedent D614G strain…..



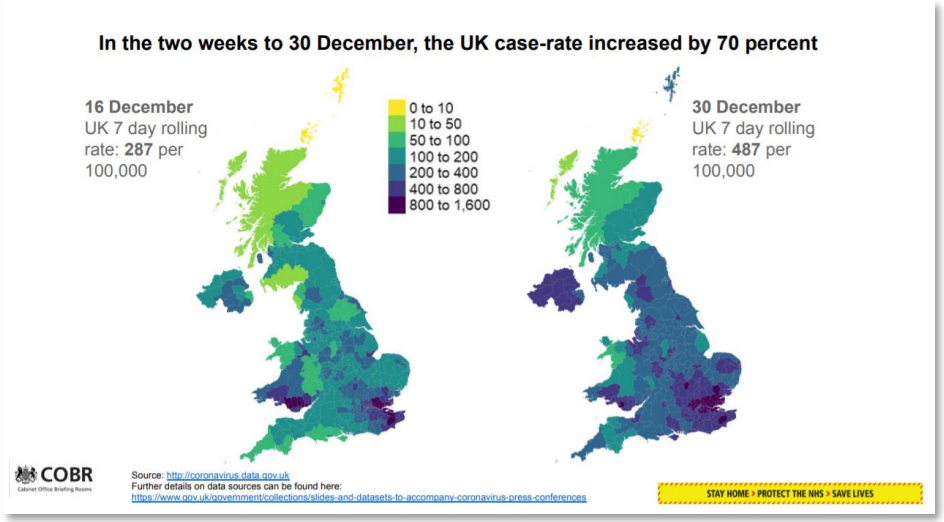
…..and spread from the Eastern Cape



[Tegally et al medRxiv Dec 21, 2020]

EMERGENCE AND RAPID SPREAD OF VARIANT LINEAGE WITH MULTIPLE MUTATIONS IN THE UK (**501Y.V1 = B.1.1.7)**

Explosion of cases in the UK between end of November and now 1:30-1:50 people estimated positive in the UK currently…



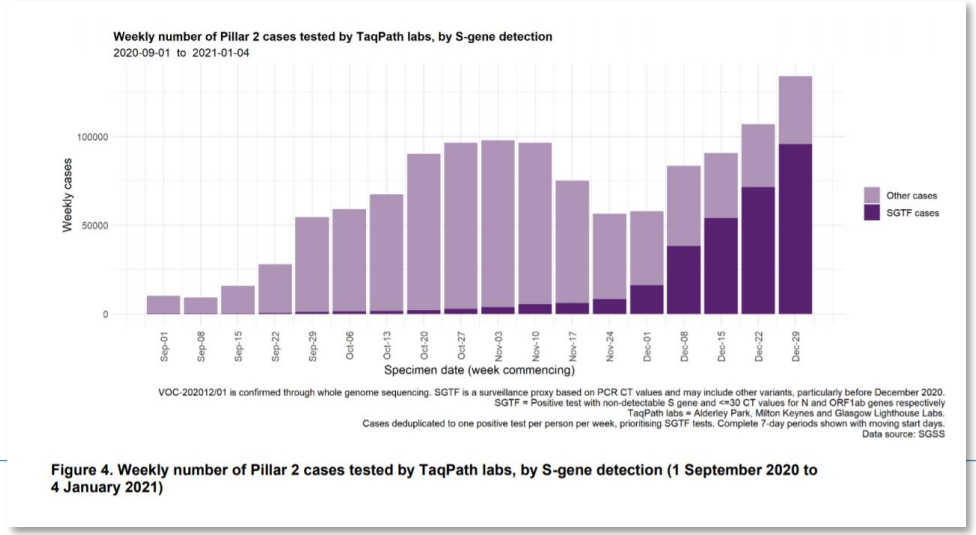


Figure 4. Weekly number of Pillar 2 cases tested by TaqPath labs, by S-gene detection (1 September 2020 to 4 January 2021)

Under the same lockdown conditions the Re for D614G was 0.95 whereas the 501Y.V1 had Re of 1.45 (range 1-2)

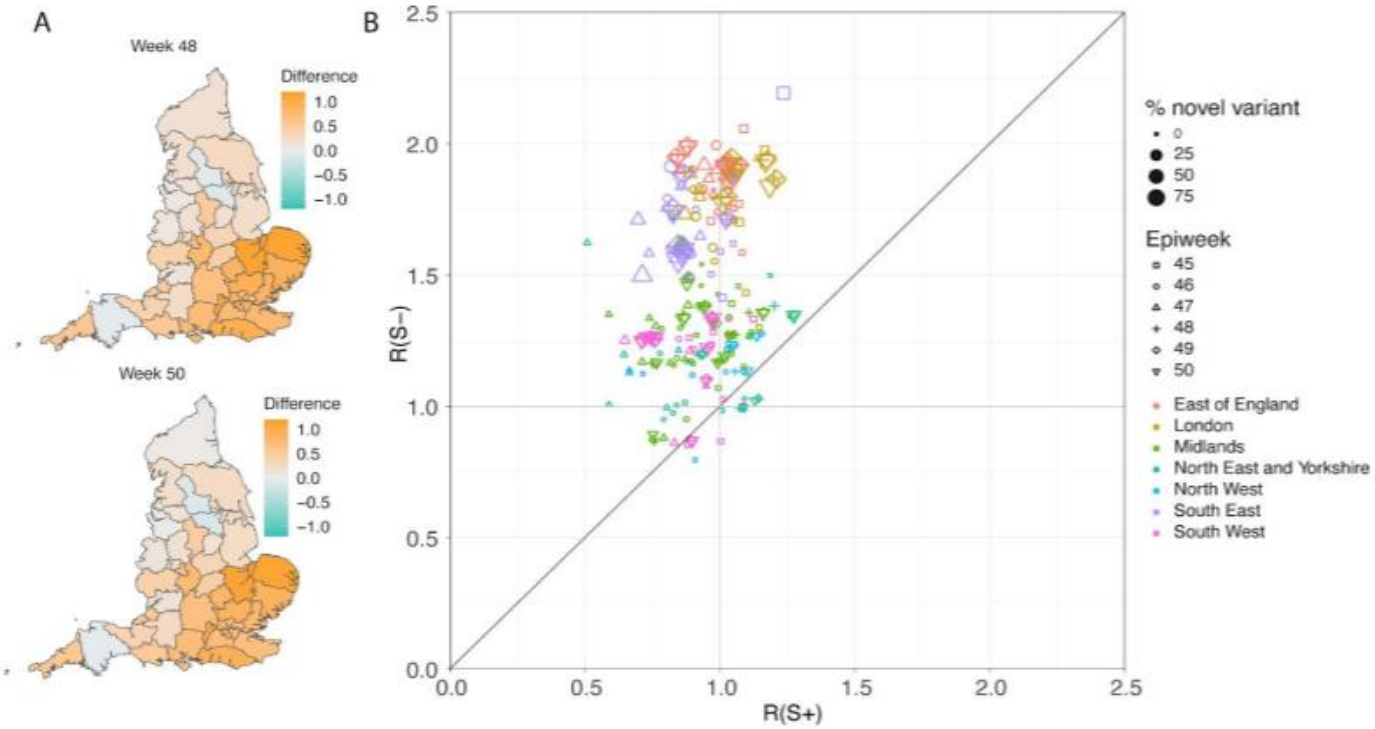
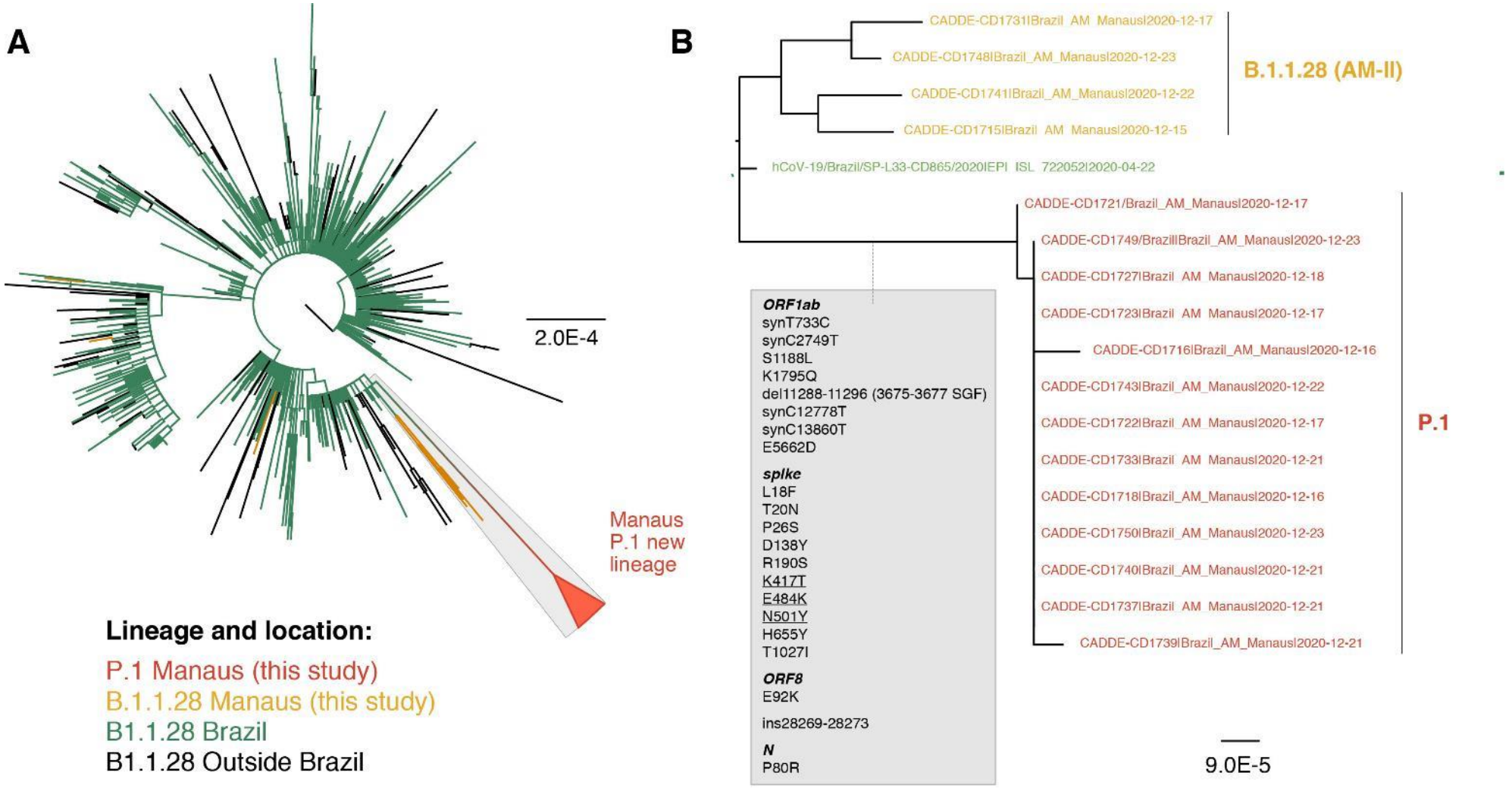


Figure 6: (A) Map of the difference in median R_t estimates for VOC and non-VOC variants for all STPs for weeks 48 and week 50. (B) Scatterplot of the reproduction numbers of VOC (S-) and non-VOC (S+) by STP and week. Point size indicates frequency of the VOC, while shape and colour signify week and NHS region, respectively.

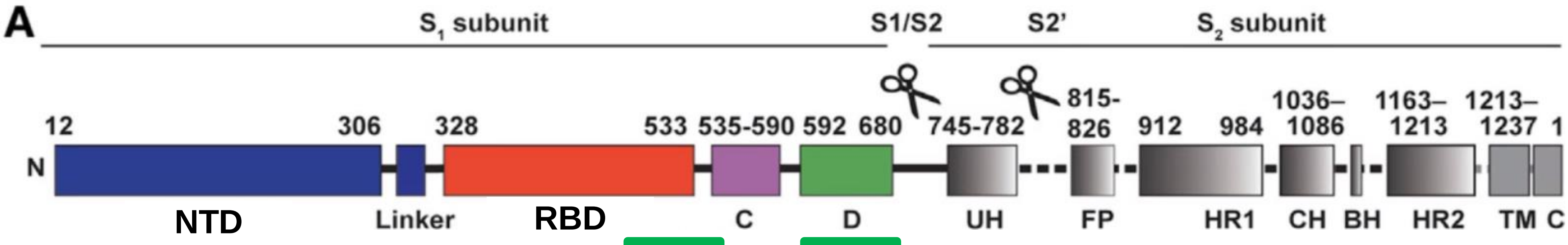
Volz et al medRxiv Dec 30th 2020

NEW VARIANTS ARE EMERGING AND THE MUTATIONS IN THE VIRUS FROM MANAUS DEFINE A NEW LINEAGE (**P.1**)



Faria et al virological.org

501Y.V2 & **B.1.1.7:** OVERLAPPING BUT DISTINCT SPIKE MUTATIONS



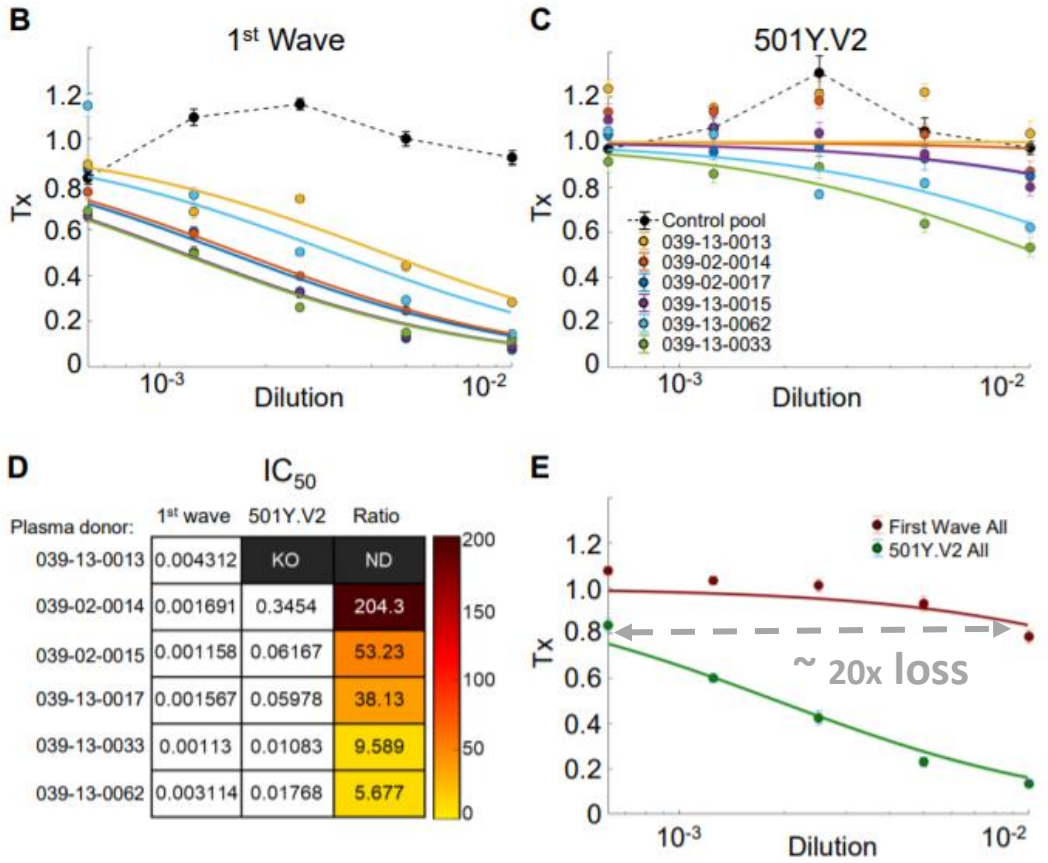
501Y.V2 (SA)	L18F D80A D215G	K417N E484K	**N501Y**		**D614G** A701V			
B1.1.7 (UK)	69-70del Y144del		**N501Y**	A570D	**D614G** P681H T716L	S982A		D1118H
P.1 (Brazil)	L18F P26S D138Y T20N R190S	K417N E484K	N501Y		D614G H655Y		T1027I	

