COVAX

COVID-19 Vaccine Development in an Increasingly Seropositive World

Clinical Development & Operations SWAT Team | Wednesday October 27, 2021

CEPI

Gavi The Vaccine Alliance

World Health Organization

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Meeting Norms and Recording Disclaimer

- Throughout the workshop, please ask any questions in the "**Q&A**" function. If you see that your question is already asked, you can "like" the question in the "**Q&A**" function.

- This workshop will be **recorded**. Please be mindful of the diverse audience attending the meeting when participating in open discussions.

Welcome & Meeting Objectives

Peter Dull, MD

Deputy Director,

Integrated Clinical Vaccine Development,

Bill & Melinda Gates Foundation (BMGF)

Workshop Agenda

Time (CET)	October 27, 2021 -Topics	Speakers
15:00-15:10	Part I - Welcome, meeting objectives and updates	Peter Dull, BMGF
15:10-15:20	Global Covid19 seroprevalence studies in unvaccinated populations, 2020-2021	Emmanuelle Espie, CEPI
15:20-15:30	Vaccination among the previously infected: Immunology and effectiveness	Florian Krammer, Icahn School of Medicine at Mount Sinai
15:30-15:40	Vaccination among the previously infected - Lessons from Clover's phase 3 efficacy study	Htay Htay Han, Clover
15:40-15:50	Covid-19 vaccine delivery update	Emily Nickels, BMGF
15:50-16:05	Heterologous COVID-19 Booster Vaccine studies Fractional doses – research gaps	Paul Oloo, CEPI Christof Vinnemeier, CEPI
16:05-16:15	Heterologous vaccination: what can we anticipate in terms of breadth and durability?	Robbert van der Most, CEPI
16:15-16:25	Q&A Session for Part I	Moderated by Peter Dull
16:25-16:35	Part II - Regulatory Considerations for Booster Vaccinations	Jakob Cramer, CEPI
16:35-16:45	How the USA Increased Its Access to Seasonal Influenza Vaccines 15 Years Ago	Bruce Innis, PATH
16:45-17:00	Surrogate markers and correlates of protection: immuno-bridging in an increasingly primed population	Edde Loeliger, CEPI
17:00-17:10	Success criteria for phase 3 immunologic non-inferiority trial for COVID-19 vaccines	Christian Taucher, Valneva
17:10-17:55	Panel Discussion: Regulatory considerations for approach to the demonstration of efficacy in setting of increased COVID-19 seropositivity – Relevance of learnings from influenza vaccines	Moderated by Peter Dull, BMGF
17:55-18:00	Wrap Up & Next Steps	Jakob Cramer

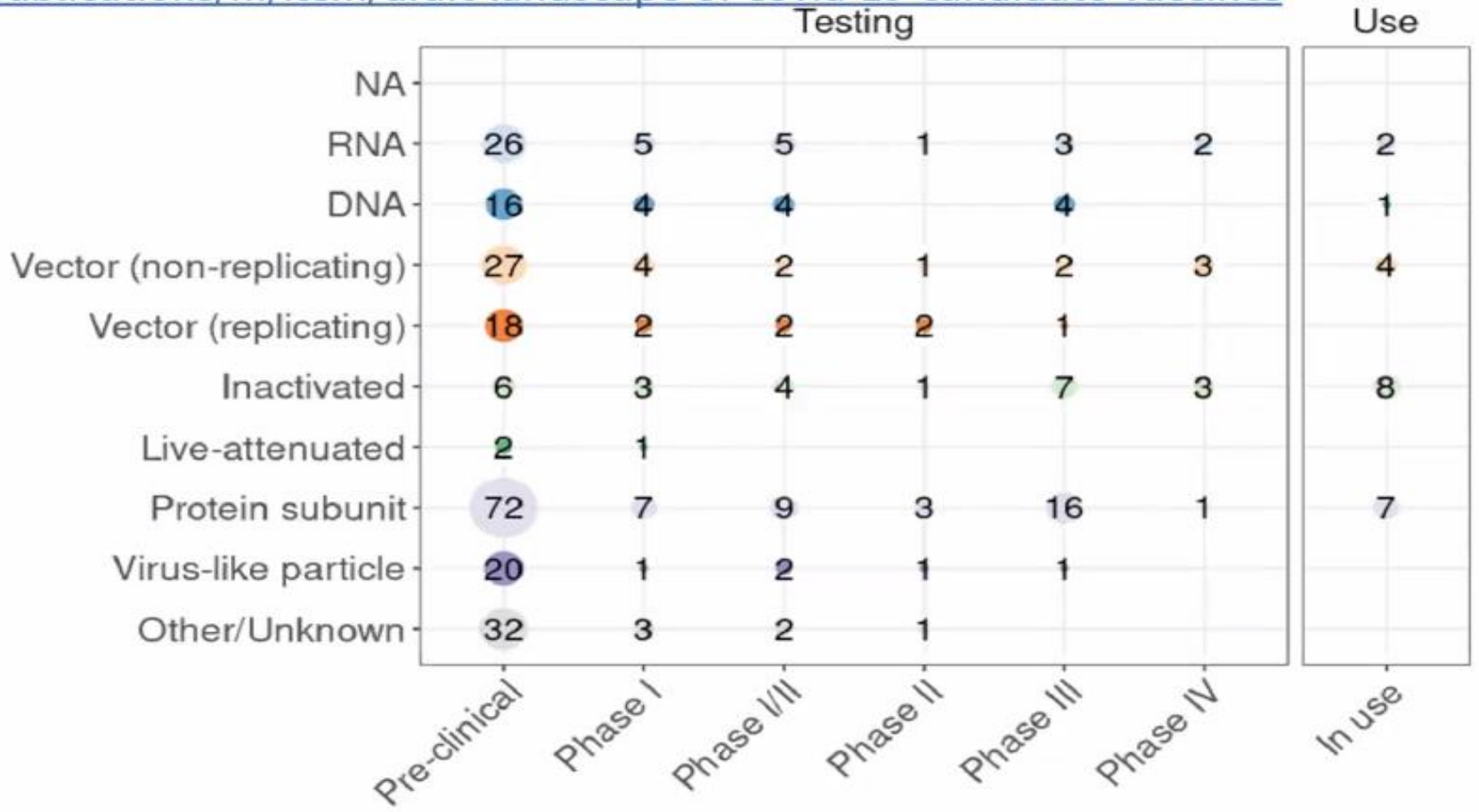
Meeting Objectives

- Review global epidemiology of past natural infection with SARS-CoV-2
- Provide update on global vaccine delivery and uptake by vaccine type
- Review vaccine immune responses and efficacy among those with prior COVID-19 infections
- Discuss current and future approaches to generating supportive efficacy data for vaccine licensure

COVID-19 vaccine development landscape

As of 14 October 2021, a total 332 candidate vaccines of which 113 in clinical trials, 22 in large scale use

https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines



https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/

SAGE on Covid-19 vaccines

thl

Covid-19 Vaccine development – new challenges

- **Diversity of vaccines available with increasing volume but remain imperfectly distributed**
- **Impressive performance across several vaccine platforms but…still gaps remain**
  - Durability of protection across different clinical endpoints, variable impact on variants, relatively high COGs / price, volume insufficient, deliverability (cold chain), safety evaluations continue to evolve
- **Environment for new vaccine development continues to shift**
  - Placebo controlled studies challenging but ongoing (e.g., WHO Solidarity Trial Vaccines)
  - Seropositivity, “natural” or vaccine induced, is increasing
  - Booster or “additional” dose as a new development target (heterologous successes)
- **Each product may have different challenges**
  - Antibody not putative driver of efficacy, NRA setting without immuno pathway, product better aligned for use among sero-positive / exposed persons
- **Never too early to look forward ---- challenges ourselves with an “influenza pathway”**

Global COVID-19 seroprevalence studies in unvaccinated populations, 2020-2021

Workshop “COVID-19 Vaccine Development in an Increasingly Seropositive World”

27th of October 2021

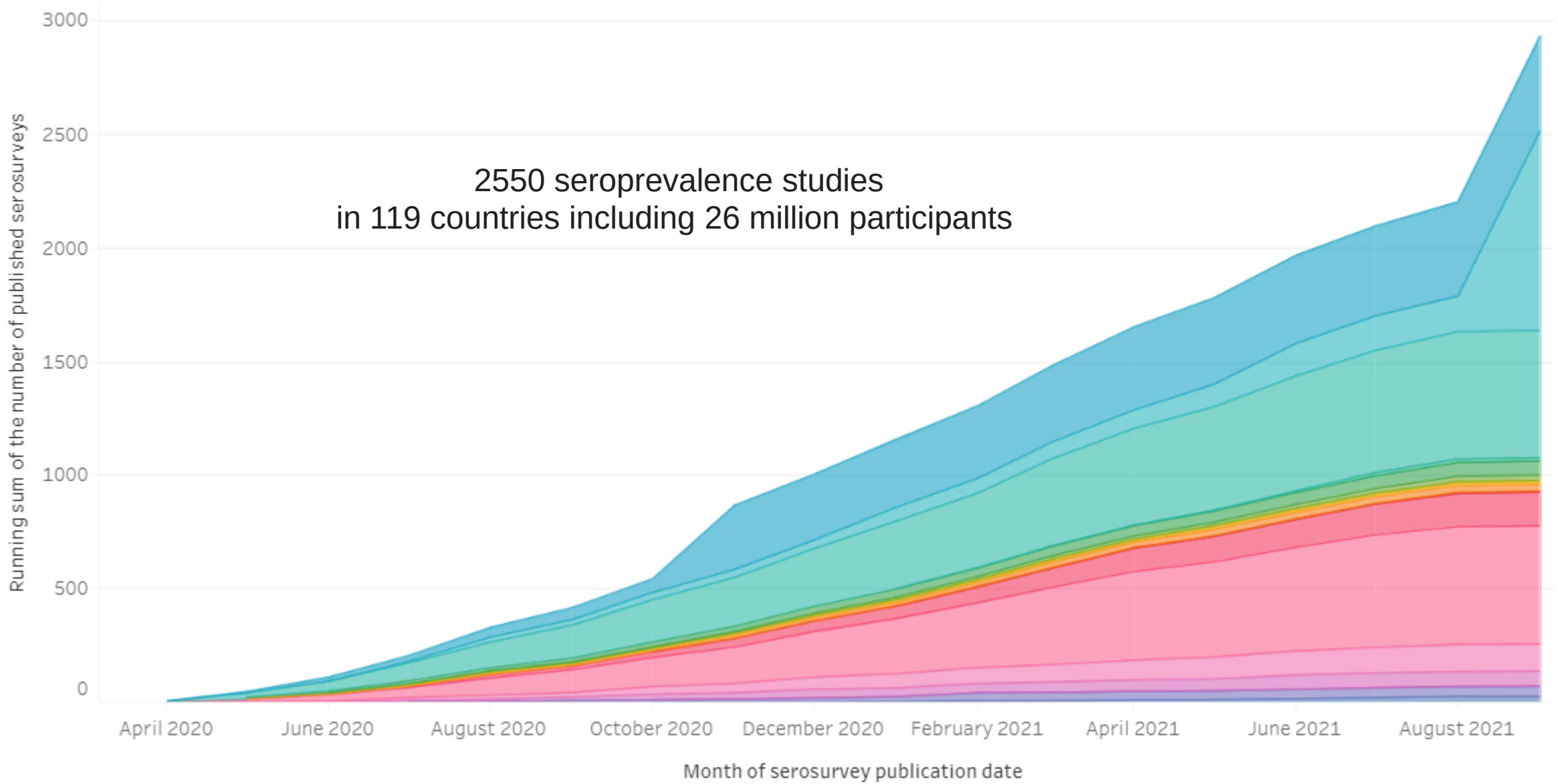
Emmanuelle Espié

Seroprevalence data from observational real-life studies

Geographic patterns and temporal trends

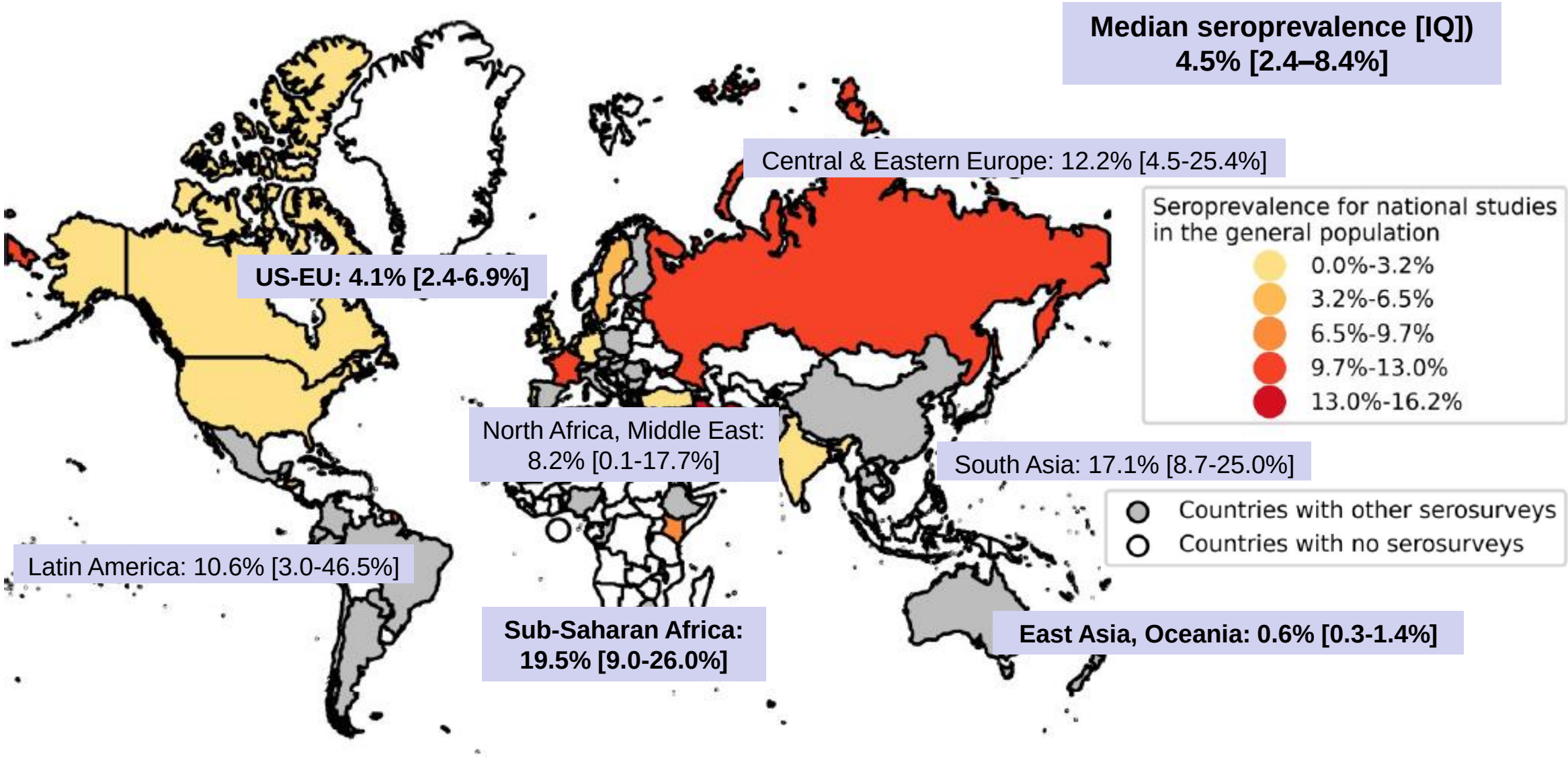
CEPI

Cumulative number of serosurveys published over time (source: SeroTracker)



https://serotracker.com/en/Explore

Geographical distribution of national seroprevalence studies reporting population-wide estimates, 2020



Bobrovitz N et al. PLOS ONE 2021;16(6): e0252617. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0252617

Seroprevalence data in Europe, 2020-2021

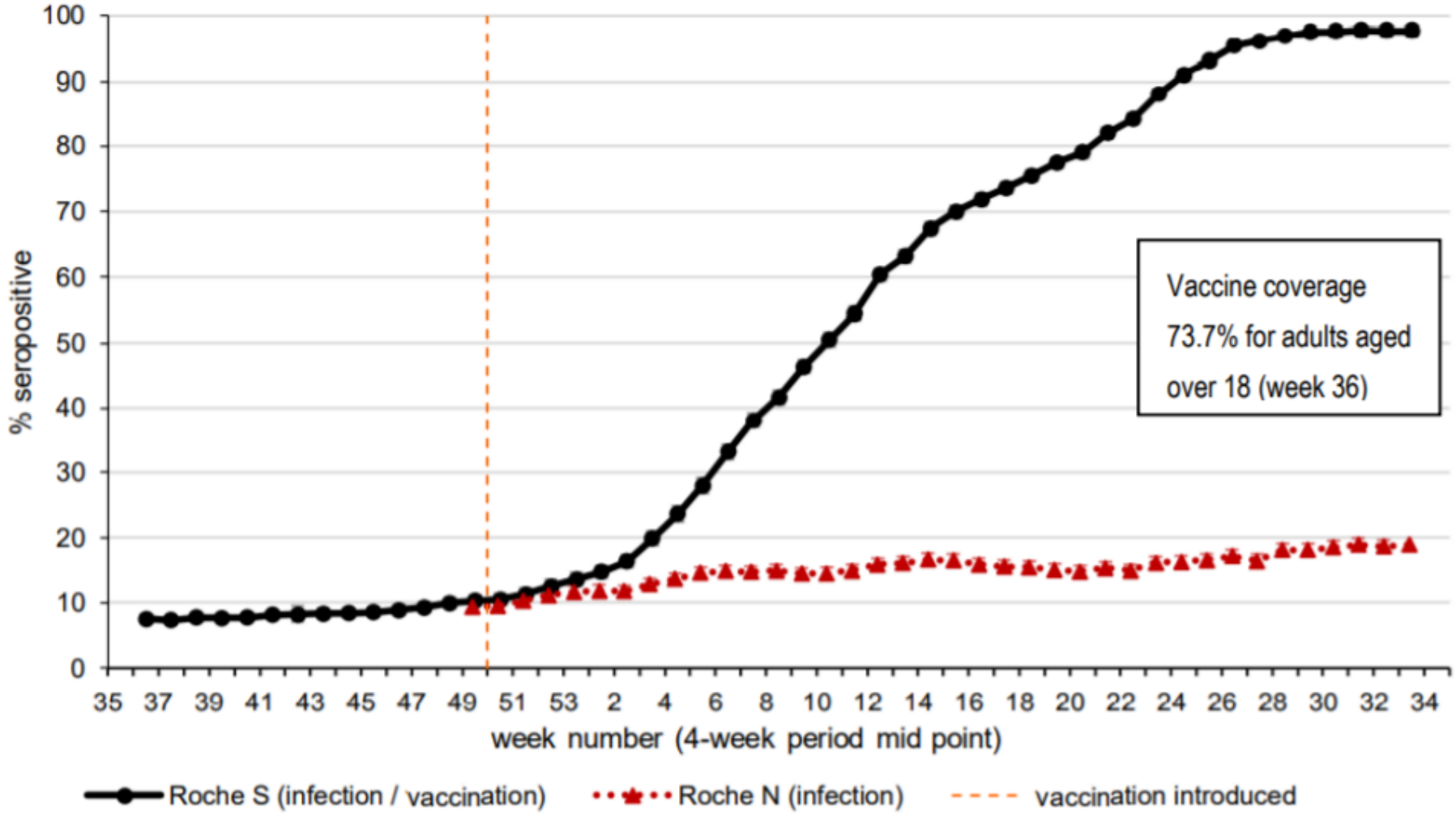
- EU/EEA: Among non-vaccinated adult population, ~ 20% had detectable antibodies against SARS-CoV-2, with a higher proportion in 11-19 years old compared to 20-64 years old.

- Sweden: March 2021 (prior to vaccination), seroprevalence among blood donors of 22% [95%CI 20.3-24.5]

- UK: August 2021 (Week 34), seroprevalence among unvaccinated blood donors aged 17 years and older of 18.9% [95%CI 17.9-20.0]

ECDC. Rapid Risk Assessment. https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-assessing-sars-cov-2-circulation-variants-concern
Public Health England (PHE). Weekly national Influenza and COVID-19 surveillance reportt. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1018187/Weekly_Flu_and_COVID-19_report_w37.pdf
Folkhälsomyndigheten. https://www.folkhalsomyndigheten.se/contentassets/376f9021a4c84da08de18ac597284f0c/pavisningantikroppar-mot-sars-cov-2-blodgivare.pdf

SARS-Cov2 antibody seroprevalence (% seropositive) in blood donors in England, 2020-2021



Public Health England (PHE). Weekly national Influenza and COVID-19 surveillance report - week 37 report (up to week 36 data). London: PHE; 2021. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1018187/Weekly_Flu_and_COVID-19_report_w37.pdf

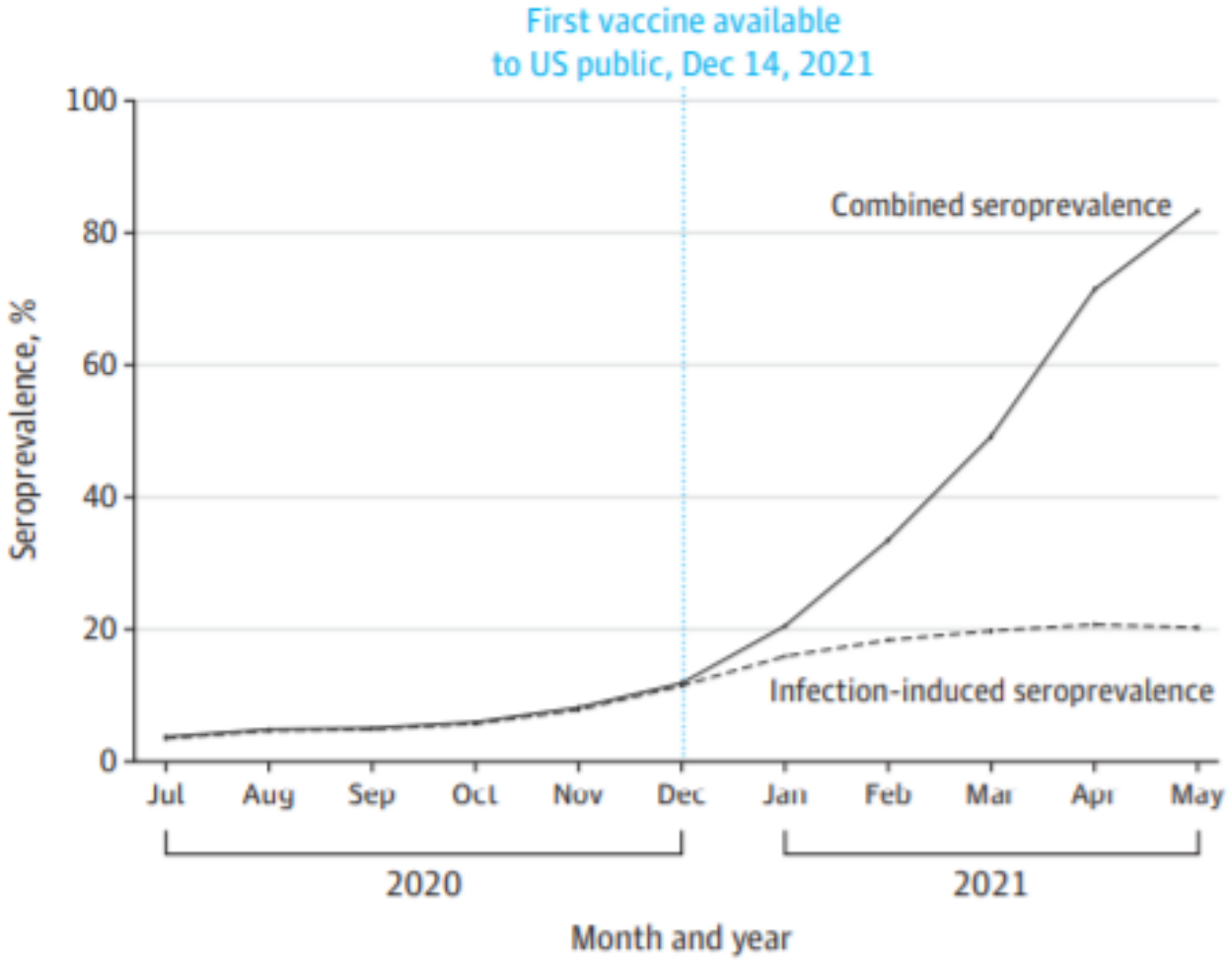
Seroprevalence data in US, 2020-2021

In repeated studies of blood donors, seroprevalence increased from 3.5% in July 2020 to 20.2% in May 2021

Number of projected cumulative SARS-CoV-2 infections with detectable antibodies, US, January-May 2021

	January	February	March	April	May
Infection-induced seroprevalence, % (95% CI)[a]	15.9 (15.6-16.2)	18.4 (18.1-18.7)	19.8 (19.4-20.1)	20.7 (20.4-21.0)	20.2 (19.9-20.6)

Weighted SARS-CoV-2 seroprevalence, US, July 2020-May 2021



Jones JM, Stone M, Sulaeman H, et al. Estimated US Infection- and Vaccine-Induced SARS-CoV-2 Seroprevalence Based on Blood Donations, July 2020-May 2021. JAMA. Sept 2, 2021. doi:10.1001/jama.2021.15161

Seroprevalence data in LMIC

- **Brazil**: Among the Sao Paulo population aged 18 years, seroprevalence increased from 13.6% in September 2020 to 25% [95%CI 21.7-28.7] in February 2021

- **Kenya**: Among blood donors (aged 16-64 years), the seroprevalence increased from 9.1% in September 2020 to 44.2% [95%CI 42.4-46.0] by March 2021.
- **South Africa**: Among bloods donors (aged 15-69 years) over the 1st quarter of 2021, the seroprevalence was estimated 47.4% [95%CI 46.2-48.6].

- **India**: In January 2021, the third national survey showed a seroprevalence of 24.3% [95%CI 23.1-25.6] in the population aged >10 years, with higher rates in urban (Delhi, Hyderabad 54-56%) versus rural areas.

July 2021: Seroprevalence in children 57.2% and 61.6% respectively in 6-9 yoa and 10-17 yoa

Albuquerque J et al. medRxiv preprint June 2021 doi: https://doi.org/10.1101/2021.06.16.21256530
Vermeulen M et al. Research Square 2021 Aug. doi: 10.21203/rs.3.rs-690372/v2
Uyoga S et al. JAMA 2021 Sept 2. doi:10.1001/jama.2021.15265
Murhekar MV et al. Int J Infect Dis. 2021 Jul;108:145-155.

