COVAX

Booster and Mix & Match COVID-19 Vaccine Strategies - Planning Ahead in an Environment of Increasing Complexity

Clinical Development & Operations SWAT Team | Thursday June 3, 2021

CEPI Gavi The Vaccine Alliance World Health Organization unicef

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.

Meeting Objectives

To support COVID-19 vaccine developers to deliver on safe, effective and appropriate vaccines with a focus on booster vaccination strategies and heterologous vaccine schedules to maximize impact on the ongoing pandemic

- Product-agnostic developer support so that regulators and policy-makers can make informed decisions on best evidence possible
- Guidance should reflect current and anticipated region-specific COVID-19 disease epidemiology including seropositivity rates and vaccine coverage
- Provide latest information from pre-clinical and clinical studies to guide “best-practice” study designs to drive efficiency in getting the right studies conducted and the right product authorized for use

Workshop Agenda

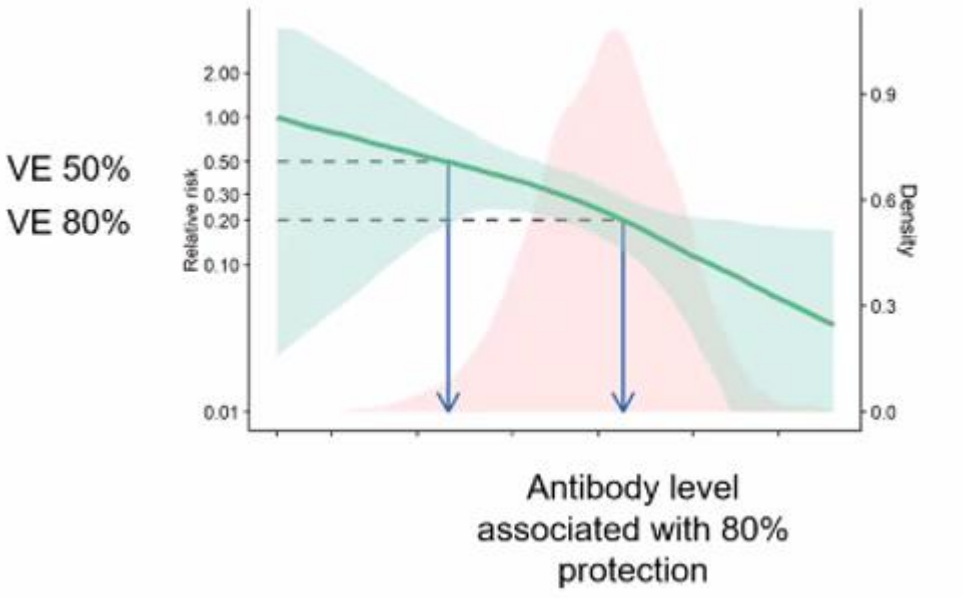
Time (CET)	June 03, 2021 -Topics	Speakers
15:00 -15:15	Welcome, meeting objectives and updates	Peter Dull, BMGF
15:15-15:25	COVID-19 global epidemiology and immunity update	Boris Pavlin, WHO
15:25-15:35	Durability of immune responses following natural SARS-CoV-2 infection & vaccination: overview of evidence	Amol Chaudhari, CEPI
15:35-15:50	Updates on post-introduction vaccine effectiveness to guide approach to booster vaccination	Daniel Feikin, WHO
15:50-16:05	Overview of single-dose strategies and scenarios	Edde Loeliger, CEPI
16:05-16:35	Panel: Discussion of regulatory pathway for product as boost-only vaccination	Moderated by Peter Dull, BMGF
16:35-16:40	Overview of heterologous COVID-19 vaccine strategies	Jakob Cramer, CEPI
16:40-16:50	Registration of Zabdeno®, Mvabea® vaccination for Ebola	Jerry Sadoff, Janssen
16:50-16:55	COVID-19 vaccine Mix & Match – Current clinical research landscape	Paul Oloo, CEPI
16:55-17:05	Update on ongoing and planned studies – Com-COV1, Com-COV2, and Cov-Boost	Matthew Snape, Oxford Vaccine Group, UK
17:05-17:20	Further evidence from heterologous studies	Cristóbal Belda-Iniesta, Spain Leif Erik Sander, Germany
17:20-17:55	Panel Discussion: Vaccine policy implications	Moderated by Jakob Cramer, CEPI
17:55-18:00	Wrap up & next steps	Jakob Cramer, CEPI

UPDATES FROM EVIDENCE ON CORRELATES OF PROTECTION

WHO Meeting on Correlates of Protection, 26 May 2021

- Neutralizing and binding antibody show strong association with short-term efficacy
- An absolute threshold (i.e., a titer above which the risk of disease = 0) may not exist, but a population-based correlate appears attainable
- Some regulators expressed comfort with immunobridging new products to authorized products, especially within the same platform and demonstrating superiority to comparator
- Standardization across labs/immunoassays, e.g. using the WHO International Standard, was again emphasized

Correlates of Vaccine Efficacy – ChAdOx UK Ph3



- Serum sample @ 28 days after dose 2
  - N=1400 vaccine recipients (i.e. non-cases)
  - N=168 breakthrough cases
    - primary symptomatic
    - non-primary symptomatic
    - asymptomatic (weekly home testing by PCR)

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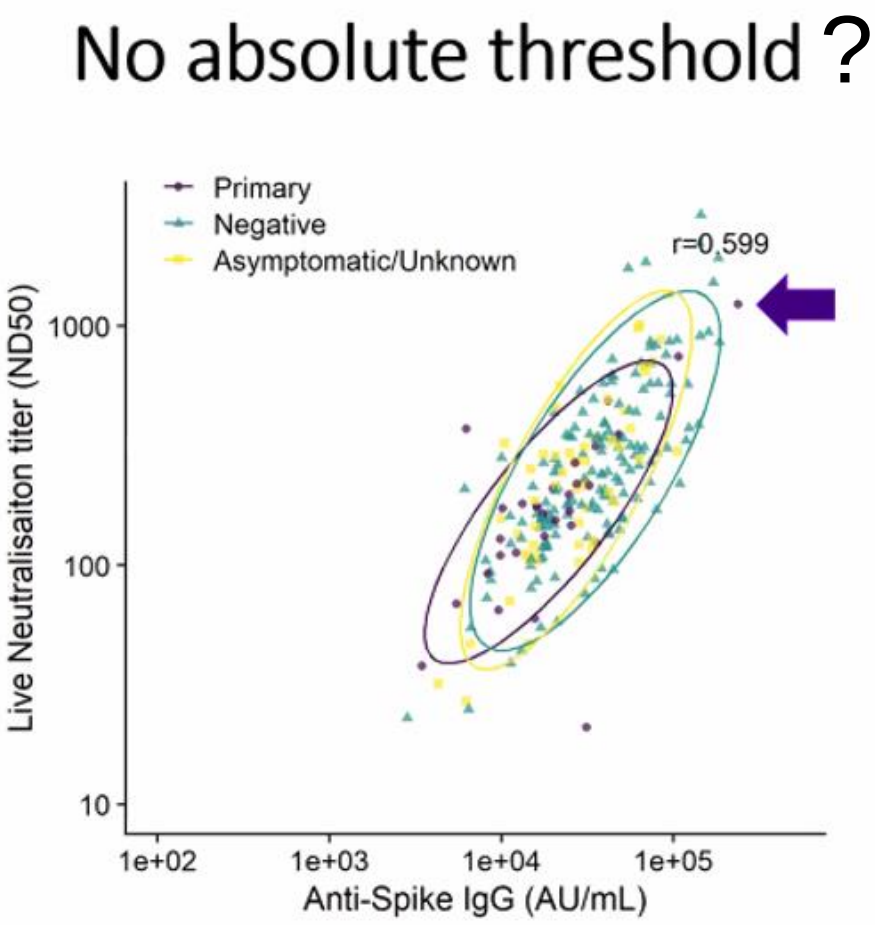


Merryn Voysey, Elaine Shuo Feng, Oxford U

Survey of 10 Companies/NGOs Executing or Anticipating Phase 3 Placebo-controlled Efficacy Trials

Phase 3 placebo-controlled efficacy trials were possible in May with negative trends emerging

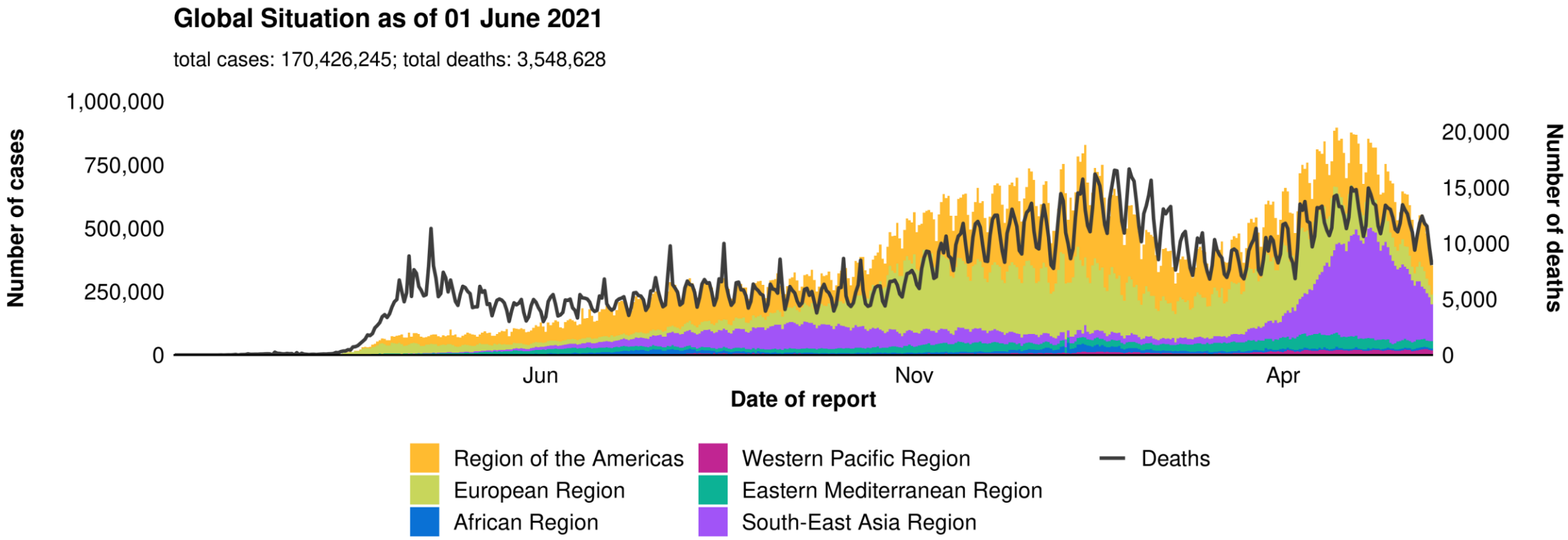
- National regulator agencies of record did not object to placebo-controlled trials in May 2021 though some saw such trials as infeasible given the state of the pandemic and availability of authorized vaccines. Some trial site countries rejected placebo-controlled trials.
- No company experienced an ethics committee objection though some ECs insisted upon subject unblinding once authorized vaccine become available and to cross-over vaccinate upon demonstration of efficacy.
- **6/8** companies say recruitment was slower than anticipated (Phase 1/2/3 trials)
- **7/10** companies say that recruiting has been especially slow for those with co-morbidities and those 65+ years of age: "*near impossible to recruit subjects 65+ in a placebo-controlled study in any country*"; "*we anticipate at least a 4 month-delay*"; "*the population prefers waiting for the authorized vaccines to come in*".
- **3/4** companies experienced a higher rate of screen failures than anticipated (some were not screening for antibody or did not yet have results): "*we have experienced screen failure rate of 60% due to seropositivity*"; "*data from the first 400 subjects indicate 39% S+*".
- **5/9** companies experienced a high rate of drop-out rate: "*we have close to 30% drop out in some sites in the US because of request to receive the approved vaccine*"; "high drop-out rate in EU countries due to unblinding requests to receive vaccination as part of National vaccination campaign".