Mutations in the RBD and NTD are of particular concern for ACE2 interactions and neutralizing antibodies:

- **N501Y** is in all three lineages. It **enhances binding affinity to ACE2 and may increase infectivity**. This is a site of recognition of some NAbs, can arise in immunocompromised individuals and is observed in mouse adapted strains-enabling efficient replication.
- **E484K** also enhances ACE2 binding and is a **key recognition site of class II NAbs** (eg Ly-COV555). Seen in mouse adapted strains and can appear under immunological selection in humans. It is associated with resistance to neutralization by polyclonal sera.
- **K417N** is a **site of recognition of class I NAb** with VH3-53. It makes direct contact with ACE2. Seen in mouse adapted strains where it is associated with increased pathogenicity.
- **69-70del** has arisen in mink mutants and in patients treated with convalescent plasma (Gupta et al)
- Neutralizing Abs directed against the **NTD domain target** a single supersite (Cerutti et al and McCallum et al)

Tegally et al medRxiv Dec 21, 2020, Nelson et al.

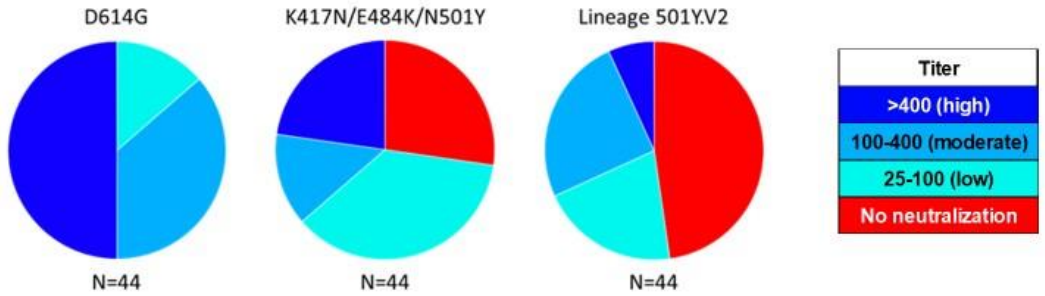
501Y.V2 VARIANT ESCAPES NEUTRALIZATION BY SOUTH AFRICAN WAVE 1 SERA



- **~ 20-fold loss (5 to >50x)** in neutralization was observed against the new variant.
- Results suggest that the majority of neutralizing activity in convalescent sera is sensitive to the mutations in this variant.

Convalescent sera vs RBD triple mutant and 501Y.V2

Preliminary data



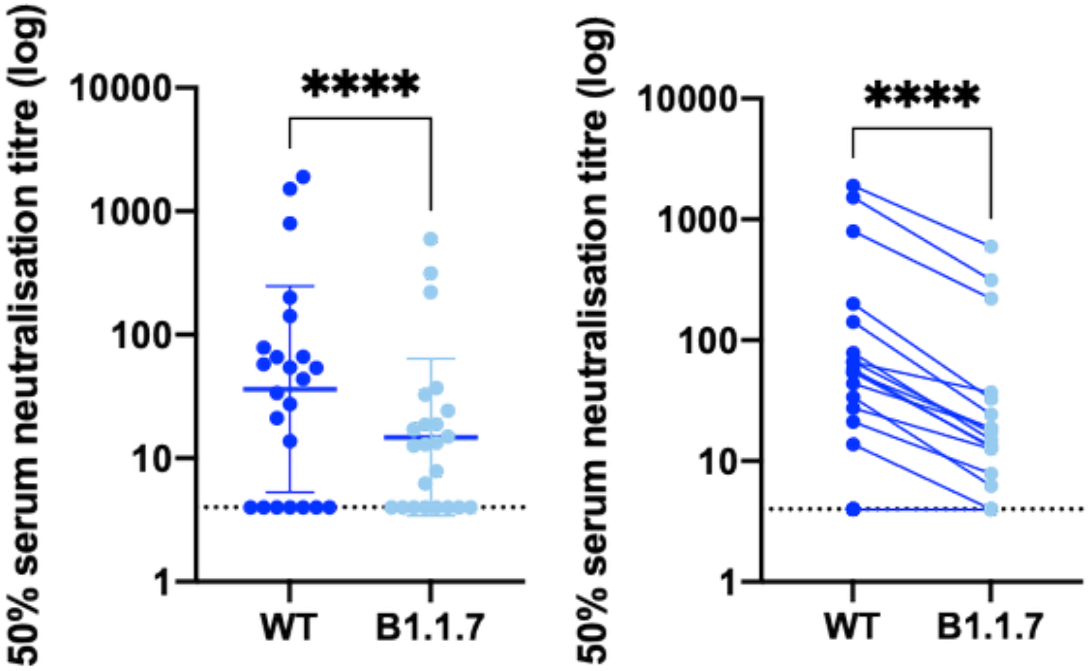
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Penny Moore, Kurt Wibmer, Jinal Bhiman, South Africa

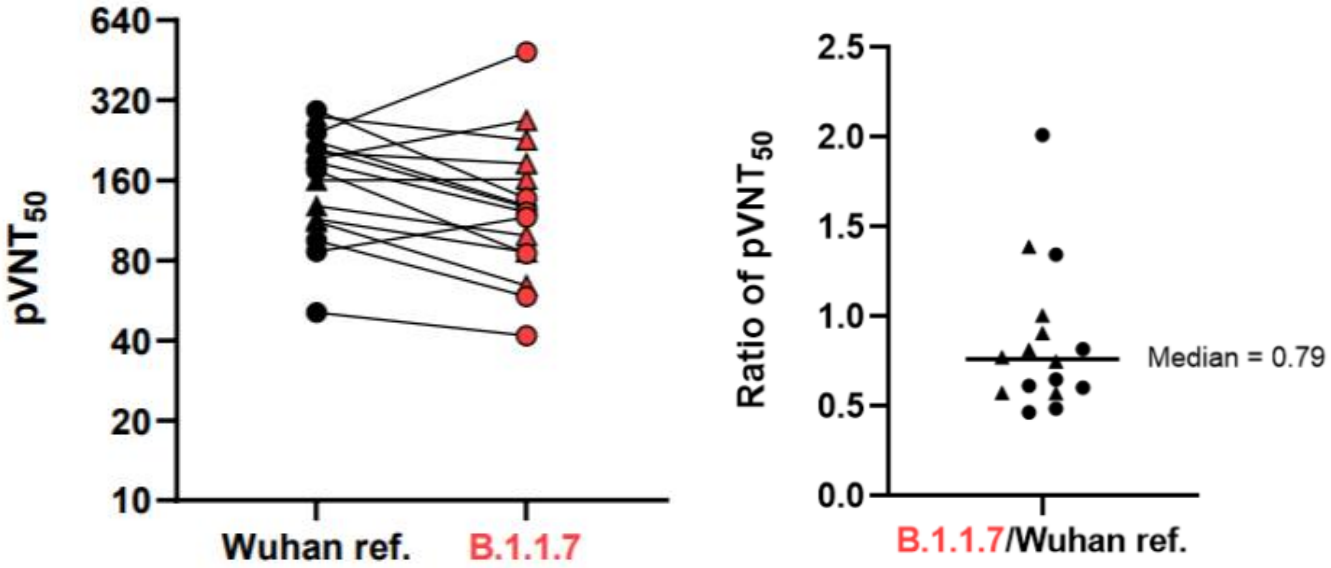
- 44 Wave 1 convalescent sera were tested against a Wave 1 pseudotype virus, pseudotype with 3 key RBD mutations, and 501Y.V2 pseudotype virus (8 mutations).
- Significant effect on neutralization seen with the 3 RBD mutations
- Further impact seen in the **fully mutated variant which demonstrates major escape**
- Inter-individual variation in escape seen across individuals, but almost all are impacted strongly.

MODEST DECREASE IN NEUTRALIZATION AGAINST **B.1.1.7** BY BNT/PFIZER VX SERA

Among 15 individuals with neutralisation activity three weeks after the Pfizer mRNA vaccine, 10 showed evidence of reduction in efficacy of antibodies against the B.1.1.7 mutant (Fold change >3).



8 young (triangles), 8 older (circles) individuals 21 days post second dose of BNT162b2. Ratio was 0.79, indicating “no biologically significant difference in neut activity”



BNT, Pfizer BioRxiv 1-19-2021

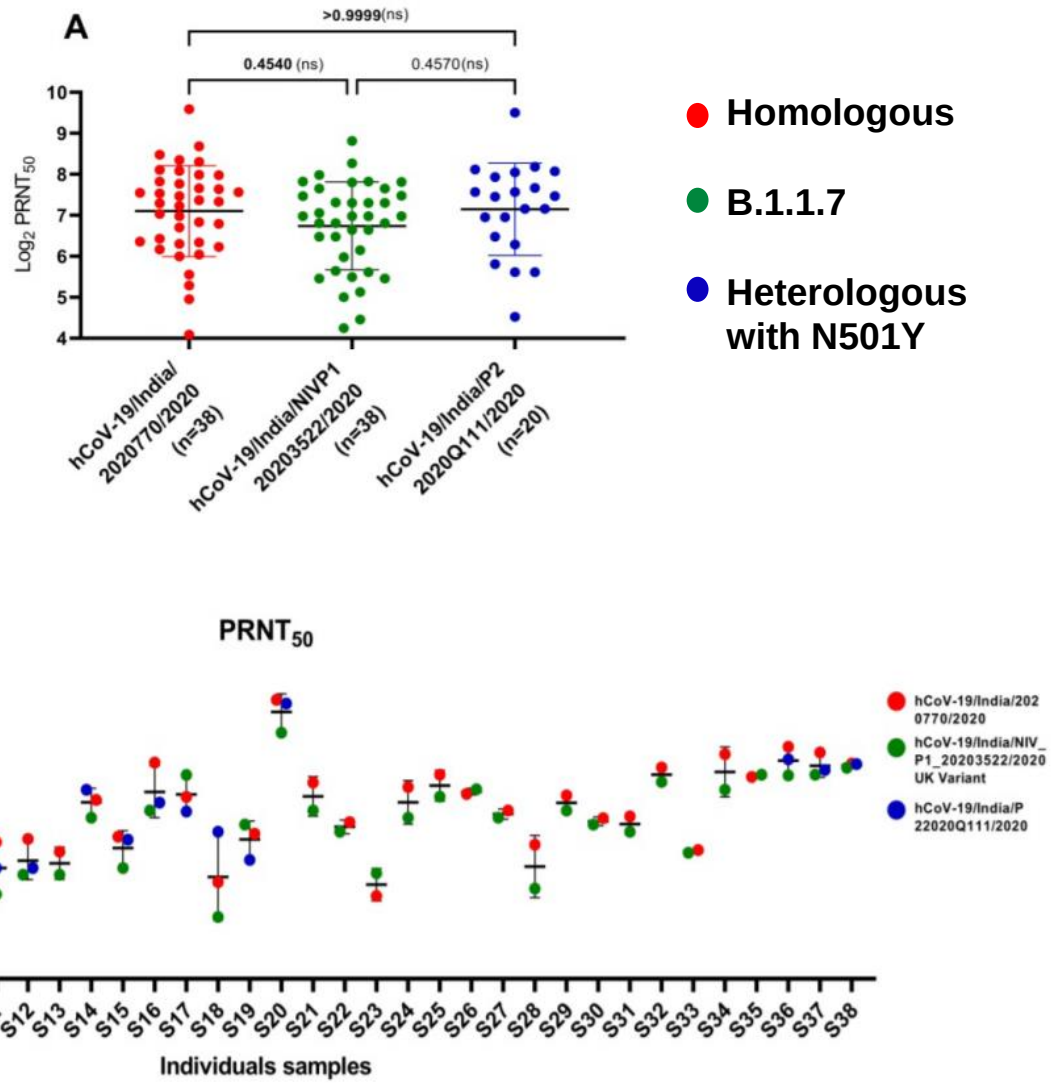
Ravi Gupta @GuptaR_lab, Cambridge
Twitter 1/18/2020, BioRxiv 1-19-2021

B.1.1.7 **pseudovirus**: del69/70, del 144/145, N501Y, A570D, P681H, T716I, S982A, D1118H

NEUTRALIZATION OF **B.1.1.7** BY COVAXIN VACCINATED HUMAN SERUM

The median ratio of 50% neutralization of sera was found to be **0.8** when compared with hCoV-19/India/2020770 against mutant hCoV19/India/20203522 (B.1.1.7)