Seroprevalence data from clinical trials setting

HERALD Phase IIB/III clinical trial
Recruitment: from December 2020 to April 2021

Country	Seropositivity % *
Germany	1.10%
Spain	4.05%
Belgium	4.22%
The Netherlands	4.56%
Argentina	4.94%
Colombia	10.7%
Panama	14.6%
Peru	18.7%
Mexico	12.4%
Dominican Republic	56.3%

* Presence of antibodies binding against SARS-Cov2 Nucleoprotein

SPECTRA Phase II/III clinical trial
Recruitment: from May 2021 to August 2021

Country	Seropositivity**
Belgium	13%
Brazil	30%
Colombia	46%
South Africa	46%
Philippines	65%

** Presence of antibodies binding against SARS-Cov2 Spike protein

Seroprevalence in unvaccinated populations, 2021

Take home messages

Summary and discussions

- **Wide variations of seropositivity in unvaccinated populations up to mid-2021**
  - HIC: seropositivity ~ 20% with high vaccination coverage (≥ 60%)
  - LMIC: seropositivity up to 50-60% with low vaccination coverage (< 20%)

- Methodological limitations
  - Study design and population (specific population subgroups vs. general population)
  - Sampling size and selection (small convenient sample vs. large representative sample)
  - Sensitivity and specificity of immunoassays

- **Impact of the increasing seropositivity rate in unvaccinated populations**
  - Public health perspective:
    - Major risk of disease transmission from infected unvaccinated individuals
    - Recommendations for vaccination of previously infected individuals
    - Vaccine effectiveness and safety in previously infected individuals
  - Future vaccine development:
    - Control / Placebo seronegative group
    - Dose ranging and dose finding

- Given pandemic progression and vaccination rollout → need for updates (especially in LMIC)

CEPI

Vaccination among the previously infected: Immunology and effectiveness

Florian Krammer

Mount Sinai Professor in Vaccinology

Icahn School of Medicine at Mount Sinai

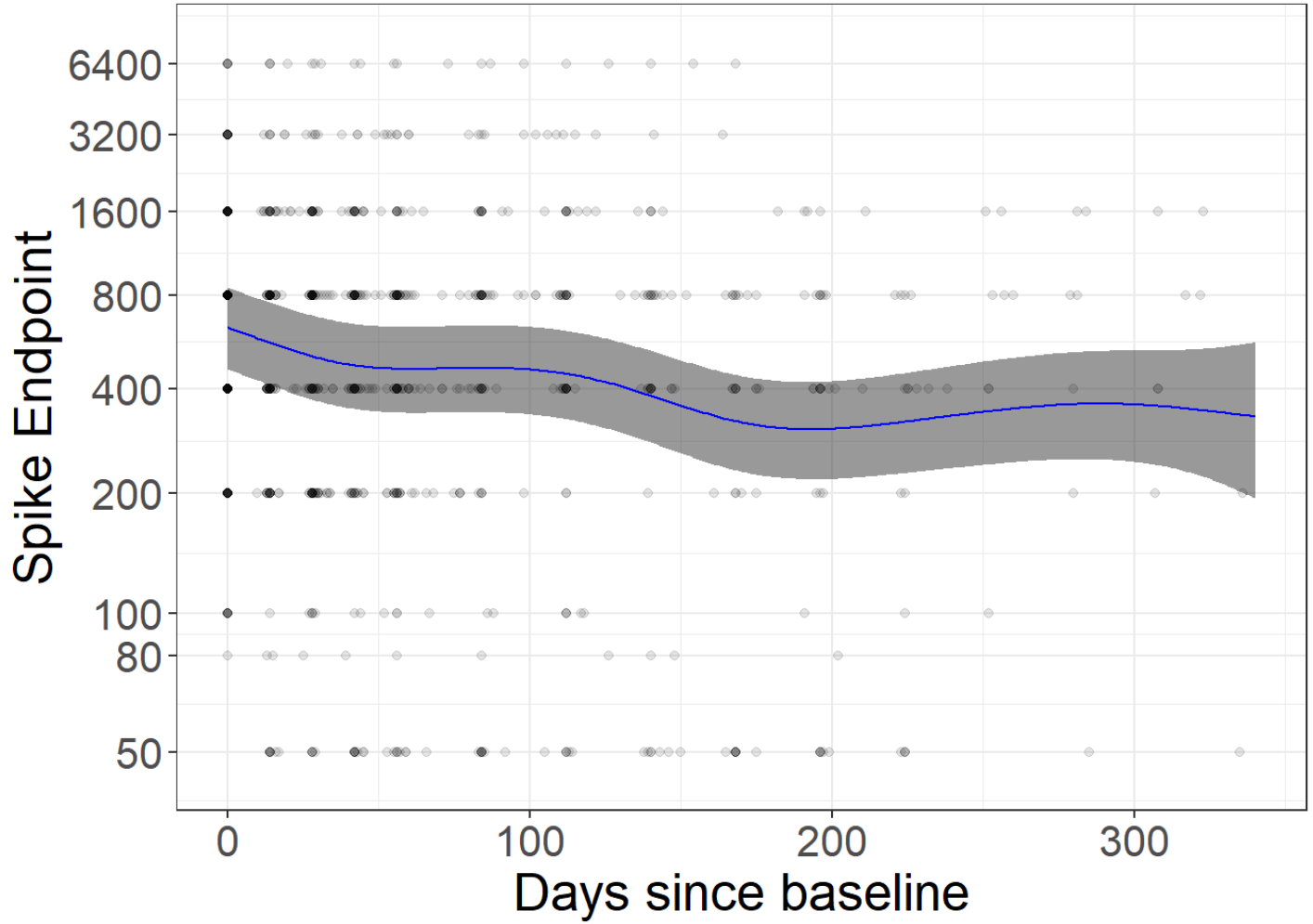
COVAX Workshop COVID-19 Vaccine Development in an Increasingly Seropositive World

October 27th, 2020

Mount Sinai

How do we find out who was previously infected?

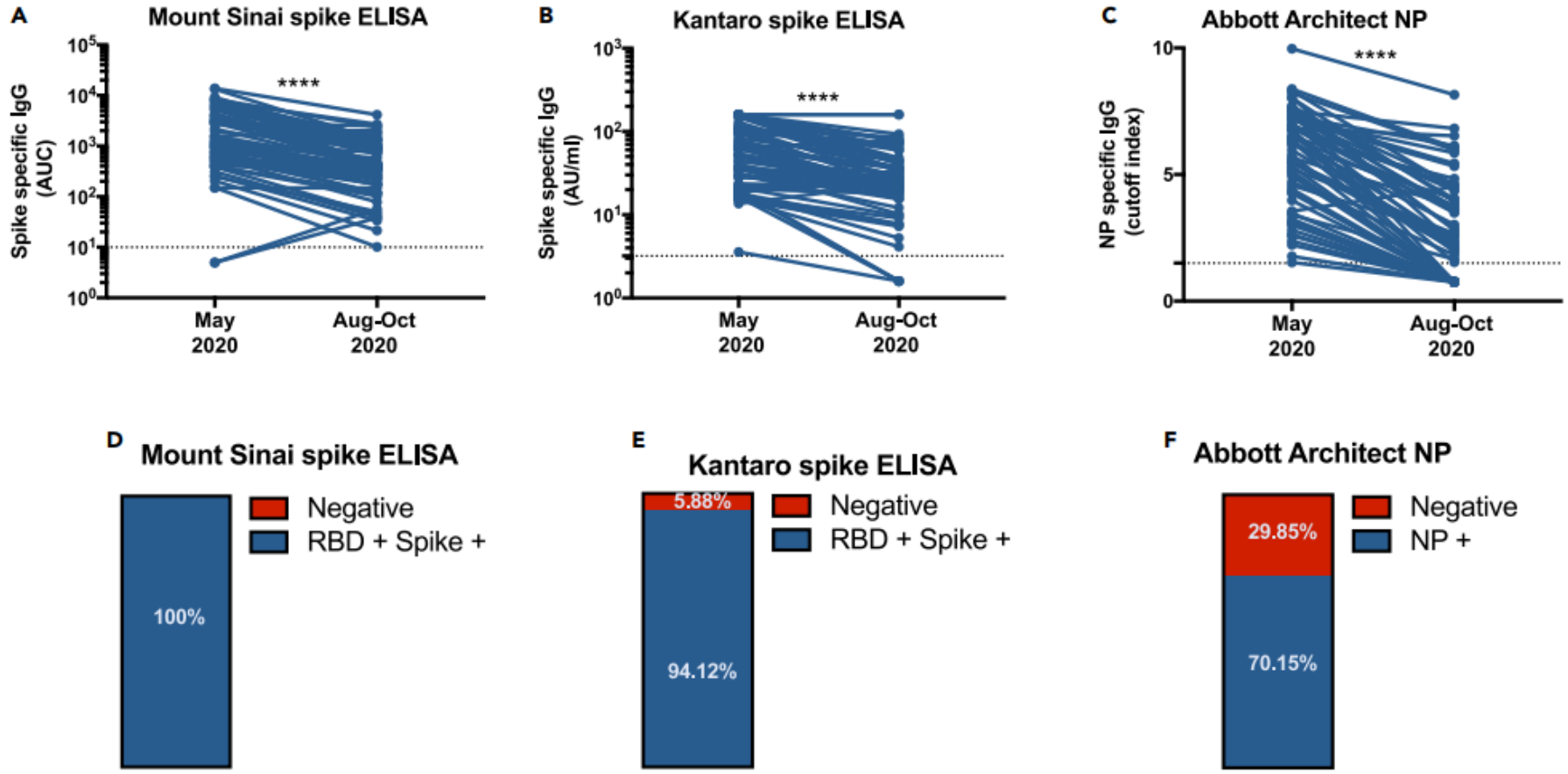
Infection induces long-lived anti-spike responses in individuals with mild COVID-19



approximately 5% of antibody positive participants sero-reverted

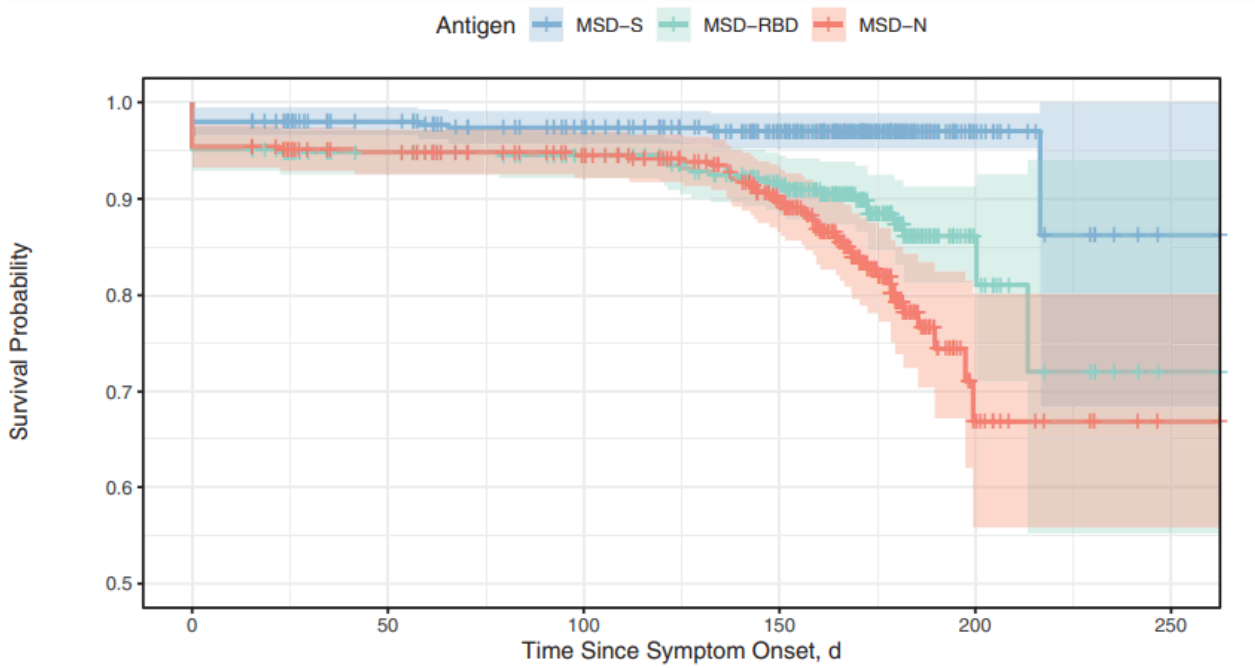
John Kubale, Aubree Gordon, Florian Krammer, **Viviana Simon** plus the **PARIS** study team

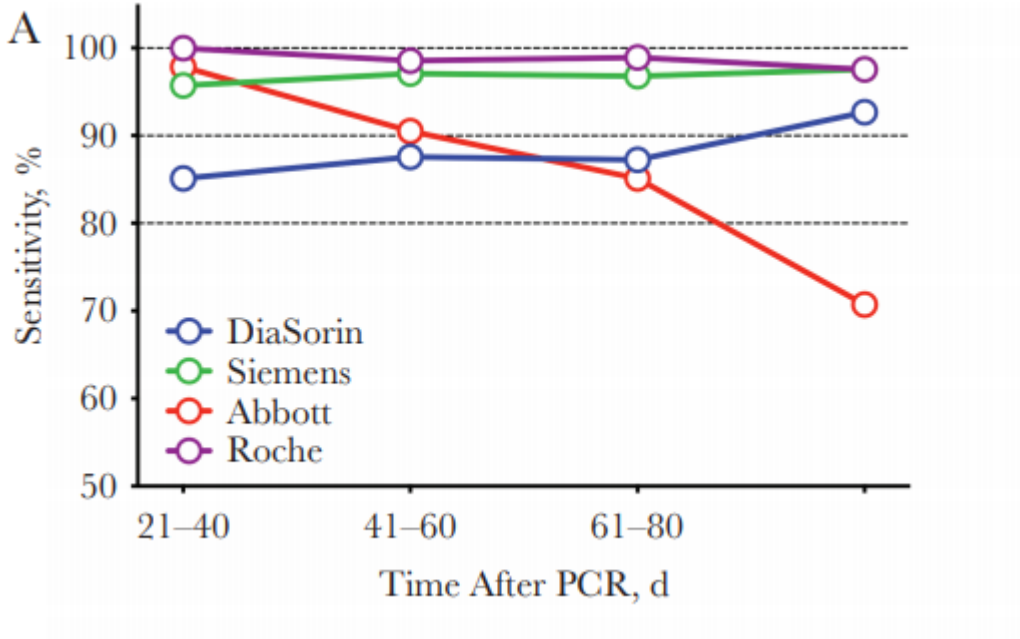
Assay sensitivity and/or persistence of immunity is influencing NP seroprevalence



Carreño et al., iScience, 2021
https://pubmed.ncbi.nlm.nih.gov/34368647/

This has also been observed by other laboratories – but it is unclear if it is caused by biology or technology

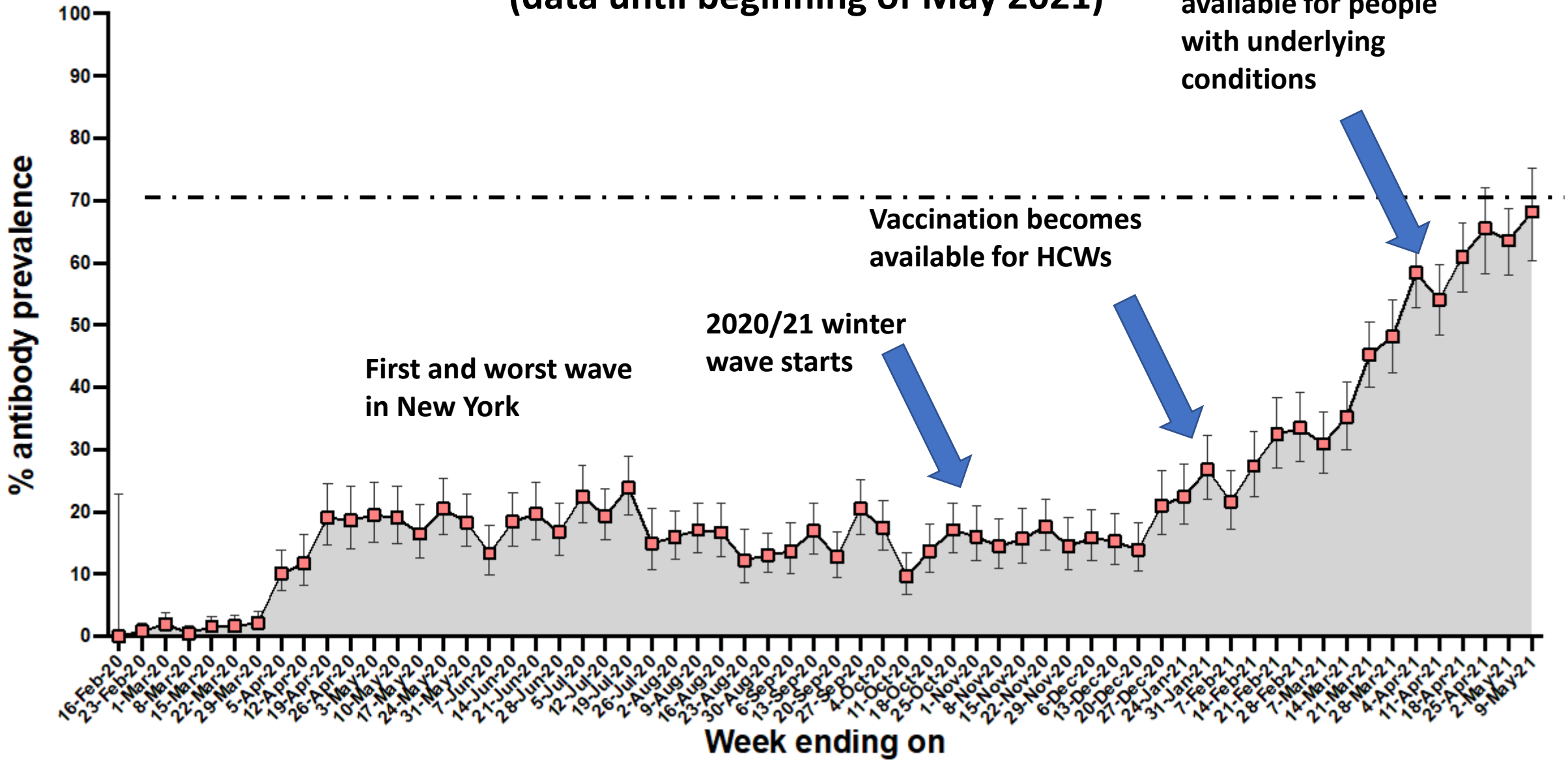




Grandjean *et al.*, CID, 2021
https://pubmed.ncbi.nlm.nih.gov/34218284/

Muecksch *et al.*, JID, 2021
https://academic.oup.com/jid/article/223/3/389/5952470

Sero-prevalence study in New York City (data until beginning of May 2021)



Juan Manuel Carreño and Krammer lab serology core

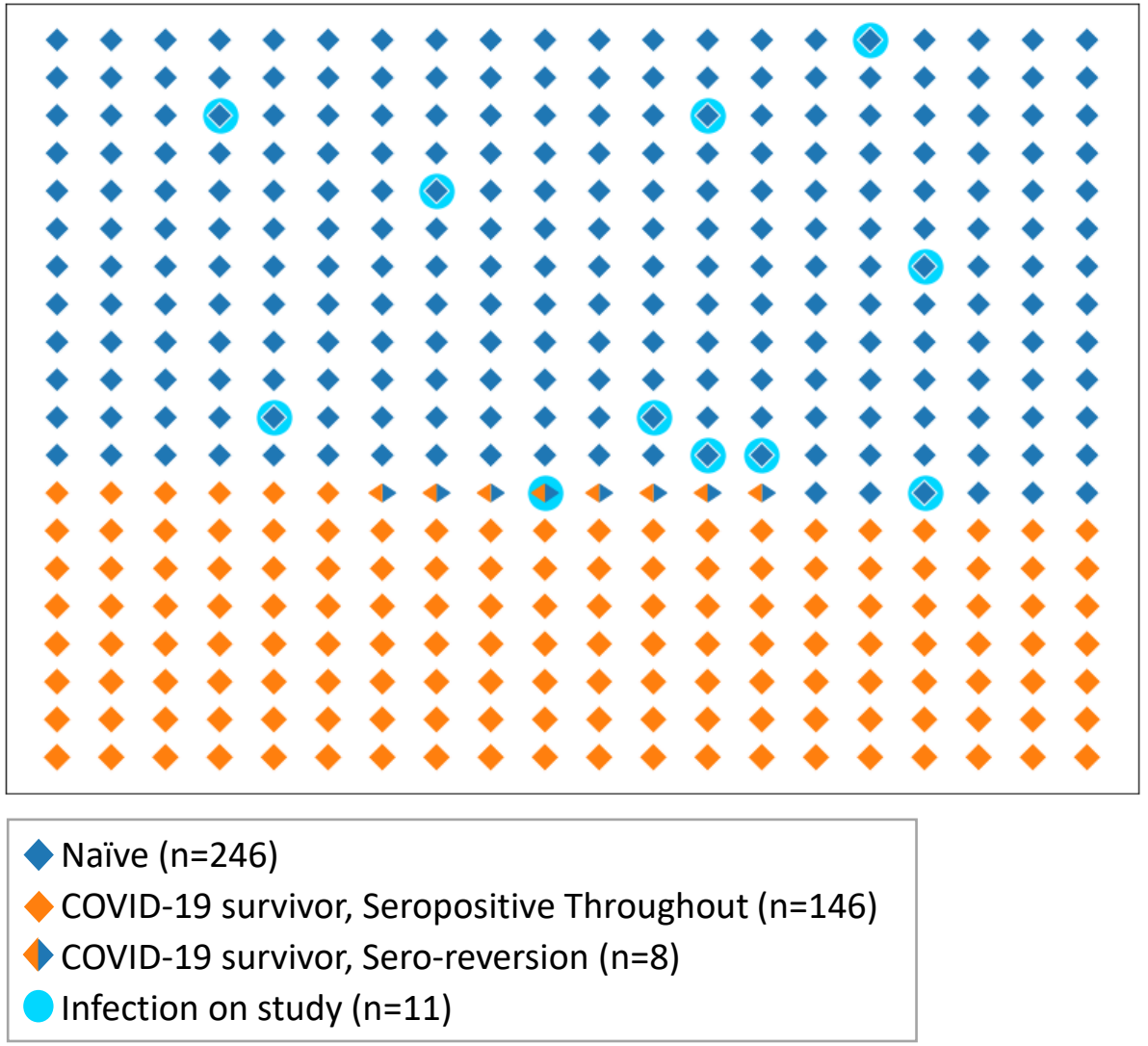
Spike-binding IgG antibodies mounted upon natural infection provide significant protection from re-infection

PARIS NYC data included in this analysis:
154 seropositive
246 seronegative

Follow up every 2-4 weeks:
Median: 102.5 days

11 documented new SARS-CoV-2 infections

- 10 in naïve participants
- 1 in a participant with COVID-19 history but no detectable antibodies (sero-reversion) at the time of re-infection
- p=0.01



Pre-Delta studies showing that natural infection affords protection from reinfection (similar to vaccines)

- https://pubmed.ncbi.nlm.nih.gov/33844963/
- https://pubmed.ncbi.nlm.nih.gov/33583018/
- https://pubmed.ncbi.nlm.nih.gov/33369366/
- https://pubmed.ncbi.nlm.nih.gov/33718968/
- https://pubmed.ncbi.nlm.nih.gov/33743221/
- https://pubmed.ncbi.nlm.nih.gov/33625463/

Post-Delta studies showing that natural infection affords protection from reinfection (similar to vaccines)

- https://www.nature.com/articles/s41591-021-01548-7

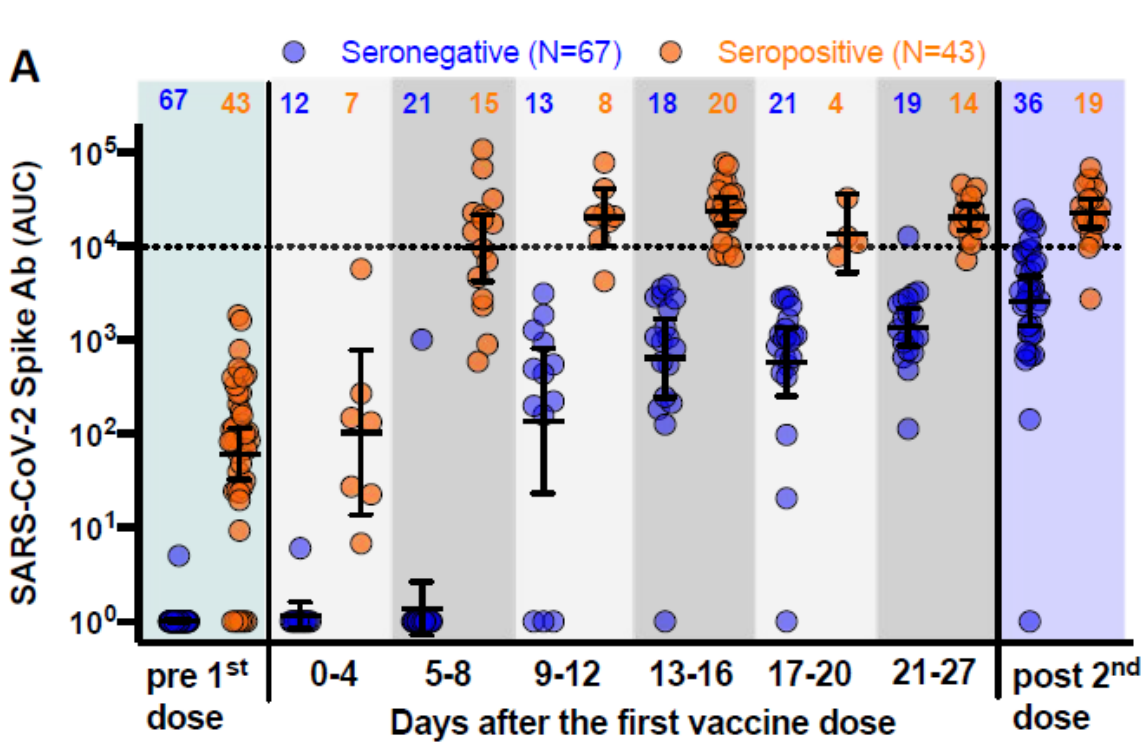
What happens if you vaccinate previously infected individuals?