World Health Organization

COVID-19 GLOBAL EPIDEMIOLOGY AND VACCINATION UPDATE

Dr. Boris Pavlin, WHO HQ COVID-19 Epidemiology Pillar Lead 3-6-2021

Global epidemiological overview



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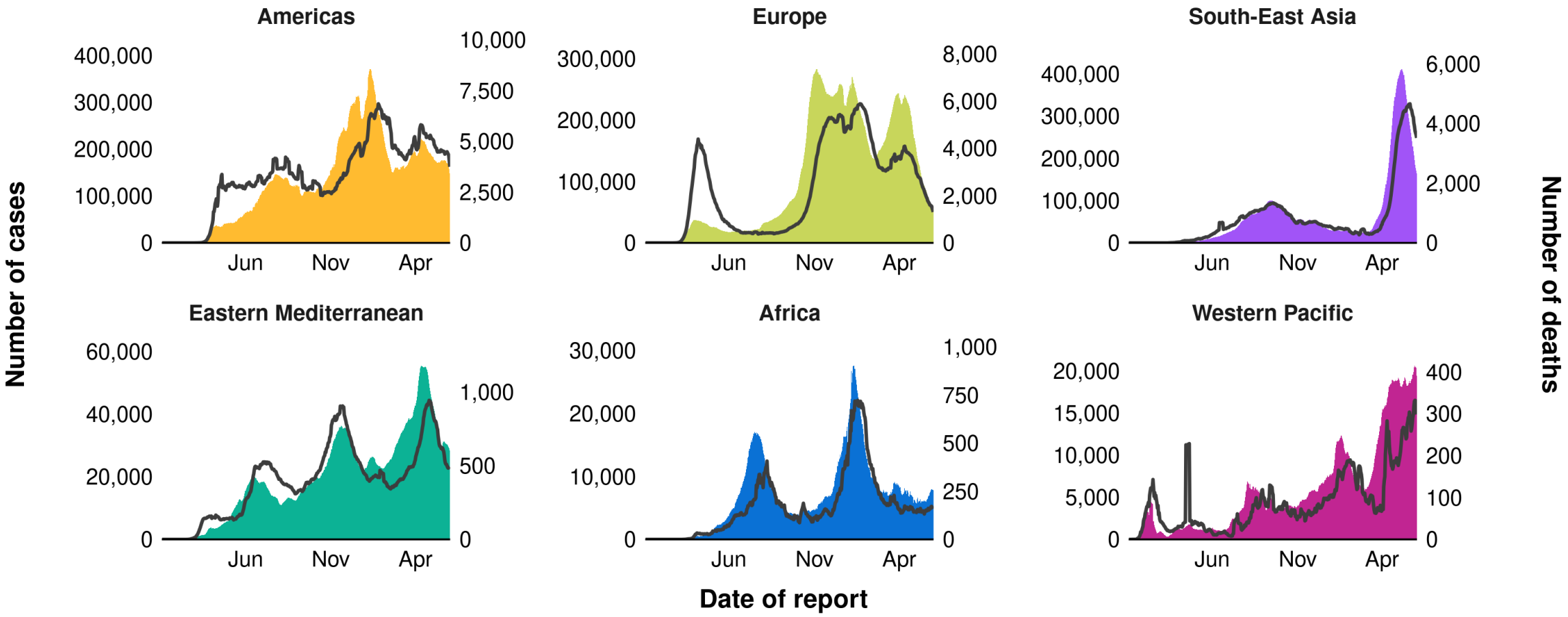
Regional epidemiological overview

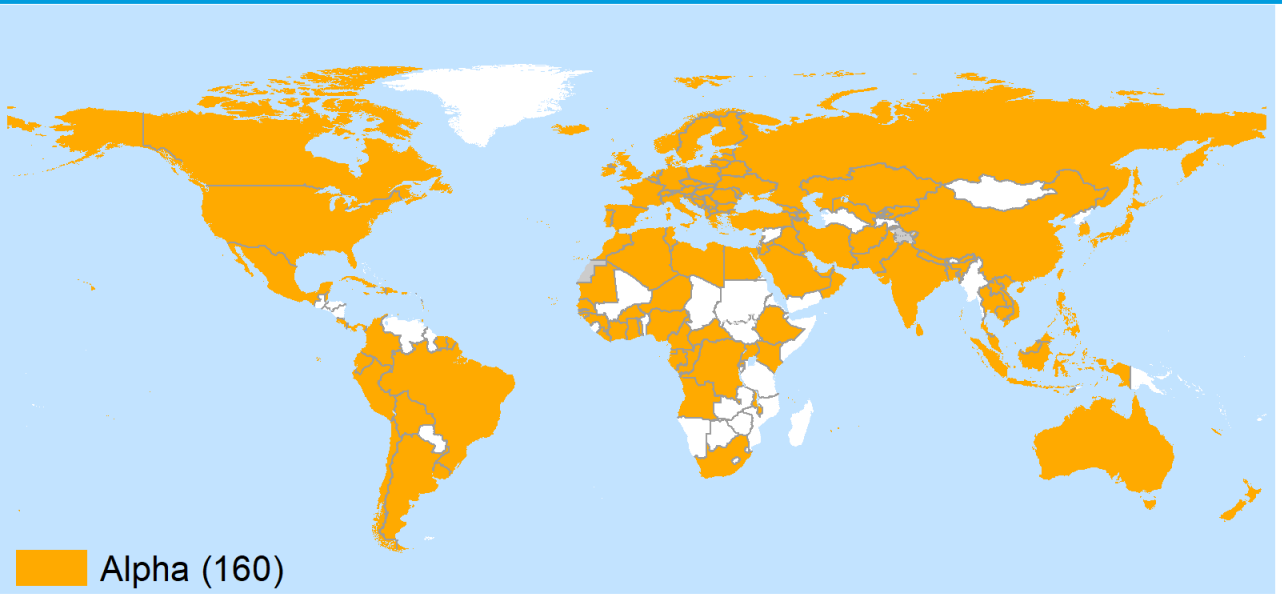


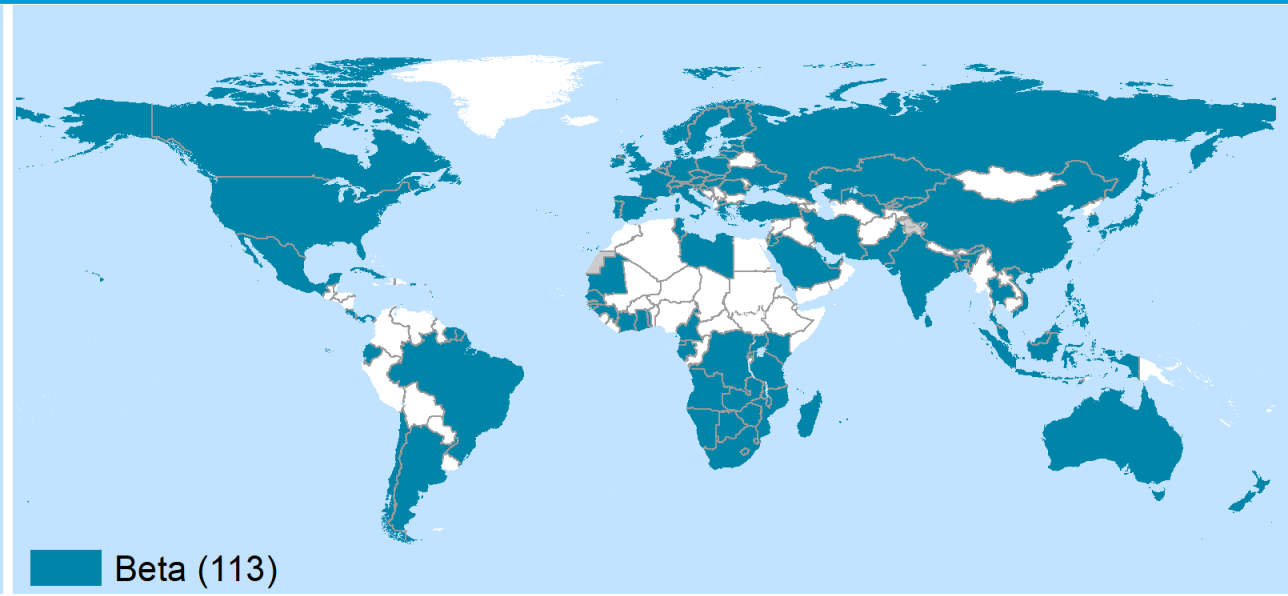
Cases depicted by bars; deaths depicted by line. Data smoothed with 7-day moving average. Note different scales for y-axes.

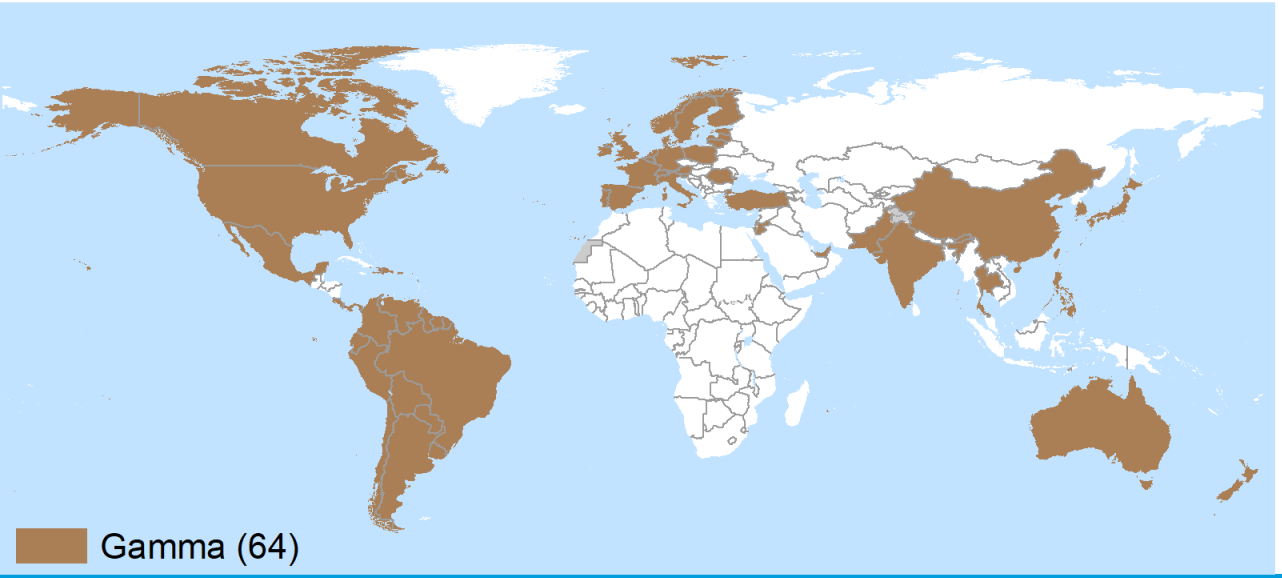
World Health Organization

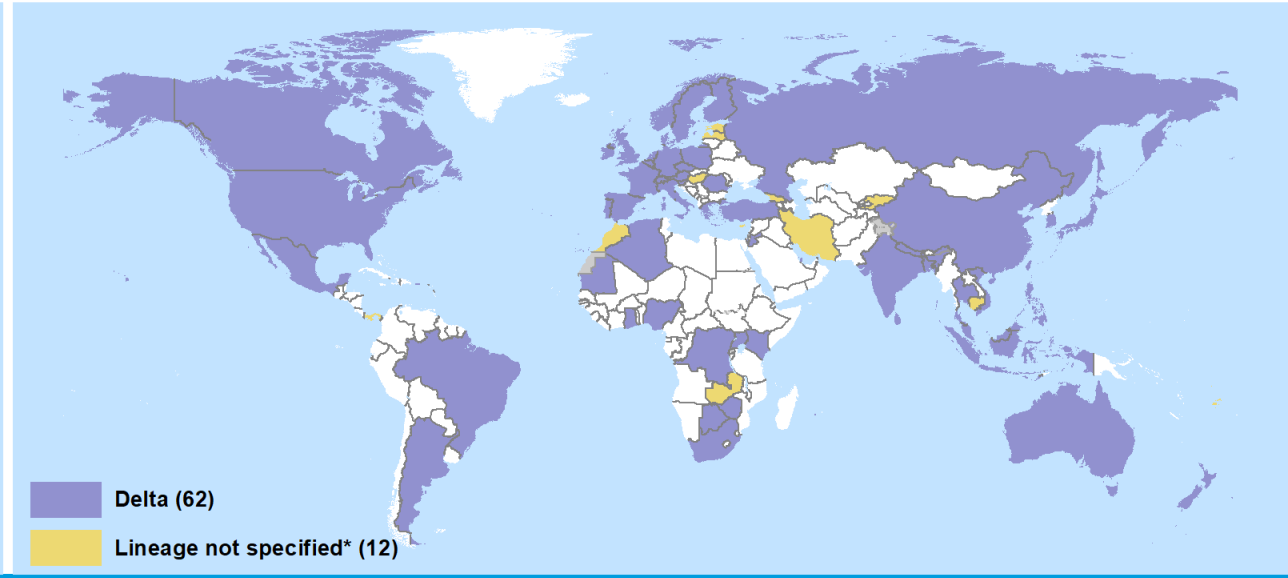
Countries, territories, and areas reporting Variants of Concern

(situation as of 01 June 2021)