Suggests that COVAXIN will be equivalently effective against B.1.1.7



Sapkal BioRxiv 1/26/2021

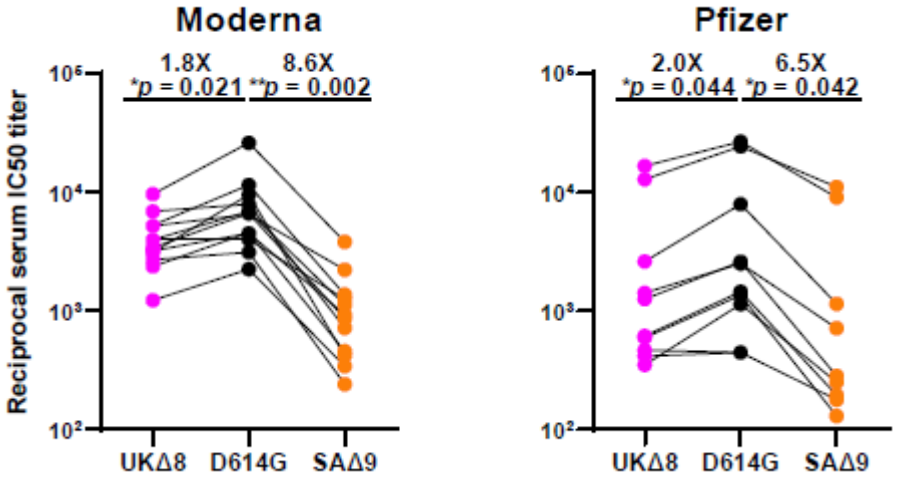
LARGER DECREASE IN NEUTRALIZATION AGAINST **501Y.V2** VS. **B.1.1.7** BY MODERNA AND PFIZER VX SERA

Neutralization profiles for 22 serum samples from vaccinees against pseudoviruses,

Change in IC50 values relative to WT pseudovirus

Fold change of IC50 from WT		Moderna vaccinee sera												Pfizer vaccinee sera									
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22
UK	UKΔ8	-2.7	-2.2	-3.0	-1.2	-1.7	-1.9	-1.2	-1.9	-1.4	1.0	-1.2	-1.8	-1.6	-1.9	-2.1	-1.8	+1.1	-2.4	-2.3	-3.2	-1.1	+1.1
	69-70del	+1.4	+1.4	-1.3	+1.2	-1.3	-1.1	+1.9	+1.1	+1.5	-1.4	+1.3	+1.3	-1.4	+1.3	-1.0	-1.0	-1.5	-1.3	+1.3	+1.3	-1.4	+2.1
	144del	-1.1	-1.2	-1.4	+2.1	-1.2	-1.2	-1.1	-1.2	-1.2	-1.1	+1.1	-1.3	-1.2	-1.7	-1.2	-1.2	-1.3	+1.1	-1.2	-1.6	+1.1	-1.3
	N501Y	+1.5	+1.1	-1.8	+1.6	-2.0	+1.9	+2.2	-2.0	-1.2	+4.6	+2.9	-1.2	-1.2	+1.2	-2.1	-1.6	-1.6	-1.5	-1.1	-2.4	-1.4	1.0
	A570D	+1.4	+2.2	+1.2	+2.4	+1.7	+1.6	+2.2	+1.5	1.0	+1.5	+1.4	+1.6	+1.2	+1.5	+1.5	+2.6	+1.2	+1.3	+1.8	+1.1	-1.2	+1.4
	P681H	+2.2	+1.2	-1.7	-1.5	-1.5	+1.0	+1.1	-1.4	1.0	-1.1	+1.1	+1.1	+1.2	+1.2	-1.3	+1.1	-1.1	-1.1	-1.0	-2.1	-1.3	-1.0
	T716I	+1.1	-1.1	-1.1	+1.6	+1.3	+1.3	+1.8	+1.1	1.0	+1.6	+1.2	+1.4	+1.7	+1.4	+1.3	+1.1	+1.1	+1.3	+1.1	+1.6	+1.1	+1.1
	S982A	-2.3	-1.5	-2.6	-1.8	-2.0	-1.6	-1.3	-2.5	-1.7	-1.5	-1.5	-1.5	-1.2	-1.6	-1.6	-1.7	-1.5	-1.9	-1.6	-2.4	-2.0	-1.3
	D1118H	-1.2	+1.1	-1.2	-1.4	+1.1	1.0	1.0	-1.5	-1.2	-1.1	1.0	+1.1	-1.2	-1.2	-1.6	-1.6	-1.2	-1.5	-1.2	-1.3	-1.7	-1.3
SA	SAΔ9	-6.9	-8.4	-22.7	-11.0	-6.1	-7.7	-2.9	-10.0	-4.8	-3.2	-13.0	-6.6	-3.0	-2.2	-9.2	-3.5	-2.5	-7.5	-10.4	-4.5	-15.0	-2.5
	L18F	+1.9	1.0	-1.8	-1.1	-1.3	1.0	+3.3	-1.5	1.0	+1.2	+1.8	1.0	+1.2	-1.3	+1.2	+1.2	1.0	-1.4	+1.4	-1.4	-1.5	+1.4
	D80A	+1.2	+1.5	-1.1	+2.1	+1.1	+1.5	+1.8	-1.5	+1.4	+3.0	+1.3	+1.1	+1.8	1.0	+1.2	+1.4	-1.5	-1.8	1.0	-1.8	-1.3	+1.1
	D215G	-1.3	+1.1	+1.1	-1.2	+1.3	+1.2	-1.1	-2.9	-1.1	+2.7	+1.1	-1.3	-1.1	+1.1	-1.8	-2.0	-1.2	-1.8	-1.3	1.0	-1.2	+1.1
	242-244del	-3.6	1.0	-1.3	-1.8	-1.7	-1.3	-1.7	-1.7	-1.4	-1.5	-1.6	-1.6	-1.4	-1.9	-1.4	-1.3	+1.5	+1.1	-1.3	-2.6	-1.6	-1.8
	R246I	-1.6	+1.1	-2.0	-1.1	-1.7	-1.2	+1.1	-2.1	-1.3	-1.1	1.0	-1.7	-1.5	-1.2	+1.6	1.0	+1.3	+2.0	+2.9	-4.0	1.0	-1.1
	K417N	+1.6	+1.4	-1.1	1.0	1.0	-1.2	+1.7	-1.3	+1.1	+1.4	-1.3	+1.5	+1.4	+1.8	+1.2	+1.4	-1.5	+1.9	+2.0	1.0	-1.8	+1.6
	E484K	-3.0	-2.3	-3.9	-4.0	-1.4	-2.8	-1.3	-3.3	-2.2	-2.6	-3.2	-1.8	-1.9	-2.7	-2.1	-1.6	-2.9	-11.3	-3.3	-3.2	-3.1	-1.8
	N501Y	+1.5	+1.1	-1.8	+1.6	-2.0	+1.9	+2.2	-2.0	-1.2	+4.6	+2.9	-1.2	-1.2	+1.2	-2.1	-1.6	-1.6	-1.5	-1.1	-2.4	-1.4	1.0
	A701V	-1.1	-1.2	-1.9	-2.2	-1.7	-1.6	-1.4	-1.7	+1.2	+1.1	+2.1	-1.1	-1.2	-1.3	-1.2	-1.1	-2.1	-1.5	-1.4	+1.1	-2.2	-1.5

Red: resistance >2 fold; Green: sensitization >2 fold

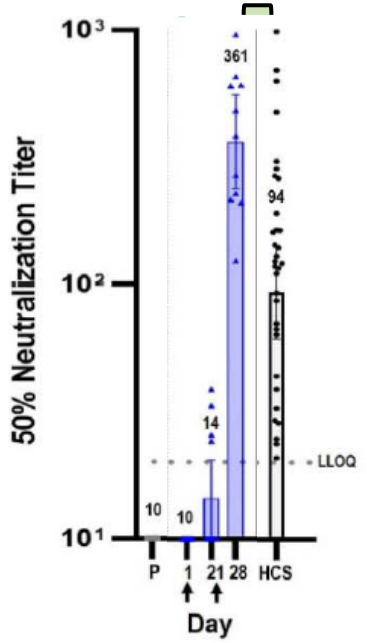
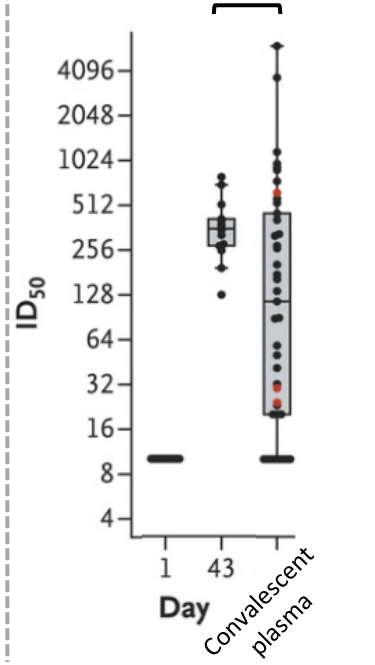
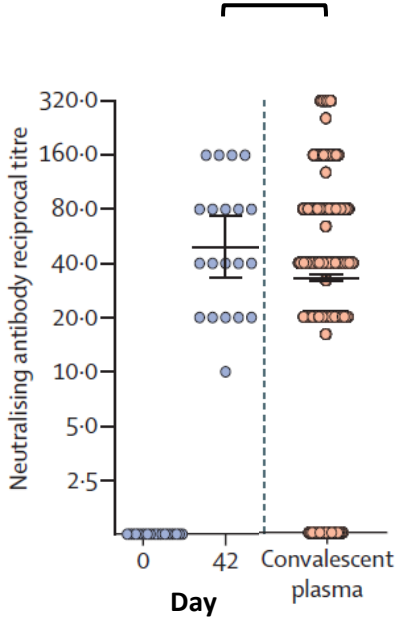
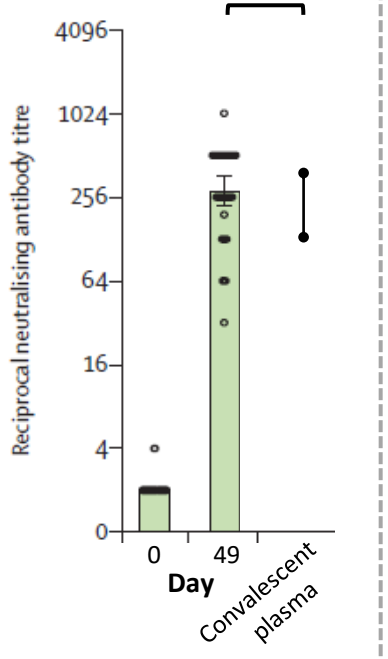
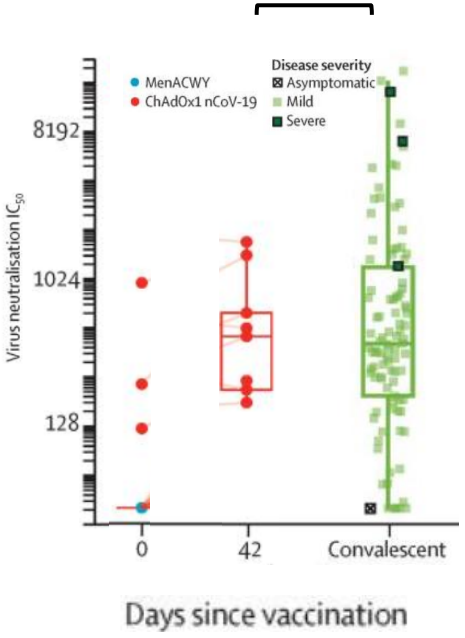


Wang &Ho BioRxiv 1-25-2021

THE D614G IS EASY TO NEUTRALIZE AS PROTECTION IS SEEN EVEN WHEN NEUTRALIZATION TITERS ARE NEAR ASSAY LLOQ

……but vaccines that induce neutralizing tires only to levels of convalescent serum may fail to control 501Y.V2

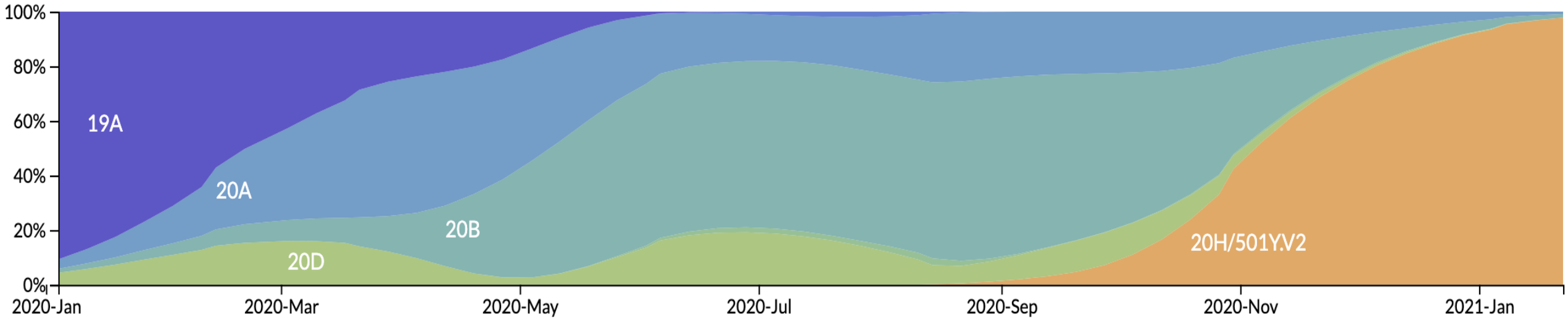
Neuts relative to convalescents:

Pfizer / BioNTech BNT162b2	**Moderna** mRNA-1273	**Gamaleya** Sputnik V	**Sinopharm** BBIP-CorV	**Oxford / Astra Zeneca** ChAdOx1
3.8-fold **higher**[1]	3.2-fold **higher**[2]	1.5-fold **higher**[3]	Comparable[4]	Comparable[5]
				
Efficacy: **95%**[6]	**94.1%**[6]	**95%**[7]	**86%**[7]	**62.1% (up to 90%)**[7]

1. 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. 2. 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. 3. wt MNA titers in subjects aged 18-60, 21 days following rAd5-S boost; HCS: mild and moderate cases only. 4. wt VNA titers (50% CPE) in subjects aged 18-59, 28 days after 2nd 4µg dose; convalescent sera 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. Primary analysis. 7. Interim analysis

Note: Figures have been cropped / re-labeled as needed to enable comparison; Convalescent sera variably sourced from severe, moderate, mild disease and asymptomatic cases