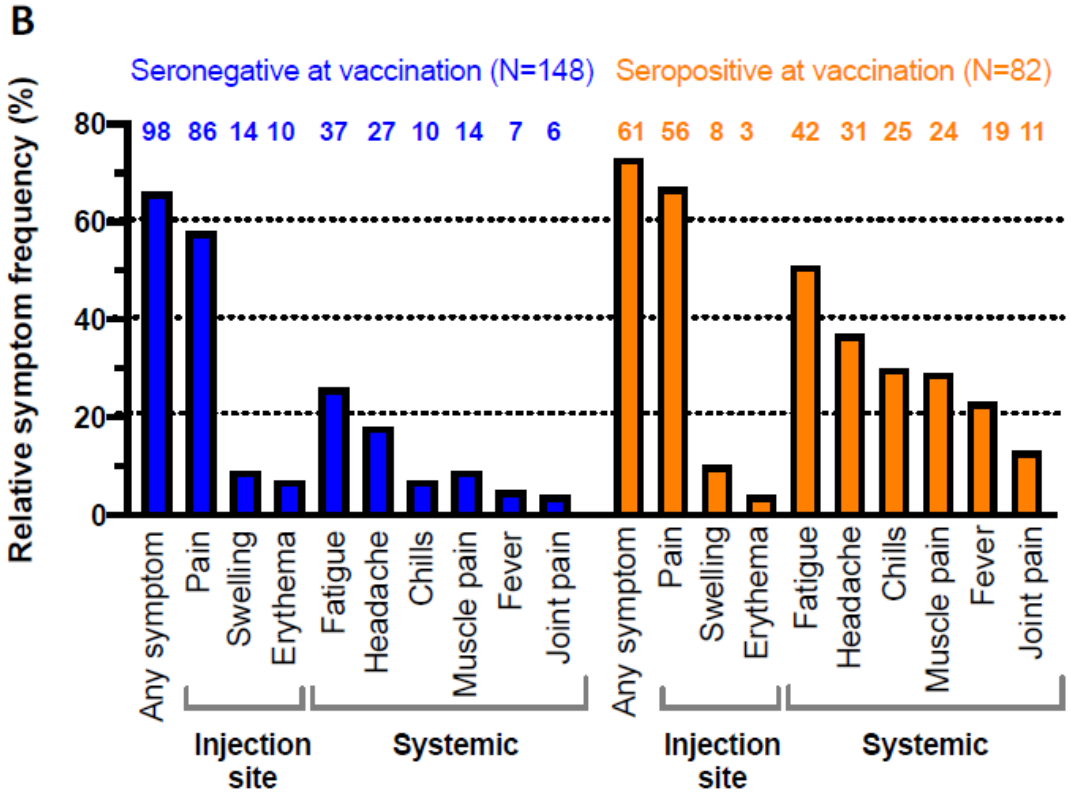
What happens if you vaccinate previously infected individuals?

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

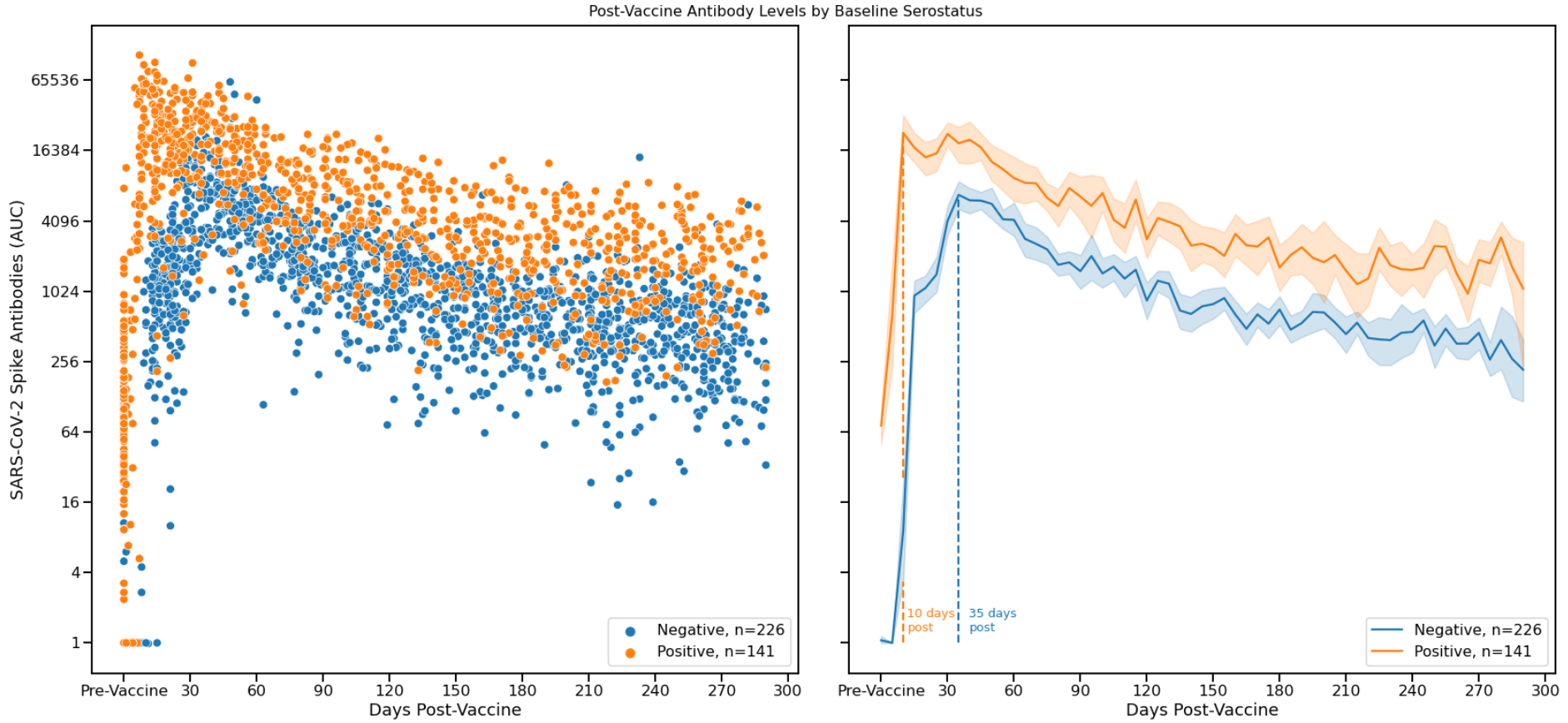
Antibody Responses in Seropositive Persons after a Single Dose of SARS-CoV-2 mRNA Vaccine





Pfizer and Moderna mRNA vaccinees

Antibody titers after mRNA vaccination in naïve individuals and individuals previously infected with SARS-CoV-2



14 breakthrough infections so far in fully vaccinated individuals, all in the naïve vaccinated group

PARIS cohort with Viviana Simon

EBioMedicine 68 (2021) 103401

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

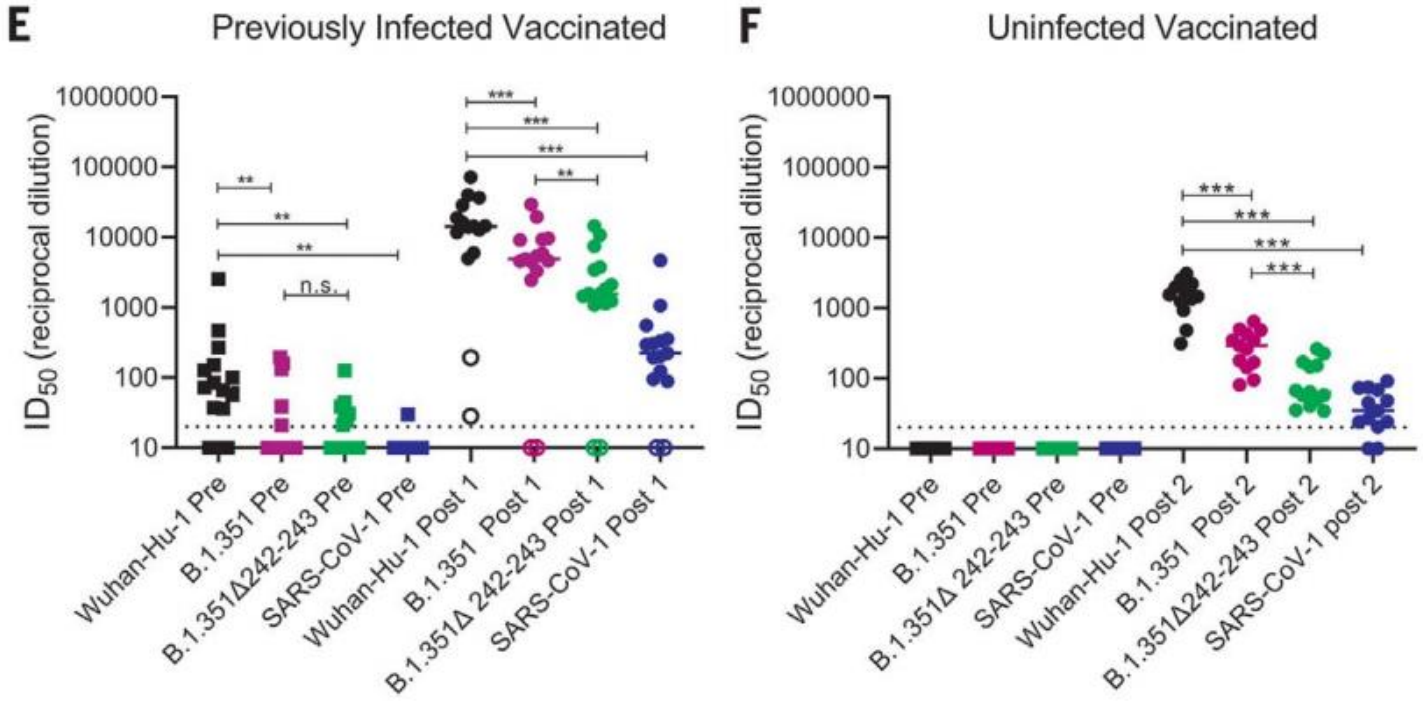
Letter

SARS-CoV-2 vaccines for all but a single dose for COVID-19 survivors

Matthew Frieman[a], Anthony D. Harris[b,c], Ramin Sedaghat Herati[d], Florian Krammer[e], Alberto Mantovani[f,g,h], Maria Rescigno[f,g], Mohammad M. Sajadi[c,i,j], Viviana Simon[e,k,l,*]

[a] Department of Microbiology and Immunology, University of Maryland School of Medicine, Baltimore, Maryland, United States
[b] Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland, United States
[c] Department of Medicine, Baltimore VA Medical Center, Baltimore, Maryland, United States
[d] New York University School of Medicine, New York City, NY, United States
[e] Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, United States
[f] Department of Biomedical Sciences, Humanitas University, Milan, Italy
[g] IRCCS Humanitas Research Hospital, Milan, Italy
[h] The William Harvey Research Institute, Queen Mary University, London, United Kingdom
[i] Institute of Human Virology, University of Maryland School of Medicine, Baltimore, Maryland, United States
[j] Global Virus Network, Baltimore, Maryland, United States
[k] Division of Infectious Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[l] Global Health Emerging Pathogens Institute, Icahn School of Medicine at Mount Sinai, New York, NY, United States

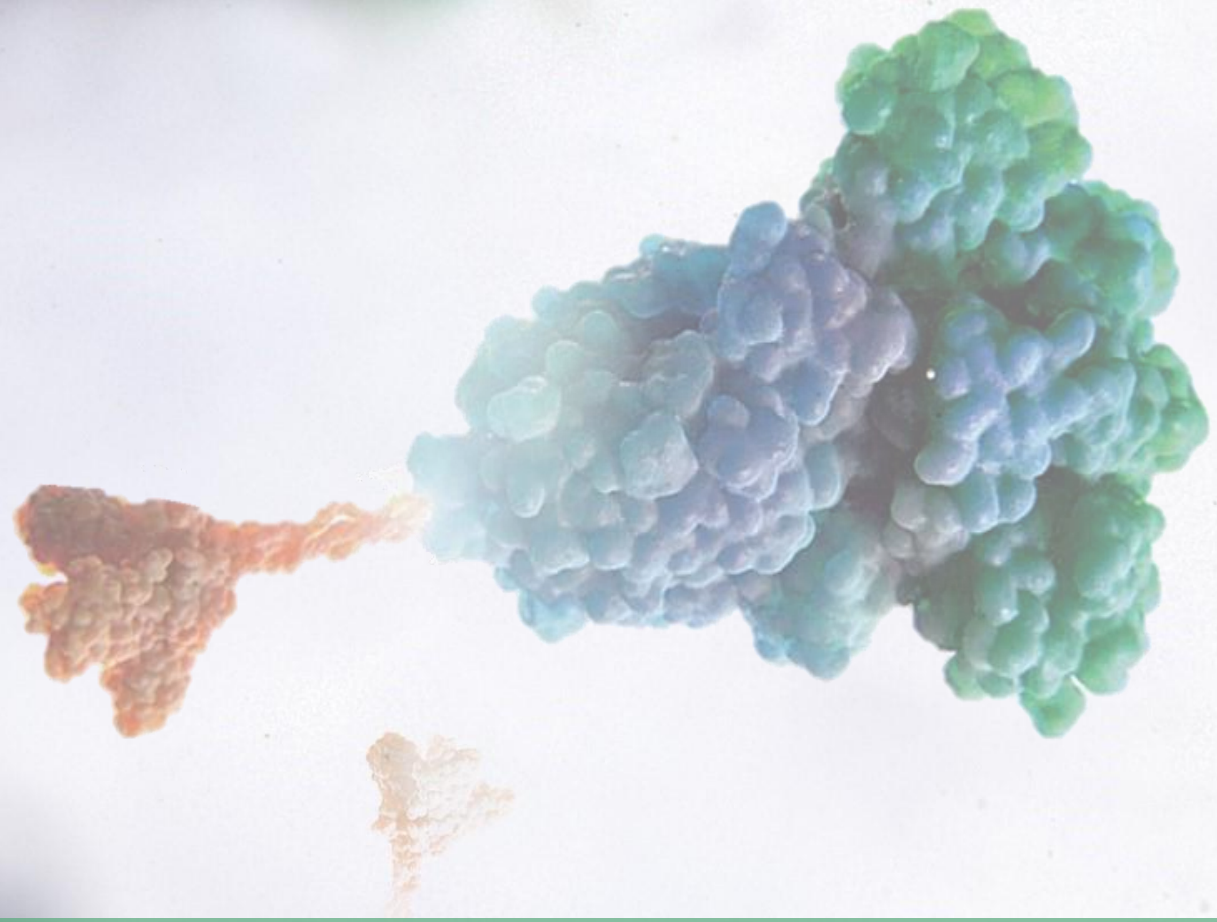
A large number of studies show that vaccinating individuals previously infected with SARS-CoV-2 leads to very robust immune responses



Stamatatos *et al.*, Science, 2021
https://www.science.org/doi/pdf/10.1126/science.abg9175

What to expect when vaccinating previously infected (or vaccinated) individuals?

- Typically a quick and robust anamnestic antibody response after one vaccination
  - This is also seen in sero-reverters
  - A second dose may not further increase the immune response
- Even after one dose peak titers are often higher in pre-exposed individuals than in naïve individuals
- Timing between infection and vaccination may matter
- Not every vaccine may boost pre-existing immunity in the same way
- Boosting vaccine-induced pre-existing immunity may be different than boosting infection-induced pre-existing immunity
- Placebo controlled trials with partially immune control groups would need to be very large



Vaccination among the previously infected - Lessons from Clover's phase 3 efficacy study

Htay Htay Han

October 27, 2021

Clover's COVID-19 Vaccine Candidate: SCB-2019 (CpG 1018/Alum)

- **Adjuvanted Protein-Based COVID-19 Vaccine Candidate**: SCB-2019 antigen (30 µg/dose) in combination with CpG 1018 adjuvant and aluminum hydroxide (alum)
  - **Two-dose** vaccine candidate (administered 21 days apart)
  - **Intramuscular (IM) injection** (0.5 mL/dose)
  - **Standard refrigeration** (2-8°C) storage & transportation conditions

SCB-2019 Antigen

- SCB-2019 is a recombinant SARS-CoV-2 Spike (S) protein, preserved in the ***native trimeric prefusion conformation*** form utilizing Trimer-Tag™

Global Collaborations

- **Up to $360.5 million** grant funding by CEPI
- Clinical & commercial supply agreements with DYNAVAX for **CpG 1018 adjuvant supply**
- Advanced Purchase Agreement (APA) signed with Gavi The Vaccine Alliance to supply up to **over 400 million doses** to the COVAX facility for global distribution

SCB-2019 Antigen Structure

S1

S2

Prefusion Spike (S) Protein of SARS-CoV-2 Original Strain

Trimer-Tag™

CLOVER BIOPHARMACEUTICALS

CLOVER BIOPHARMACEUTICALS

SPECTRA

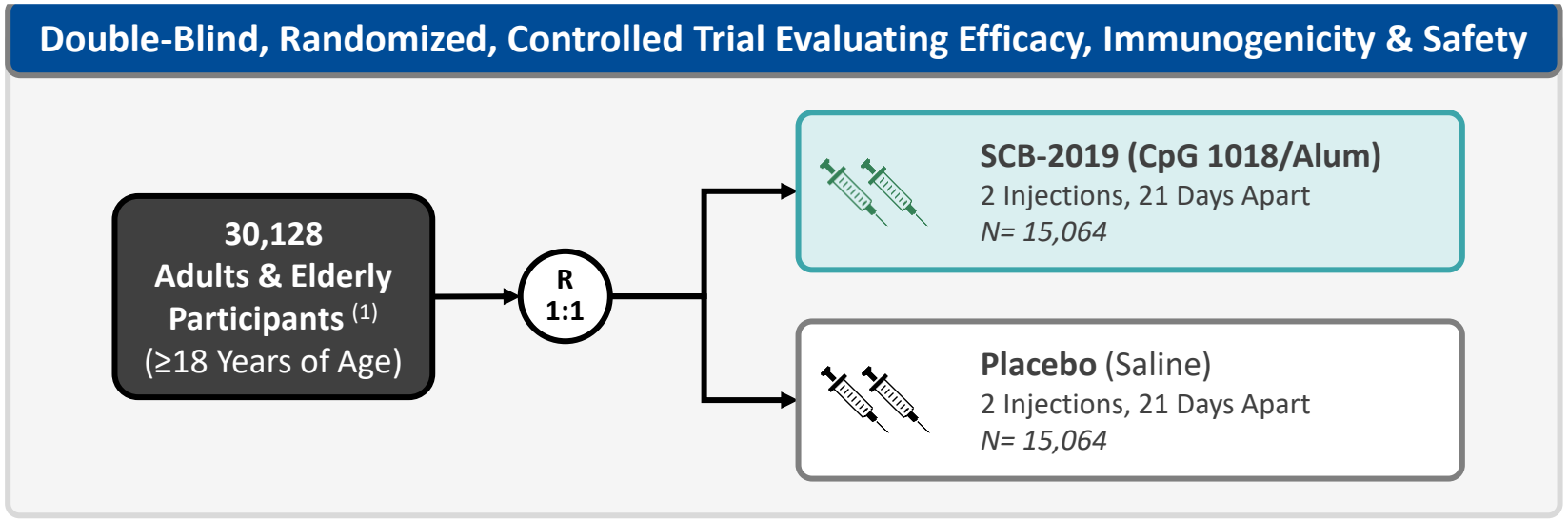
Study Evaluating **P**rotective-**E**fficacy and
Safety of **C**lover's **T**rimeric **R**ecombinant Protein-based
and **A**djuvanted COVID-19 Vaccine

Phase 2/3 Efficacy Trial Initiated on 24 MARCH 2021

- *Over **30,000 participants** aged 18 years or older enrolled in SPECTRA in **5 Countries** across **4 Continents** (South America, Asia, Europe and Africa)*

 Philippines
 ***Colombia***
 ***Brazil***
 ***S. Africa***
 ***Belgium***

SPECTRA Global Phase 2/3 Pivotal Trial Design



➢ **Primary Efficacy Endpoint:**

- **Prevention of PCR-confirmed COVID-19 of Any Severity ≥14 Days After Second Dose (in baseline seronegative participants)**

➢ **Secondary Efficacy Endpoints(2):**

- Prevention of **moderate-to-severe COVID-19**, **severe COVID-19**, **hospitalization due to COVID-19**
- **SARS-CoV-2 strain-specific** prevention of any, moderate-to-severe, and severe COVID-19
- Efficacy in **baseline seropositive (previously-infected) participants**
- **Immunogenicity** (including neutralizing antibodies)

➢ **Primary Safety Endpoints:**

- **Solicited AE – Systemic & Local** (within 7 days after each dose)
- **Unsolicited AEs** (up to day 43)
- **SAE, MAAE, AESI** (all participants)

Abbreviations: AE (adverse event), SAE (serious adverse event), MAAE (medically-attended adverse event), AESI (adverse event of special interest).
(1) Number of participants randomized and dosed in trial.
(2) Prespecified secondary efficacy endpoints in protocol for which data are available at time of topline results.

CLOVER BIOPHARMACEUTICALS

Key Takeaways from SPECTRA Global Phase 2/3 Trial

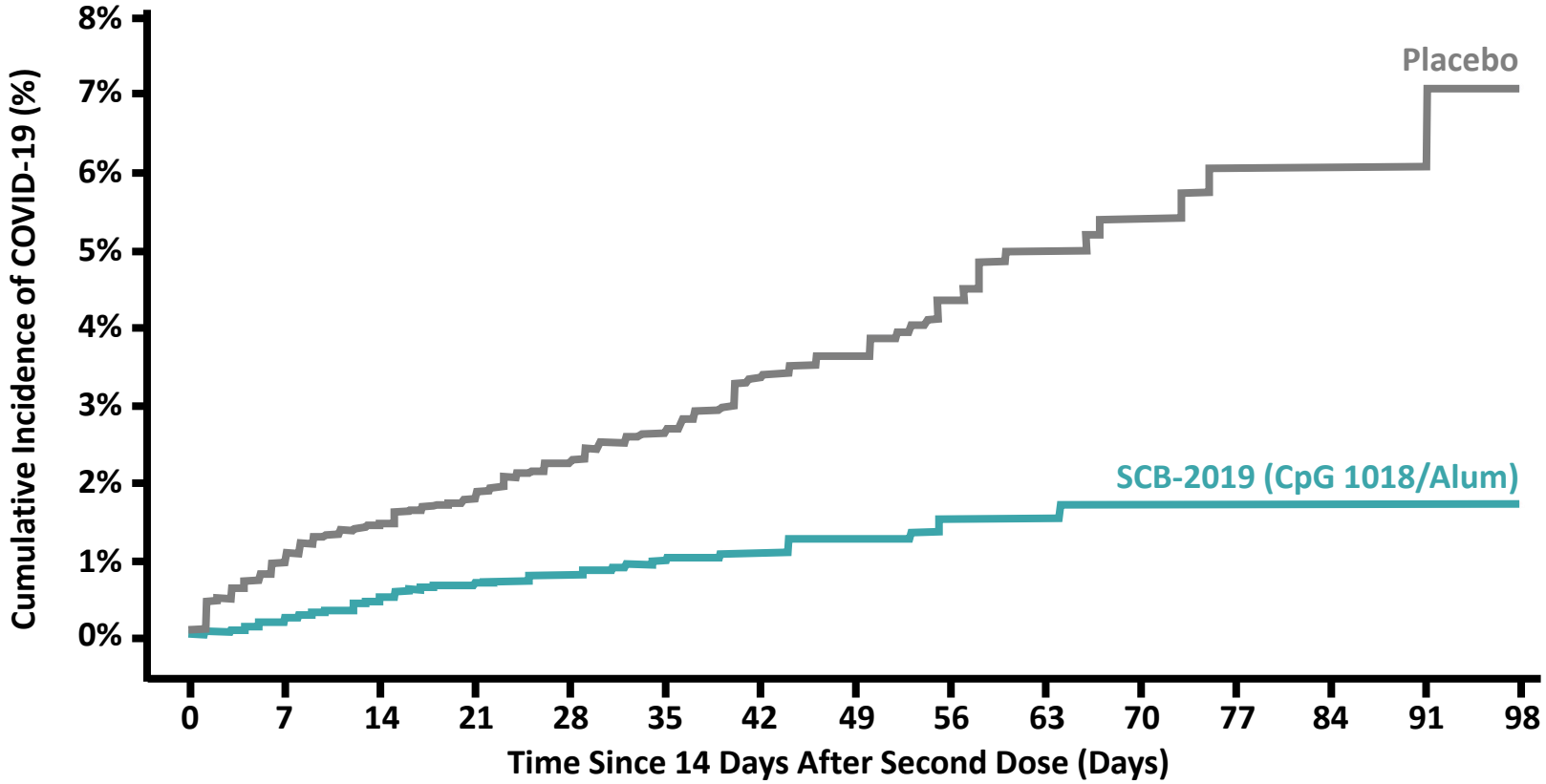
- *SPECTRA successfully enrolled over 30,000 adult & elderly participants in 5 countries across 4 continents*
- *100% of SARS-CoV-2 strains observed in the efficacy analysis were variants (Delta was predominant strain)*

- ✓ **Primary and secondary efficacy endpoints were successfully met**
- ✓ **100% efficacy against severe COVID-19 & hospitalization, 83.7% efficacy against moderate-to-severe COVID-19, 67.2% efficacy against COVID-19 of any severity** caused by any strain of SARS-CoV-2 in SPECTRA
- ✓ **Delta: 78.7% efficacy** against **COVID-19 of any severity** caused by the **globally-dominant Delta strain**
- ✓ **Favorable safety profile:** No significant differences in systemic adverse events or severe/serious adverse events compared to placebo
- ✓ First COVID-19 vaccine to demonstrate **significantly reduced risk of COVID-19 disease in previously-infected individuals**, a growing & increasingly important population as SARS-CoV-2 continues to spread globally

Note: Abbreviations of "SCB-2019 (CpG 1018/Alum)" are used in the following slides, including "SCB-2019". SARS-CoV-2 variants are identified in the following slides by their WHO assigned labels based on the letters of the Greek alphabet (e.g., Delta for Delta Variant)."