World Health Organization

***Data Source**: World Health Organization*
***Map Production**: WHO Health Emergencies Programme*

Not applicable

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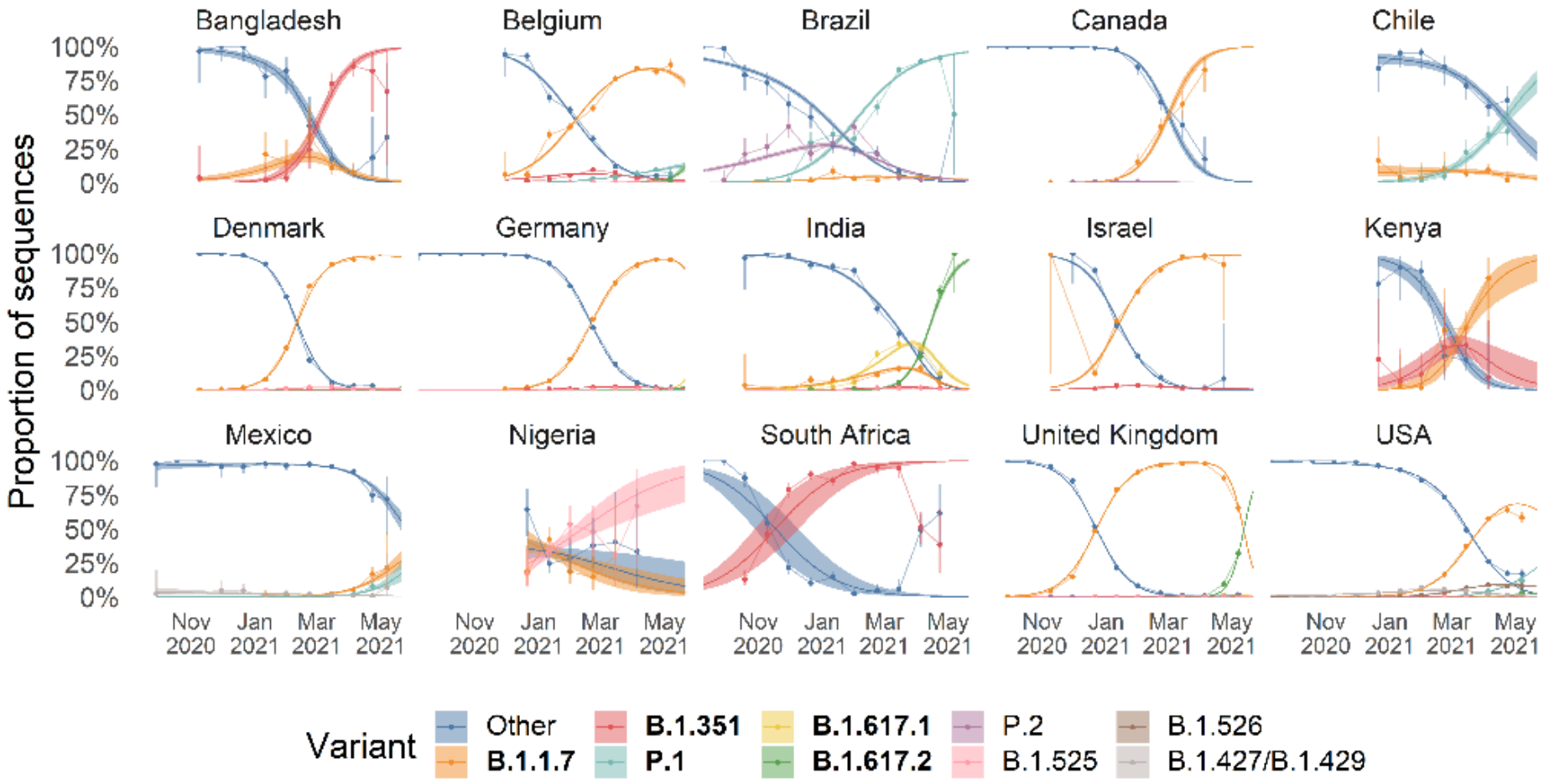
SARS-CoV-2 variant evolution over time



World Health Organization

Performance against Alpha (B.1.1.7) - variant first identified in the UK)

PRELIMINARY and ongoing assessment of evidence, including study quality

Reduction of neutralizing activity in laboratory assays	Clinical efficacy against variant	Clinical efficacy against non-variant	Clinical efficacy/ness criteria
None-9x [5,7,90]	1) 29% (NS) 2) 66-70% [7; effectiveness: E26]	1) 70% 2) 82%	1) Asymptomatic 2) Symptomatic
None [43,68]	-	78%[1]	Symptomatic
None [52]	-	92%	Symptomatic
-	-	1) 74% 2) 78%	1) Moderate to severe 2) Severe
None-2.3x [6,20,9,28,33,45,78,84]	1) 90% 2) 94% [E27]	1) 94%	1) Symptomatic 2) Hospitalization/Death
2.1x [20]	86% [77]	96%	Symptomatic
None-3.9x [3,5,9,10,13,18,21,23,28,45,49,50,51,57, 58,64,75,76,78,87,90]	1) 82-90% 2) 90-93% 3) 94-100% [effectiveness: E7, E16, E22, E26, E27]	2) 95%	1) Infection 2) Symptomatic 3) Severe/fatal
None [53]	-	78%	Symptomatic
None [53,89]	-	51-84%	Symptomatic

1. Interim analysis of phase III clinical efficacy

Performance against Beta (B.1.351) - variant first identified in South Africa)

PRELIMINARY and ongoing assessment of evidence, including study quality

	Reduction of neutralizing activity in laboratory assays	Clinical efficacy against variant	Clinical efficacy against non-variant	Clinical efficacy criteria
Anhui	**1.6-2.5x** [11,85]	-	-	-
AstraZeneca	**2.5-31x / undetectable** **[5,15,36]**	1) 10% (NS) [15]	2) 62-90%	1) Mild & moderate 2) Symptomatic
BHARAT BIOTECH	-	-	78%[1]	Symptomatic
THE GAMALEYA NATIONAL CENTER OF EPIDEMIOLOGY AND MICROBIOLOGY	**6.1x** [52]	-	92%	Symptomatic
Johnson&Johnson	**14-41x** [88]	1) 52% 2) 73% [65]	1) 74% 2) 78% [65]	1) Moderate to severe-critical 2) Severe
moderna	**3.8-28x** [9,24,28,29,31,33,44,45,47,48,56,78,84]	-	94%	Symptomatic
NOVAVAX	**11.1-14.5x** [56,86]	60% (HIV-) 49% (HIV- and HIV+) [71]	96%	Symptomatic
Pfizer	**3-42x** [5,9,10,12,13,21,23,28,29,34,36,40, 45,47,48,49,50,51,57,58,64,75,78,87.90.91]	1) 75% 3) 100% [effectiveness: E22]	2) 95%	1) Infection 2) Symptomatic 3) Severe
Sinopharm	**1.6-2.4x** [11,53]	-	78%	Symptomatic
sinovac	**3.3-5.3x** [53,85,89]	-	51-84%	Symptomatic

1. Interim analysis of phase III clinical effi

Performance against Gamma (P.1) - variant first identified in Brazil)

PRELIMINARY and ongoing assessment of evidence, including study quality

	Reduction of neutralizing activity in laboratory assays	Clinical efficacy against variant	Clinical efficacy against non-variant	Clinical efficacy criteria
AstraZeneca	**2.9x** [5]	-	62-90%	Symptomatic
Bharat Biotech	-	-	78%[1]	Symptomatic
The Gamaleya National Center of Epidemiology and Microbiology	-	-	92%	Symptomatic
Johnson & Johnson	-	-	1) 74% 2) 78% [65]	1) Moderate to severe-critical 2) Severe
moderna	**2.8x-4.8x** [9,24,29,33,59,84]	-	94% 100%	1) Symptomatic 2) Severe
NOVAVAX	-	-	96%	Symptomatic
Pfizer	**1.7x-10x** [5,9,10,12,13,29,33,40,51,59]	-	95%	Symptomatic
Sinopharm	-	-	78%	Symptomatic
sinovac	**No loss - Full loss (preliminary study)** [60, 22, 89]	42-50% (symptomatic) 35.1% (any infection) [effectiveness: E9, E25]	51-84%	Symptomatic

Performance against Delta (B.1.617.2) - variant first identified in India

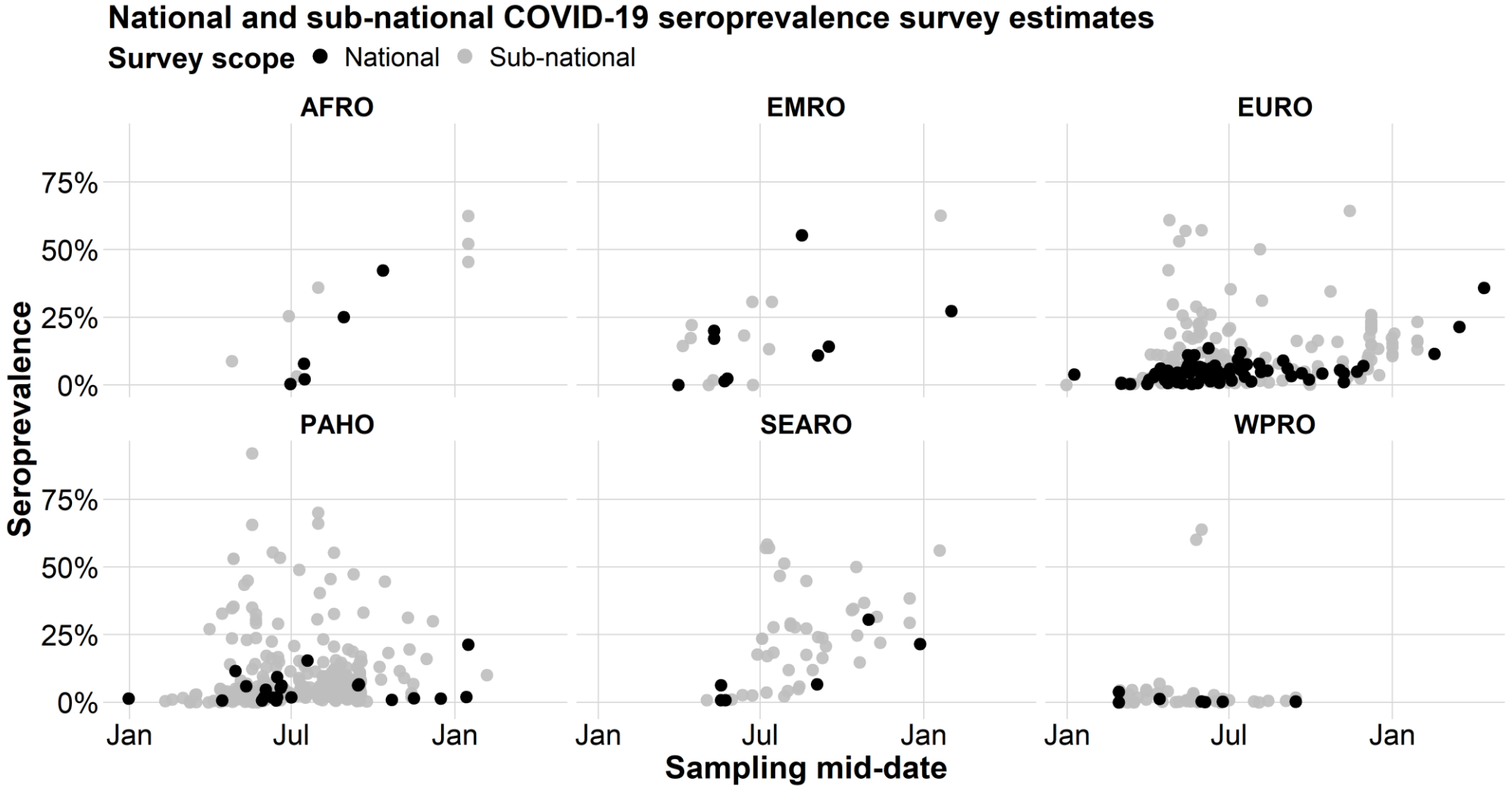
PRELIMINARY and ongoing assessment of evidence, including study quality

	Reduction of neutralizing activity in laboratory assays	Clinical efficacy against variant	Clinical efficacy against non-variant	Clinical efficacy criteria
AstraZeneca	**Full loss (1 dose)** [90]	**59.8%** **(1-dose: 32.9)** [E26]	62-90%	**Symptomatic, all severity**
Bharat Biotech	**2x*** [68]	-	78%[1]	Symptomatic
The Gamaleya National Center of Epidemiology and Microbiology	-	-	92%	Symptomatic
Johnson & Johnson	-	-	1) 74% 2) 78%	1) Moderate to severe-critical 2) Severe
Moderna	-	-	94%	Symptomatic
Novavax	-	-	96%	Symptomatic
Pfizer	**3x** [90]	**87.9%** **(1-dose: 33.2)** [E26]	95%	**Symptomatic, all severity**
Sinopharm	-	-	78%	Symptomatic
Sinovac	-	-	51-84%	Symptomatic

*Unknown sublineage

1. Interim analysis of phase III clinical efficacy

Infection-derived immunity



Point estimates from 788 surveys with low or moderate risk of bias, from serotracker.com as of 20 May 2021
Produced by WHO COVID-19 analytics team