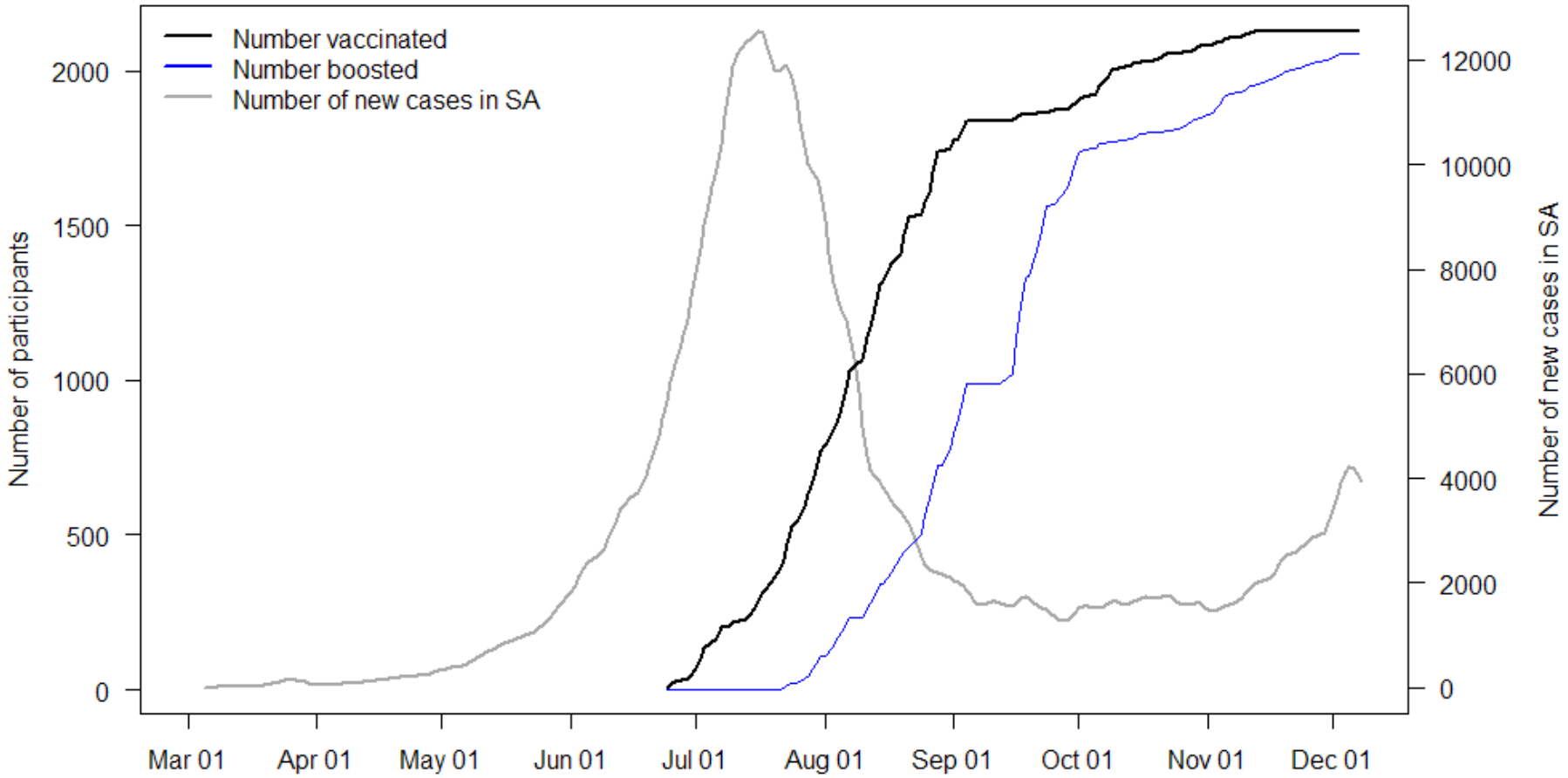
EVOLUTION OF STRAINS IN SOUTH AFRICA (NEXTSTRAIN.ORG)
501Y.V2 DOMINANT DURING EFFICACY COLLECTION WINDOW



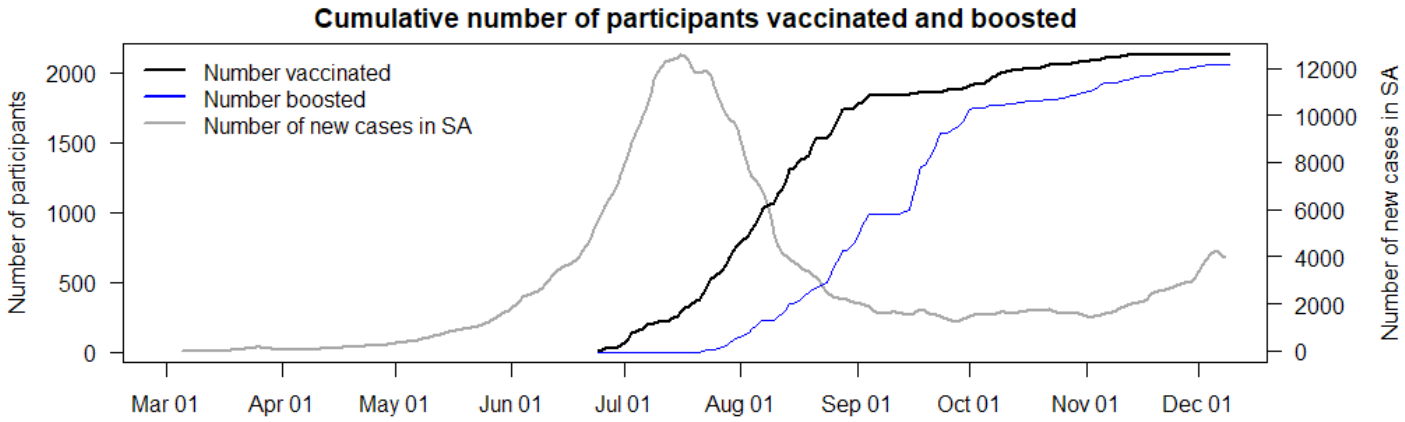
Participants entering Per-Protocol efficacy evaluation period

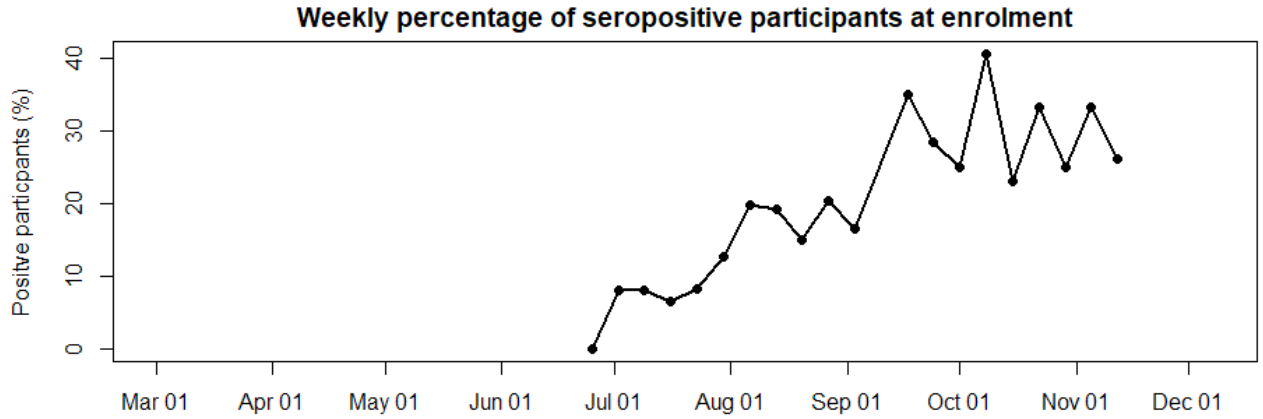
Per-Protocol efficacy endpoint accrual

TEMPORAL ASSOCIATION OF COVID-19 CASES IN SOUTH AFRICA AND RECEIPT OF 1ST AND 2ND ASSIGNED ALLOCATED DOSE IN THE CHADOX1 PHASE IIA STUDY.



SERO-POSITIVITY (N-PROTEIN) OF PARTICIPANTS ENROLLED INTO CHADOX1 VACCINE TRIAL IN SOUTH AFRICA.





Overall sero-positivity at enrolment 16.8% (356/2106)

DISCUSSION

- Early evolution of variant with multiple mutations involving the immunodominant RBD and NTB domains.
- B1.1.7 only modestly resistant to neutralization by convalescent plasma (~3 fold) and mRNA vaccines (~2 fold)
- N501Y.V2 variant >10-30 fold more resistant to neutralization by convalescent plasma and ~6.5-8.6 fold for mRNA vaccinee sera.
- Differences in immunogenicity of vaccines designed based on prototype virus may have differential effect on efficacy against N501Y.V2 variant.
- Imminent vaccine efficacy readout for Novavax, AZ and J&J vaccines from South Africa will provide efficacy readout against N501Y.V2 variant.
-

Heterologous prime-boost & prolonged dosing interval: Immunologic considerations

Arnaud Didierlaurent, PhD
Associate Professor
Translational Immunology
University of Geneva, Switzerland

Heterologous prime-boost & prolonged dosing interval

Immunological considerations

Pr. Arnaud Didierlaurent

Center of vaccinology, Geneva

Workshop: Emerging Challenges to the Development of Covid-19 Vaccines

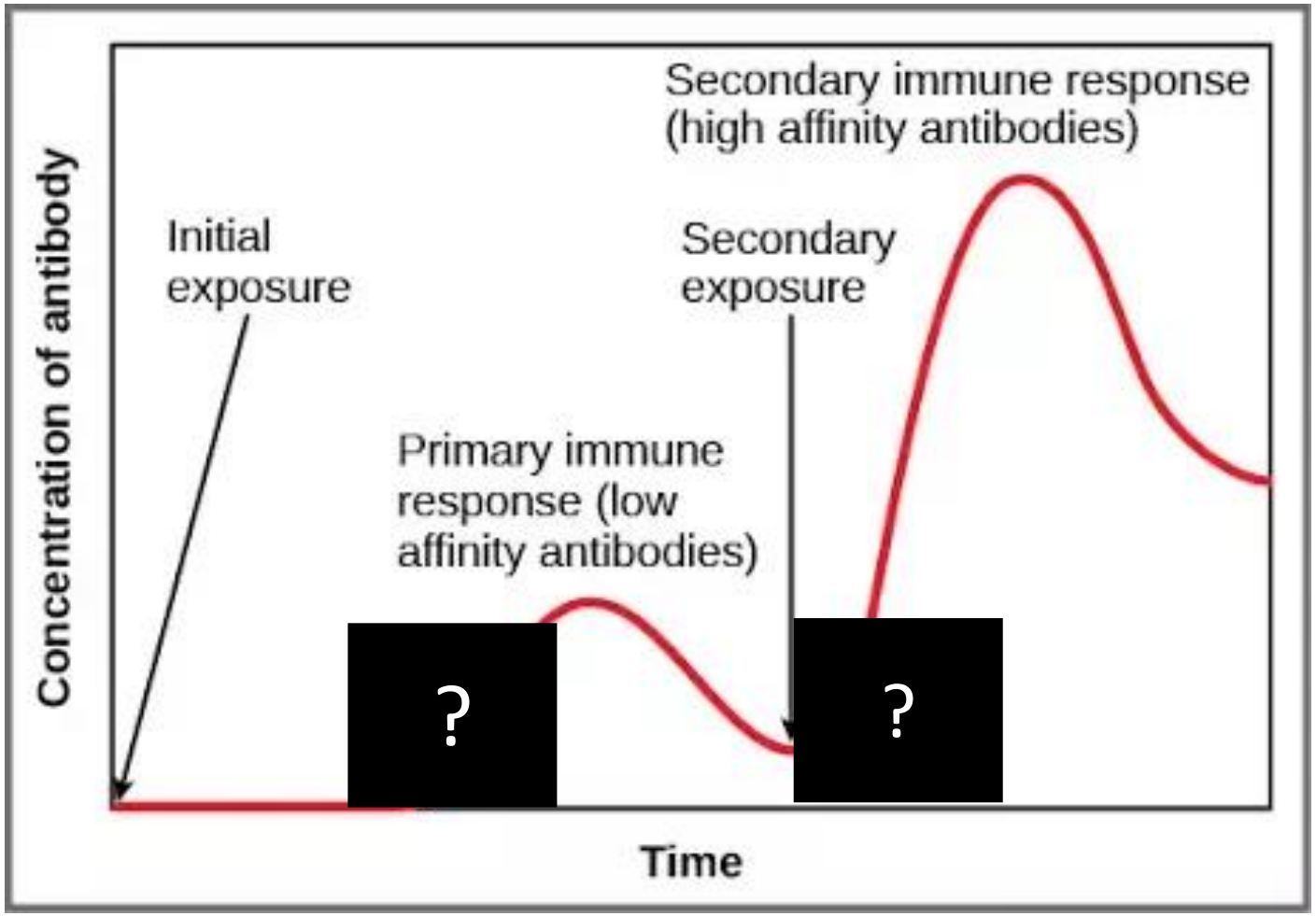
January 28th 2020

Questions

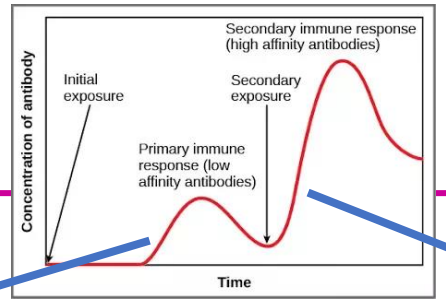
- Immunological considerations related to Mix&Match approach, including dosing intervals

- Can we expect **to modify immune response** with a mix&match approach- how would that impact recognition of current/future variants?