Significant Overall Efficacy Against COVID-19 (Including Globally-Dominant Delta Strain)

✓ **Vaccine efficacy appears to be persistent through 112 days after second dose in environment dominated by Delta and other concerning variants**



Participants at Risk															
Placebo	5806	5180	4505	3386	2476	2070	1782	1393	968	572	368	231	171	94	48
SCB-2019	5935	5313	4682	3526	2546	2075	1791	1410	995	571	349	226	166	81	46

Cumulative Number of Events															
Placebo	7	61	81	97	109	118	132	136	145	150	152	154	154	155	155
SCB-2019	3	15	28	36	39	44	44	45	48	51	51	52	52	52	52

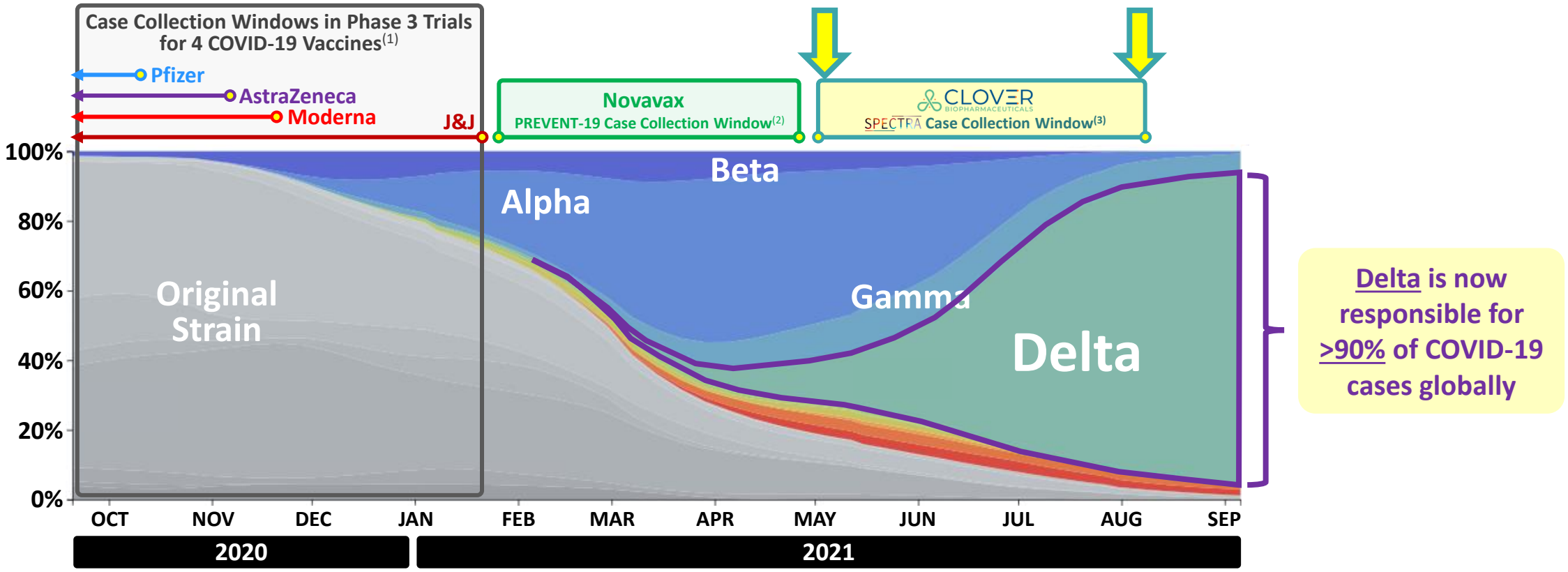
Notes: Figure shows data for PCR-confirmed COVID-19 of any severity (against any strain) at ≥14 days after second dose in participants without evidence of prior SARS-CoV-2 infection (baseline seronegative). Primary endpoint in protocol.

CLOVER BIOPHARMACEUTICALS

SPECTRA Enables Clover to Evaluate Efficacy Against Delta in a Randomized Clinical Trial

- Delta was the predominantly circulating strain globally during SPECTRA enrollment
- SPECTRA evaluated SCB-2019 (CpG 1018/Alum) against concerning variants including Delta

Global SARS-CoV-2 Strain Distribution (GISAID Database)



Delta is now responsible for >90% of COVID-19 cases globally

Source: Strain distribution data from Nextstrain.org (GISAID data) as of 06-SEP-2021

(1) Case collection cutoff dates for primary efficacy endpoint used to support EUL/conditional approvals: Moderna (25-NOV-2020; DOI: 10.1056/NEJMoa2035389), Pfizer (09-OCT-2020; DOI: 10.1056/NEJMoa2034577), AstraZeneca (04-NOV-2020; DOI: 10.1016/S0140-6736(20)32661-1), J&J (22-JAN-2021; DOI: 10.1056/NEJMoa2101544).

(2) Novavax case collection window for primary efficacy endpoint from 25-JAN-2021 to 30-APR-2021 (PREVENT-19 Final Data Announcement Presentation; 14-JUNE-2021).

(3) Clover case collection window for primary efficacy endpoint in SPECTRA from 28-APR-2021 to 10-AUG-2021.

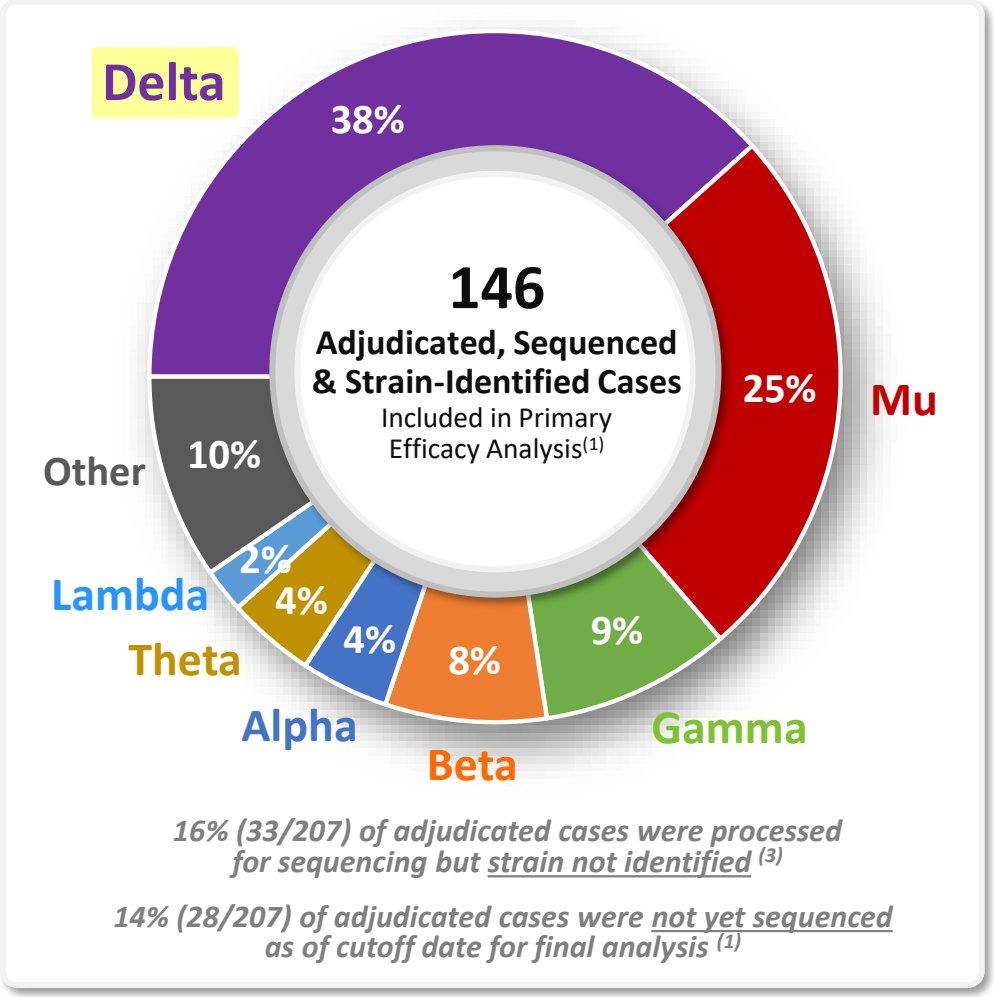
CLOVER BIOPHARMACEUTICALS

Delta was the Dominant SARS-CoV-2 Strain in SPECTRA

- ✓ **100% of identified SARS-CoV-2 strains observed in the efficacy analysis were variants**
- ✓ **Globally dominant Delta was the strain most observed in SPECTRA (38% of all sequenced cases)**
- ✓ **>85% of strains in SPECTRA were VOCs/VOIs with suspected escape mutations (Delta, Mu, Gamma, Beta, Theta, Lambda)**

- COVID-19 Cases included in **primary efficacy analysis**[1]:
  - **Total Adjudicated Cases**[2]**:** **207 cases**

- Strain sequencing provides basis for **strain-specific efficacy analysis** in SPECTRA:
  - Adjudicated + Sequenced Cases: 179 cases
  - **Adjudicated + Sequenced/Identified: 146 cases**
    - **100% of these strains were variants**
    - **Top 3 Variants (Delta, Mu, Gamma) represented 73% of strains**
    - **No cases were caused by Original Strain** of SARS-CoV-2



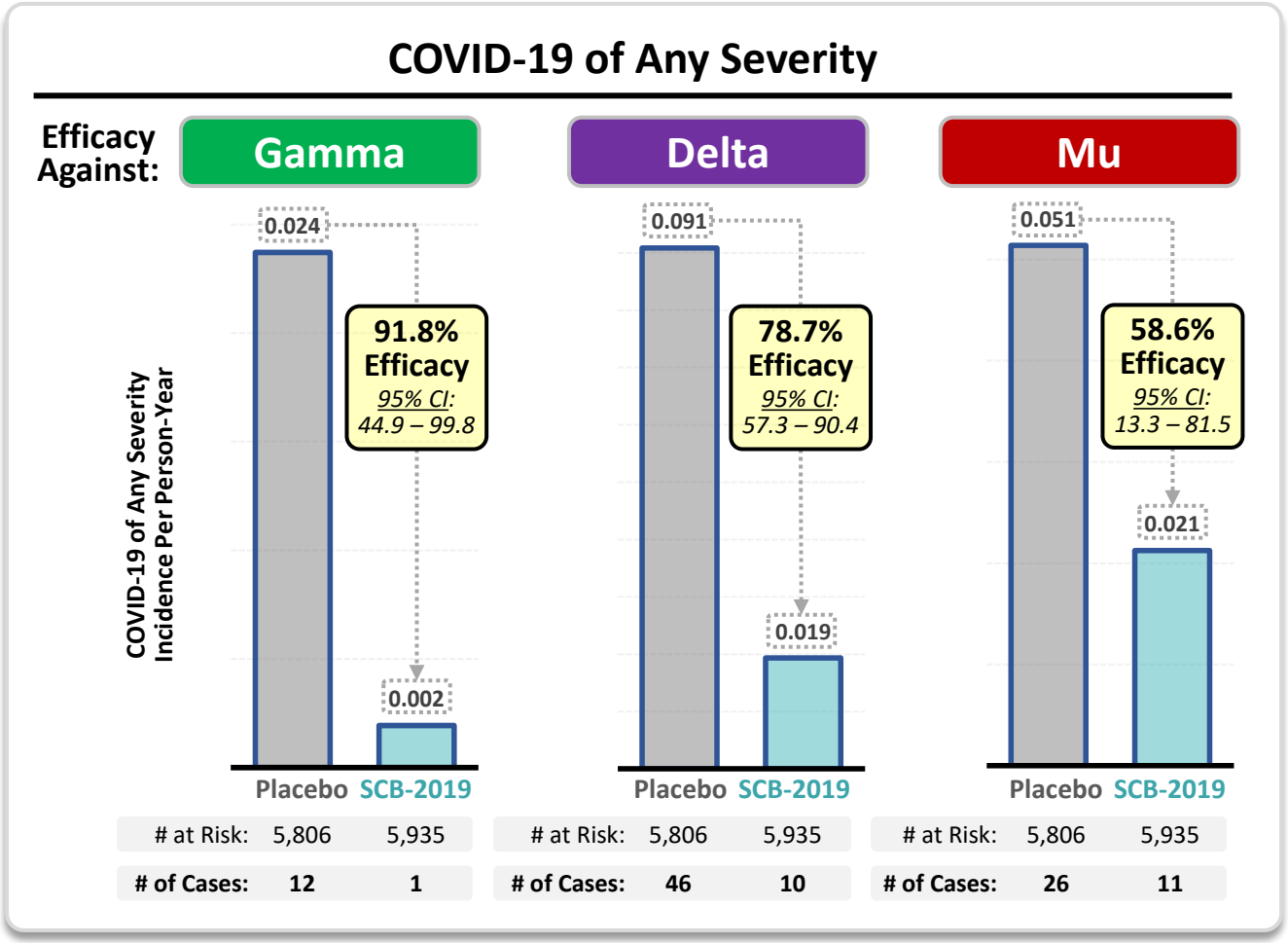
16% (33/207) of adjudicated cases were processed for sequencing but strain not identified (3)

14% (28/207) of adjudicated cases were not yet sequenced as of cutoff date for final analysis (1)

Note: VOC (Variant of Concern). VOI (Variant of Interest).
(1) Counting of cases for primary efficacy analyses begins at ≥14 days after second dose. Cutoff date for primary efficacy analyses was 10-AUG-2021 in all countries in SPECTRA.
(2) 207 cases included in primary efficacy analyses in baseline seronegative participants were adjudicated by an independent endpoint adjudication committee (EAC). 41 additional cases in baseline seropositive participants were adjudicated and included for secondary efficacy analyses.
(3) Samples processed for sequencing, but strains were not identified (e.g. lack of sufficient nasopharyngeal swab sample collected, unsuccessful RNA-sample extraction, etc.).

Significant Efficacy Also Observed Against Gamma (VOC) and Mu (VOI)

- ✓ **First COVID-19 vaccine to demonstrate significant efficacy against Delta, Gamma & Mu variants** (Top 3 strains in SPECTRA, comprising 73% of all strains identified)
- **Differences in vaccine efficacy likely driven by unique mutation profiles of each variant strain**



- **Gamma: 91.8% efficacy against Gamma (any severity)**
  - Gamma (P.1) harbors E484K escape mutation in RBD, and demonstrated high transmissibility in Brazil and other Latin American countries(1)
- **Mu: 58.6% efficacy against Mu (any severity)**
  - Mu (B.1.621) is predominant strain in Colombia(1), and believed to be 'Beta-like' based on spike protein mutation profile and cross-neutralization studies(2)
  - A Phase 2b/3 clinical trial of an mRNA COVID-19 vaccine candidate demonstrated lowest efficacy against Mu (41.5% vaccine efficacy) among all variant strains evaluated(3)
- **Other: Against all other sequenced strains (including Alpha, B.1.623, Beta, Lambda, Theta, Other & Not Identified), efficacy against moderate-to-severe COVID-19 was 90.2% (95% CI: 31.2,99.8), and efficacy against COVID-19 of any severity was 55.0% (95% CI: 24.9%, 73.8%)**
  - No hospitalizations or severe COVID-19 cases in vaccine group (2 severe COVID-19 cases in placebo group)
  - Insufficient number of cases of each individual variant strain to enable statistical analyses of vaccine efficacy

Notes: VOC (variant of concern); VOI (variant of interest). RBD (receptor binding domain of spike protein). Figures show data for PCR-confirmed COVID-19 at ≥14 days after second dose in participants without evidence of prior SARS-CoV-2 infection (baseline seronegative).

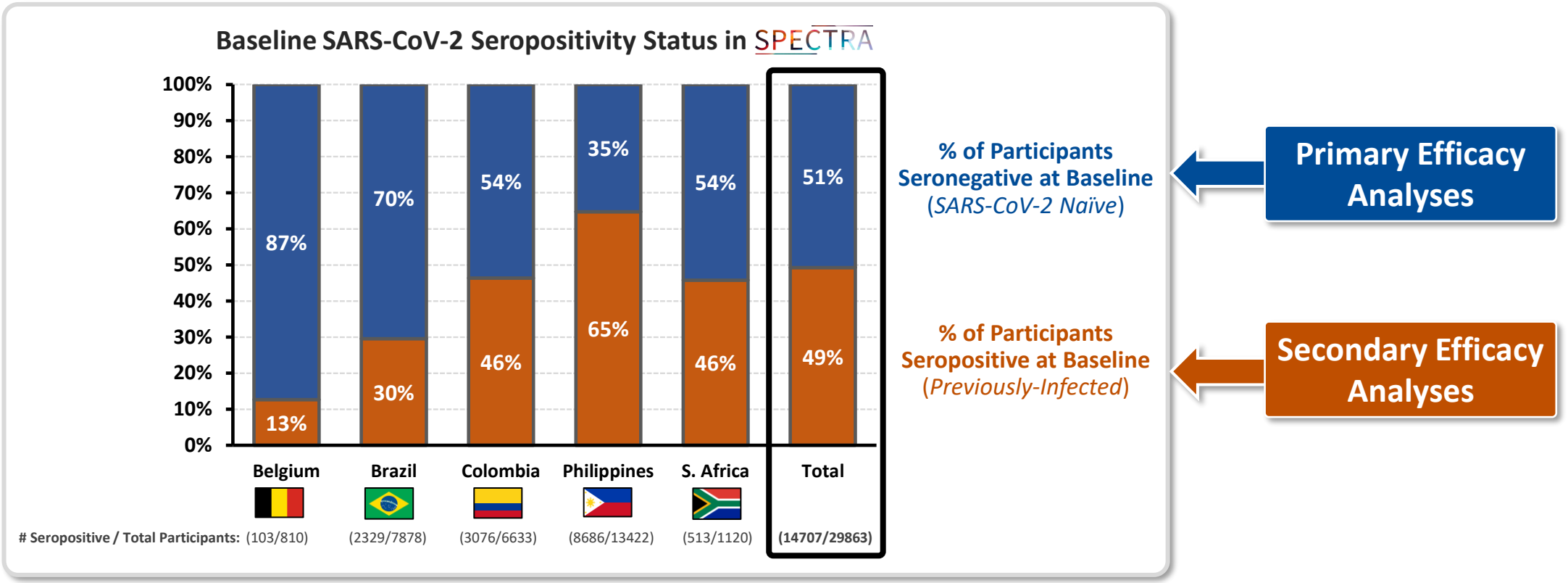
(1) NextStrain.org (GISAID database) as of 06-SEP-2021.
(2) DOI: 10.1101/2021.09.06.459005
(3) DOI: 10.2139/ssrn.3911826

CLOVER BIOPHARMACEUTICALS

Enrollment of Previously-Infected Individuals in SPECTRA

☑ *SPECTRA enrollment enables evaluation of efficacy & safety in previously-infected individuals in a randomized clinical trial*

- **Previous COVID-19 vaccine clinical trials** evaluated efficacy & safety primarily in **SARS-CoV-2 naïve individuals** ('baseline seronegatives')
- As SARS-CoV-2 continues to spread globally, evaluation of vaccine efficacy & safety in **previously-infected individuals ('baseline seropositives')** is becoming increasingly important
- **~49% of all participants enrolled in SPECTRA were baseline seropositive**, providing basis for landmark analysis of vaccine efficacy in this population
- Analysis for vaccine efficacy in SPECTRA were stratified by baseline seropositivity status



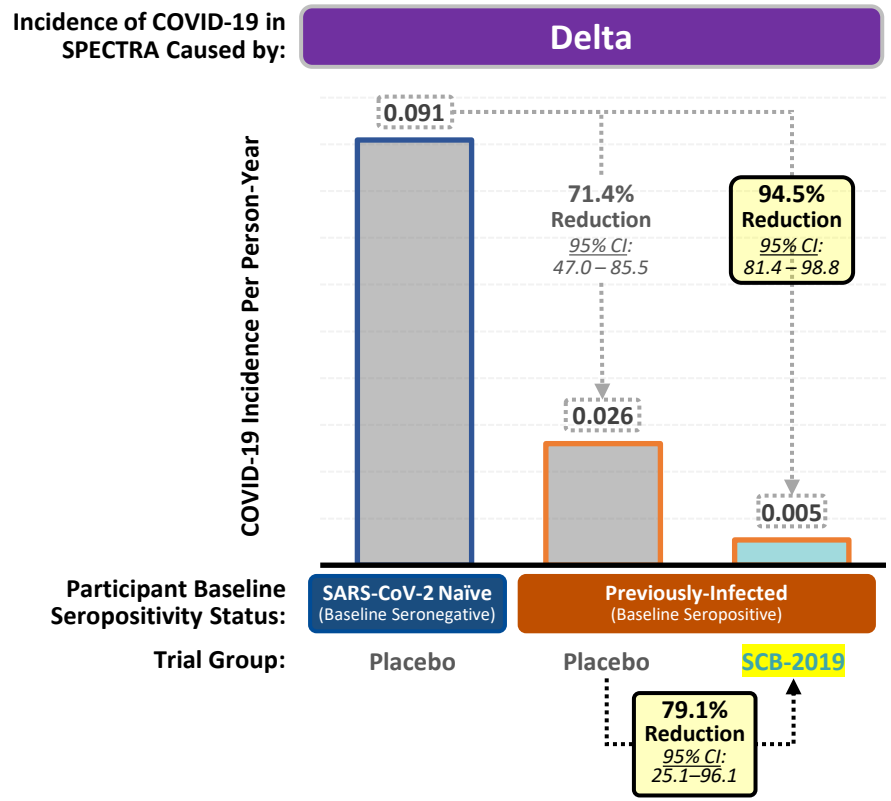
Note: Baseline seropositivity status determined by presence of antibodies binding to SARS-CoV-2 Spike (S) protein in Day 1 serum samples (Roche Elecsys® anti-S test) or known history of COVID-19 disease.
Data shown for all participants with available seropositivity testing results.

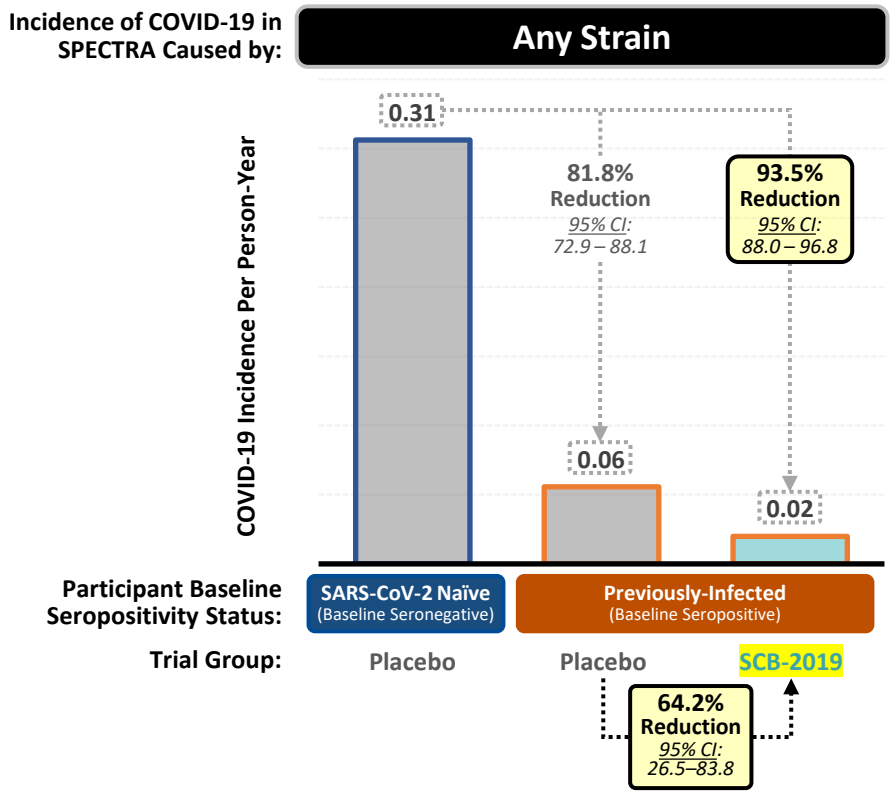
CLOVER BIOPHARMACEUTICALS

Unprecedented Analysis of Efficacy in Previously-Infected Population

- **Previous SARS-CoV-2 natural infection provides significant protection against symptomatic re-infection; however,**
- ✓ **SCB-2019 vaccination can significantly boost protection in previously-infected subjects**
- ✓ SCB-2019 is the first COVID-19 vaccine globally to demonstrate **vaccine efficacy & safety in previously-infected individuals**

COVID-19 of Any Severity





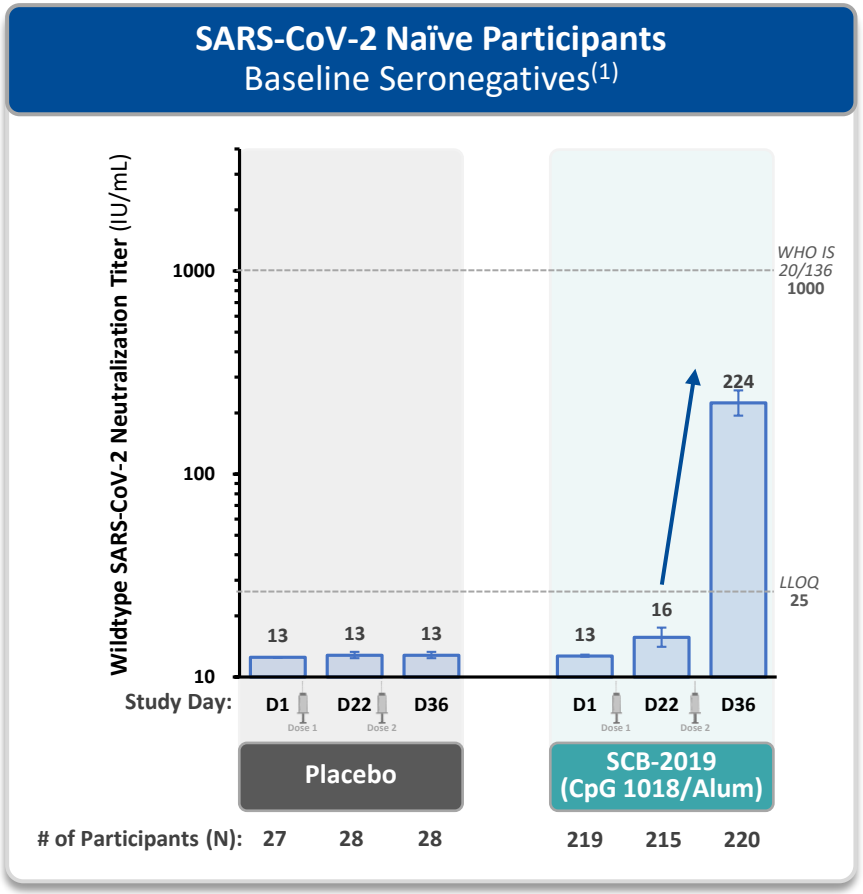
Source: Adapted from Clover Public Presentation for SPECTRA Ph 2/3 Trial Data (22 SEP 2021).
Notes: Figures show data for PCR-confirmed COVID-19 at ≥14 days after second dose. Preliminary efficacy in baseline seropositives relative to baseline seronegative placebo group is exploratory post-hoc analysis. "Reduction" refers to reduction in risk of COVID-19 compared to placebo group in SARS-CoVI-2 naïve (baseline seronegative subjects).