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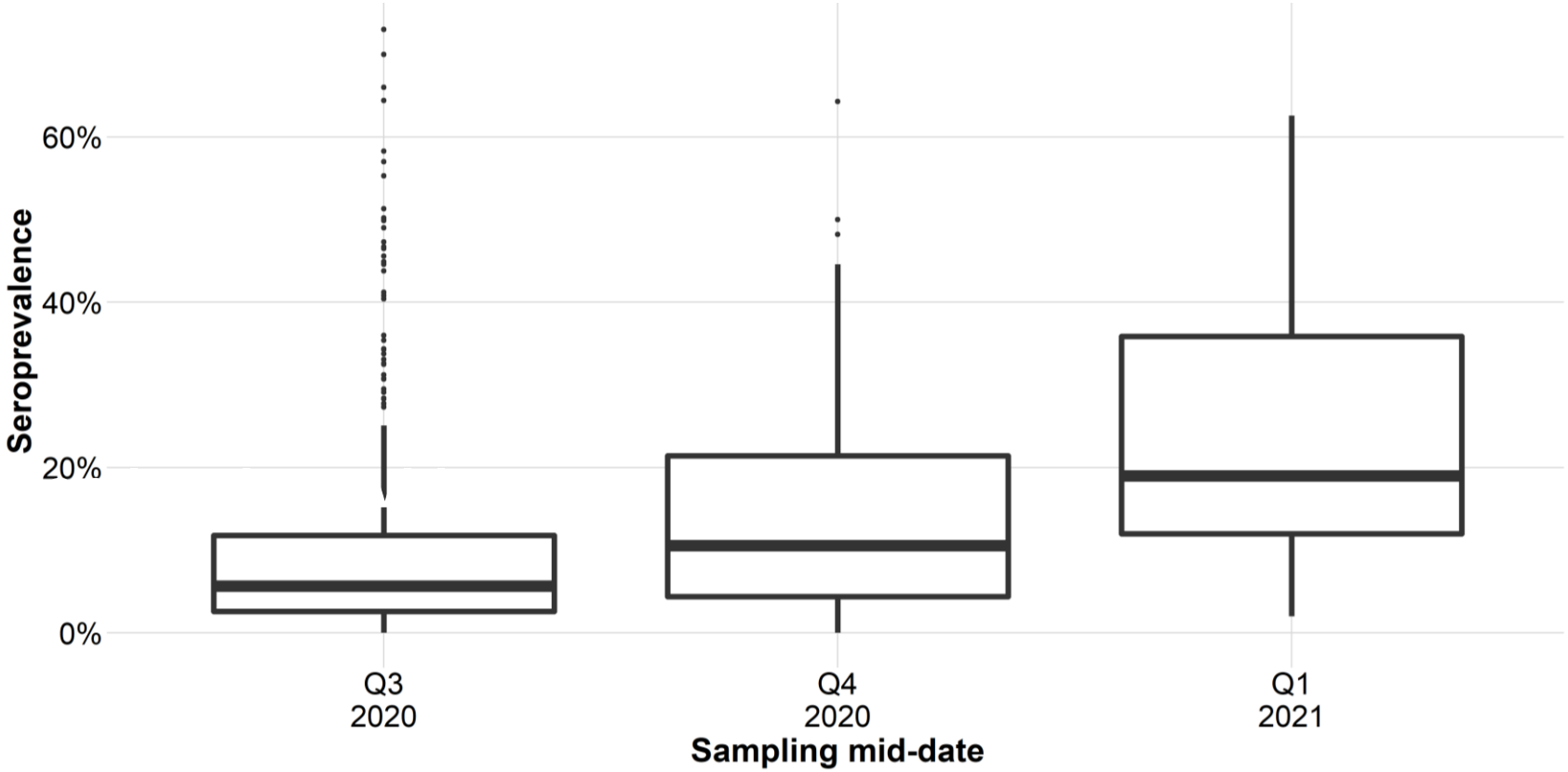
Infection-derived immunity

COVID-19 seroprevalence survey estimates

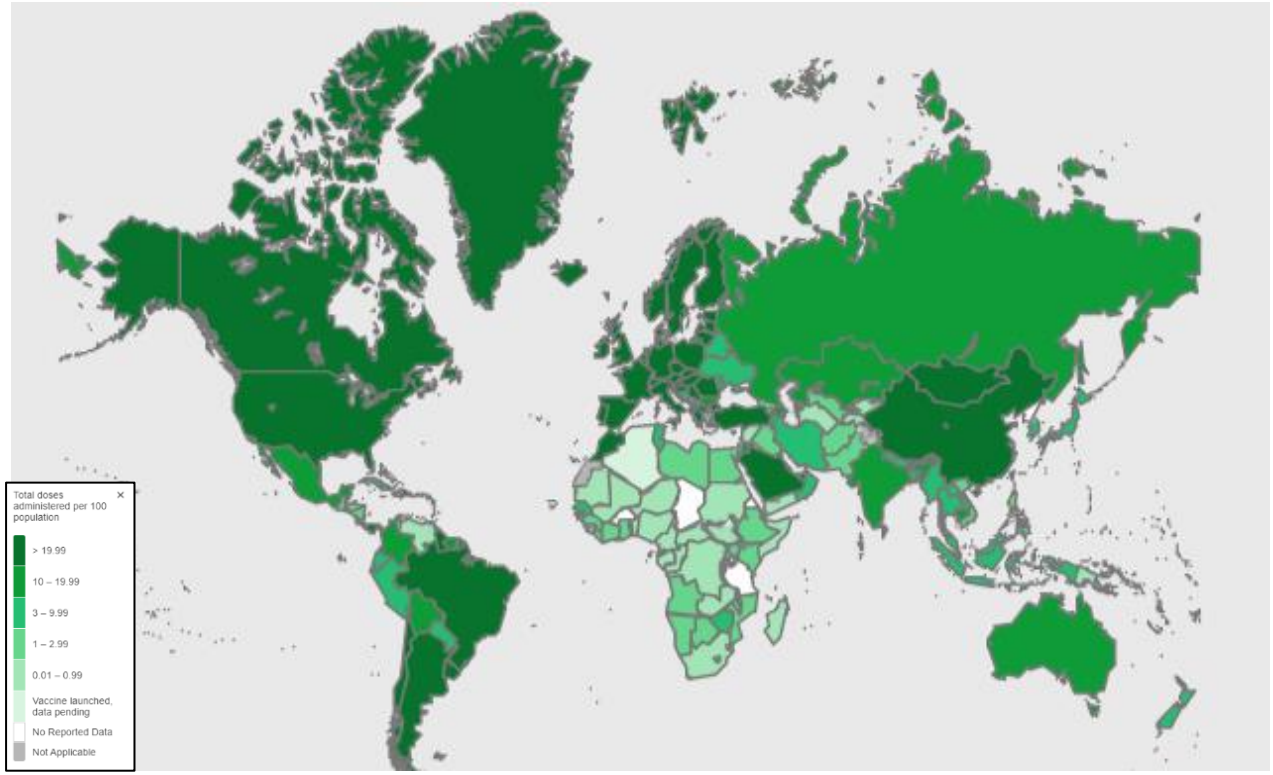


World Health Organization

1,870M doses of COVID-19 vaccine have been administered[1] in 211 countries, areas, territories & economies[2]

DATA AS OF 31 MAY, 11AM CET

Total doses administered per 100 population[3]

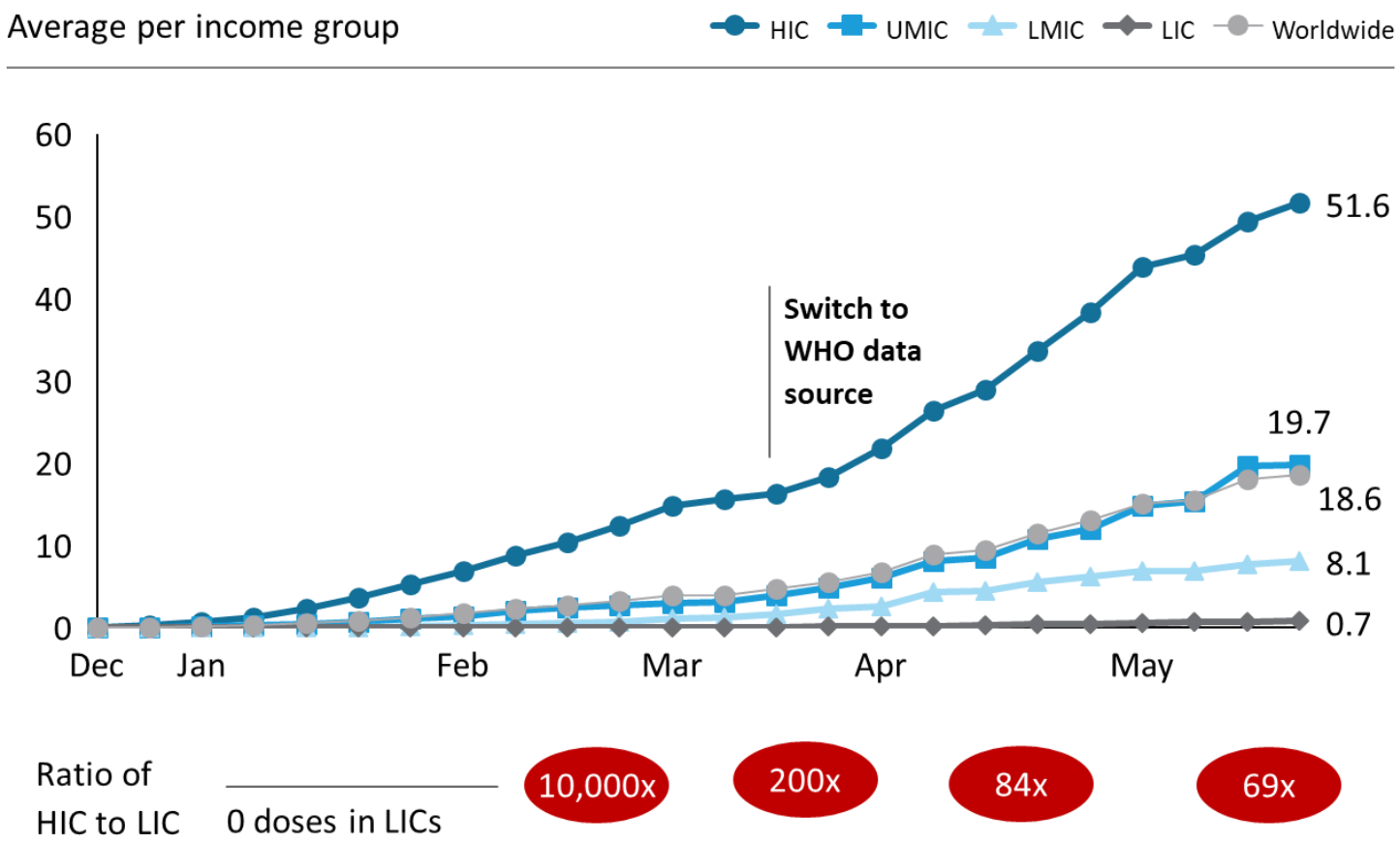


- **1,870M vaccine doses[1]** have been administered
- **COVAX has shipped 77.7M doses to 127 participants4**
- Campaigns have **not yet started in 9 countries**, economies & territories[2]

Note: (1) Source of data: Bloomberg; (2) Total of 220 countries, areas, territories & economies: 218 economies listed by World Bank + WHO Member states Cook Islands + Niue; (3) WHO COVID-19 Dashboard at https://covid19.who.int/ ; 4. Including donations of doses through COVAX.; The designations employed and the presentation of these materials do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Vaccine inequities

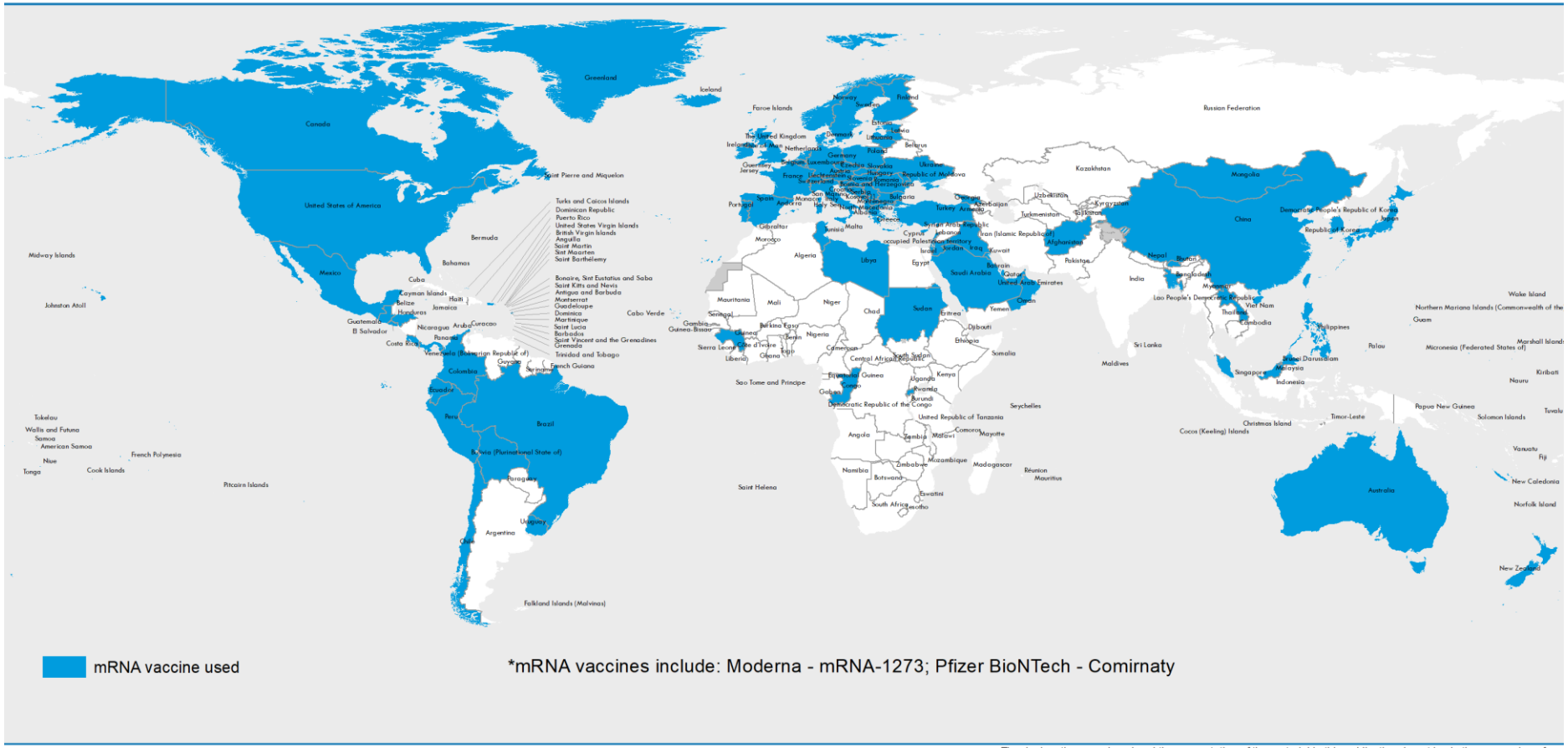
Cumulative COVID-19 doses administered per 100 population



Vaccine distribution by type - mRNA

COVID-19: Countries, territories, areas using mRNA vaccines
data as of 02 June 2021