Prime/boost response- a complex interplay of T and B cell response



Prime/boost response- a complex interplay of T and B cell response

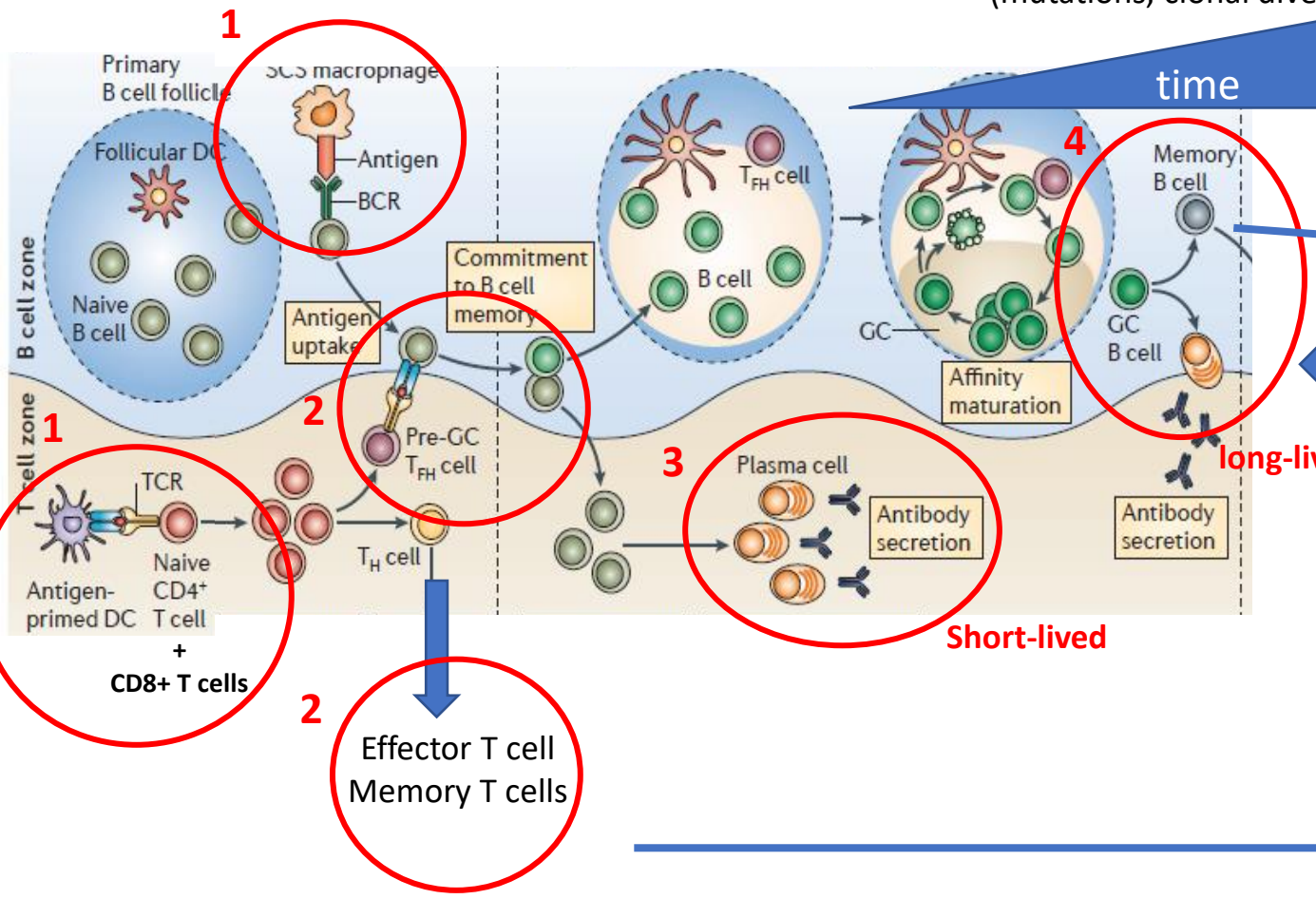


1st dose

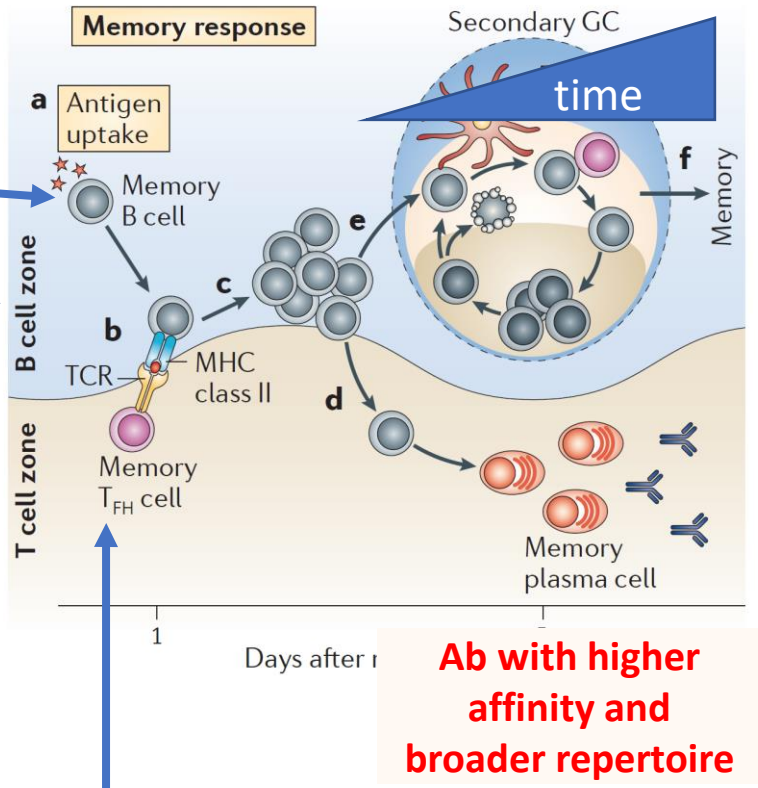
2nd dose

Affinity maturation
(mutations, clonal diversity)

Further maturation



Week/months



Ab with higher affinity and broader repertoire

McHeyzer-Williams, Nature Reviews 2012

Learnings from adjuvanted Flu vaccines on shaping antibody response

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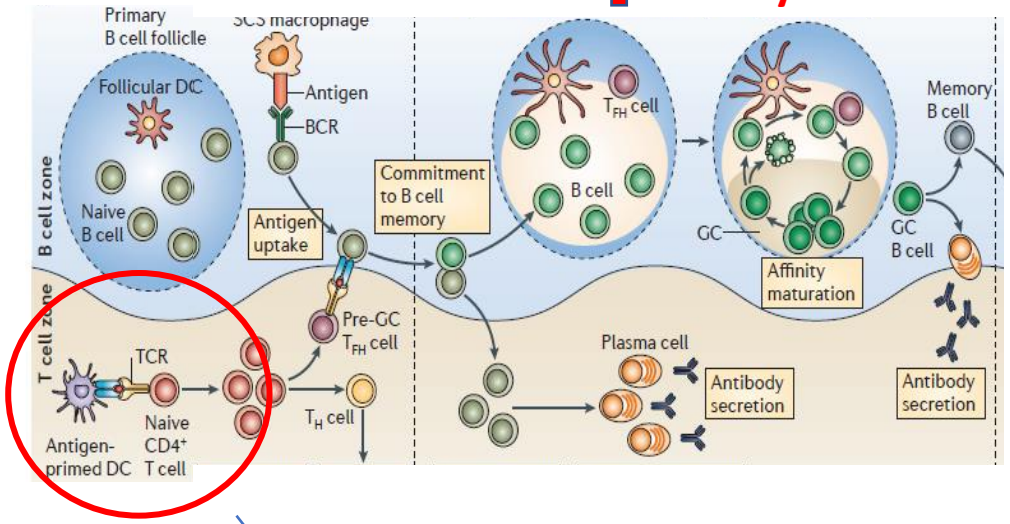
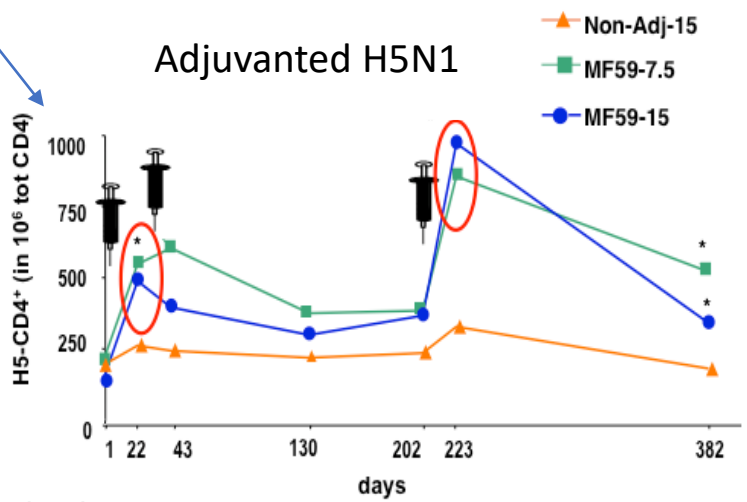
1st dose

Affinity maturation



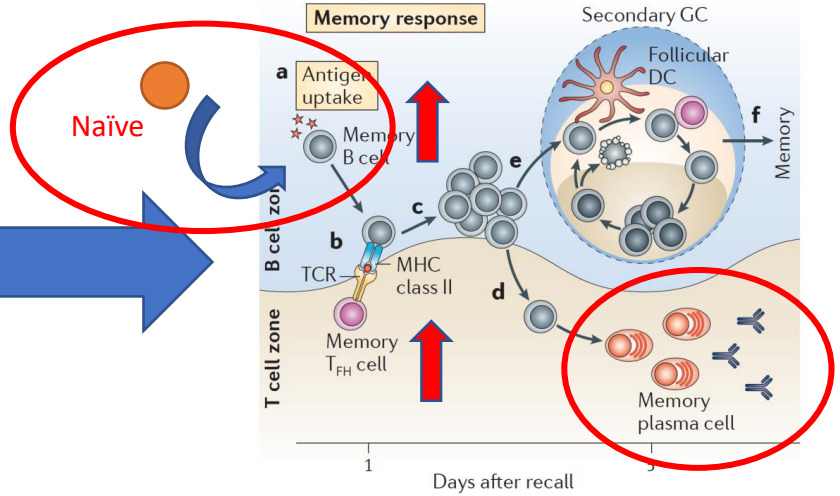


Increased T cell Response

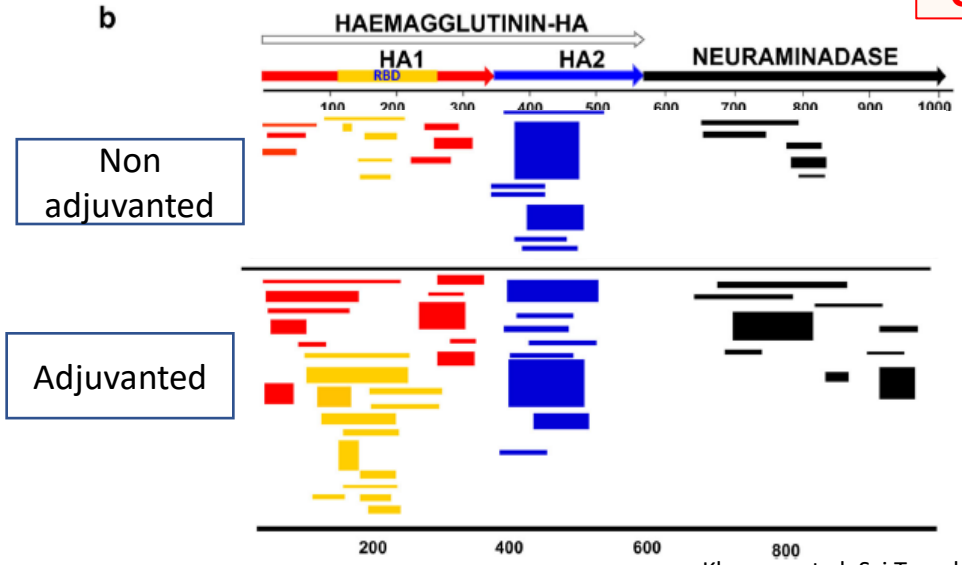
Galli et al, Proc Natl Acad Sci USA 2009

2nd dose

Affinity maturation

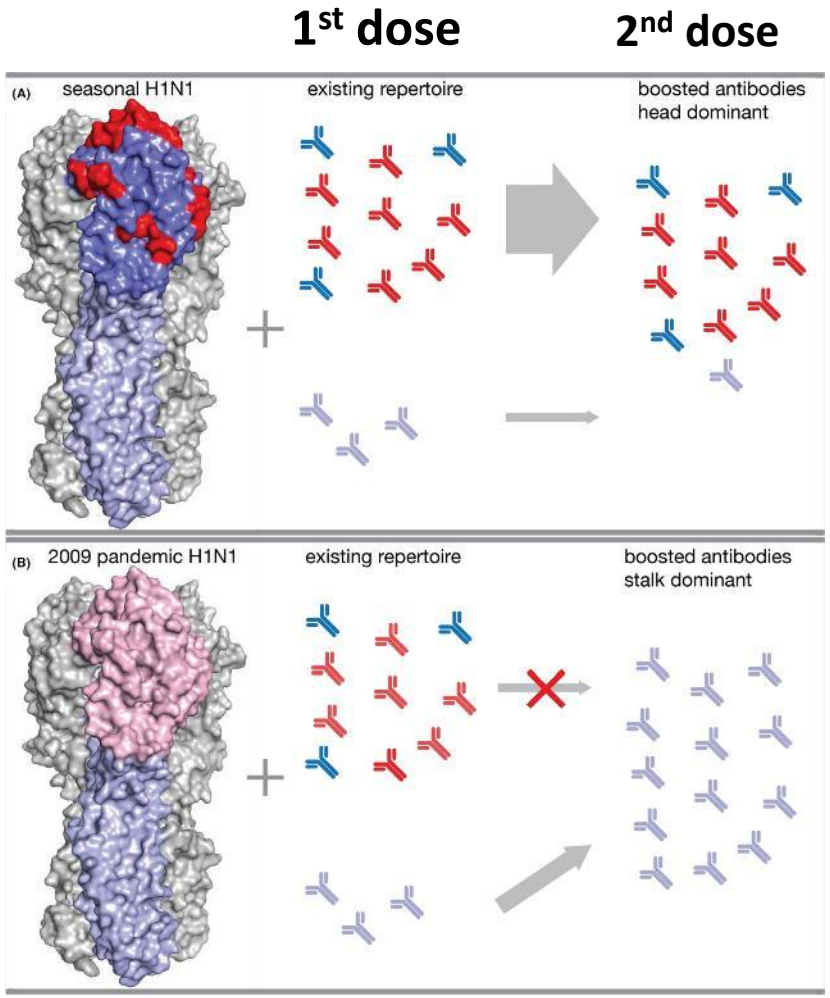


Broader repertoire
Higher affinity
Cross-neutralizing



Khurana et al. Sci Transl Med. 2011; Npj Vaccine, 2018

The “original antigenic sin” applied to vaccine interference



“drifted” strain with different head

preferential boosting of pre-existing memory B cells to repeated exposure to the same antigen