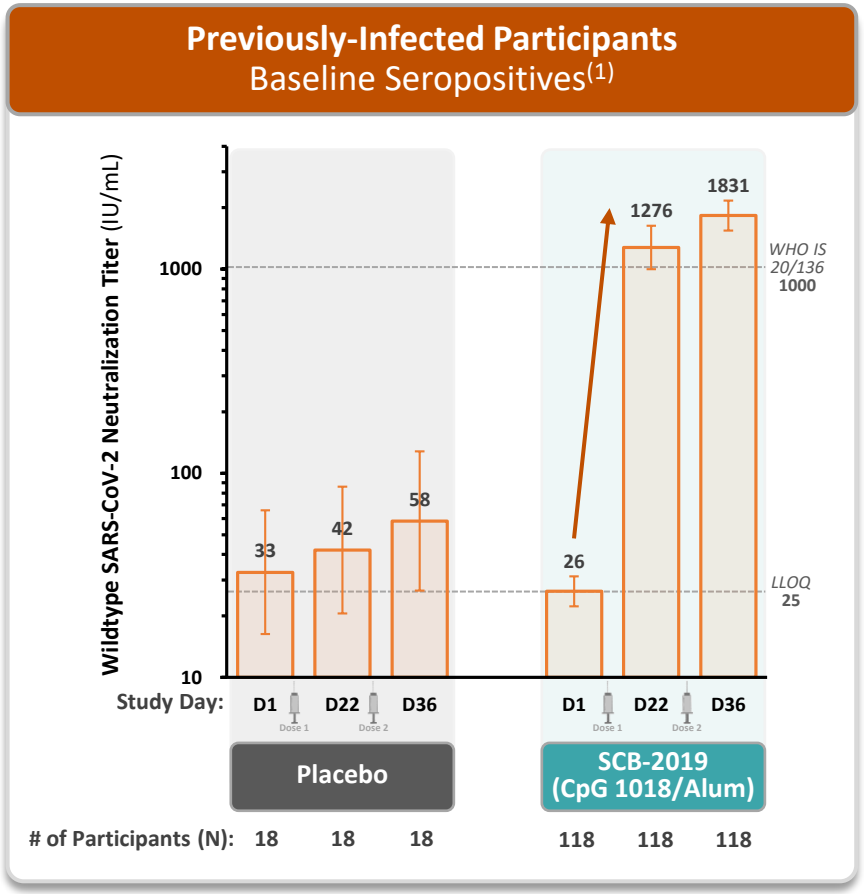
Neutralizing Antibodies (Wildtype SARS-CoV-2 Neutralization Assay)

☑ *Strong Neutralizing Immune Responses Induced by SCB-2019 (CpG 1018/Alum)*

✓ **High neutralizing antibodies induced in SARS-CoV-2 naïve participants after 2 doses of SCB-2019 (CpG 1018/alum); results are in-line with Clover's Phase 1 clinical trial**

✓ **Rapid & strong boosting effect induced in previously-infected participants after 1 dose, supporting further evaluation of SCB-2019 (CpG 1018/alum) as a booster vaccine**





Notes: Bars represent Geometric Mean Concentrations (GMC) ± 95% confidence intervals (95% CI). Validated Wildtype neutralization assay against the original strain of SARS-CoV-2 (VisMederi). Titers expressed was international units/mL (IU/mL) based on WHO international standard sera (WHO IS 20/136). Samples with titers below LLOQ were assigned a value of 12.5.
(1) Baseline seropositivity status determined by presence of antibodies binding to SARS-CoV-2 Spike (S) protein in Day 1 serum samples (Roche Elecsys® anti-S test).

CLOVER BIOPHARMACEUTICALS

Key Takeaways from SPECTRA Global Phase 2/3 Trial

- *SPECTRA successfully enrolled over 30,000 adult & elderly participants in 5 countries across 4 continents*
- *100% of SARS-CoV-2 strains observed in the efficacy analysis were variants (Delta was predominant strain)*

- ✓ **Primary and secondary efficacy endpoints were successfully met**
- ✓ **100% efficacy against severe COVID-19 & hospitalization, 83.7% efficacy against moderate-to-severe COVID-19, 67.2% efficacy against COVID-19 of any severity** caused by any strain of SARS-CoV-2 in SPECTRA
- ✓ **Delta: 78.7% efficacy** against **COVID-19 of any severity** caused by the **globally-dominant Delta strain**
- ✓ **Favorable safety profile:** No significant differences in systemic adverse events or severe/serious adverse events compared to placebo
- ✓ First COVID-19 vaccine to demonstrate **significantly reduced risk of COVID-19 disease in previously-infected individuals**, a growing & increasingly important population as SARS-CoV-2 continues to spread globally

Thank You

Clover Biopharmaceuticals

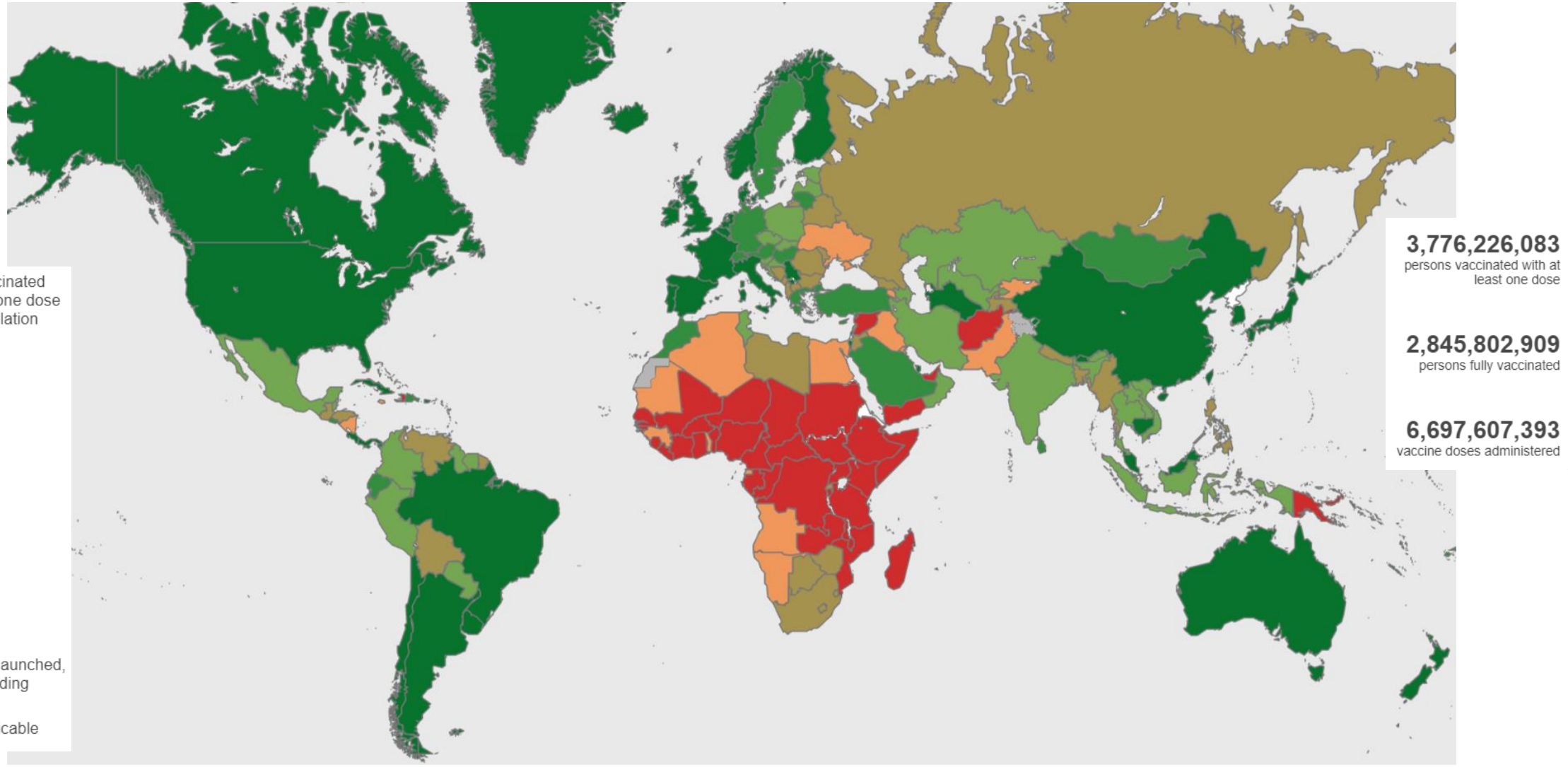
www.cloverbiopharma.com

COVID-19 VACCINE DELIVERY UPDATE

COVAX Clinical Dev & Ops Workshop, Oct 27, 2021

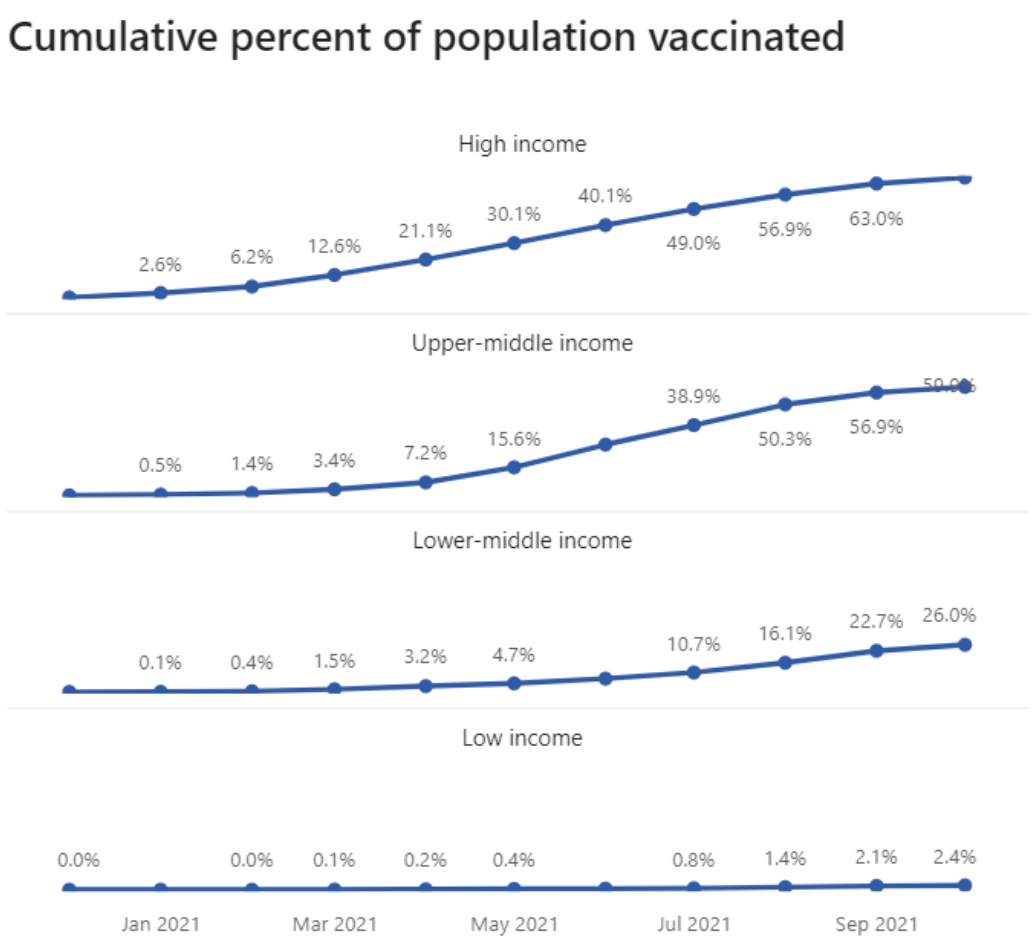
Emily Nickels
Program Officer
Bill & Melinda Gates Foundation

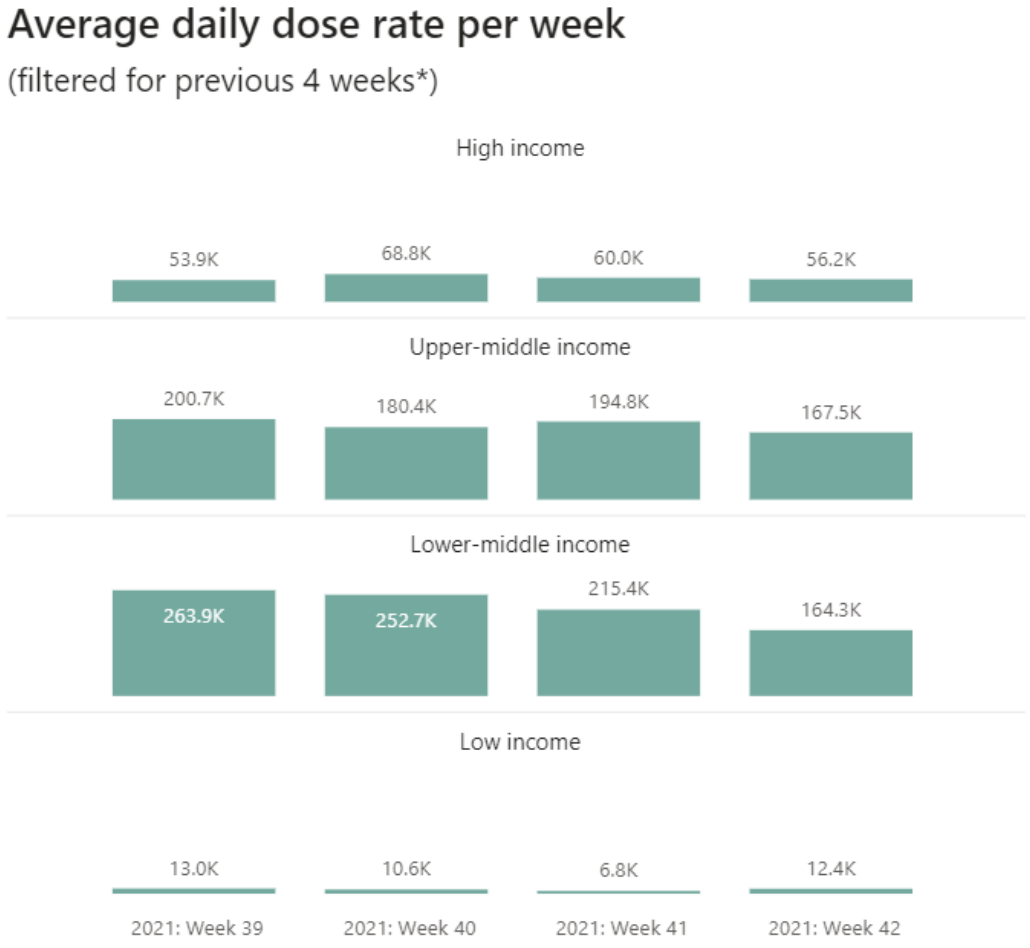
GLOBAL COVID-19 VACCINE COVERAGE



Source: [WHO COVID-19 Dashboard](), accessed Oct 25, 2021

COVERAGE INEQUITY: HIC 66%, UMIC 60%, LMIC 26%, LIC 2%





OWID source accessed: 10/21/2021 | Power BI refreshed: 10/21/2021

* Note: this looks at the most recent 4 complete weeks. Weeks start on Sunday and end the following Saturday. As a result, this does not show the most recent daily information - it will be anywhere from 3 days old on a Tuesday to 7 days old on a Saturday.

Data source: Our World in Data, World Bank.

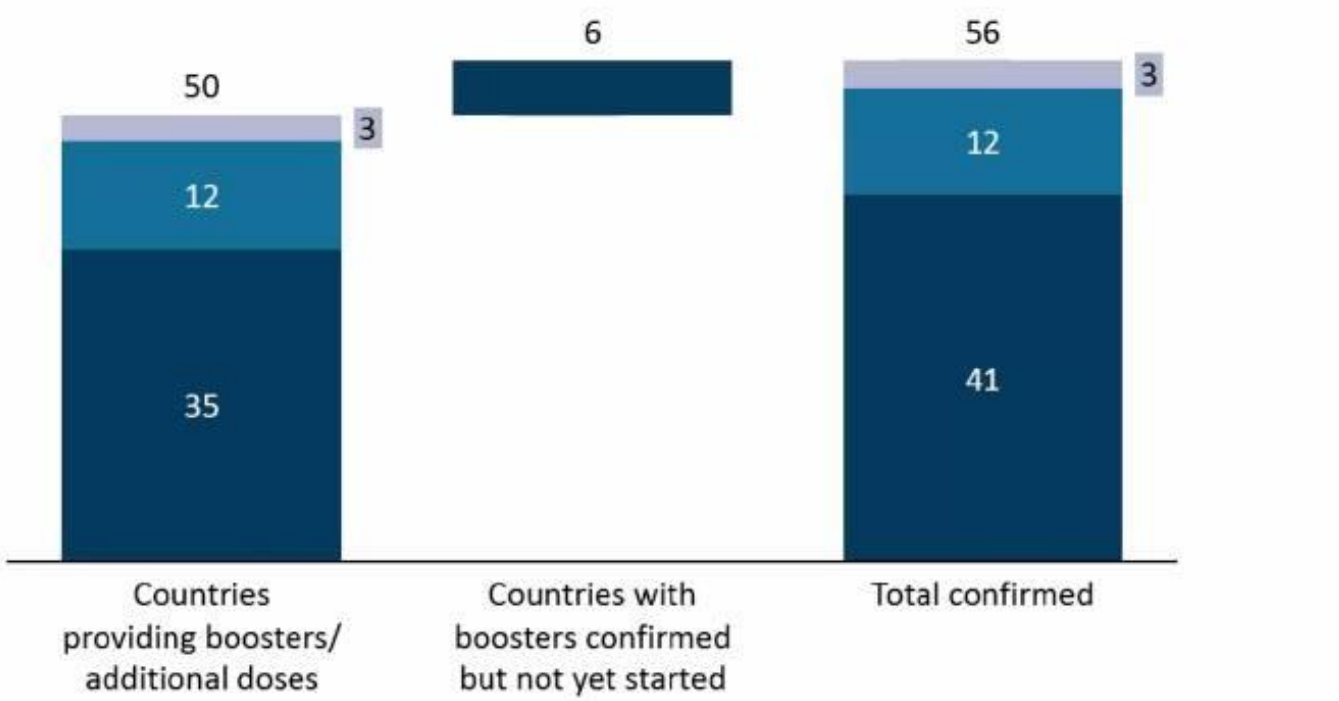
At least 56 countries have confirmed COVID-19 vaccine boosters/additional doses

PLEASE NOTE: WHO DOES NOT RECOMMEND BOOSTER DOSES, AND HAS CALLED FOR A VACCINE BOOSTER MORATORIUM UNTIL END OF 2021

DATA AS OF OCT 05, 2021

INDICATIVE // NON-EXHAUSTIVE

Status of COVID-19 booster administration, # of countries



Source: Government statements, press search

Key takeaways

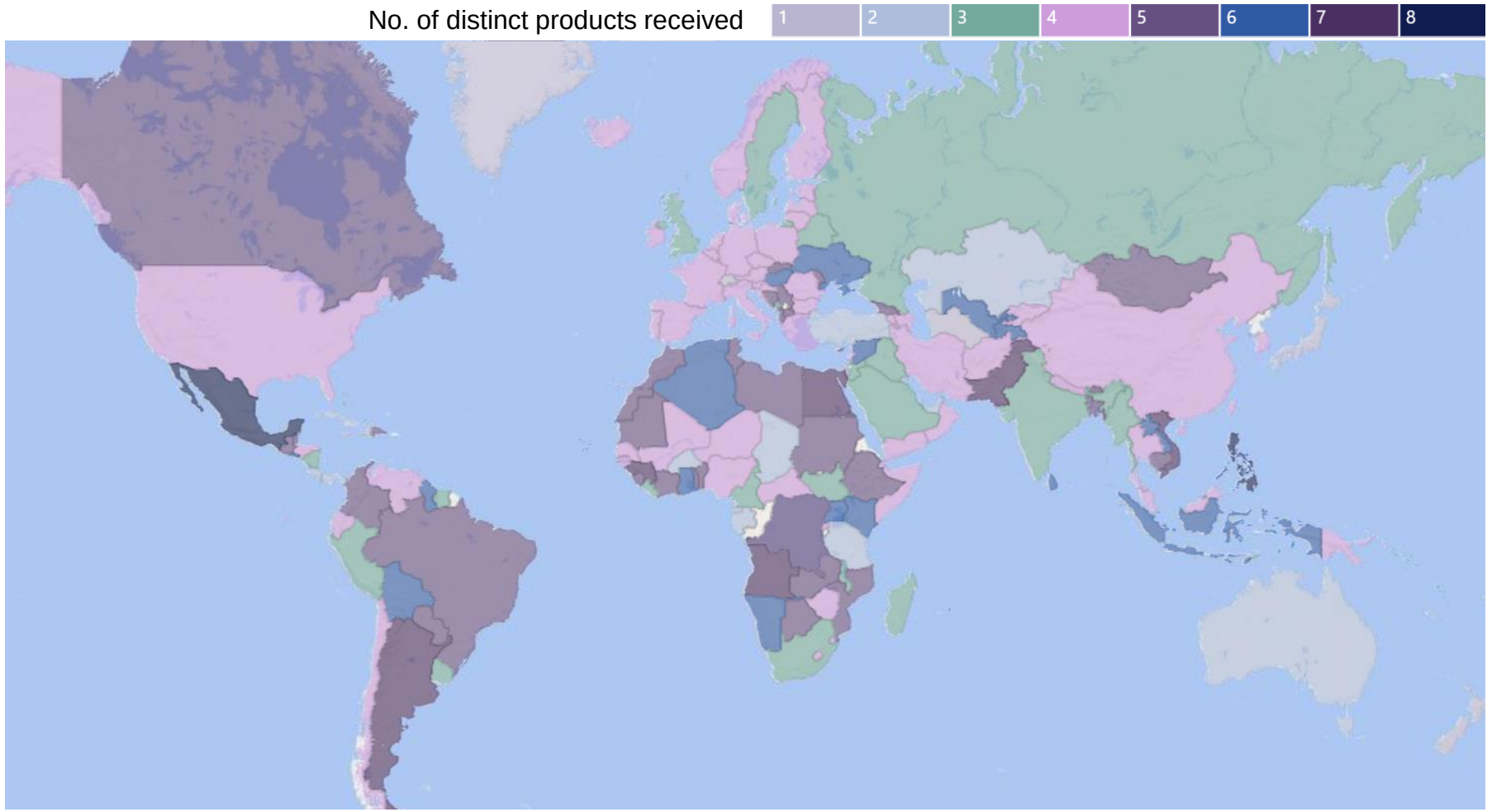
50 countries (70% are HICs) started administering boosters/ additional doses as of Oct 5th:

6 HICs confirmed a booster program but yet to start

At least 12 other countries are considering a booster program

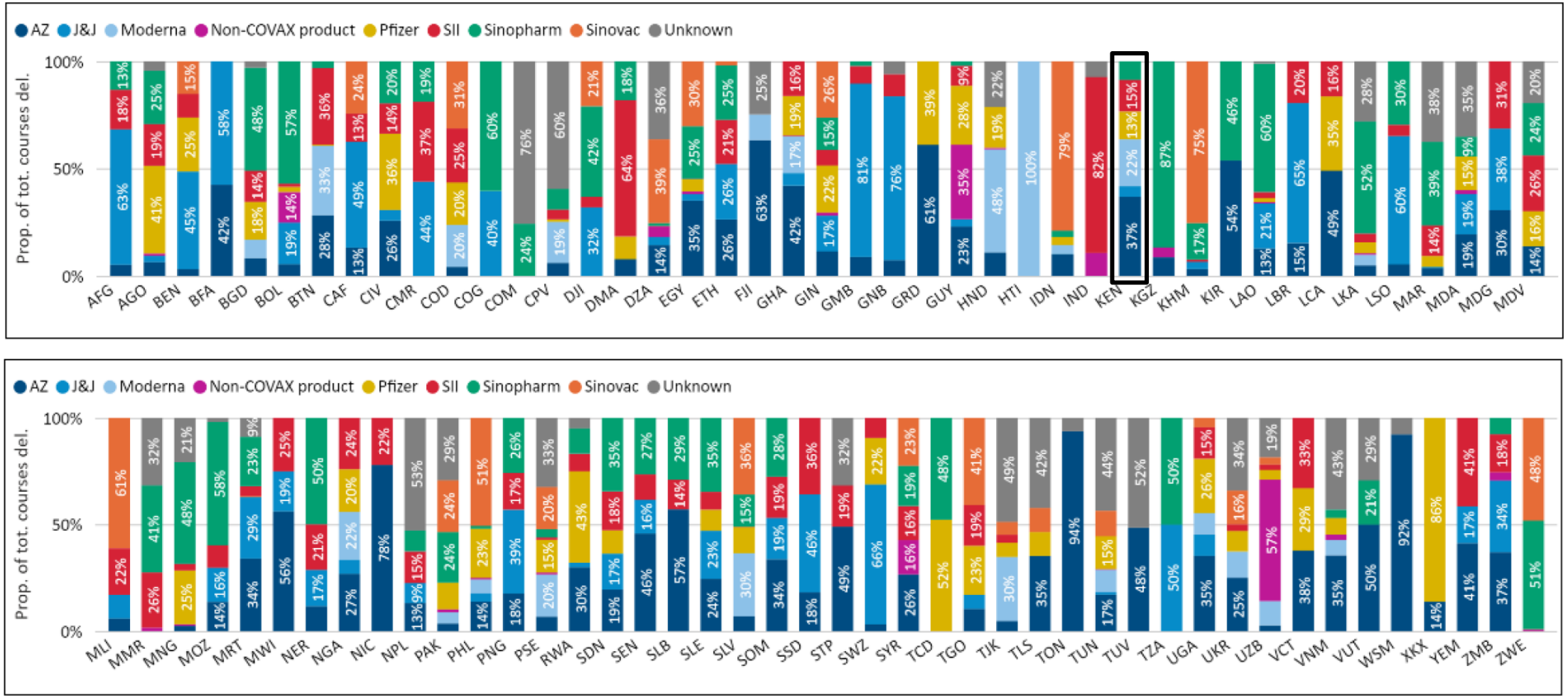
At **least 3x as many** booster doses are administered **daily** as there are primary doses in LICs

MOST COUNTRIES HAVE RECEIVED 4+ PRODUCTS



Source: UNICEF COVID-19 Market Dashboard, accessed Oct 25, 2021

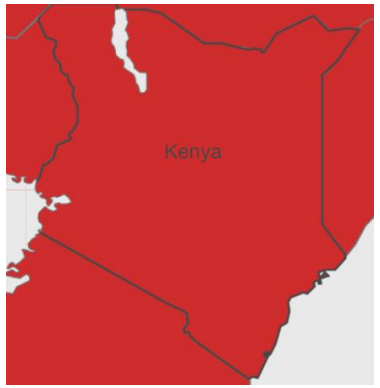
PROPORTION OF TOTAL DOSES RECEIVED BY PRODUCT ACROSS AMC92 PARTICIPANTS



Source: [UNICEF COVID-19 Market Dashboard](), visual courtesy of WHO, data as of Oct 20, 2021