World Health Organization



Data Source: *World Health Organization,*
Map Production: *WHO Health Emergencies Programme*
Request ID: COVID19_36

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World Health Organization

Vaccine distribution by type – inactivated/subunit

COVID-19: Countries, territories, areas using inactivated or/and protein subunit vaccines
data as of 02 June 2021

World Health Organization

Inactivated or/and protein subunit vaccine used

*Inactivated or/and protein subunit vaccines include: Anhui ZL - Recombinant; Beijing CNBG - Inactivated; Bharat - Covaxin; Novavax - Covavax; RIBSP - QazCovid; Sinovac - CoronaVac; SRCVB - EpiVacCorona; Wuhan CNBG - Inactivated

Data Source: *World Health Organization,*
Map Production: *WHO Health Emergencies Programme*
Request ID: COVID19_36

Not applicable

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World Health Organization

Vaccine distribution by type – adenovirus vector

COVID-19: Countries, territories, areas using adenoviral vector vaccines
data as of 02 June 2021

World Health Organization

*Adenoviral vector vaccines include: AstraZeneca - AZD1222; CanSino - Ad5-nCOV; Gamaleya - Sputnik V; Janssen - Ad26.COV 2.5; SII - Covishield

Data Source: *World Health Organization,*
Map Production: *WHO Health Emergencies Programme*
Request ID: COVID19_36

Not applicable

0 3,000 6,000 km

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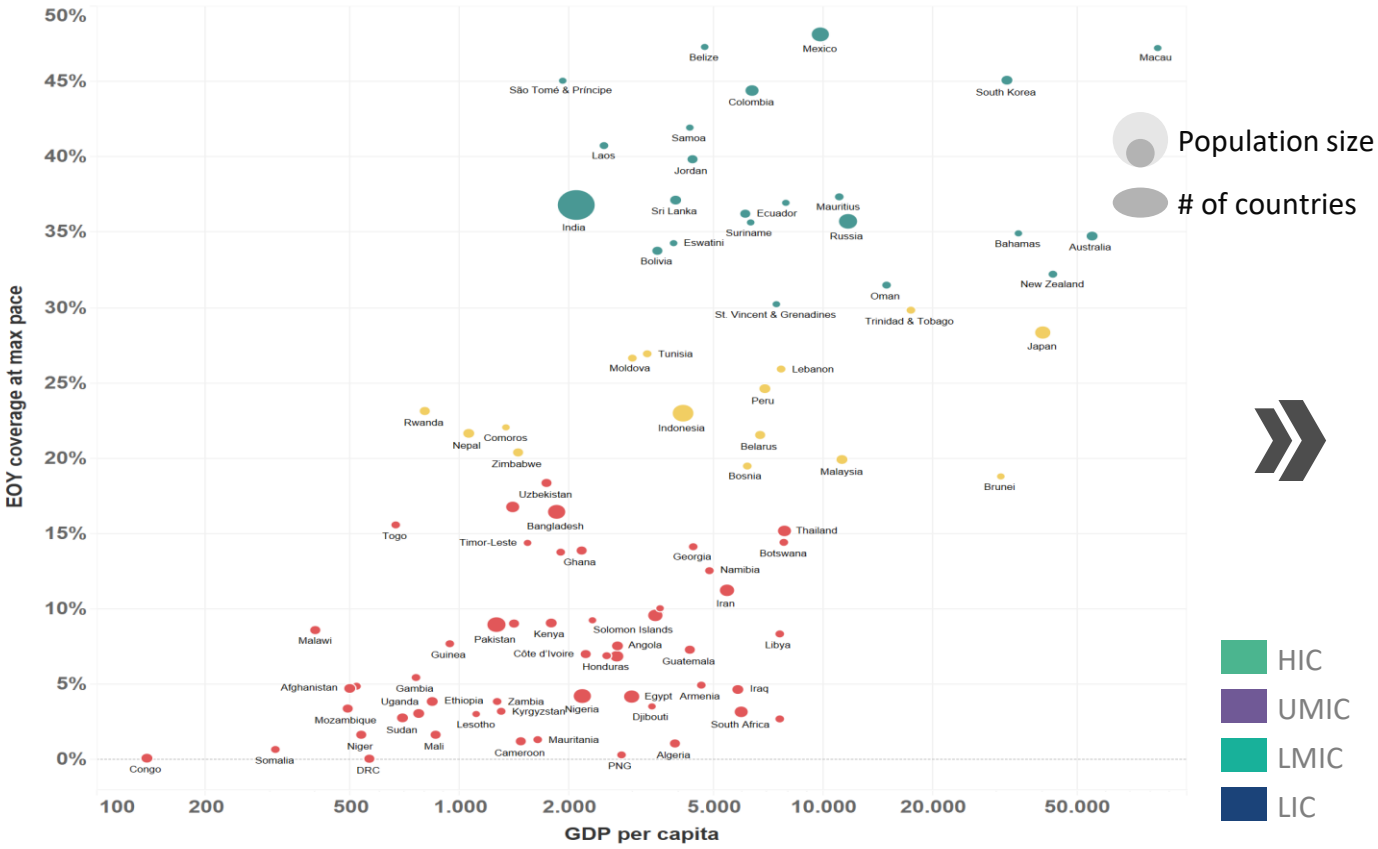
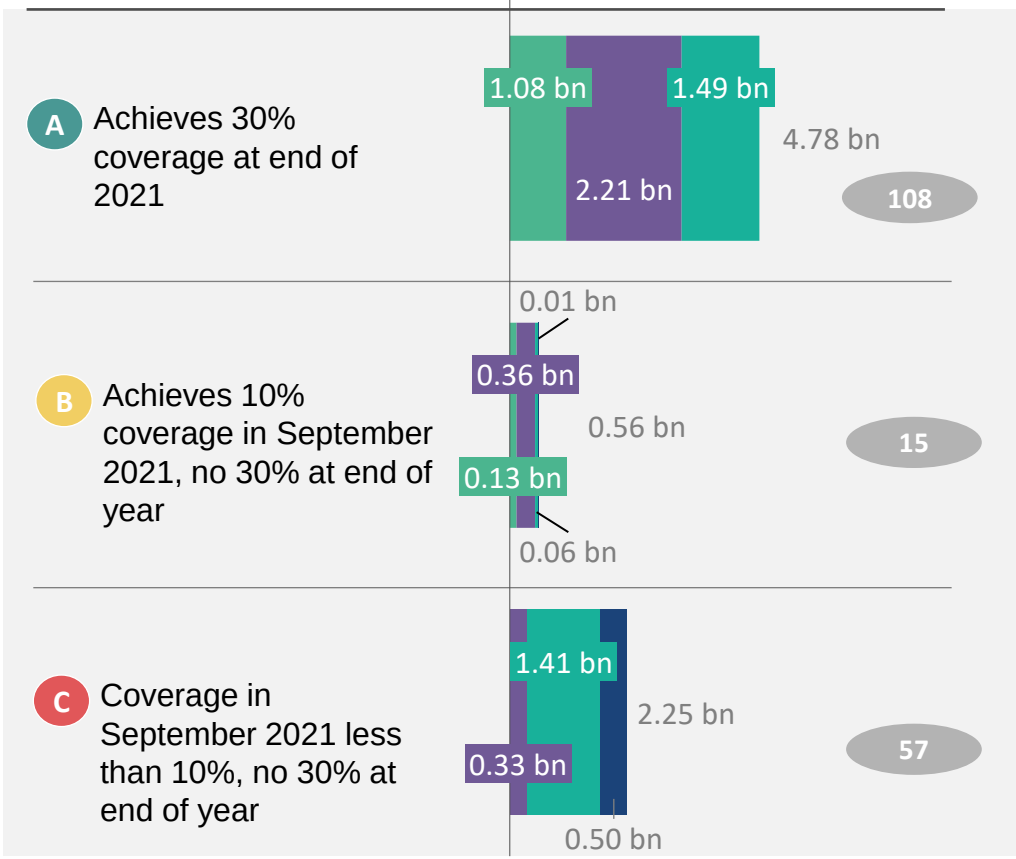
World Health Organization

2.8bn people live in areas where they will not reach 30% coverage at the end of 2021

EOY coverage at maximum administration pace



DATA AS OF 24 May



1. September coverage rate is calculated as the population coverage per May 17th augmented with theoretical coverage rate they could achieve if they were to continue at maximum administration pace assuming doses are available in country

Excludes Bhutan, Mongolia
Source: OWID, WB

Current situation: key trends summary

Epidemiological situation: 2021 is on course to be more deadly than 2020. More cases of COVID-19 were reported globally in the two weeks to May than during the first six months of the pandemic.
The increase in the incidence of new cases globally has slowed in recent weeks, but this masks marked variations between countries. Acute crises are ongoing in a number of countries due to premature relaxation of public health and social measures combined with low vaccination rates and high proportion of population susceptible to infection.

Variants of interest and concern: Tracking the evolution and geographical spread of SARS-Cov-2 variants, and evaluating their impacts on vaccines, therapeutics, and diagnostics, will be crucial; but capacity to detect and monitor variants in many countries is underpowered and requires urgent investment.

Risk and vulnerability: Evidence from serology studies tells us that the vast majority of countries remain susceptible to large-scale outbreaks. Lowering prevalence remains the best way to both reduce mortality and reduce the risk of significant variants arising.

Vaccine inequity: The development of COVID-19 vaccines in record time promises to significantly increase our ability to control and limit the impact of the pandemic. In countries that have access to large quantities of vaccine, age-groups with high vaccination coverage have experienced commensurate declines in death, severe disease, and transmission. Only 0.4% of global vaccine supply has made it to low-income countries. Limited supplies and limited capacities to roll vaccines out rapidly risks prolonging the pandemic for all and requires urgent action to redress the balance.


World Health Organization
Thank you
World Health Organization

CEPI

Durability of immune responses following natural SARS-CoV-2 infection & vaccination: overview of evidence

03 June 2021

Amol Chaudhari, MD

Introduction

- Anti-SARS-CoV-2 antibodies (Abs) are likely key to immune protection against COVID-19[1] but they may wane over time potentially making the individual prone to infection/re-infection
- Cellular immunity (its role not fully understood) is expected to contribute additional longer-term protection especially against severe disease and death[2]
- An overview of important evidence on long term immune persistence following natural infection & vaccination is summarized here
- The data may help understand the need and timing of future booster doses
- There may also be lessons from other coronaviruses…

1. Harvey et al. Association of SARS-CoV-2 Seropositive Antibody Test With Risk of Future Infection. JAMA Intern Med. 2021;181(5):672-9. doi:10.1001/jamainternmed.2021.0366.
2. COVID-19 natural immunity. WHO Scientific brief. 10th May 2021. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci-Brief-Immunity-passport-2021.1. [Accessed on: 31 May 2021]

Data from other CoVs

- Common cold CoVs show a rapidly waning Ab response leading to annual re-infections

- SARS-CoV-1
  - High Ab titres for 2 years in most patients but disappeared in almost half patients within 3rd year; a few reports of persistence up to 13 years
  - Memory T cells in 70-100 % patients at 4 and 6 years

- MERS-CoV
  - Duration of Ab persistence directly correlates with disease severity; low or undetectable Ab titres by 2 years in subclinical or mild infection
  - Memory T cells (despite absent Abs) persist in all till 2 years post infection

1. Sariol A. Lessons for COVID-19 Immunity from Other Coronavirus Infections. Immunity. 2020 Aug 18;53(2):248–63.
2. COVID-19 natural immunity. WHO Scientific brief. 10th May 2021. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci-Brief-Immunity-passport-2021.1. [Accessed on: 31 May 2021]

CEPI

Immune persistence following natural infection

Data at 6 months or longer

Study description	Assays	Main findings
Ripperger et al *(Immunity. 17 Nov 2021)*[1]	Anti-N, RBD & S IgG; NAbs	• Ab titres dependent on COVID-19 severity • Anti-S & RBD and NAbs persisted till ***7 months***;
L'Huillier et al *(Clin Microbiol Infect. 2021)* [2]	Anti-N & RBD IgG; NAbs	• Ab titres dependent on COVID-19 severity • Anti-RBD Abs and NAbs persisted till ***6 months***;
Dan et al *(Science. 2021)*[3]	IgG; NAbs; Memory B cells	• Higher Ab & memory B cells in hospitalised VS non-hospitalised cases • $t_{1/2}$: Anti-S IgG – 103 days; memory B cells – no decay ***(8 months FU)***
Muena et al *(MedRxiv. 18 May 2021)*[4]	NAbs at 6 & 12 months	• Higher VNTs in hospitalised; (t1/2 – 225 in outpatients & 195 in hospitalised) • NAbs persisted till ***12 months***;
Laing et al *(Medrxiv. 02 May 2021)*[5]	Anti- S IgG; NAbs	• Higher titres in hospitalised cases (IgG $t_{1/2}$ - > 1000; NAb – 88-132) • IgG & NAbs persisted till ***12 months***

NAb: neutralising antibody; Anti-N: Anti-neucleocaspid; RBD-receptor binding domain; S-Spike;