Knight, Immunological review, 2020

The “original antigen sin” applied to vaccine interference

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Priming **Boost**

0 Day 21 14mo 14mo+21d

14 months

A

B +Adj +Adj +Adj +Adj

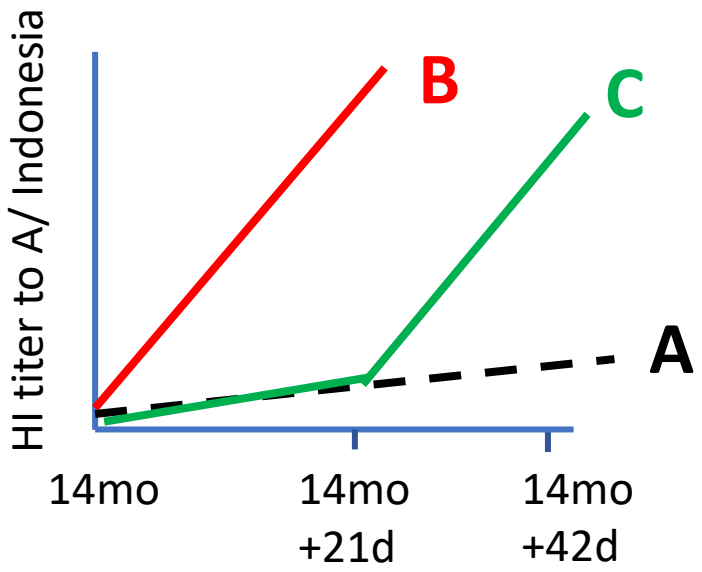
C No priming

Prime: A/Vietnam/1194/2004

Boost: A/Indonesia/5/2005

Priming with adjuvant increases Ab breadth / cross-reactivity of memory B cells

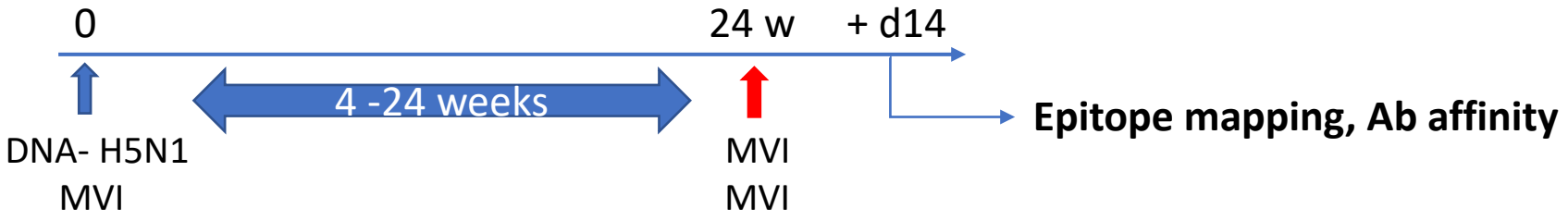
Better adaptability to variants

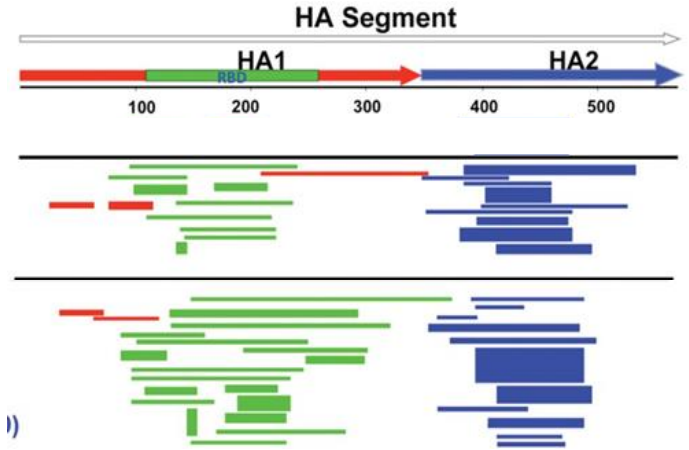


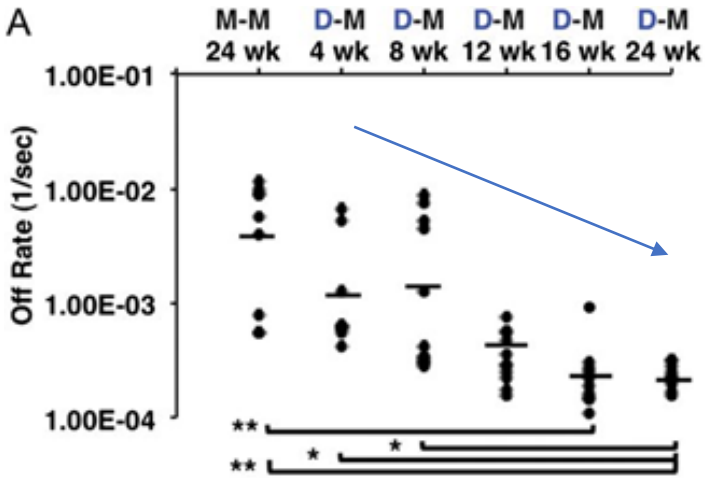
Adapted from van der Most, Science translational Medicine, 2014
Leroux-Roels, The Lancet, 2007; Leroux-Roels, Vaccine, 2010

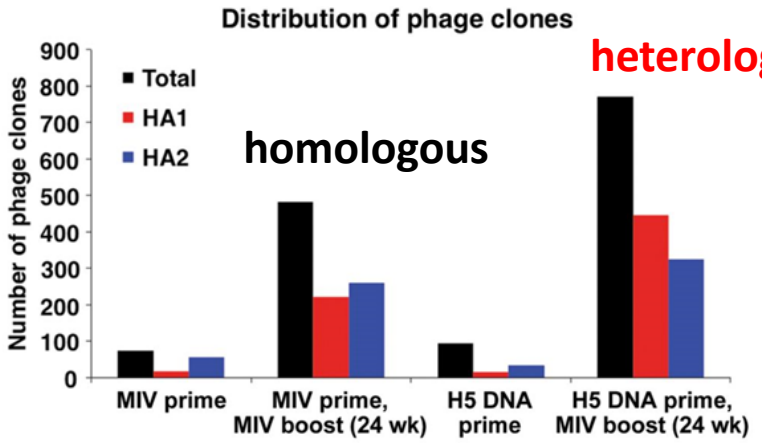
Heterologous priming can improve antibody quality (ex: DNA/inactivated Flu)

MVI: Monovalent Inactivated H5N1 Virion









Increased Ab epitope repertoire

Increased affinity with increased time interval

Khurana, JID, 2013; Ledgerwood, JID, 2013

Does the interval between 1st and 2nd dose matter? Yes, but may only be short term

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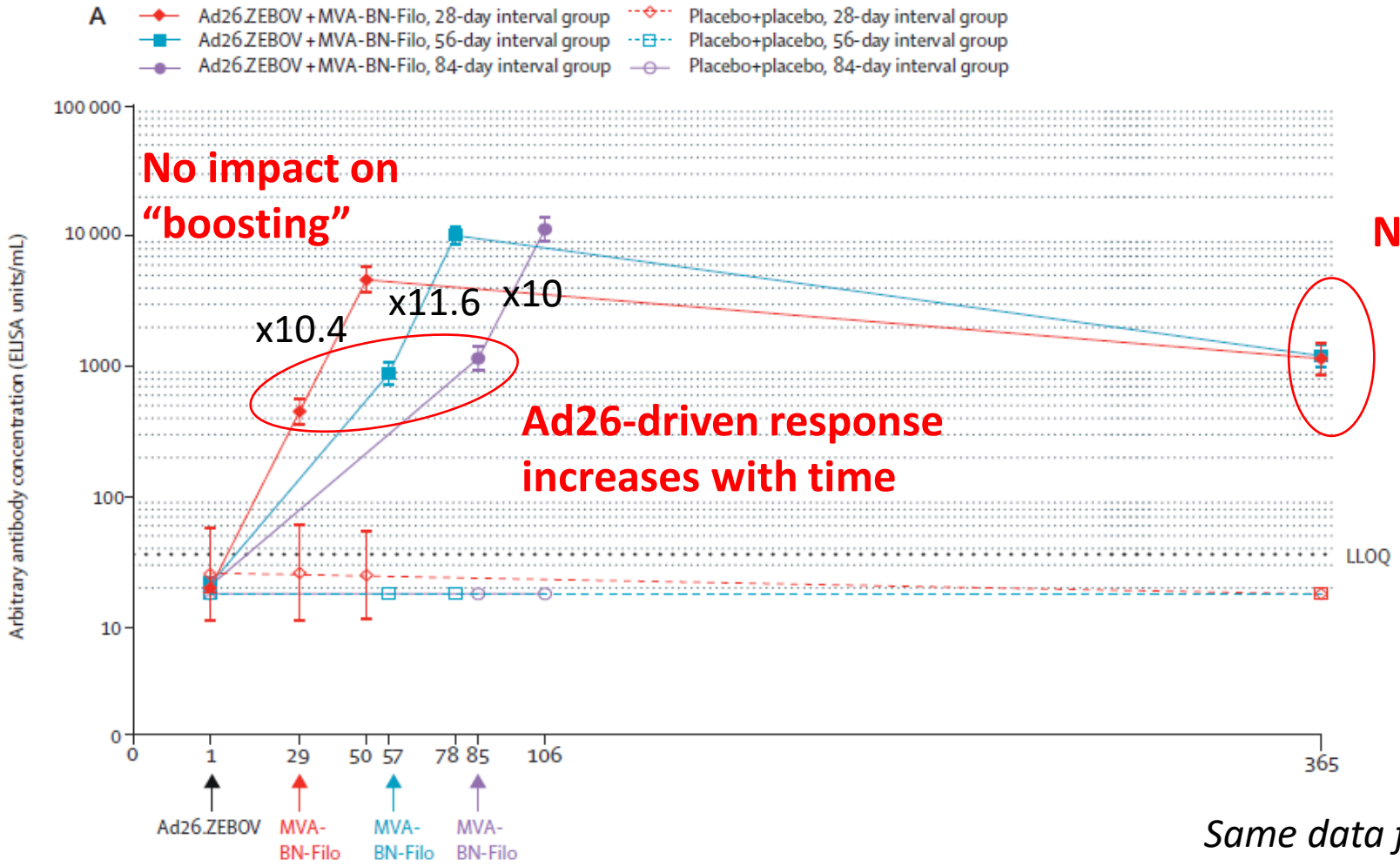
Phase II – Ad26/MVA

Compare 28 days, 56 days and 84 days intervals



No long term change

Same data for neutralizing Ab
No difference for T cell response

Pollack, Launay, NEJM, 2020

The type of vaccine used in boost influences the quality of the response

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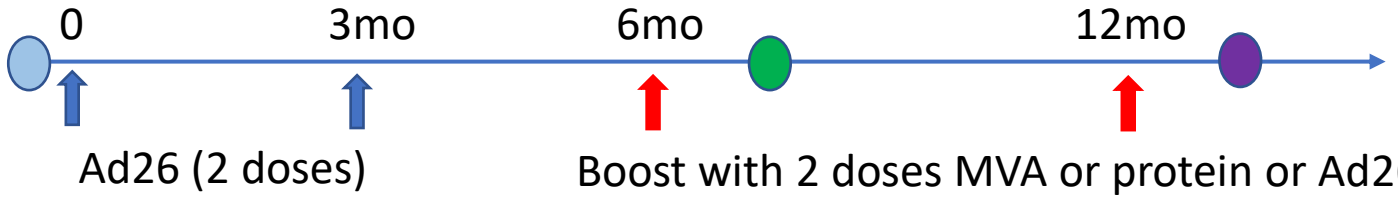
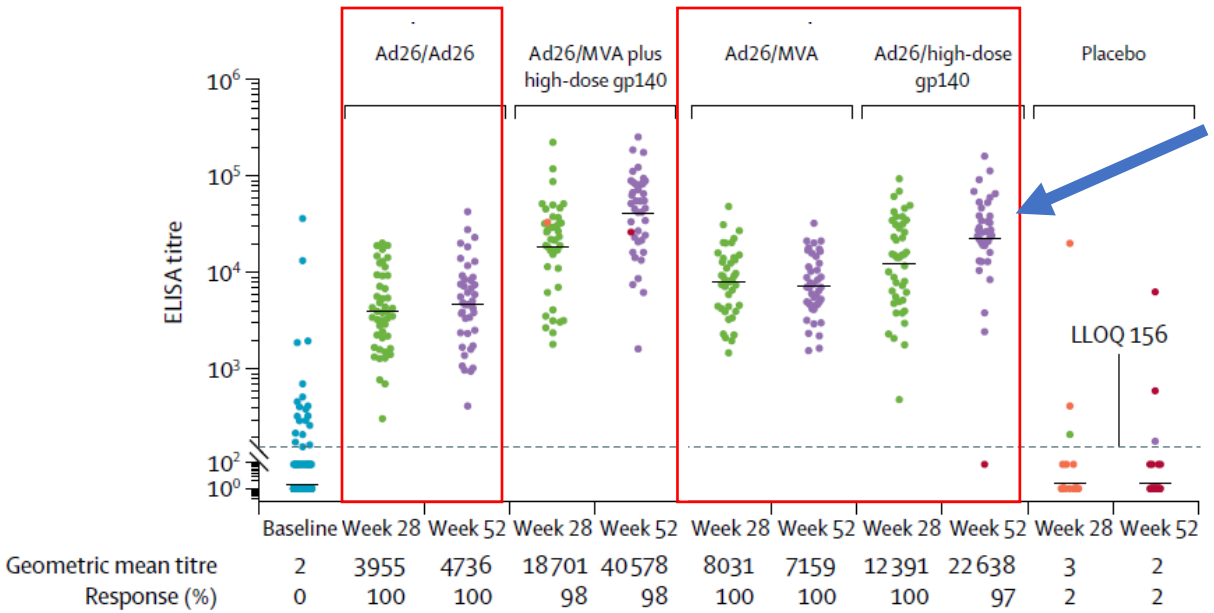
APPROACH study (phase 1/2a)
Ag: mosaic **HIV-1** (Env)/Gag/Pol
Env gp140