EXAMPLE: PRODUCT INFLUX IN KENYA

Summary of vaccination program



4.9M doses administered

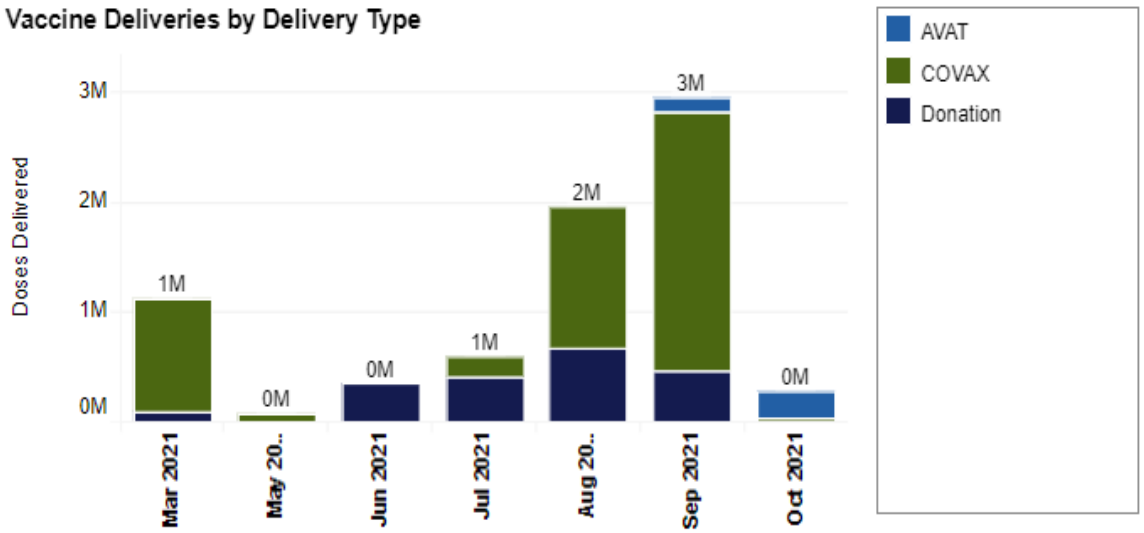
9.2 doses administered / 100 population

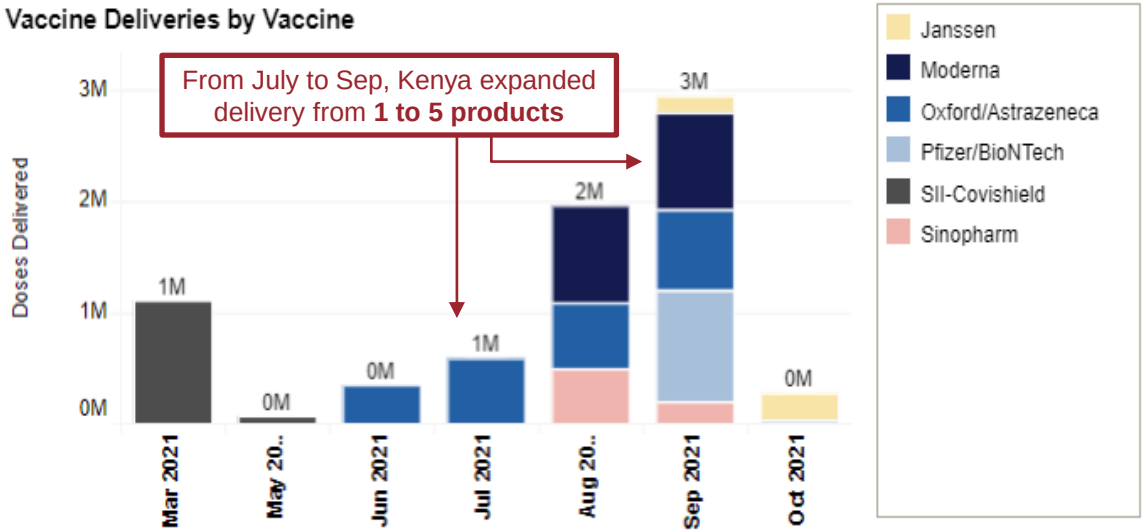
6.4% first dose coverage

2.6% fully vaccinated

Key challenges

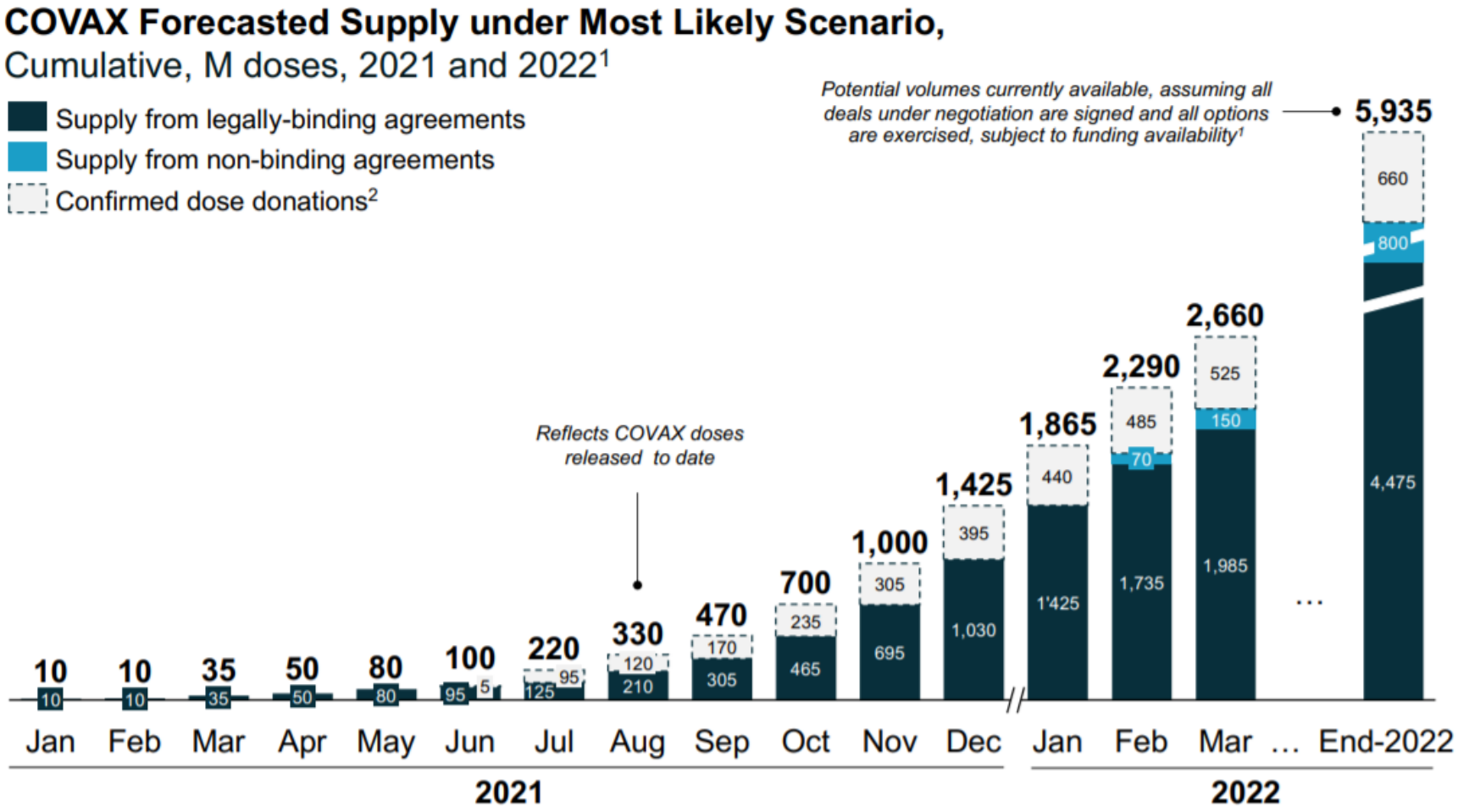
- Microplanning with limited supply visibility
- Managing different product profiles:
  - Cold chain requirements
  - Immunization schedules
  - Training and administration
  - 2nd dose follow-up
- Prioritization based on expiration
- Availability of ancillary products (notably 0.3ml syringes)





Source: Our World in Data; UNICEF COVID-19 Market Dashboard, accessed Oct 25, 2021

COVAX FACILITY GLOBAL SUPPLY FORECAST



1 Forecasts are based on best available information from manufacturers and analysis from Gavi and UNICEF. Timing of available supply is based on anticipated date of release by manufacturer, at which point doses become available for delivery; as such, timing of delivery to countries will be lagged. Volumes for expected single-dose regimen candidates doubled to ensure comparability across vaccines. Volumes have been rounded to nearest 5M, except those less than 10M, and so totals may not equal sum of segments.
2 "Dose donations" estimated based upon donor commitments to share new doses bilaterally with COVAX. The transfer of COVAX allocations from SFPs to AMC Participants are already included in "Supply from legally-binding agreements".

Heterologous COVID-19 Booster Vaccine Studies

COVAX Workshop on COVID-19 Vaccine Development in an Increasingly Seropositive World

27.10.2021

Paul Oloo

Overview- Planned and Ongoing Heterologous Boost studies

Sponsor	Dose interval (in months)	Location	Status	Preliminary data
Vaccine Task Force, NIH, Uni Hosp of Southampton (COV Boost)	>3 after 2nd dose	UK	Ongoing	No
NIAID	3	USA	Ongoing	Yes (Preprint)
University of Birmingham (OCTAVE DUO)	*At least 14 days after completing primary series*	UK	Ongoing	No
Erasmus Medical Centre (SWITCH)	3	Netherlands	Ongoing	Yes (WHO consultation)
Christian Medical College (CMC) Vellore	6	India	Ongoing	No
Jiangsu CDC+Cansino	3-6	China	Active. not recruiting	No
Jiangsu CDC	3	China	Ongoing	No
Qihan Li	6	China	Not yet recruiting	No
Medical University Innsbruck, Austria	3	Austria	Ongoing	No

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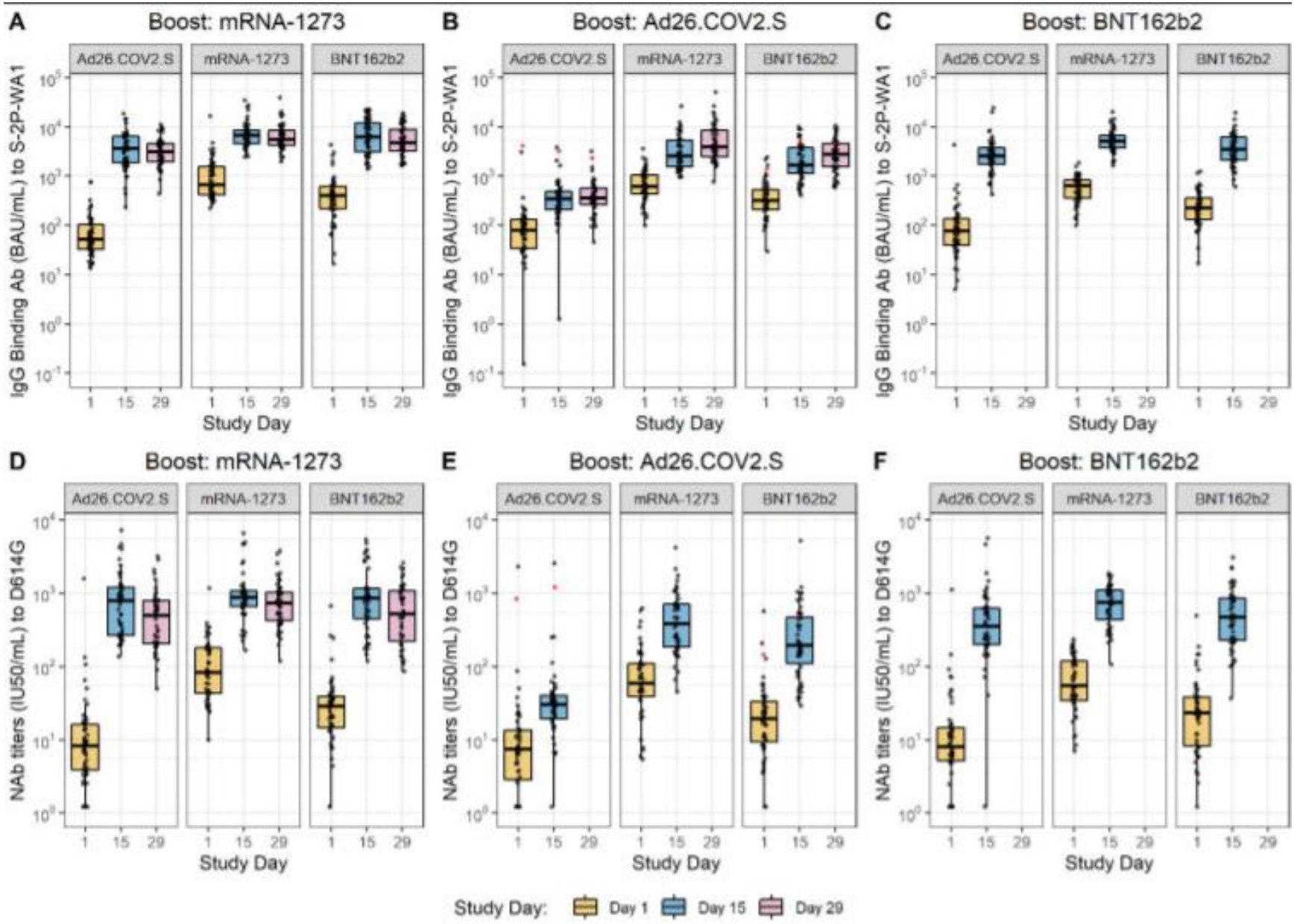
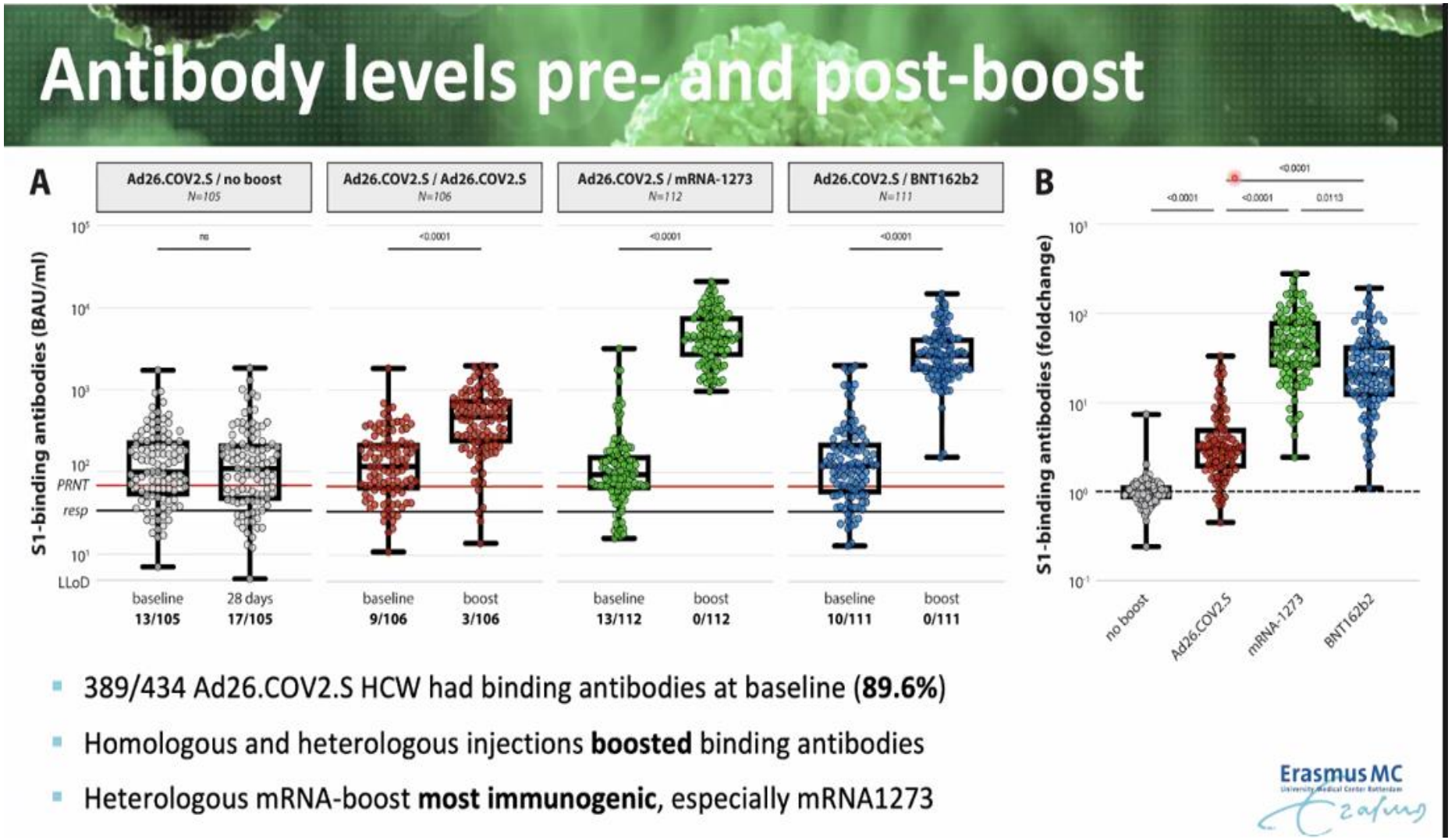
NIAID US Heterologous Platform Boost study



- Adults received Moderna, JnJ or Pfizer vaccines followed by booster after 12 weeks in 9 combinations
- mRNA peaks at D15, stable at D29
- JnJ incremental rise to D29
- Limitations:
  - Non-randomized
  - Study did not control for intervals between primary vaccines and boosts
  - Only antibody data available- cellular immune data pending
  - Data from early timepoints only

Atmar, R. et al (2021) heterologous SARS-CoV-2 Booster Vaccinations- preliminary report, NIAID, https://www.medrxiv.org/content/10.1101/2021.10.10.21264827v1

Erasmus Medical Centre Heterologous Boost study in Health Care Workers 18-65 years old (SWITCH Trial)



- Primary vaccine – Janssen vaccine single dose
- Booster dose after 12 weeks
- Primary outcome: IgG Ab titers 28 days after booster

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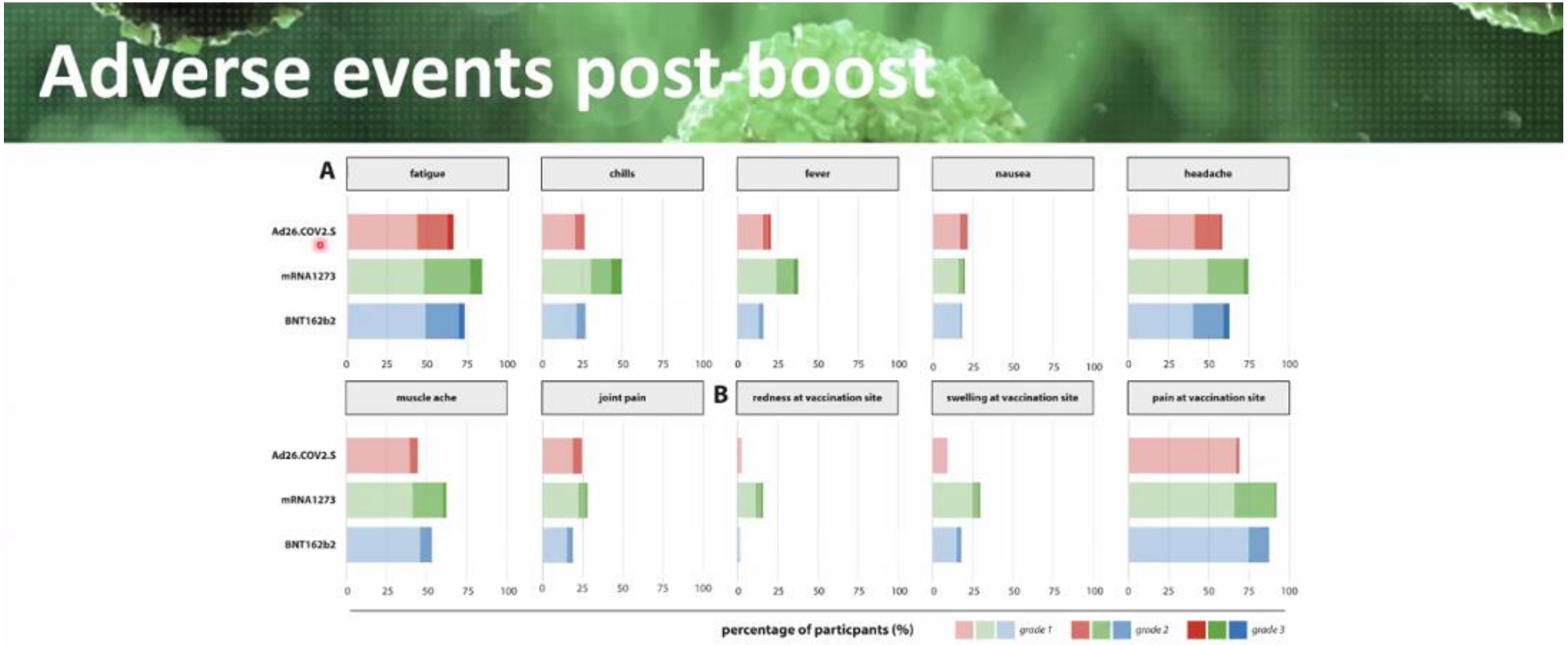
Vries, R. Erasmus MC, Adopted from WHO consultation on COVID-19 Vaccine research, 25.10.2021, NCT04927936

Erasmus Medical Centre Heterologous Boost study in Health Care Workers 18-65 years old (SWITCH Trial)



- Only mild systemic and local adverse events reported
- Adverse events generally resolved within 48hrs
- mRNA1273 was most **reactogenic**

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Erasmus MC

Vries, R. Erasmus MC, Adopted from WHO consultation on COVID-19 Vaccine research, 25.10.2021, NCT04927936

Key Learnings

- mRNA vaccines most reactogenic particularly mRNA-1273
- Use of mRNA-1273, Ad26.COV2.S and BNT162b2 as booster vaccines leads to anamnestic serologic responses after priming with Moderna or Pfizer or Janssen vaccines
- mRNA vaccines result in higher antibody titers in the first 28 days after boost compared to viral vectored vaccines
- No safety concerns identified so far
- Most trials focus on mRNA platform vaccines and Janssen vaccine. There is urgent need to close corresponding gaps for vaccines used in LMICs

Discussion

- More data on heterologous boost studies expected in coming weeks and months through Q1 2022
- Clinical trials ongoing: Which vaccine works best as a booster jab?
- The order of prime-boost administration may be important: may be antigen-dependent, influenced by the type(s) of immune responses to be achieved
- Benefits of booster doses should be clear in order to make a benefit:risk assessment
    - Primary vaccination may not induce adequate immunity in immunocompromised persons and recipients of vaccines with low efficacy
- More data on how long immunity lasts following the primary series of COVID-19 vaccines
- Risk of booster doses:
    - safety concerns (platform specific? Dose specific?);
    - unknown long-term consequences;
    - adverse public health outcomes
- Not all vaccines have controlled or systematic analyses of post-authorization safety data
- Data on administration of booster vaccine(s) together with flu vaccine(s)- studies ongoing

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Fractional doses – research gaps

COVAX Clinical Development and Operations SWAT Team Workshop Oct 27, 2021

Christof Vinnemeier

Urgent need for data on fractional doses of COVID-19 vaccines

- Terminology

Booster dose:	To **maintain immune response** over time
Additional dose:	as **part of** / to complete **primary immunisation** (e.g. 2+1), 1 dose given months (>6 months) after priming (for vaccines with a rapid decline in Ab-levels, in special populations)

- Why fractional doses? → Supply shortages / **safety considerations**
- Fractional doses have been proven to be **feasible with other vaccine platforms** (e.g. live-attenuate YFV-17D (1/5 dose) or non-adjuvanted protein HBs Ag (1/4 dose)
- First data available (e.g. Moderna 50 µg, BNT/Pfizer 10 µg/3µg, Janssen $1.25x10^{10}$), intradermal application of 10ug/20ug mRNA-1273, more data to be published soon (e.g. CoV-BOOST study)

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Fractional doses – Questions and Challenges

- **Fractional doses in un-primed populations:** Primary immunisation?

- **Fractional in doses in primed populations:**

  - only for special populations (e.g. elderly, immunocompromised) given the recent SAGE recommendation and continuing supply shortages ?

  - for individuals after natural infections (particular importance in LMICs)

    - Lancet data from Ethiopa indicates seroprevalence rates up to 73% in **unvaccinated urban communities** (as of April 2021) Gudina, EK et al. Lancet Glob Health 2021

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Fractional doses – Questions and Challenges

- **Durability** of antibody responses when boosted (with fractional doses):
  all available data reflects short-time follow-up periods (up to 8 weeks)

- **Selection of vaccine**, dose selection (benefit/risk; dose dependent safety aspects),
  timing of booster

- **Practical challenges**: secure vaccine supply for trials, administration of small volumes of vaccines, shortages of syringes

Open call

A platform trial approach to assess the immunogenicity and safety / reactogenicity of fractional COVID-19 vaccine(s) as an additional dose in primed populations (FraCT-CoV)

Technical and administrative questions about this Call should be directed to cfp@cepi.net

Fractional dose platform trial: Core elements

1. **Full versus fractional single dose** of a selected vaccine. If the "booster" vaccine differs from vaccine given for priming, a control group including the same vaccine (full dose) given for primary vaccination should be considered
2. **4-week interval** between „booster" dose and primary immunogenicity endpoint
3. Immune response for primary endpoint assessed based on **binding antibodies** (IgG ELISA)
4. **Reactogenicity / safety** assessment (as co-primary objective)
5. Follow-up (safety) for at least **3 months**

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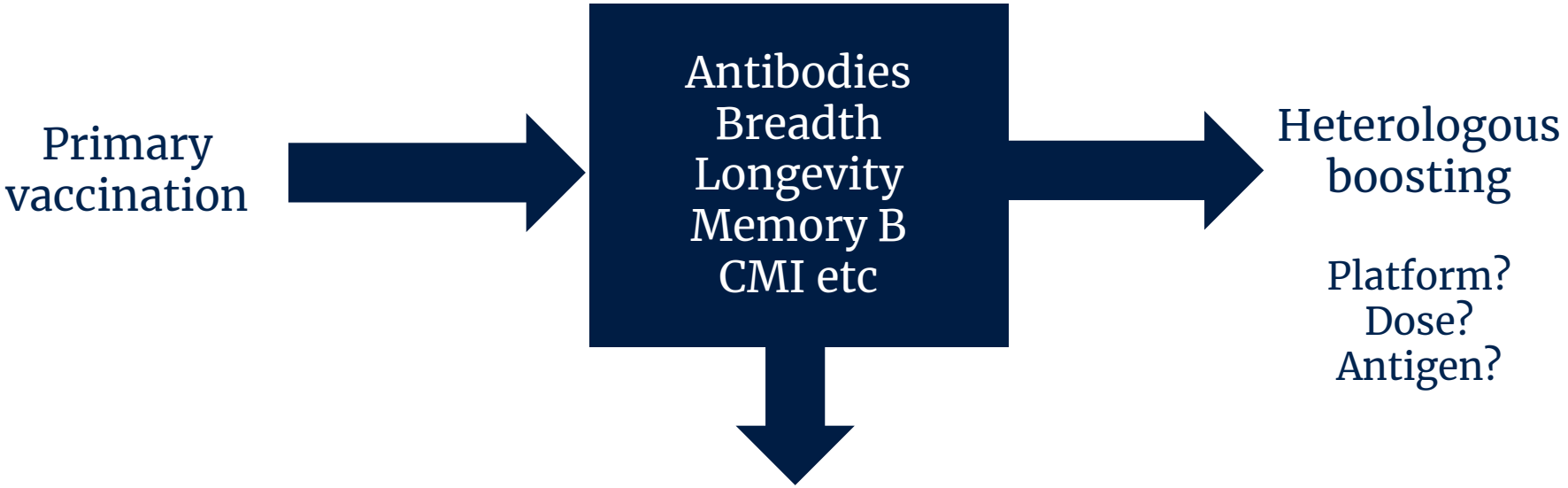
Heterologous vaccination: what can we anticipate in terms of breadth and durability?