1. *Ripperger TJ et al. Orthogonal SARS-CoV-2 Serological Assays Enable Surveillance of Low-Prevalence Communities and Reveal Durable Humoral Immunity. Immunity. 17 Nov 2020;53:925–33.*
2. *L'Huillier AG et al. Antibody persistence in the first 6 months following SARS-CoV-2 infection among hospital workers: a prospective longitudinal study. Clin Microbiol Infect 2021;27:784.e1e784.e8.*
3. *Dan JM et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science 371, eabf4063 (2021). DOI: 10.1126/science.abf4063.*
4. *Muena NA et al. Long-lasting neutralizing antibody responses in SARS-CoV-2 seropositive individuals are robustly boosted by immunization with the CoronaVac and BNT162b2 vaccines. 18 May 2021. doi: https://doi.org/10.1101/2021.05.17.21257197.*
5. *Laing ED et al. SARS-CoV-2 antibodies remain detectable 1 12 months after infection and antibody 2 magnitude is associated with age and COVID-19 severity. 02 May 2021 doi: https://doi.org/10.1101/ 2021.04.27.21256207*

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Key trends & learnings from natural infection data

- Direct correlation of disease severity with Ab response but no clear relation with kinetics
- Abs remain detectable in most cases for the duration of follow-up (6-12 months)
- Half life estimates (from few published reports so far):
  - Anti-S IgG - 100 - > 1000 days
  - Anti-RBD IgG - ~ 69 days
  - NAbs – 90-225 days
  - T cells - 94-225 days
- Memory B cells persisted without decay for up to 8 months (just one study)
- Re-infection: Few studies have shown seropositivity is 80-90% protective[1] against re-infection, however the correlation to Ab titres is not fully established

1. COVID-19 natural immunity. WHO Scientific brief. 10th May 2021. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci-Brief-Immunity-passport-2021.1. [Accessed on: 31 May 2021]

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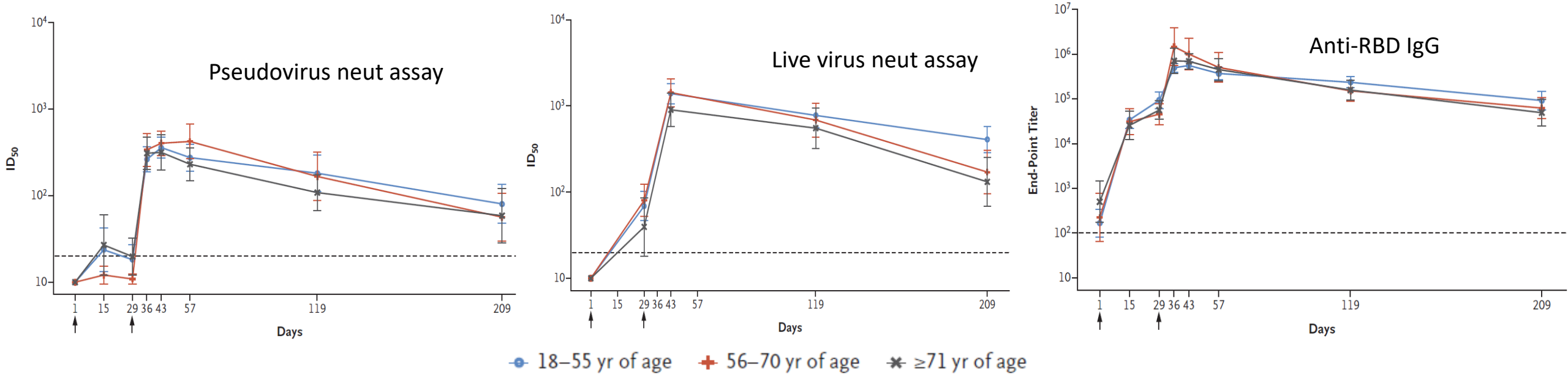
Immune persistence following vaccination

- Moderna[1]: immune persistence data up to Day 209 (~6 months)
  - Anti-S Ab & NAbs (pseudo- [PsV] and live-[LV] virus) remained detectable at 6 months
  - Estimated $t_{1/2}$:
    - Anti-RBD IgG – 52 days (steady rate model) & 109 days (decreasing rate over time)
    - Pseudovirus NAb - 69 & 173 days
    - Live virus NAb – 68 & 202 days



1. *Doria-Rose N et al. Antibody Persistence through 6 Months after the Second Dose of mRNA-1273 Vaccine for Covid-19. NEJM. 13 May 2021. DOI: 10.1056/NEJMc2103916.*

Immune persistence following vaccination

- Pfizer[1] has reported vaccine efficacy of 91.3% at 6 month follow-up in its Phase 3 trial but no immune response results available
- Immunogenicity from other vaccines beyond 3 months of FU is presently not available and more data is needed for assessing persistence following vaccination
- Post roll-out data has consistently shown reduction in hospitalization, severe COVID-19 and death but no long-term (6 months and beyond) data at present
- More data is needed….

1. *https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-confirm-high-efficacy-and-no-serious.*

Plasma cells (post - natural infection & vaccination)

- Bone marrow plasma cells (BMPCs) derived from B cells are an important source of Abs in long term

- Following natural infection[1]
  - Biphasic Ab decline due to transition from short-lived plasmablasts to long-lived BMPCs which appear later
  - BMPCs & memory B cells (n=18) detected at 7 months; BPMCs also detected at 11 months in 5 subjects

- Following vaccination with BNT162b2[2]
  - Plasmablasts at 3 weeks in 19/25 with no h/o SARS-CoV-2 infection but in 0/7 of previously infected
  - Germinal center B cells were found post vaccination & persisted till 7 weeks after dose 1 (n=12)

- These findings, while from small studies are indicative of long-lasting humoral immune responses following natural infection and vaccination

1. *Turner JS. et al. SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans. Nature https://doi.org/10.1038/s41586-021-03647-4 (2021).*
2. *Turner JS et al. SARS-CoV-2 mRNA vaccines induce robust plasmablast and germinal centre responses in humans. Available at: https://www.researchsquare.com/article/rs-310773/v1. [Accessed on: 02 June 2021]*

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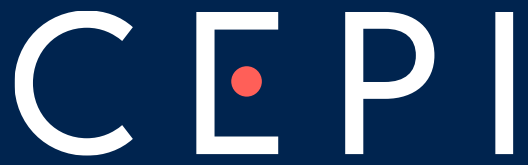
To conclude…

- Anti-SARS-CoV-2 Abs while waning, have been reported to persist up to 6-12 months following natural infection; Ab titres directly correlate with disease severity
- If post-vaccination immune responses follow similar trend, vaccines may remain protective for a year or beyond; however, data is currently limited & inconclusive
- The memory B cells have shown to persist for months without decay and may contribute to long term protection especially against severe COVID-19 and death
- The impact of variants of concern on immune response needs to be monitored closely; distinguish:
  - Impact on prevention of infection and all-severity COVID-19?
  - Impact on severe and critical disease, hospitalization, death?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Post-introduction Covid-19 Vaccine Effectiveness; *Evidence of need for boosters?*

Daniel Feikin, MD

June 3, 2021

Department of Immunizations, Vaccines and Biologicals/WHO

Where might need for booster become apparent in post-implementation VE studies?

- Waning VE with duration since vaccination
- VE against variants of concern

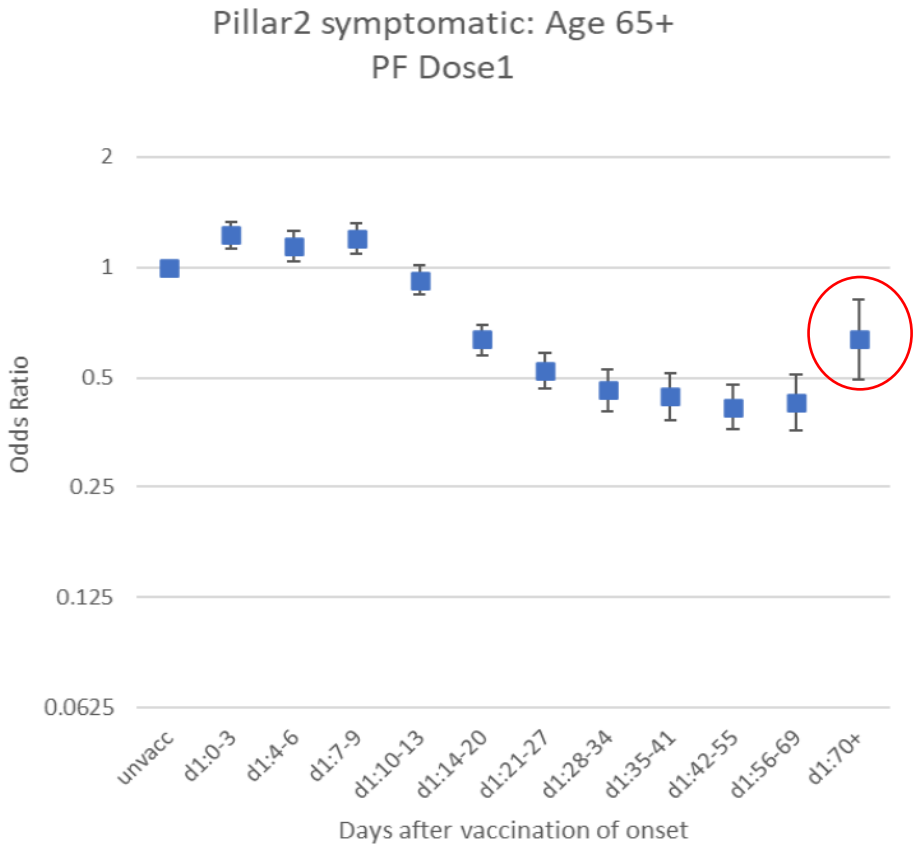
Duration of protection from vaccine clinical trials

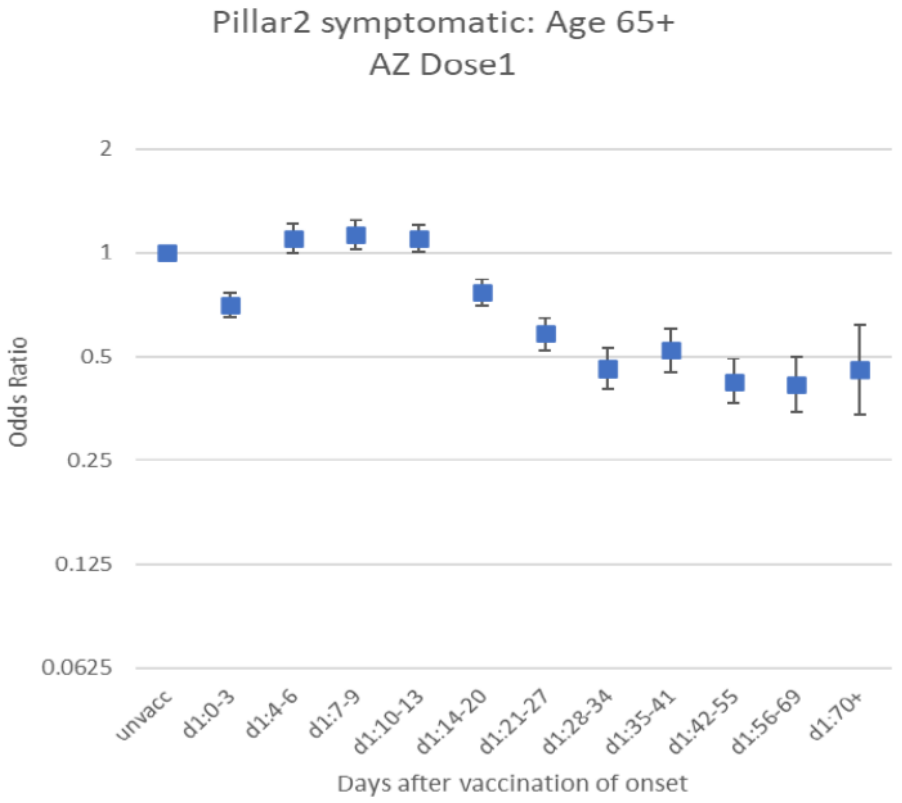
- Efficacy vs Effectiveness

- BNT162b2 at 6 months after 2nd dose found efficacy of 91.3% (95% CI, 89.0, 93.2]) against symptomatic disease
  - Vs. 95% though 3 months
  - 100% VE against severe disease at six months
- mRNA-1273 at 6 months after 2nd dose found efficacy >90% against symptomatic disease
  - Vs. 94% at 3 months
  - >95% against severe disease at 6 months

VE through 10 weeks in UK

- PHE, Test Negative Design using national databases, 12 week interval between doses