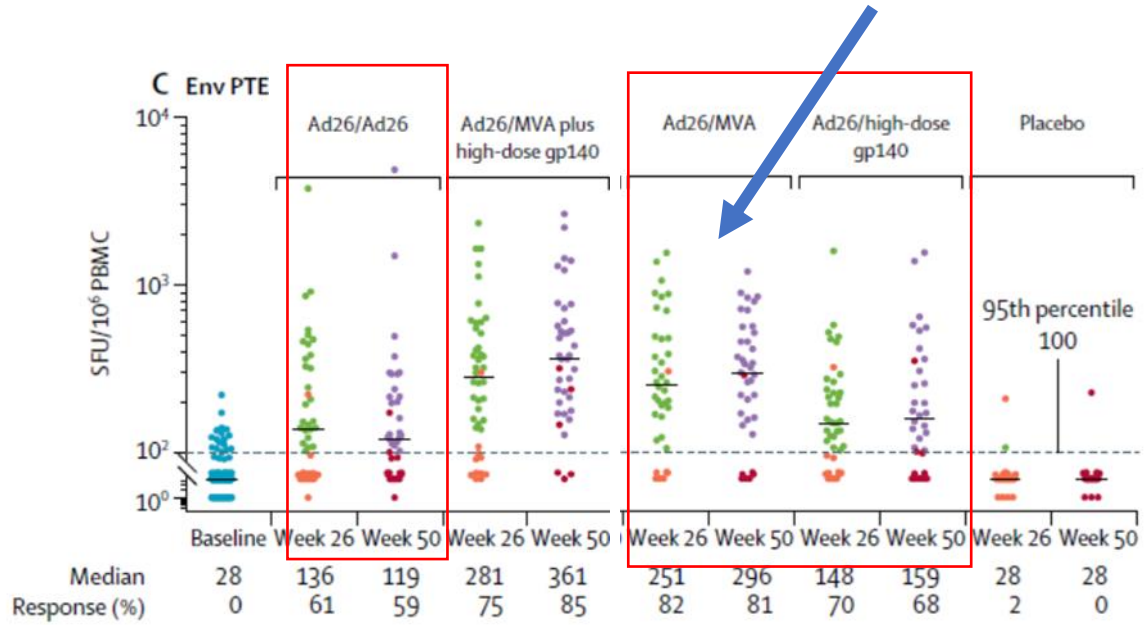


Binding Ab to gp140



<u>Protein</u> performed better than MVA at boosting antibody response

Cellular response to Env



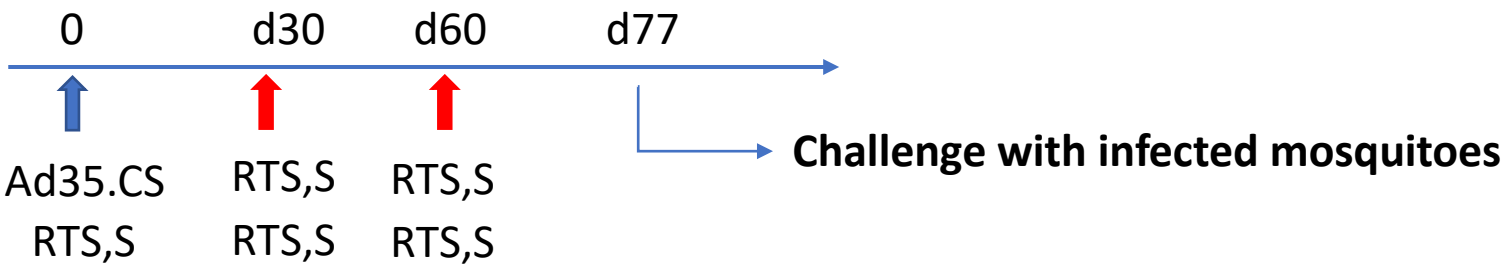
<u>MVA</u> performed better than protein at boosting cellular response

Adapted from Barouch, The Lancet, 2018

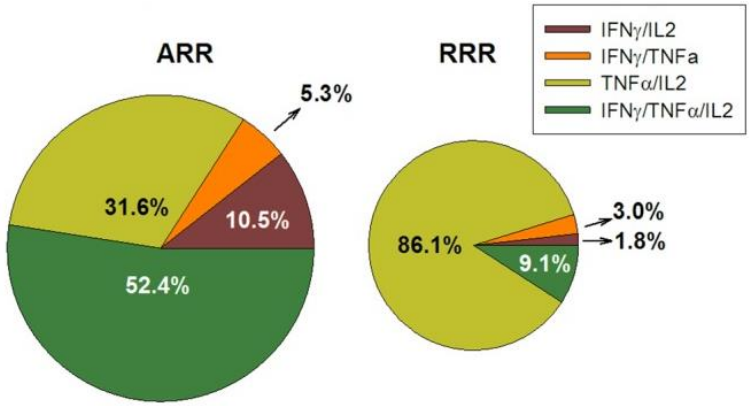
Heterologous prime/boost does not always improve outcome

Antigen: Malaria CS protein

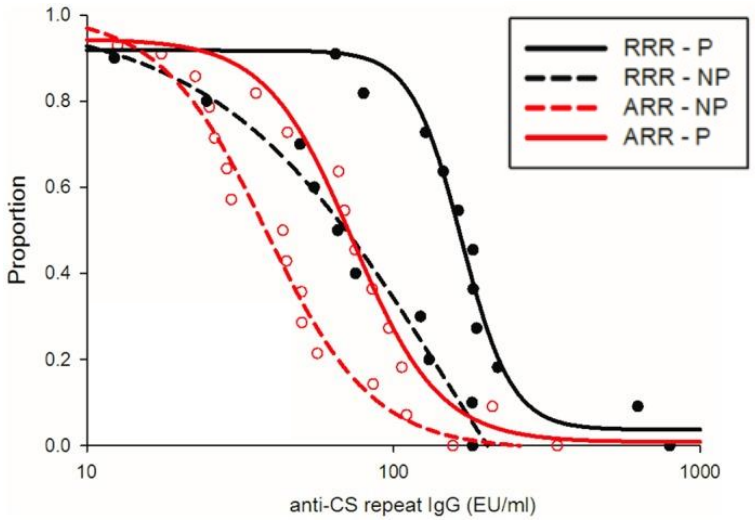
Priming with Adeno (Ad35.CS) versus RTS,S (CS/HepB in AS01)



Heterologous priming enhances CD4 T cell response

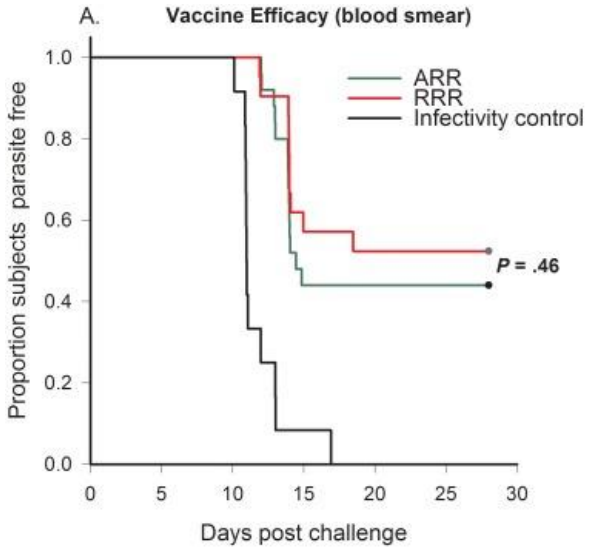


Heterologous priming reduces CS-specific Ab



P= protected
NP= non protected

No advantage for efficacy

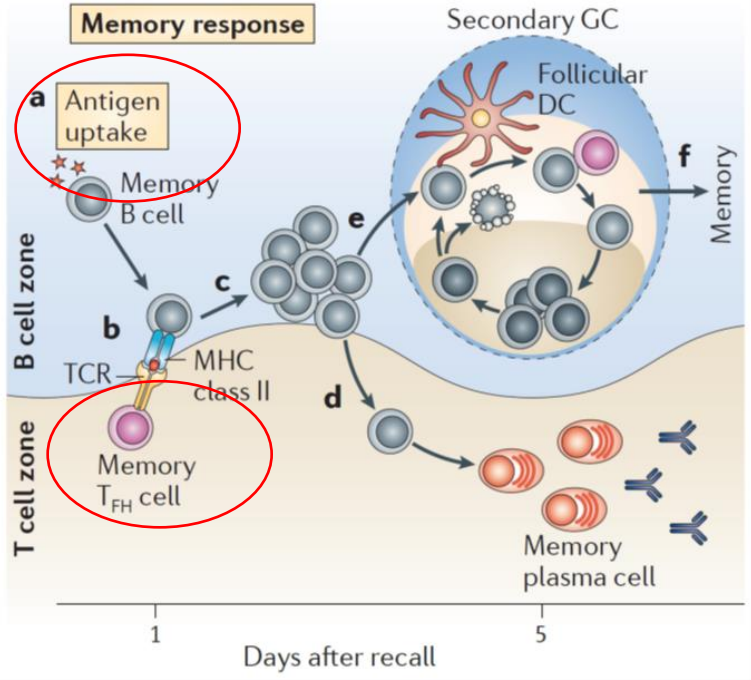


Ockenhouse, Plos one, 2015

Key points

- Priming is key! (needs good memory TFh and B cells, affinity maturation)

- Factors associated with the 2nd vaccine impacting of the quality of antibody response
  - Homology of sequence/conformation?
  - Antigen availability and presentation to memory B cells/TfH
  - Ability to stimulate innate immunity (improved Ag presentation)



- A longer interval may favour a broader repertoire and increase affinity of antibodies but may require months rather than weeks

- Boosting of T cells is likely to be less sensitive to mix & match although preferential T cell boosting (CD8 vs CD4 T for ex) cannot be excluded

Implications-future studies

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- **Clinical data are needed!**
  - Quality of response after one dose, across platforms
  - Go beyond antibody level: measure affinity, breadth, BCR repertoire, Fc function -> implication for response/efficacy against current and future variants
  - assess memory response at 1 year (revaccination?)

- Assess response in **previously infected** individuals due to pre-existing immunity-Bridging studies in animal models (NHP)

- **Variant-adapted antigens** may be required to further broaden antibody repertoire and cross-reactivity

Thank you

Workshop: Emerging Challenges to the Development of Covid-19 Vaccines

January 28th 2020

Comparing COVID-19 Vaccine Schedule Combinations (Com-COV)

Matthew Snape, MBBS FRCPCH MD

Associate Professor
Paediatrics and Vaccinology
University of Oxford

Oxford Vaccine Group
University of Oxford

Comparing COVID-19 Vaccine Schedule Combinations (Com-COV)

Matthew Snape

Associate Professor Paediatrics and Vaccinology

COM-COV
Comparing COVID-19 Vaccine Schedule Combinations

Study commencing Feb 2021

Funded by UK Vaccine Task Force

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Brief to assist flexibility in vaccine delivery

- If vaccine A given for dose 1, can we use vaccine B for dose 2?
  - Improves flexibility for mass immunisation
  - Protects against disruption in vaccine supply

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Comparing COVID-19 Vaccine Schedule Combinations

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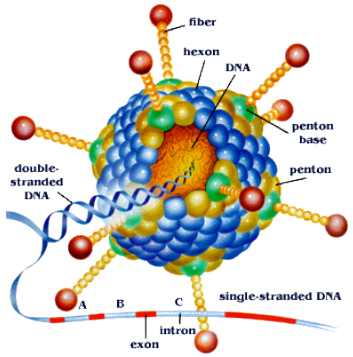
AstraZeneca/Oxford ChAdOx1 nCOV-19



Chimpanzee Adenovirus vector

Pfizer/BioNTech BNT162b2

mRNA, lipid nanoparticle

Potential to add additional vaccines (e.g. protein/adjuvant, whole virus) as they are approved

Background

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Comparing COVID-19 Vaccine Schedule Combinations

Public Health England | Department of Health

Immunisation against infectious disease

Provisional guidance subject to MHRA approval of vaccine supply

14a

COVID-19 - SARS-CoV-2 NOTIFIABLE

The virus

Previous incomplete vaccination

If the course is interrupted or delayed, it should be resumed using the same vaccine but the first dose should not be repeated. There is no evidence on the interchangeability of the COVID-19 vaccines although studies are underway (JCVI, 2020). Therefore, every effort should be made to determine which vaccine the individual received and to complete with the same vaccine. For individuals who started the schedule and who attend for vaccination at a site where the same vaccine is not available, or if the first product received is unknown, it is reasonable to offer a single dose of the locally available product. This option is preferred if the individual is likely to be at immediate high risk or is considered unlikely to attend again. In these circumstances, as both the vaccines are based on the spike protein, it is likely the second dose will help to boost the response to the first dose. For this reason, until additional information becomes available, further doses are not required.

Britain Opens Door to Mix-and-Match Vaccinations, Worrying Experts

If a second dose of one vaccine isn't available, another may be substituted, according to the guidelines.

Britain has been moving away from the dosing regimens tested in late-stage clinical trials of the vaccines the country is deploying. Oli Scarff/Agence France-Presse — Getty Images

By Katherine J. Wu

Jan. 1, 2021

Coronavirus: BMJ urges NYT to correct vaccine 'mixing' article

2 January

The editor of the British Medical Journal has asked the New York Times to correct an article that says UK guidelines allow two Covid-19 vaccines to be mixed.

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- Subsequent developments
  - Adaptation of UK schedule to include 12 week dosing interval
  - Emergence of novel SARS-Cov-2 variants

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Single-Blind, Non-Inferiority RCT

Cohort	Number	1st dose (Day 0)	2nd dose		Blood tests
			Day 28	Day 84	
General (n=720)	90	ChAdOx1 nCOV-19	ChAdOx1 nCOV-19		Day 0, 28, 56, 182, 364 (28 day interval groups)
	90	ChAdOx1 nCOV-19		ChAdOx1 nCOV-19	
	90	ChAdOx1 nCOV-19	BNT162b2		Day 0, 56, 84, 112, 182, 364) 84 day interval groups)
	90	ChAdOx1 nCOV-19		BNT162b2	
	90	BNT162b2	BNT162b2		
	90	BNT162b2		BNT162b2	
	90	BNT162b2	ChAdOx1 nCOV-19		
	90	BNT162b2		ChAdOx1 nCOV-19	

Inclusion/Exclusion

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- Population
  - Adults aged 50 and over, allowing controlled mild-moderate co-morbidities
  - BAME recruitment to be representative of UK population
- Exclusion
  - Severe co-morbidities
  - Pregnancy or intent to become pregnant
  - Known confirmed previous SARS-CoV-2 infection
  - Immunosuppression
  - History of angioedema/anaphylaxis/carry epi-pen

Immunogenicity Assays:

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Assay	Laboratory/Assay
Anti-spike IgG	Nexelis
Neutralising antibodies against SARS-CoV-2	Porton Down
Anti-nucleocapsid immunoglobulins	Roche (Porton Down)
Pseudo neutralising antibodies	Nexelis
Cellular immune responses by ELISpot	Oxford Immunotech
Cellular immune responses by ICS (Th1/Th2)	Oxford Immunotech

UK Vaccine Task Force preferred suppliers – allows standardization across multiple studies

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- Primary Outcome
  - Non-inferiority of immunogenicity of heterologous with homologous prime/boost schedules administered at 4 week intervals (Anti-spike IgG)

Number (Immunology and General combined, 4 week interval)	1st dose	2nd dose
115	ChAdOx1 nCOV-19	ChAdOx1 nCOV-19
115	ChAdOx1 nCOV-19	BNT162b2
115	BNT162b2	BNT162b2
115	BNT162b2	ChAdOx1 nCOV-19

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- Primary Outcome
  - Non-inferiority of immunogenicity of heterologous with homologous prime/boost schedules administered at 4 week intervals (Anti-spike IgG)