25 October 2021

Robbert van der Most

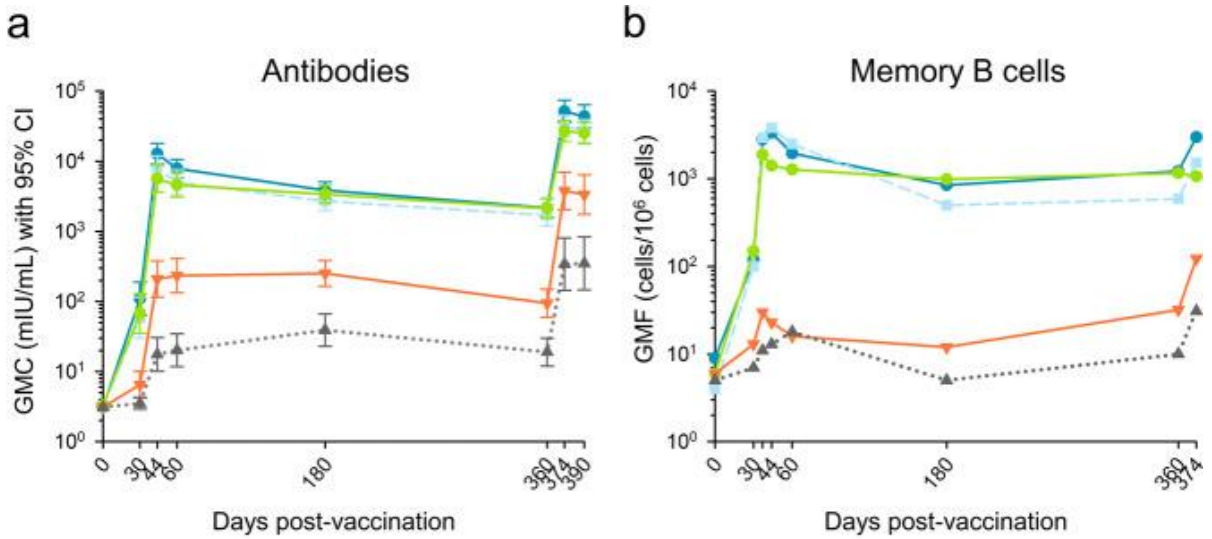
Situation

- How to define heterologous boosting? *Platform and/or antigen*
- Consider **protection** as a function of antibody titer, durability, CMI and innate immunity
- Consider **boostability** as a function of memory B cells => numbers and specificities



Example 1: it works

- **Hepatitis B fractional dose boosting**
- Subjects were immunized with different HBsAg vaccines => *different memory levels*
- Memory B cell numbers well maintained
- Boosted with 1/5 dose non-adjuvanted HBsAg => clear boost in responses
- However, this is not really heterologous



[Budroni et al., 2021: NPJ Vaccines DOI: 10.1038/s41541-021-00337-0]

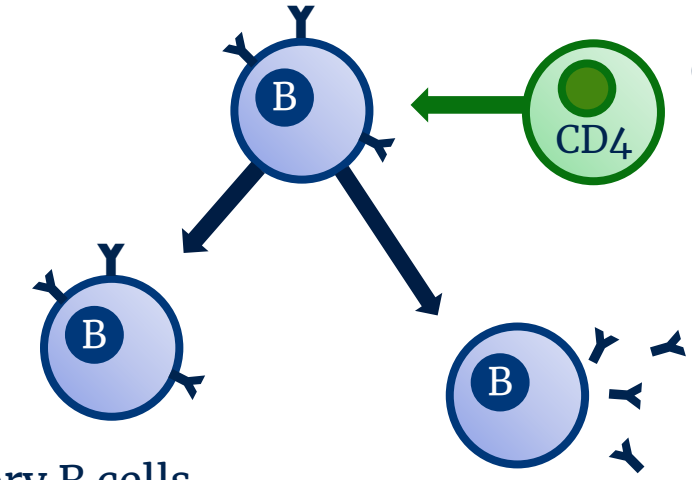
Example 2: it may work *or not*

- **H5N1 influenza heterologous boosting**
- Same platform but different antigens (H5N1/Indonesia versus H5N1/Vietnam)
- H5N1/Vietnam-prime => H5N1/Indonesia boost => measure Indonesia-specific HAI-response
- Good news (1) & bad news (2): depending on the nature of immunological memory
- Hypothesis: difference between (1) and (2) explained by CD4 T helper cells
- *Continuous improvement*: with CD4 help, B memory cells can deal with antigenic differences: go from (2) to (1)

[Van der Most RG et al., 2014: Science Translational Medicine 6, 246 DOI: 10.1126/scitranslmed.3008409]

An immunological framework for heterologous boosting

- **A B-cell centric world view**
- Primary vaccination induces B cell responses that depend on CD4 help
- B cells differentiate into plasma cells and B memory cells



CD4 help: *class switching, affinity, BCR hyper-mutation*

Memory B cells

Their existence allows boosting

Plasma cells => homing to the bone marrow

Their survival determines Ab durability

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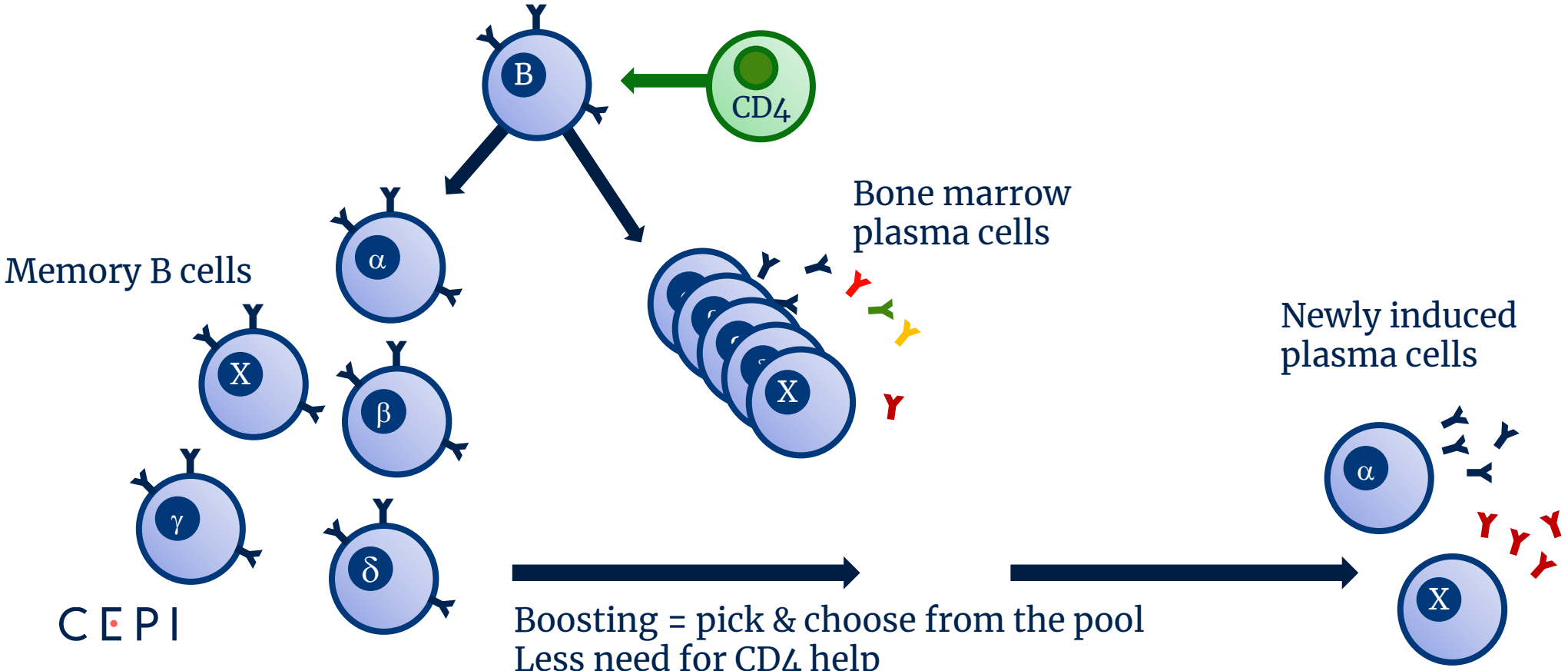
An immunological framework for heterologous boosting

- **Strain specificity is determined by the B cell receptor**
- The memory pool has different specificities, including α/β/γ/δ –specific or cross-reactive X



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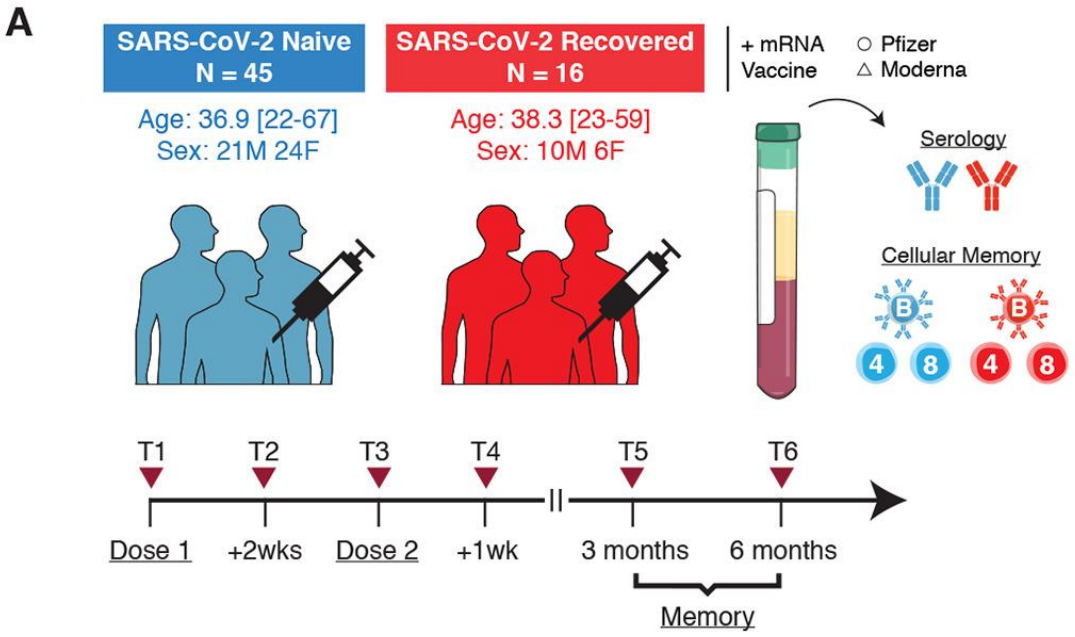
Example 2 revisited

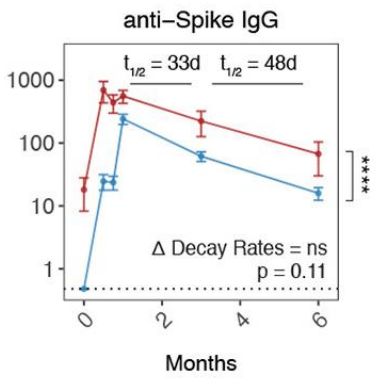
- **H5N1 influenza heterologous boosting after priming with or without adjuvant**
- The difference between success (1) and failure (2) is driven by memory
- (2) is an example of original antigen sin => *wrong-footing the system*
- Which B memory cells are being picked? OR:
- How to get Indonesia-antibodies with Vietnam-memory cells?

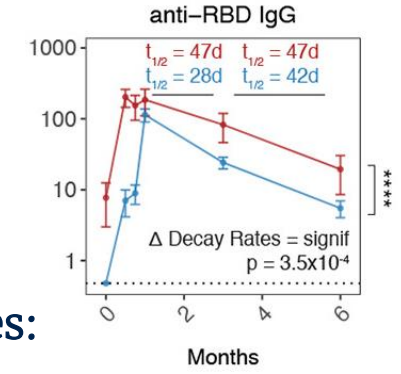
[Van der Most RG et al., 2014: Science Translational Medicine 6, 246 DOI: 10.1126/scitranslmed.3008409]

Translation to SARS-CoV-2 vaccines

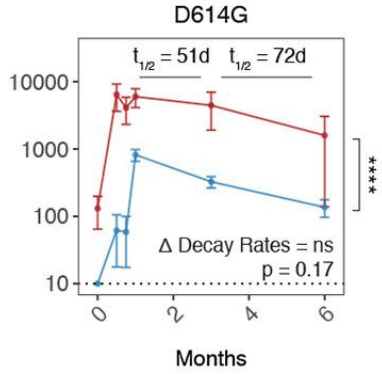


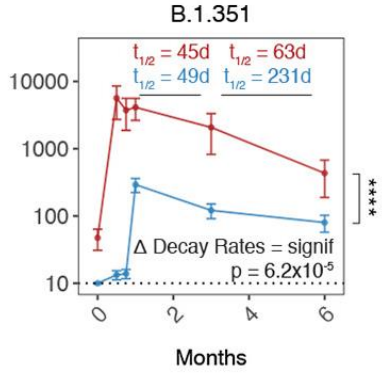
Binding antibodies



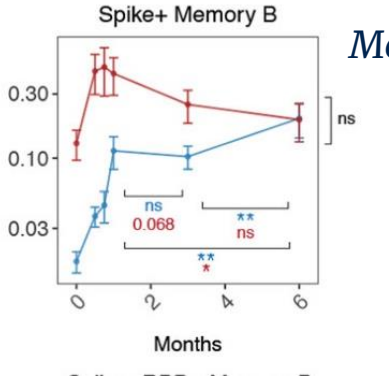


Ps-neutralizing antibodies





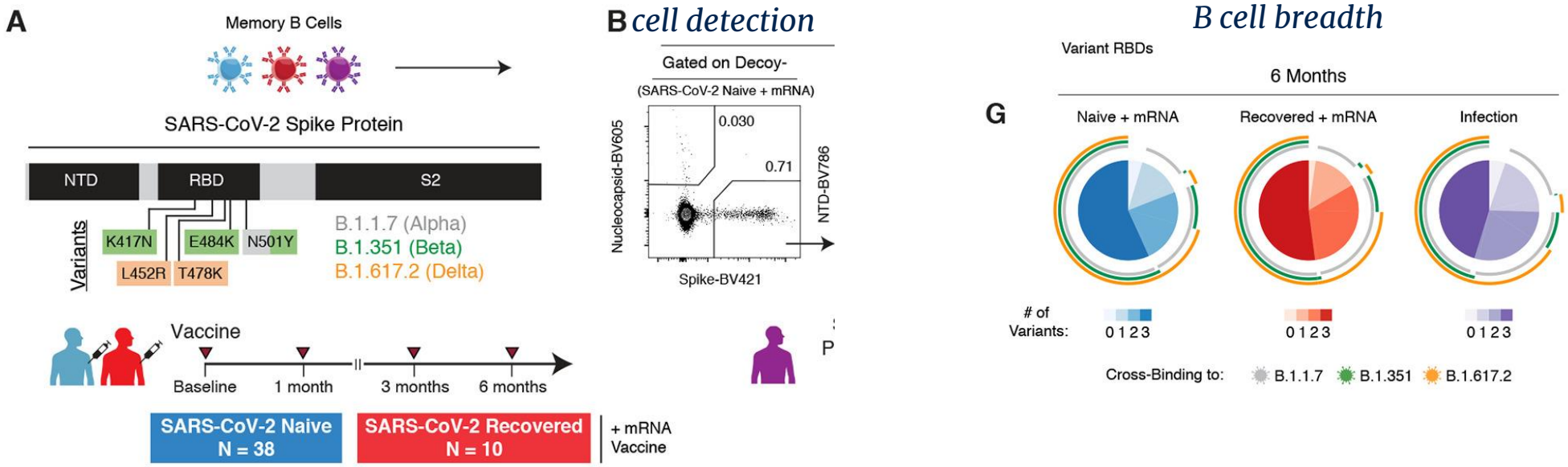
Memory B



- **Longitudinal analysis of mRNA vaccine-induced responses:**
- Binding and neutralizing antibodies + memory B
- B memory => *what is the breadth and diversity?*
- Breadth => *which variant sequences are recognized?*

[Goel et al., 2021: Science Oct 14 DOI: 10.1126/science.abm0829]

Breadth of Spike-specific memory B cells



- At 6 months: memory B cells pool is diverse with many cells being cross-reactive
- This facilitates heterologous boosting because there are memory cells to choose from

[Goel et al., 2021: Science Oct 14 DOI: 10.1126/science.abm0829]

Real life: MixMatch data from ComCov

COM-COV
Comparing COVID-19 Vaccine Schedule Combinations

'COM-COV 2'

Enrolled those
- immunized with a single dose of Pfizer or ChAdOx1 between 25th January and 20th March
- Randomisation at 2nd dose

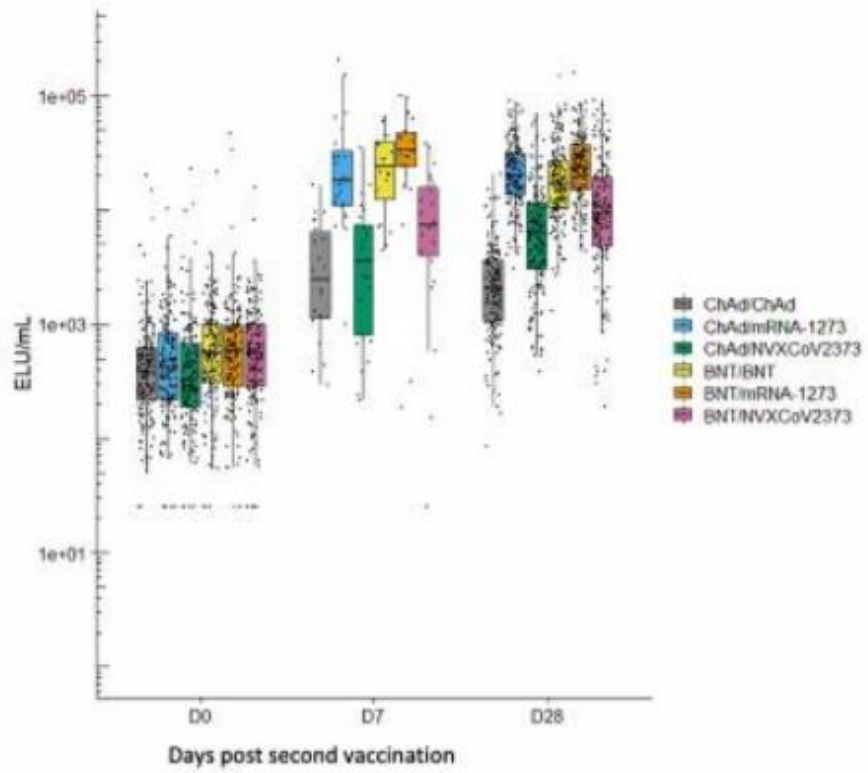
Non-inferiority of immune response to 'alternate' vs 'same' boost

1070 > 50 year olds

General and Immunology cohort		number	Enrolment
1	primed with **Pfizer** at 8 to 12 weeks previously	175	Pfizer
2		175	Moderna
3		175	Novavax
4	Primed with **ChAdOx** 8 to 12 weeks previously	175	ChAdOx
5		175	Moderna
6		175	Novavax
Total		1050	

Real life: MixMatch data from ComCov

28 days post boost dose-Immunogenicity plots: ELISA



Rank order at day 28 post boost

Schedule	Anti-spike IgG	95% C.I.
BNT/Moderna	22953	(20589-25590)
ChAd/Moderna	20116	(18150-22296)
BNT/BNT	16929	(15025-19075)
BNT/Novavax	8886	(7393-10680)
ChAd/Novavax	5597	(4756-6586)
ChAd/ChAd	1971	(1718-2262)

Data presented at D7 based on immunology cohort only (N=25 per group)

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Question & Answer Session for Part I

Moderated By:

Peter Dull, MD

Deputy Director,

Integrated Clinical Vaccine Development,

Bill & Melinda Gates Foundation (BMGF)

Question & Answer Session for Part I

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Participants

- **Emmanuelle Espie, CEPI**

“Global Covid19 seroprevalence studies in unvaccinated populations, 2020-2021”

- **Florian Krammer, Icahn School of Medicine at Mount Sinai**

“Vaccination among the previously infected: Immunology and effectiveness”

- **Htay Htay Han, Clover Pharmaceuticals**

“Vaccination among the previously infected - Lessons from Clover’s phase 3 efficacy study”

- **Emily Nickels, BMGF**

“Covid-19 vaccine delivery update”

- **Paul Oloo, CEPI**

“Heterologous COVID-19 Booster Vaccine studies”

- **Christof Vinnemeier, CEPI**

“Fractional doses – research gaps”

- **Robbert van der Most, CEPI**

“Heterologous vaccination: what can we anticipate in terms of breadth and durability?”

Please submit questions through the Q&A function on Zoom

Part II - Regulatory Considerations for Booster Vaccinations

Jakob Cramer, MD

Head of Clinical Development

Coalition for Epidemic Preparedness Innovations (CEPI)

How the USA Increased Its Access to Seasonal Influenza Vaccines 15 Years Ago

Bruce Innis, MD

October 27, 2021

PATH

Presentation Objective

- Impart a history lesson relevant to the present-day challenge of increasing access to next generation COVID-19 vaccines

History: Problem & Response

- 15 Oct 2004, US FDA blocked import of all 48M doses of Chiron's IIV from its Liverpool facility
- US had a severe vaccine shortage for its influenza immunization campaign

- GSK submitted an IND (Nov), did a phase 3 immuno/safety study vs placebo with HHS (Dec-May), filed a BLA (Jun), got a marketing authorization (Sep) with commitments to conduct an efficacy trial in adults, and to immunobridge via NI to Sanofi's IIV3 for children and adults >49 YOA
- Vaccine marketed in 2005/6 season
- CBER released Guidance for Industry 18 months later, May 2007

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Guidance for Industry

Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
MAY 2007

CBER clarified that the **Accelerated Approval Pathway** was available for new egg-, cell-, and recombinant HA-based IIVs

Accelerated Approval

- Granted for vaccines studied for safety and effectiveness in treating **serious or life-threatening illness** and for which there is **unmet need**
- Approval will be based on adequate and well-controlled clinical trials establishing that the vaccine has an effect on a **surrogate endpoint that is reasonably likely to predict clinical benefit,** based on epidemiologic, therapeutic, pathophysiologic, or other evidence,.
- CBER's guidance proposed the **HI antibody response to vaccination as an acceptable surrogate endpoint for seasonal IIVs**

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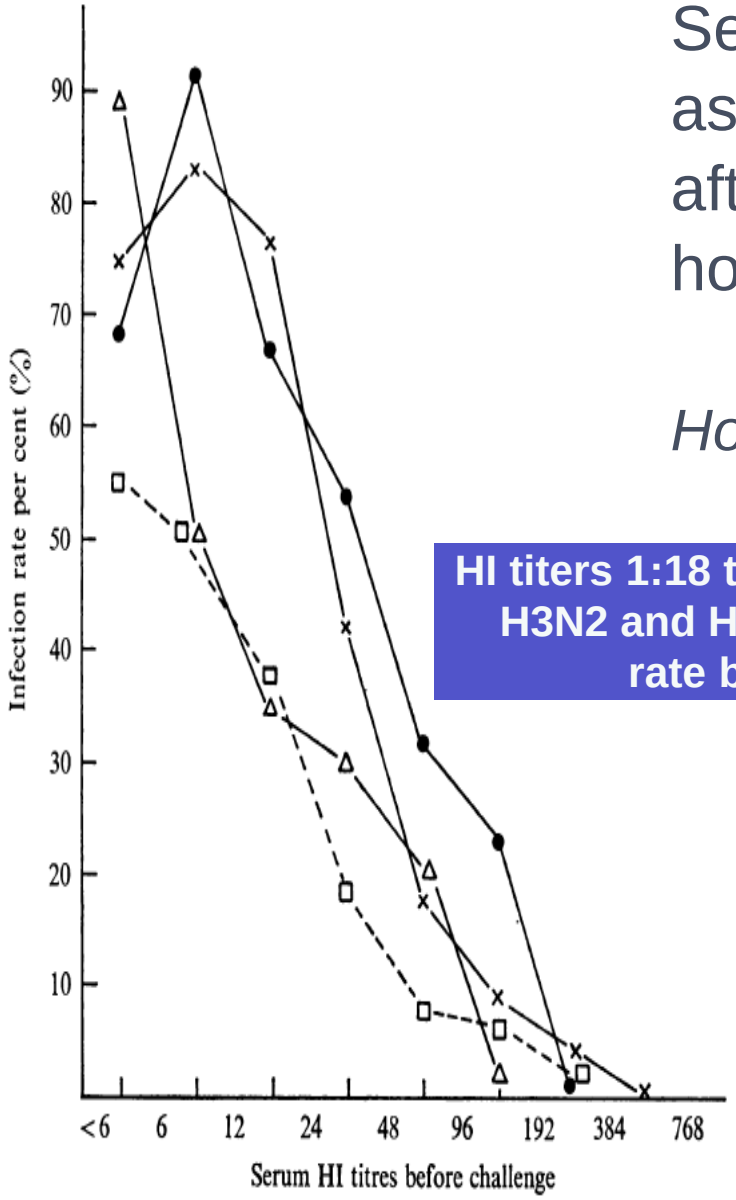
Serum hemagglutination inhibiting antibody titer is associated with a reduction in the risk of infection after experimental intranasal inoculation of the homologous influenza virus strain, types A and B

Hobson et al, J Hyg, Camb. 1972

HI titers 1:18 to 1:36 reduced H3N2 and H2N2 infection rate by ~50%



1032 volunteers

- Influenza A2, 570 volunteers
  - HK Salisbury trial
  - Pre-1968 A2 Salisbury trial
  - HK field trial
- Influenza B, 462 volunteers
  - B/Eng/13/65 field trial

Evidence Needed for Licensure

- BLA for a new seasonal IIV should include results from one or more **well-controlled studies designed to meet immunogenicity endpoints** and a **commitment to conduct confirmatory post-marketing studies of clinical effectiveness in preventing influenza** in the next influenza season
    - The risk to CBER that an ineffective vaccine would be conditionally approved was mitigated by the sponsor's post-marketing commitment
- A non-inferiority immunogenicity trial of HI antibody responses to the new vaccine as compared to a U.S. licensed seasonal IIV may support an accelerated approval. The study should assess co-primary endpoints for HI antibodies to each viral strain in the vaccine: GMT and seroconversion rates

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The Outcome & Relevance to 2nd Gen COVID-19 Vaccines

- Numerous sponsors used the immunobridging pathway to license new IIVs in the US
- Post-marketing VE studies confirmed clinical benefit in preventing influenza
- The US has unmatched access to IIVs

- We can expect the same beneficial impact on the supply of 2nd gen COVID-19 vaccines, if immunobridging for authorization is adopted widely
- Evidence supporting the HI surrogate endpoint was **no more robust** than the current evidence supporting the correlation of SARS-CoV-2 spike antibody with VE in trials of diverse COVID-19 vaccines that elicit immunity to S protein
- Intra-pandemic, effectiveness may be confirmed in observational studies (e.g., test-neg case-control design)

PATH


PATH

Surrogate markers and correlates of protection: immuno-bridging in an increasingly primed population

27 October 2021

Edde Loeliger

Introduction

Objective: to discuss development of new of COVID-vaccine based on immuno-bridging (not including development of strain-adapted vaccines)

Medicines & Healthcare products Regulatory Agency

Decision

Access Consortium: Alignment with ICMRA consensus on immunobridging for authorising new COVID-19 vaccines

Published 15 September 2021

ICMRA

ICMRA COVID-19 Vaccine development: Future steps Workshop

What is Immuno-bridging in a primed population ?