VE against infection at 6 weeks: Pfizer/Moderna in USA

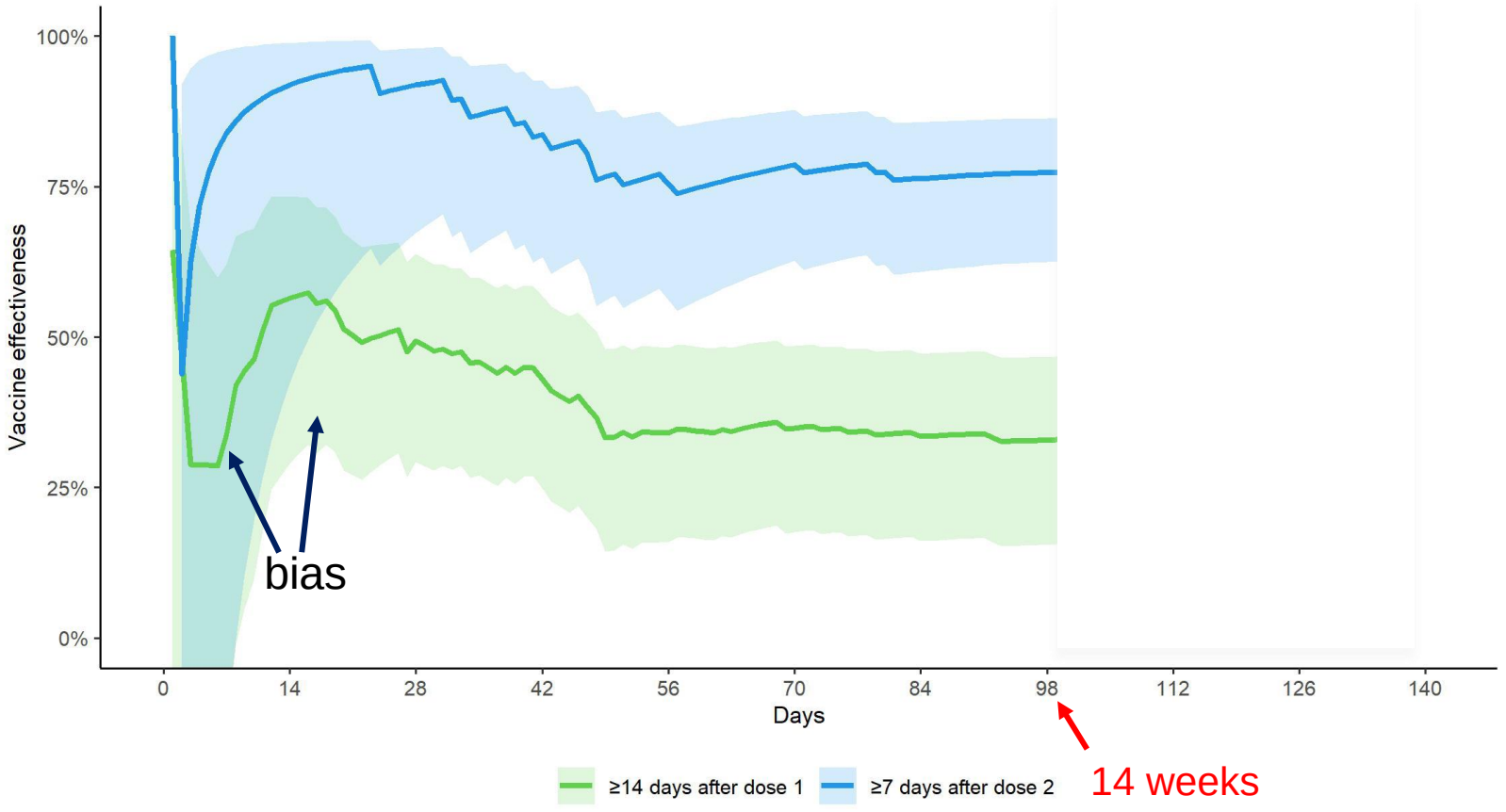
- Retrospective cohort from Mayo Clinic between Dec 1-Feb 8 who underwent PCR testing for SARS-CoV-2
- 31,069 unvaccinated versus 31,069 at least one dose (8041 2 doses)

Day post injection 1	VE (95% CI)
1-7	53.6% (40.9-63.8%)
8-14	46.7% (31.1-58.9%)
15-21	69.2% (54.1-79.8%)
22-28	74.2% (58.4-84.7%)
29-35	83.0% (63.6%-93.1%)
36-42	92.5% (70.2%-99.1%)

Pawlowski C, Lenehan P, Puranik A, Agarwal V, Venkatakrishnan AJ, Niesen MJ, et al. FDA-authorized COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system. MedRxiv 2021. https://www.medrxiv.org/content/10.1101/2021.02.15.21251623v1.full.pdf

mRNA vaccines with little waning to 14 weeks in Canadian/BC HCWS

- Pfizer (93%), longer dosing interval 7 weeks-16 weeks. Symptomatic disease outcome comparing vaccinated to unvaccinated HCWs



From Yassi A et al, medRxiv, May 25, 2021

Assessment of waning VE

- Increase % of breakthrough cases among vaccinated with time since vaccination
- Compare incidence in vaccinated recently vs. vaccinated a longer time ago
  - Relative VE of recent vs. remote vaccination
- Change in incidence of Covid-19 with increasing time since vaccination
  - See first in the earliest vaccine cohort (e.g., > 80 y.o.)
- Change in severity (e.g., hospitalization) or higher viral loads among those with remote vaccination.

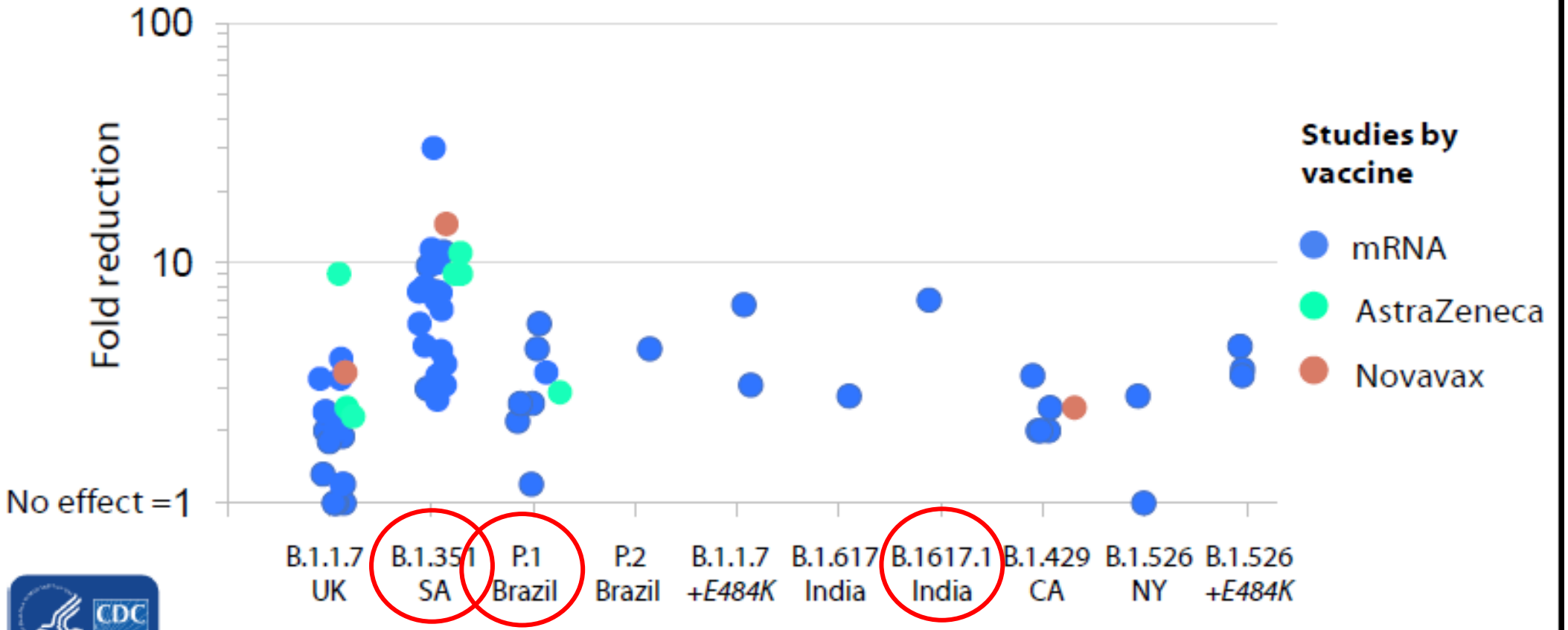
Summary of VE evidence on duration of protection

- Minimal waning of VE through 3-4 months
  - Watch UK
- Mostly 1 dose data
- Mostly Pfizer, Moderna, and AZ data
- Need to continue to have sequential VE data over time with discreet time intervals assessed

Where might need for booster become apparent in post-implementation VE studies?

- Waning VE with duration since vaccination
- VE against variants of concern

Reduced Neutralization Activity of Vaccine Sera Relative to Wildtype/Dominant Strain, by Study (n=31)

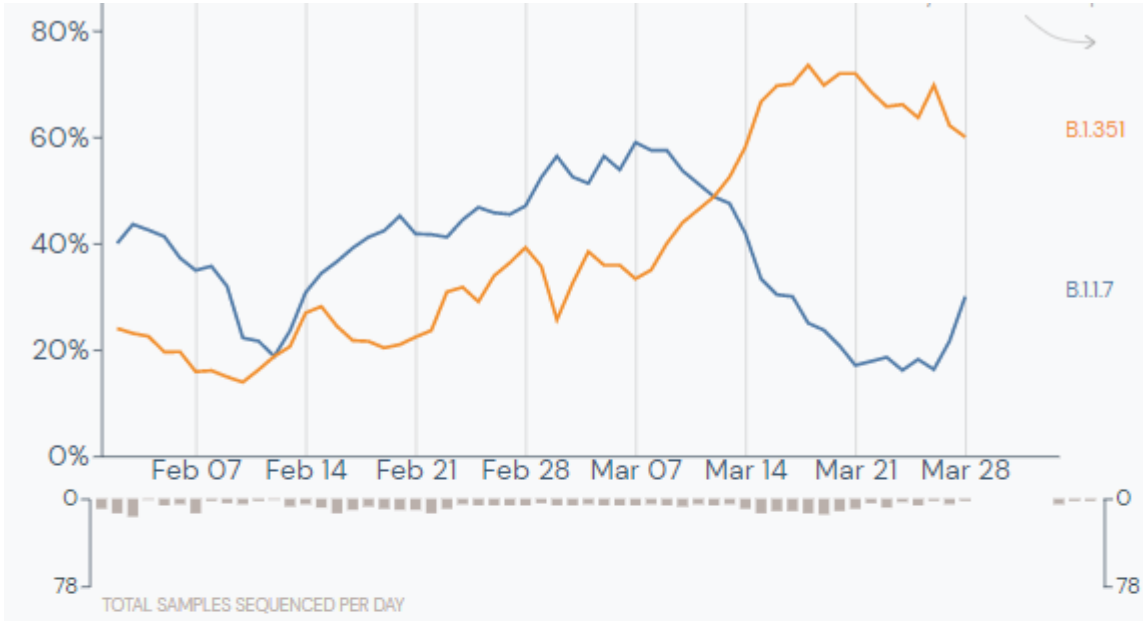


* Slide courtesy of Heather Scobie, CDC

- **Evidence from post-implementation VE studies against B1.351 (Beta)**

Background Qatar

- Pfizer vaccination started Dec 21; end of March ~20% had one dose
- Feb 23- March 18
  - After March 7 only identified B1.351 and B1.1.7
    - Use SGTF not sequencing
  - TND case-control study
  - Match 1:1 on age, sex, nationality, reason for PCR testing; sensitivity analysis by time of test



Abu-Raddad et al, NEJM

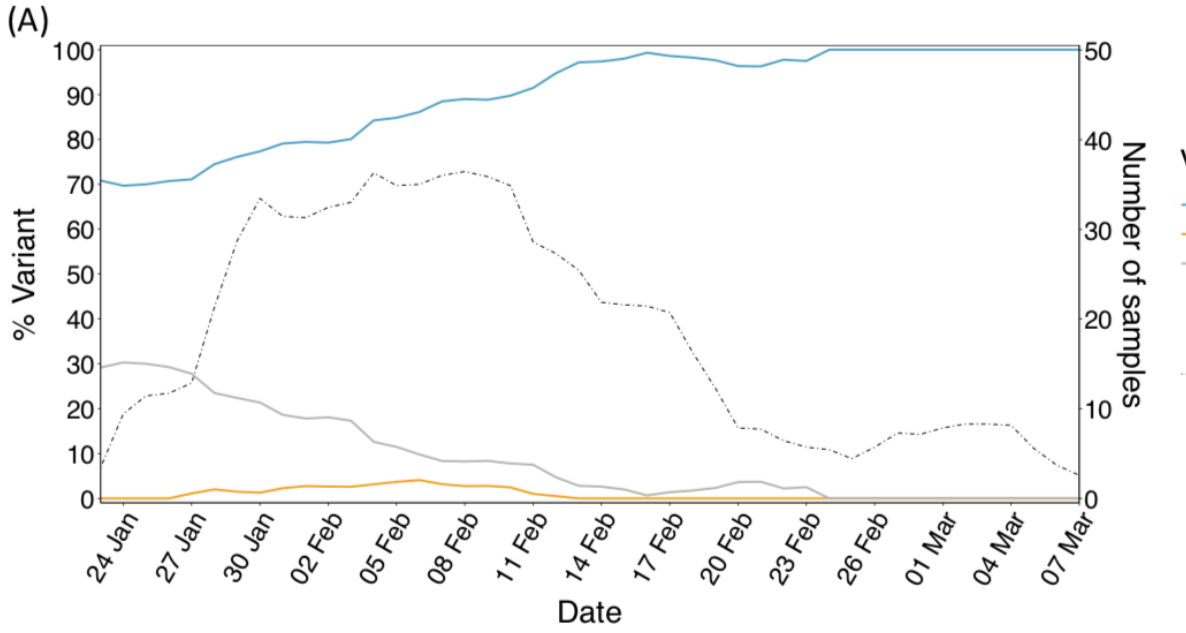
Results Qatar TND study

TND CaCo VE	B1351	B117
Infection		
≥14 days post dose 2	75% (70.5-78.9)	89.5% (85.9-92.3)
Severe, critical, fatal disease		
≥14 days post dose 2	100.0 (81.7–100.0)	100.0 (73.7–100.0)

Abu-Raddad et al, NEJM

Evaluation of B1.351 vaccine breakthrough cases

- Clalit HMO, Israel.