- Secondary
  - Immunogenicity – Anti-Spike IgG 4 weeks post second dose (all groups)
  - Safety & reactogenicity
  - Further immunogenicity assays including neutralising antibodies and pseudo-neutralising antibodies
  - Immunogenicity, reactogenicity and safety of COVID-19 vaccines in participants sero-positive at baseline
  - Characterise SARS-CoV2 infections (and immune response) in participants immunised with COVID-19 vaccines: WGS of viral strains

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Comparing COVID-19 Vaccine Schedule Combinations

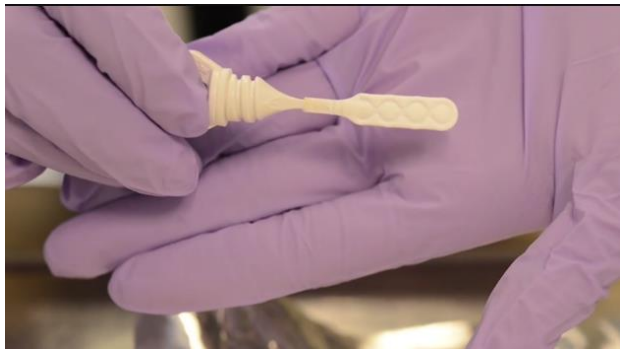
Single-Blind, Non-Inferiority RCT

Cohort	Number	1st dose (Day 0)	2nd dose	
			Day 28	Day 84
General (n=720)	90	ChAdOx1 nCOV-19	ChAdOx1 nCOV-19	
	90	ChAdOx1 nCOV-19		ChAdOx1 nCOV-19
	90	ChAdOx1 nCOV-19	BNT162b2	
	90	ChAdOx1 nCOV-19		BNT162b2
	90	BNT162b2	BNT162b2	
	90	BNT162b2		BNT162b2
	90	BNT162b2	ChAdOx1 nCOV-19	
	90	BNT162b2		ChAdOx1 nCOV-19
Immunology (n=100)	25	ChAdOx1 nCOV-19	ChAdOx1 nCOV-19	
	25	ChAdOx1 nCOV-19	BNT162b2	
	25	BNT162b2	BNT162b2	
	25	BNT162b2	ChAdOx1 nCOV-19	

Exploratory objectives

- Systems serology on immunology cohort
  - ADMP (antibody-dependent monocyte phagocytosis)
  - ADNP (antibody-dependent neutrophil phagocytosis)
  - ADCD (antibody-dependent complement deposition)
  - ADNKA (antibody-dependent NK cell activation)
  - Quantification of antibody class and subclasses via multiplex ELISA

- Mucosal immunity on immunology cohort
  - IgA & secreted IgG using SAM-strips



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The following are optional and additional, answering "No" to any will not affect your ability to participate in the study.		
15. I agree my contact details may be stored so that I may be informed of opportunities to participate in future vaccine related research. I understand that agreeing to be contacted does not oblige me to participate in any further studies.	**15** ___ ___	No o
16. I agree that any unused or leftover samples may be stored with a licenced Biobank for future research, here and abroad.	**16**___ ___	No o
17. I agree that cells from my blood may be used to produce specific antibodies ('monoclonal antibodies') which could be used in commercial activity in the future. I understand that I will not gain any direct personal benefit from this.	**17** ___ ___	No o
18. I agree that DNA (genetic material) from my study samples may be stored with a licenced Biobank for future research.	**18** ___ ___	No o

Serum and PBMC store for testing against newly emergent strains

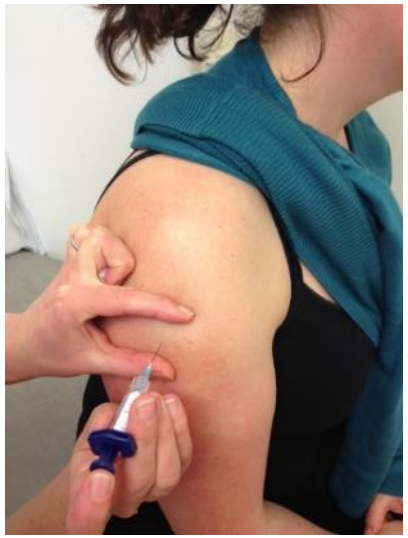
Safety & Reactogenicity

- Solicited reactions 7 days post vaccine

Symptoms (graded daily)	
Temperature	Myalgia
Feverishness	Nausea
Chills	Vomiting
Headache	Arthralgia
Generally unwell	Fatigue
Injection site reactions: pain, pruritus, heat, redness, oedema, induration	

- Unsolicited reactions 28 days post vaccine
  - Free-text for participants to enter

- Medically-attended events to 3 months post boost
  - Unscheduled medical appointments



Adverse Events of Special Interest

(Brighton collaboration definition1)

- Immunologic
  - Anaphylaxis
- Neurological
  - Isolated anosmia/ageusia*
  - Guillain-Barre Syndrome
  - Acute disseminated encephalomyelitis (ADEM)
  - Aseptic meningitis
  - Meningoencephalitis
  - Peripheral facial nerve palsy
  - Generalised convulsion
  - Myelitis
- Haematological
  - Thrombosis**
  - Stroke
  - Coagulation disorder (includes coagulopathy, thrombosis, thromboembolism, internal/external bleed and stroke)
  - Thrombocytopaenia***
  - Eosinophilia****
  - Lymphadenopathy
- Cardiac
  - Acute cardiovascular injury (includes myocarditis, pericarditis, arrhythmias, heart failure, infarction)
- Dermatological
  - Chilblain-like lesions
  - Single organ cutaneous vasculitis
  - Erythema multiforme
  - Alopecia
- Gastrointestinal
  - Acute liver injury †† †
  - Appendicitis
- Respiratory
  - ARDS (In the absence of infective aetiology, inc. COVID-19)
- Renal
  - Acute kidney injury
- Other
  - COVID-19

COVID-19 Pathway (C19P)

Purpose

1. Safety – Assessment for disease enhancement
2. Identify possible vaccine escape (viral WGS)

Eligibility

- After boost
- Within 7 days (+/- 2) of a positive test
- SARS-CoV-2 positivity (asymptomatic or symptomatic)
- Initial testing done outside trial (NHS, occupational)

Pathway structure

- Participant should be assessed for severity of disease at first contact with positive result
- Symptom e-diary to commence from notification to trial team and for at least 7 days

In-person visit

- Assessment by study doctor
  - Examination
  - Observations including Sp02
- Immunology and safety bloods
- Nasopharyngeal swab for SARS-CoV-2
  - For WGS. Will not be processed in real-time. Results will not be available clinically

NB: will still ask participants to notify us of positive tests before boost, but will not be invited for visit

Approval status & Timelines

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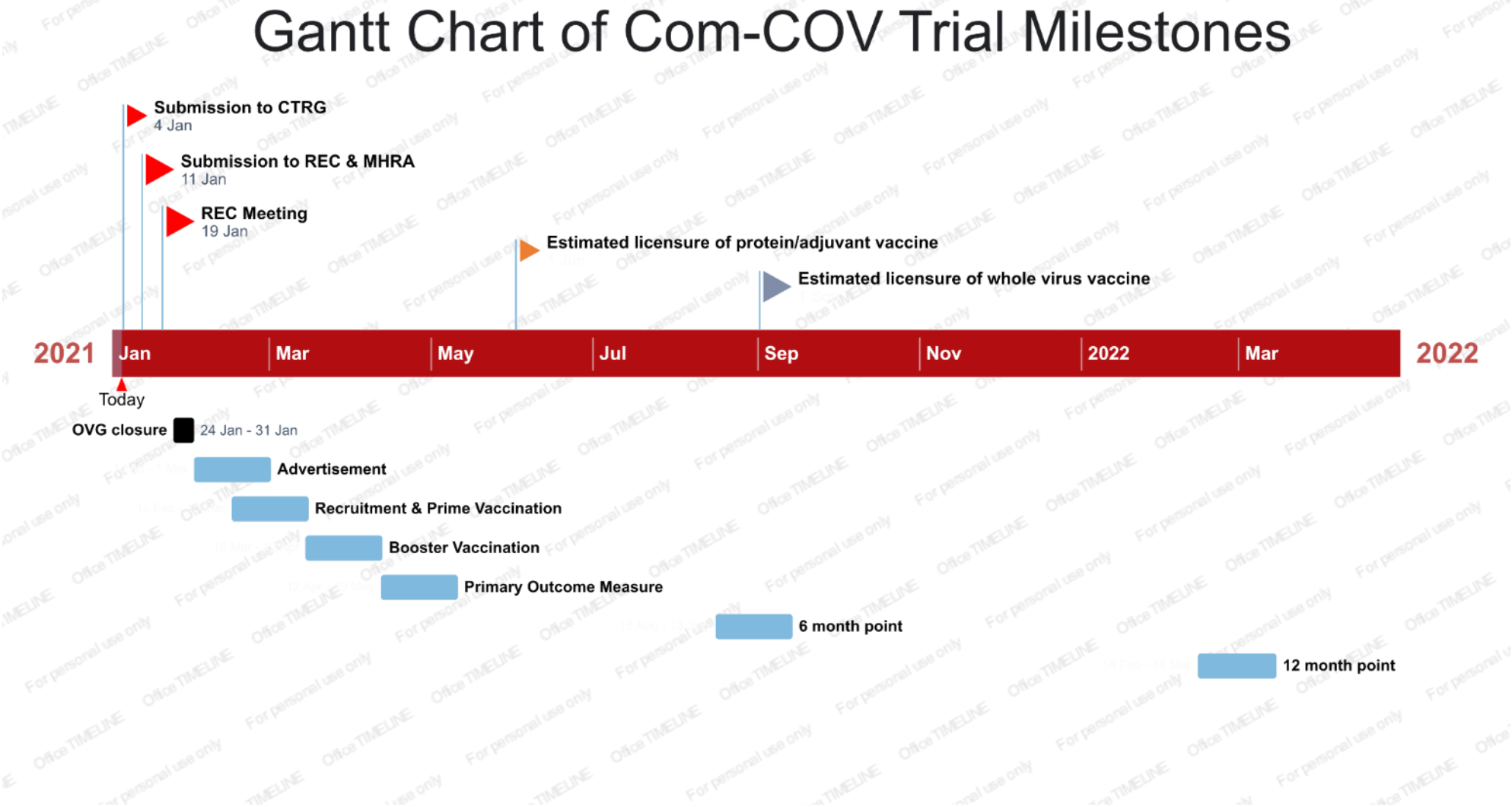


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NIHR
Oxford Biomedical
Research Centre


Public Health
England


University of Nottingham Health Service
NHS


UCL


HM Government


University of
BRISTOL


LSTM
LIVERPOOL SCHOOL
OF TROPICAL MEDICINE


Oxford University Hospitals NHS
NHS Foundation Trust


St George's University Hospitals NHS
NHS Foundation Trust


UNIVERSITY OF
OXFORD


NHS
University Hospitals
Birmingham
NHS Foundation Trust


NHS
North Bristol
NHS Trust


NHS
University Hospital Southampton
NHS Foundation Trust

Panel Discussion

Moderated By:

Jakob Cramer, MD

Head of Clinical Development

Coalition for
Epidemic Preparedness
Innovations (CEPI)

Discussion Panel Members and Example Questions

Panel Members

- **Phil Krause, MD, MBA**
  Deputy Director
  US FDA

- **Marco Cavaleri, PhD**
  Head of Biological Health Threats and Vaccines Strategy
  European Medicines Agency

- **Andrew Pollard, MBBS, PhD**
  Professor of Paediatric Infection and Immunity
  University of Oxford

+ Presenters from Part 2

Potential Discussion Questions

1. Will regulators require evidence on cross-neutralization against new variants?

2. Some countries strictly adhere to licensure / labels because of liability issues – what data would be required to expand label claims accordingly? Interchangeability versus heterologous prime-boost: Specific regulatory considerations?

3. In case of future vaccine adaptation, what clinical evidence should be generated now with existing vaccines to fill in gaps and to accelerate / facilitate vaccine adaptation in future (e.g. as a variation to existing licensures)?

4. For some of the COVID-19 vaccines and new platform technologies, do we need to understand more about immune responses post single dose in order to be able to consider booster dosing / heterologous prime-boost?

5. Should we in particular have a closer look at the immune response post single dose in seropositive subjects to prepare for future strategies with vaccines adapted to new variants?

Expanding access to vaccine/filling-in clinical development gaps: CEPI new Call For Proposals (CFP) on clinical trials

Jakob Cramer

Head of Clinical Development

Coalition for Epidemic Preparedness Innovations (CEPI)

Call for Proposals

Expand access to COVID-19 vaccines and rapid response to clinical development gaps

January 28, 2020

Objectives

Support clinical trials / trial amendments to rapidly **expand access to and confidence in** COVID-19 vaccines by

- generating clinical evidence in **special / sub-populations / age groups** or
- addressing **clinical development gaps**.

Clinical trials which expand access and capacity in **low- and middle-income countries (LMICs)** are particularly encouraged.

A new Call for Proposals will address significant gaps in Clinical Trials to ensure all vulnerable populations will be protected

SCOPE

- Support **new / separate trial(s) or amendment(s)** (pre- or post-licensure)
- Vaccines must have **entered clinical development phase**
- Have a CDP available & pathway to EUA or similar
- Evidence generated with the funded trial(s) must generate **new evidence / investigate new objectives** considered relevant to expand access to vaccines or fill-in research gaps
- It is not the intent of this CfP to support clinical trials already included in the core Clinical Development Plan towards EUA or similar (e.g., dose selection, general vaccine efficacy)
- Funded clinical trials should be able to **start within 6 months after contracting**.
- **Clinical trials in and applicants from LMICs** are particularly encouraged

Examples of Clinical gaps CEPI aims to address particularly for LMICs

GAPS

- Studies in pregnant and lactating women
- Paediatric studies
- Other special populations (e.g., immunocompromised)
- Booster studies
- Increasing / broadening the immune response, for example
- Prolonged dosing interval for primary immunisation
- Heterologous prime-boost regimen (also addresses ‘mix-&-match’)
- Dose sparing strategies including single-dose primary vaccination regimens
- Concomitant administration of routine immunizations
- Vaccine efficacy against viral shedding, asymptomatic infection and transmission
- Vaccine efficacy against new SARS-CoV-2 variants: Sequencing breakthrough cases in clinical trials
- Correlate-of-Protection studies

See WHO Consultation on COVID-19 Research Agenda in 2021, held January 15th 2021

Call for Proposals

- Rolling call: Open Jan 28th to May 28th
- https://cepi.net/get_involved/cfps/
- Contact: cfp@cepi.net

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/
- 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 vaccine

Clinical Development & Operations SWAT Team