- With a CoP
- Without a CoP

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ICMRA Future steps workshop: https://www.icmra.info/drupal/en/covid-19/24june2021

Access Consortium (15 Sept 2021) : Alignment with ICMRA consensus on immuno-bridging for authorising new COVID-19 vaccines www.gov.uk

Bridging studies - History

- ICH E5 (1998) “A bridging study is defined as a supplemental study performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the new region.

- ECH E5: An adequate a well-controlled trial: a design that permits a valid comparison with a control to provide a quantitative assessment of treatment effect to rule out a clinically significant difference (i.e. a NI trial)

- In the drug area, many generic drug approvals are based on the NI of an accepted surrogate – the blood level of the drug’s active ingredient.

Immuno-bridging studies - History

- In analogy with ICH E5 for drugs and biologicals, for vaccines, the original purpose was for supplemental studies performed in new populations.
- For vaccines, the surrogate for bridging is unique.
- Fritzell 1998: “The duplication of usually large-scale efficacy trials to generalise the clinical database of a new vaccine to other populations can be avoided by bridging studies”.
  - “Immunogenicity data can easily be used to extrapolate efficacy results when the immune response correlates with vaccine induced immunity”.
  - “In the absence of such a correlate of protection, the bridging process will be more controversial”.

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Fritzell. Bridging studies. Developments in Biological Standardization 1998;95:181-8. 1998;95:181-8.

Bridging and non-inferiority

- A NI trial seeks to determine whether a new intervention is no worse than a reference intervention
- Because proof of exact equality is impossible, a pre-stated margin of noninferiority (Δ ; NI-margin; M2) for the treatment effect is defined.
- The pre-stated NI margin represents as the smallest value that would be a clinically important effect; this can be directly measured as a clinical outcome, or indirectly using a surrogate marker.
  - Non-inferiority of clinical outcomes (e.g. blood pressure; disease prevention)
  - Non-inferiority of surrogate endpoints (e.g. drug levels; antibodies)

COVID-19 and Seasonal Influenza vaccine immune bridging

- Similarities both for COVID-19 and Influenza: surrogate marker (endpoint)
  - Immune markers "that are reasonably likely to predict the clinical benefit of vaccines”
  - Influenza surrogate marker: anti-HA (HI) titres
  - COVID-19 surrogate marker: virus neutralizing antibodies; IgG binding antibodies
  - Both: protection from illness is increased for vaccines with higher antibody titres
- Key difference: between COVID-19 and Influenza: correlate of protection (CoP)
  - Influenza CoP: 4-fold increase in anti-HA titres provides 50% protection against illness
  - No CoP for COVID-19: no “established humoral and/or cellular immune parameters that correlate to clinical protection against disease” (ACCESS/ICMRA)
  - Ecological studies do not allow a quantitative assessment of treatment effect COVID-19
  - Threshold for neutralizing antibodies differ mRNA-1273 ChAdOx-1

FDA (2007) Guidance for Industry Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines
Weir and Gruber (2016) An overview of the regulation of influenza vaccines in the United States. Influenza and Other Respiratory Viruses 10(5), 354–360
Access Consortium (15 Sept 2021 : Alignment with ICMRA consensus on immuno-bridging for authorising new COVID-19 vaccines www.gov.uk
Feng et.al (2021) Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. Nat Med (2021). https://doi.org/10.1038/s41591-021-01540-1
Gilbert et.al. (2021) Immune correlate analysis of the mRNA-1273 COVID-19 vaccine efficacy trial. medRxiv 2021, doi: 10.1101/2021.08.09.21261290

Cross platform bridging

- With CoP: example: FDA seasonal influenza accelerated approval
  - HI titres: GMTs; SCR based on four-fold increase HI titres
  - US FDA: NI margin 0.67 for GMT ratios; 10% SCR
  - Recent example: Novavax novel nanoparticle platform against Fluzone
- Without CoP: COVID-19 ICMRA consensus
  - immunogenicity bridging studies can be used if clinical endpoint efficacy studies are no longer feasible
  - Neutralising antibody titre as immune marker to predict vaccine effectiveness may be used in immunogenicity bridging studies for new vaccines
  - Study designs should be based on
    - NI immunogenicity if the comparator vaccine has high efficacy
    - Superiority trial if the comparator vaccine has modest efficacy

FDA (2007) Guidance for Industry Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines
Access Consortium (15 Sept 2021 : Alignment with ICMRA consensus on immuno-bridging for authorising new COVID-19 vaccines www.gov.uk
Khoury et al. Neutralizing antibody levels are highly predictive of immune protection. Nat Med. 2021, 27:1205-1211. doi: 10.1038/s41591-021-01377-8
Earle KA et al. Evidence for antibody as a protective correlate for COVID-19 vaccines. Vaccine 2021, 39:4423-4428. Doi: 10.1016/j.vaccine.2021.05.063
Novavax: Shinde et.al. Lancet Infect Dis 2021 Published Online September 23, 2021 https://doi.org/10.1016/ S1473-3099(21)00192-4

COVID-19 cross platform bridging considerations

- The inclusion of SCR (in naives) or sero-response rates (SRR) as endpoints in primed population is not a measure of clinical benefit but to ensure non-inferior distribution of GMTs
  - Unlike Influenza, the surrogate marker for COVID-19 established in naïve population
  - Unlike Influenza, the clinical benefit a 4-fold increase in titres; it as yet unknown
  - No clinically substantiated SCR or SPR to guide SRR
- Additional considerations: NI on the GMT against a highly effective comparator because Ab titres are important, but not sufficient
  - The protection equation P = f (Ab, nAb, CD4, CD8, B, innate)
  - Characterisation of comparative immunogenicity profiles, including CMI
- Recent examples COVID-19 cross platform bridging: Valneva; SK Biosciences

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Access Consortium (15 Sept 2021): Alignment with ICMRA consensus on immuno-bridging for authorising new COVID-19 vaccines www.gov.uk
SK Bio: NCT05007951 https://clinicaltrials.gov/ct2/show/record/NCT05007951
Valneva:: NCT05007951 https://clinicaltrials.gov/ct2/show/NCT05007951

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VLA2001 Cov-Compare Topline Results

October 27, 2021

Christian Taucher

valneva

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INTRODUCTION

Valneva's Response to the Global COVID-19 Crisis

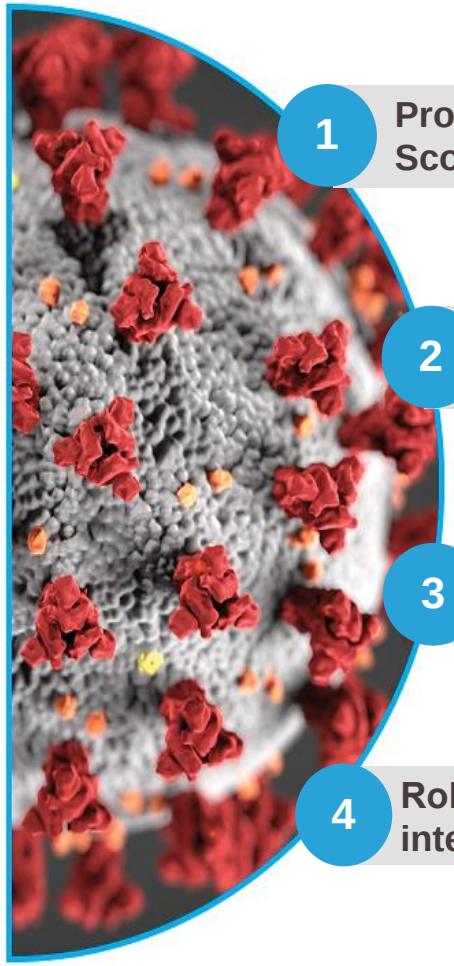
Well-Known Inactivated Approach Based on Proven Technology

VLA2001:

- Inactivated, adjuvanted SARS-Cov 2 whole virus vaccine

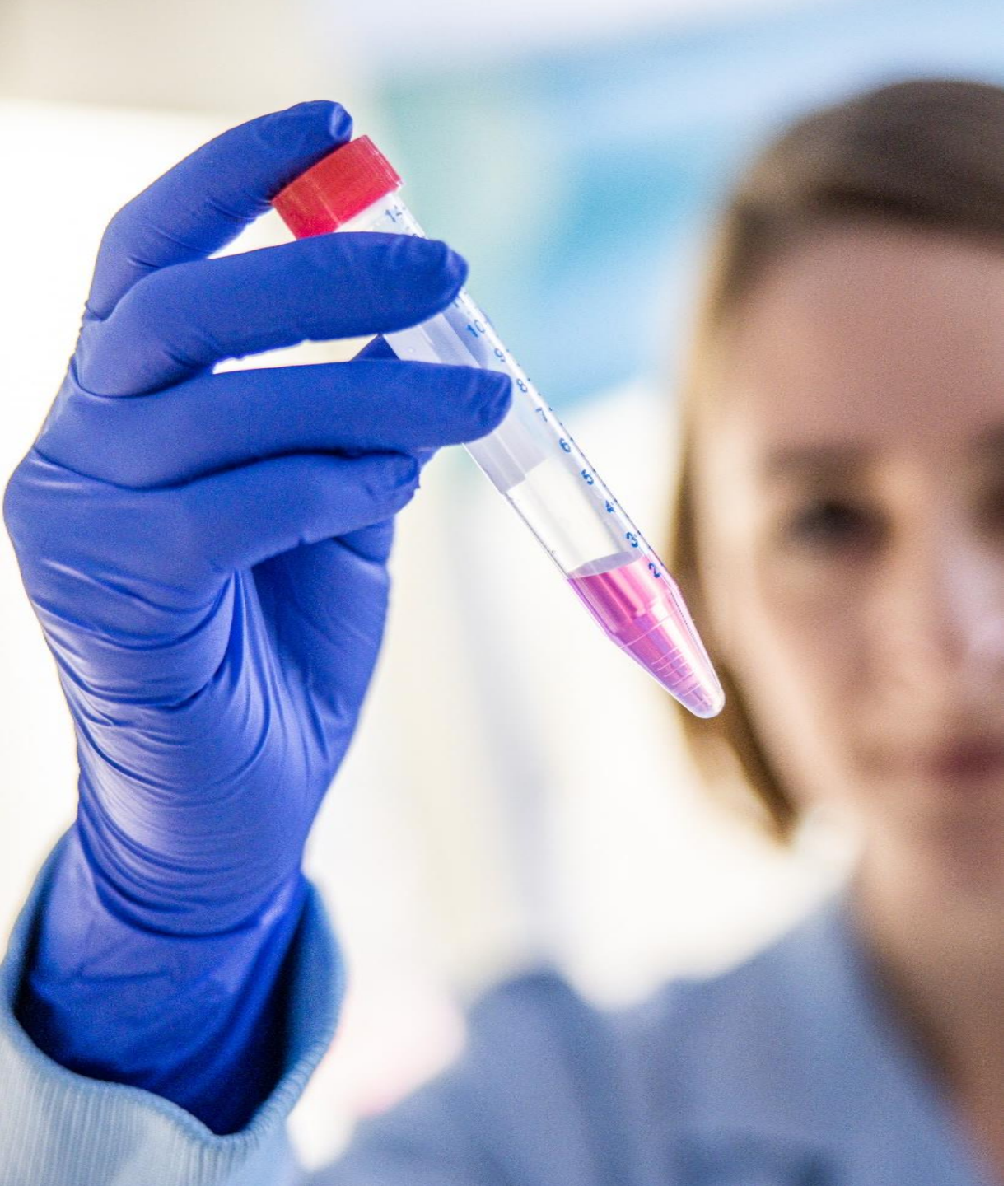
- Intended for active immunization of **at-risk populations** to prevent carriage and symptomatic infection with COVID-19 during the **ongoing pandemic** and potentially **later for routine vaccination,** including addressing **new variants**

VLA2001 – The Only Inactivated Vaccine Against COVID-19 in Clinical Development in Europe



1. Program acceleration enabled through use of Valneva's FDA-registered facility in Scotland, where commercial manufacturing commenced January 2021[1]
2. Combines Valneva's proven expertise with inactivated vaccines and Dynavax's advanced CpG 1018 adjuvant[2]
3. Phase 1/2 clinical trial results reported in April 2021[3]
4. Rolling submission to MHRA commenced in Aug. 2021; Phase 3 "Cov-Compare" results intended to form the basis for potential regulatory approval in adults

Note: Photo credit: CDC/Alissa Eckert, MSMI; Dan Higgins, MAM.**1** Valneva commences manufacturing of its Inactivated, Adjuvanted COVID-19 vaccine, completes Phase 1/2 study recruitment. **2** Valneva and Dynavax announce commercial supply agreement for Inactivated, Adjuvanted COVID-19 vaccine; **3** Valneva Reports Positive Phase 1/2 Data for Its Inactivated, Adjuvanted COVID-19 Vaccine Candidate, VLA2001



COV-COMPARE TRIAL AND TOPLINE RESULTS

About Phase 3 Cov-Compare Trial (VLA2001-301)

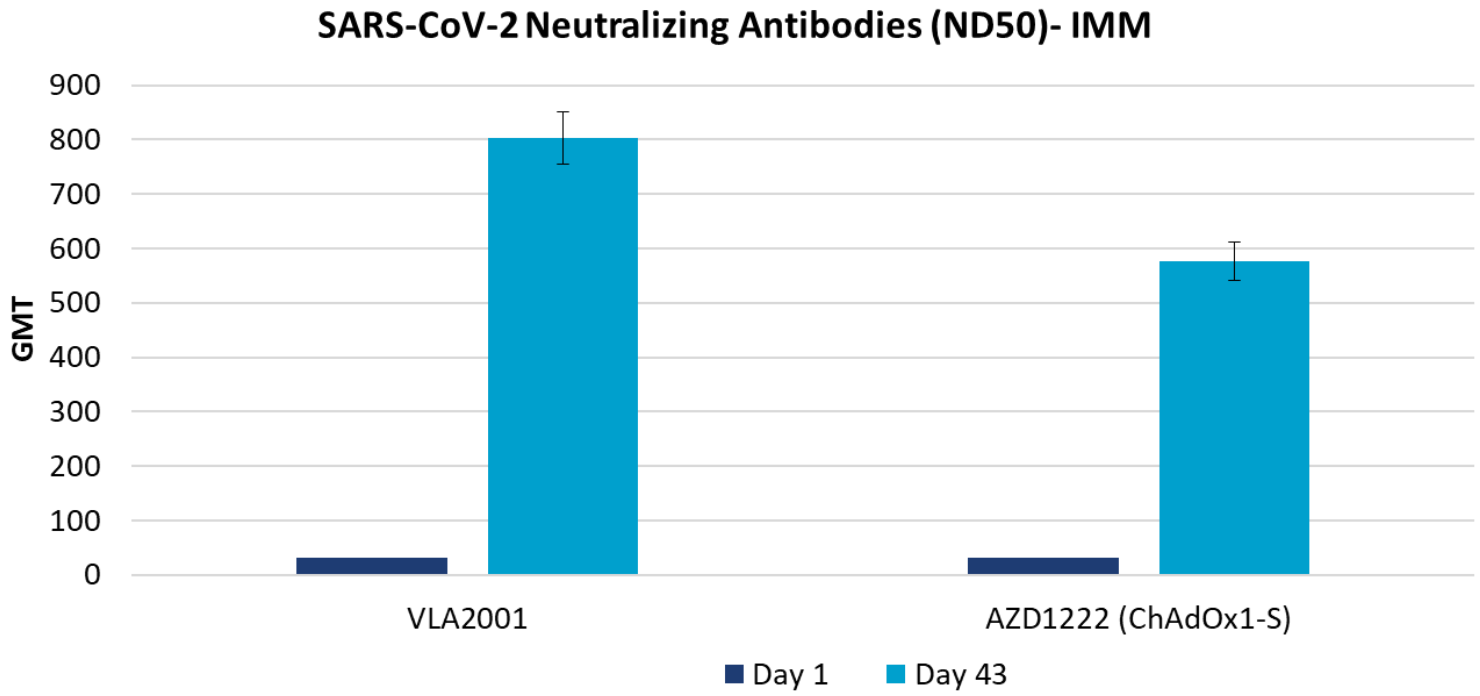
- **Randomized, observer-blind, controlled, immunogenicity trial comparing VLA2001 to AstraZeneca's conditionally approved vaccine, AZD1222 (ChAdOx1-S)**

- **2,972 participants 30 years of age and older randomized (2:1) received two doses of either VLA2001 (n=1977) or AZD1222 (ChAdOx1-S) (n=995) at the recommended dose level, 28 days apart**

- **Primary objective: Compare VLA2001 to AZD1222 (ChAdOx1-S) administered as above, to determine:**
  1. Superiority in terms of Geometric Mean Titer ratio of SARS-CoV-2-specific neutralizing antibodies at two weeks after the second vaccination (Day 43) in adults aged 30 years and older; and
  2. Non-inferiority in terms of seroconversion rate and
  3. Frequency and severity of any Adverse Events

- **Also evaluating the safety and tolerability of VLA2001 in additional adults 18-29 years of age (n=1040), two weeks after the second vaccination**

SARS-CoV-2 Neutralizing Antibody Levels (ND50)- IMM – VLA2001 Higher Than AZD1222 at Day 43



IMM includes all **randomized and vaccinated participants of the IMM subset** for the primary endpoint evaluation, **who were SARS-CoV-2 seronegative and have at least one evaluable post-baseline antibody titer** measurement after vaccination. Participants who met the case definition of **confirmed COVID-19** during the study are not **included in the IMM**.

GMT: Geometric Mean Titre, CI: Confidence Interval:
Note: [1] p-value and CI calculated using a two-sided t-test applied to log10 transformed data.

A final assay validation required by the MHRA to verify the integrity of the VLA2001-301 data remains ongoing and is a prerequisite for final submission of the clinical study report.

Immunogenicity Results – Primary Endpoint Met

SARS-CoV-2 Neutralizing Antibodies (ND50)- IMM – VLA2001 1.39 x AZD1222

Co-Primary Endpoint: Ratio of geometric mean titer (IMM population) of SARS-CoV-2-specific neutralizing antibodies, at two weeks after the second vaccination (i.e. Day 43) in adults aged 30 years and above.

Visit	Statistic	VLA2001 Age 30 and Above (N=492)	AZD1222 (ChAdOx1-S) (N=498)	Overall (N=990)
Day 1	n	492	498	990
	GMT (95% CI)	31.0 (31.00, 31.00)	31.0 (31.00, 31.00)	31.0 (31.00, 31.00)
	GMT Ratio (95% CI)			1.00 (1.00, 1.00)
	p-value [1]			NE
Day 43	n	492	493	985
	GMT (95% CI)	**803.5** (748.48, 862.59)	**576.6** (543.59, 611.66)	680.6 (649.40, 713.22)
	GMT Ratio (95% CI)			**1.39 (1.25, 1.56)**
	p-value [1]			**<.0001**

IMM includes all **randomized and vaccinated participants of the IMM subset** for the primary endpoint evaluation, **who were SARS-CoV-2 seronegative and have at least one evaluable post-baseline antibody titer** measurement after vaccination. Participants who met the case definition of **confirmed COVID-19** during the study are not **included in the IMM**.

GMT: Geometric Mean Titre, CI: Confidence Interval:
Note: [1] p-value and CI calculated using a two-sided t-test applied to log10 transformed data.

Immunogenicity Population, Table 14.3.1.1

High Proportion of Participants With Seroconversion in Terms of Neutralizing Antibodies – PP

Co-primary Endpoint: Seroconversion (PP population) (defined as 4-fold increase from baseline) of SARS-CoV-2-specific neutralizing antibodies, at two weeks after the second vaccination (i.e. Day 43) in adults aged 30 years and above.

Visit	VLA2001 (N=489) N(%)	AZD1222 (ChAdOx1-S) (N=498) N(%)	Overall (N=987) N(%)
Day 43			
Number of patients with eligible samples at visit	456	449	905
Participants with seroconversion (≥ 4- fold increase)			
n(%)	444 (**97.4**)	444 (**98.9**)	888 (98.1)
95% CI [1]	(0.954,0.986)	(0.974,0.996)	(0.970,0.989)
p-value [2]			0.0911

The Per-Protocol population (PP) will consist of the IMM population subjects who have no major protocol violations that impact the immune response.

[1] Exact 95% Clopper-Pearson confidence interval for proportion.

[2] P value or Two-sided CI is for the difference in proportions (VLA2001-AZD122) of Participants with seroconversion at each particular visit.

\+ Per-Protocol Population, Table 14.3.2.1

VLA2001-301 Immunogenicity Conclusions – Endpoints Met

- The trial **met its co-primary immunogenicity endpoints** at two weeks after the second vaccination (i.e. Day 43) in adults aged 30 years and above
  - VLA2001 demonstrated **superiority** against AZD1222 (ChAdOx1-S) in terms of geometric mean titer for neutralizing antibodies as measured by live virus microneutralization assay. (GMT ratio=1.39, p<0.0001) (VLA2001 GMT 803.5 (95% CI: 748.48, 862.59))
  - VLA2001 demonstrated non-inferiority in terms of seroconversion rates (SCR above 95% in both treatment groups)
- At Day 43, 74.3% of a subset of study participants in the VLA2001 group had T-cells that were reactive against peptide pools spanning the full-length S-protein.
- In addition, in the VLA2001 group 45.9% had T-cells that were reactive against the N-protein and 20.3% against the M-protein.

Overall Clinical Data Conclusions

All Endpoints Achieved

- The trial met its co-primary endpoints. VLA2001 demonstrated:
  - **superiority** against AZD1222 (ChAdOx1-S), in terms of **geometric mean titer** for neutralization antibodies, as well as
  - **non-inferiority** in terms of **seroconversion rates** at two weeks after the second vaccination (i.e. Day 43) in adults aged 30 years and above.

- **VLA2001 was generally well tolerated**
  - The **tolerability profile** of VLA2001 was **significantly more favorable compared** to the **active comparator** vaccine.
  - Participants **30 years and above** reported **significantly fewer solicited adverse events** up to seven days after vaccination**, both** with regards to **injection site reactions**, and **systemic reactions**
  - Participants in the **younger age group** vaccinated with **VLA2001 showed** an **overall safety profile comparable** to the **older age group.**

- The **occurrence of COVID-19** cases (exploratory endpoint) was **similar between treatment groups** in the participants **30 years and above.**

- The **complete absence** of **any severe COVID-19 cases** may suggest that **both vaccines** used in the study **prevented severe COVID-19 caused by the circulating variant(s) (predominantly Delta).**

- **T-cell responses** analyzed in a **sub-set of participants** showed that **VLA2001 induced broad** antigen-specific IFN-gamma producing T-cells **reactive against the S, N and M proteins.**

Thank you
Merci
Danke
Tack

valneva

Panel Discussion:

Regulatory considerations for approach to the demonstration of efficacy in setting of increased COVID-19 seropositivity – Relevance of learnings from influenza vaccines

Peter Dull, MD

Deputy Director,

Integrated Clinical Vaccine Development,

Bill & Melinda Gates Foundation (BMGF)

Panel: Regulatory considerations for approach to the demonstration of efficacy in setting of increased COVID-19 seropositivity – Relevance of learnings from influenza vaccines

Panel Members

- **Adam Hacker, CEPI**
- **Dean Smith, Health Canada**
- **Rogerio Gaspar, WHO**
- **Gustavo Santos, ANVISA**
- **Phil Krause, FDA**
- **In-sook Park, MFDS**

Sample Questions

- *Will the licensure pathway for future COVID-19 vaccines follow a similar pathway to that of influenza vaccine over the past few decades?*
- *In pivotal phase 3 non-inferiority trials where the primary objective is to confirm a vaccine candidate's acceptable immunogenicity in vaccine-naïve adults relative to an authorized comparator vaccine, what vaccine-homologous endpoints are most informative?*
- *How should immunogenicity of a vaccine candidate be assessed in adults who have previously been vaccinated?*
- *Is there a recommended threshold of response that could be considered clinically beneficial (either an absolute value or a fold-rise)?*
- *Is there value in characterizing the induction of antibody responses to SARS-CoV-2 variants of concern by a vaccine candidate relative to an authorized comparator vaccine?*

Wrap Up & Next Steps

Jakob Cramer, MD

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
- COVAX Enabling Science SWAT Workshop on 'Interpreting SARS-CoV-2 immune assay data involving variants and the use of the WHO International Standard for anti-SARS-CoV-2 immunoglobulin' (28 Oct 2021, 15:00-19:00 CET)
- WHO BP team and COVAX Clin Dev SWAT team to co-organise a workshop on 'fractional dosing' – date TBC

Clinical Development & Operations SWAT Team