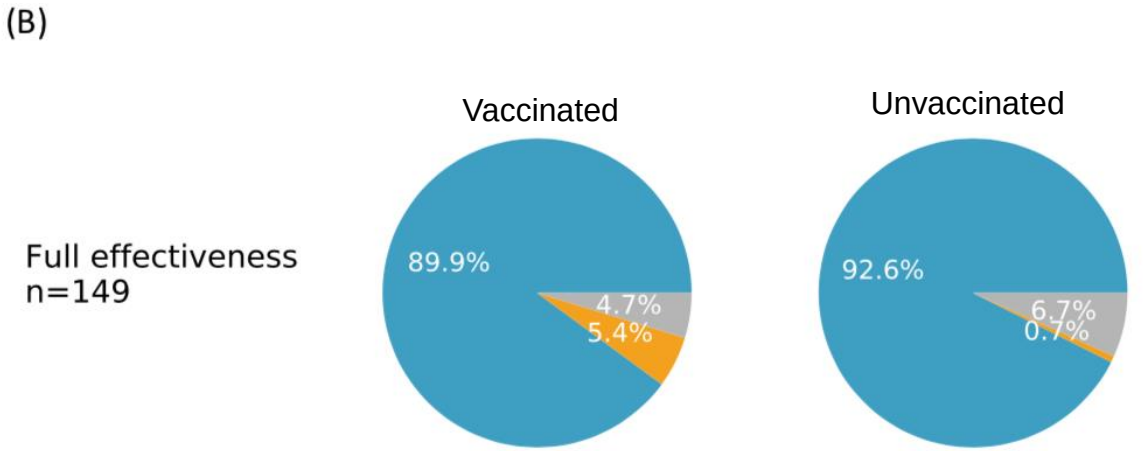


- Time period when B.1.1.7 and B.1.351 circulating
- B.1.351 came and went
- Case only analysis
  - Compare vaccinated to unvax cases
    - 14 d post-dose 1, 7 days post-dose 2
  - Matched by date, age, residence

- Kustin T, MedRxiv, https://doi.org/10.1101/2021.04.06.21254882

Evaluation of B1.351 vaccine breakthrough cases

- Clalit HMO, Israel, B1.351 is orange slice



B1.351, OR=8.0, p=0.02

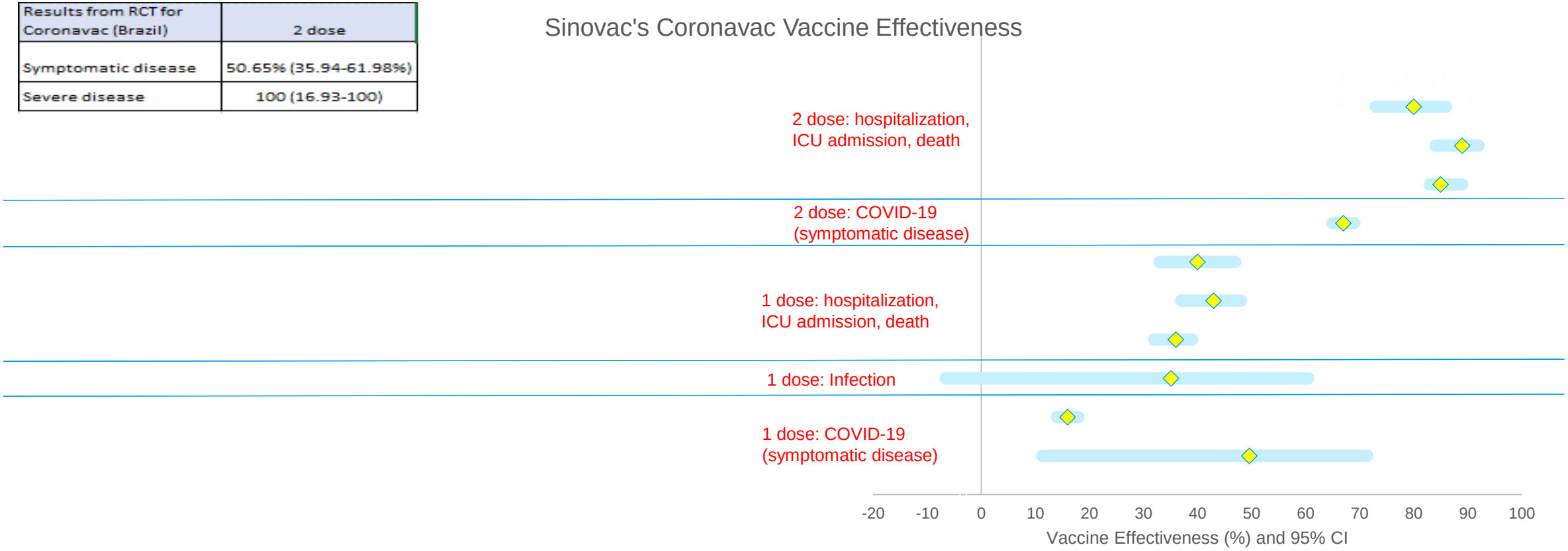
Kustin T, MedRxiv, https://doi.org/10.1101/2021.04.06.21254882

- **Evidence from post-implementation VE studies against P.1 (Gamma)**

Coronavac VE against P.1 variant in Brazil and Chile

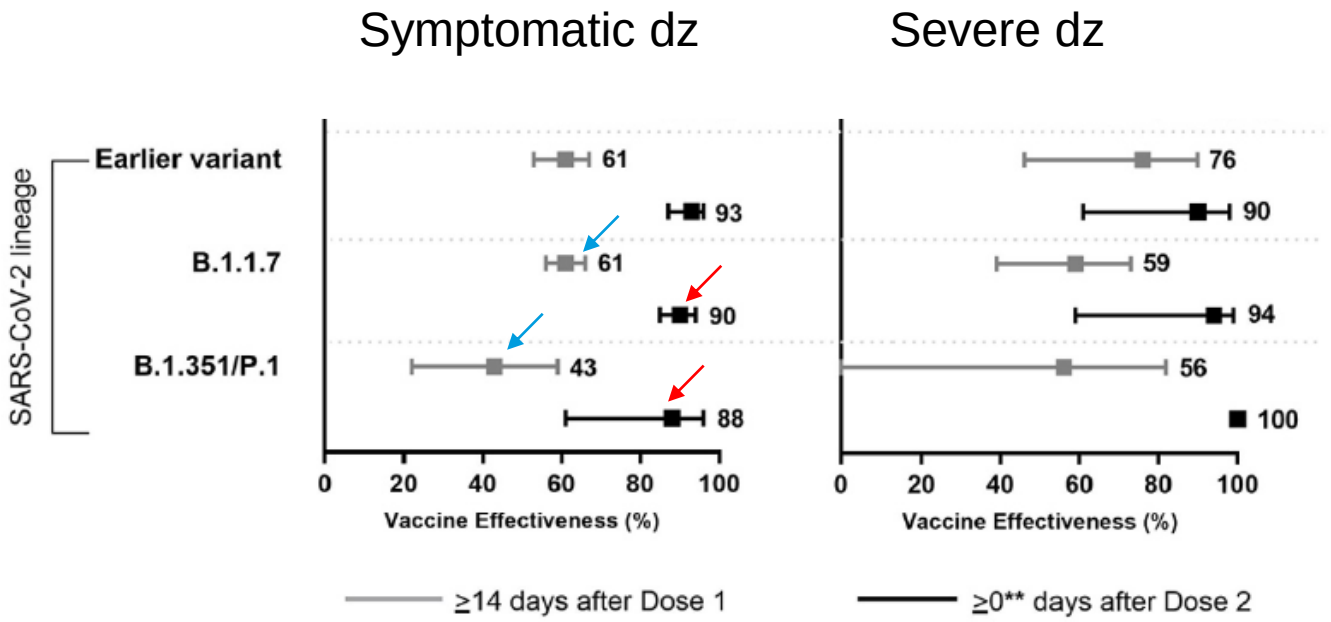
- Not all cases had typing; 75% in the community in Brazil was P1, 20-30% in Chile

Results from RCT for Coronavac (Brazil)	2 dose
Symptomatic disease	50.65% (35.94-61.98%)
Severe disease	100 (16.93-100)



Combined P1/B.1.351 in Ontario

- Based on N501Y and E484K mutations being present after March 22, about 20% total; both mRNA vaccines
- Adjusted for multiple variables in Test-negative design of linked databases



-Possible decreased VE with one dose against symptomatic, not severe, wide CI

From Chung H et al, medRxiv, May 25, 2021

- **Evidence from post-implementation VE studies against B.1.617.2 (Delta)**

VE B1.617.2 in England

- TND case-control study, PHE, VE against symptomatic disease

		VE for B.1.1.7	VE for B.1.617.2
BNT162b (Pfizer)	1 dose	51% (47-55)	34% (21-44)
	2 doses	87% (83-90)	81% (71-88)
AZ (ChadOx1)	1 dose	51% (47-55)	33% (19-44)
	2 doses	66% (54-75)	60% (29-77)

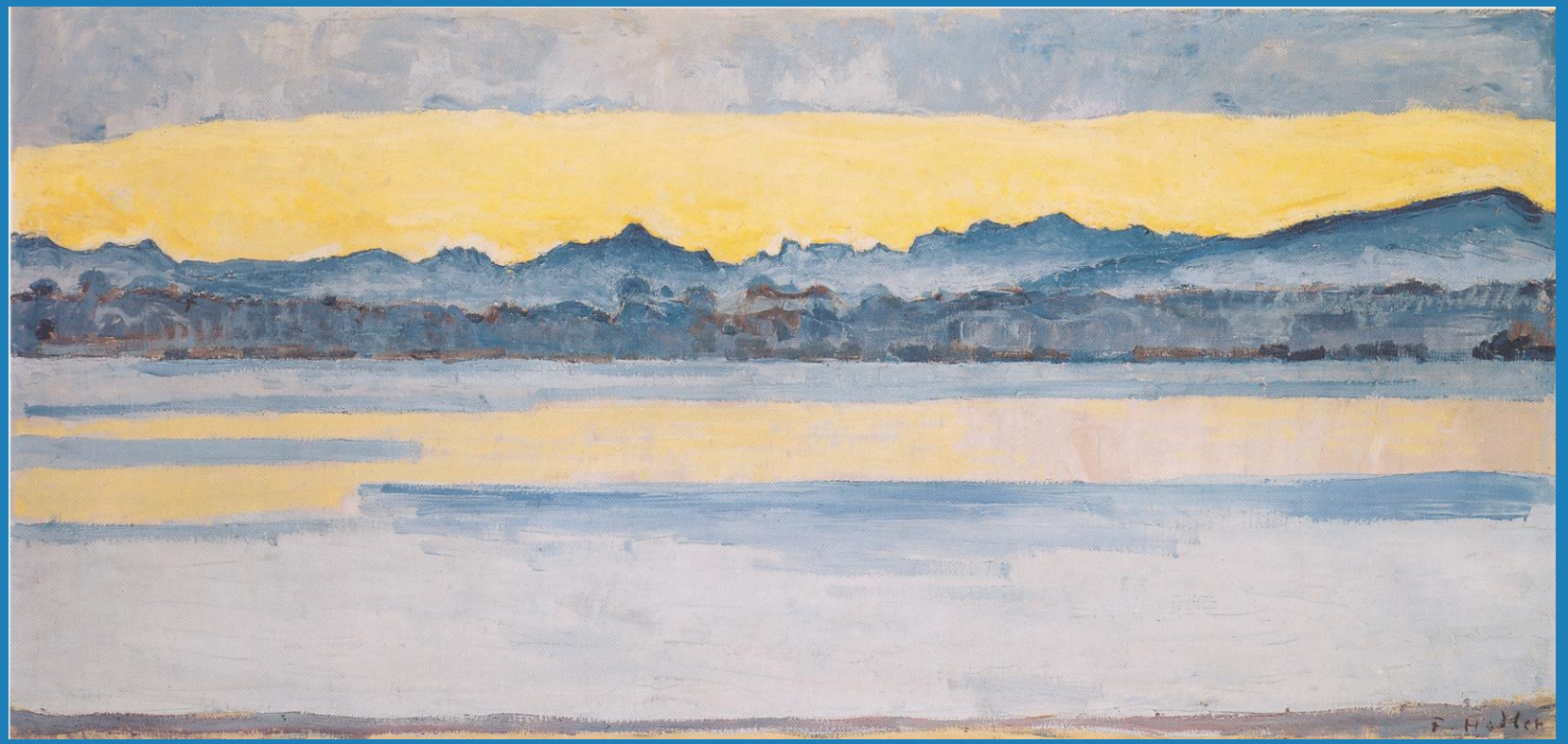
- Reduced VE with one dose of both vaccines for B1.617.2,
- But only slight reduction with 2 doses (overlapping CI)

From Lopez Bernal, J, et al. MedRxiv, https://www.medrxiv.org/content/10.1101/2021.04.08.21255108v2

Summary of VOC data

- Reduced neutralization might be reflected in slightly lower VE
  - Decreased VE with 1 dose, but less so 2 doses
  - Decreased VE mild/moderate disease, but not severe disease
- VE for VOCs is still high enough to prevent the majority of disease
- Will waning of protection be seen sooner with VOCs?

WHO policy decision on need for booster doses



World Health Organization

Overview of single dose strategies and scenarios

Edde Loeliger MD, MSc

Purpose & Objectives

- To briefly summarize single vaccine dose (SD) evidence to ADDRESS the following QUESTIONS:
- Why ADDRESS the topic of SD of COVID-19 vaccines?
  - Reduces global vaccine shortage instantly by 50%
  - Faster increase in vaccine coverage – saves lives & lowers population viral load reducing the risk of new variants of concern
- QUESTIONS to consider:
  1. Could a first, single vaccine dose act as *de facto* booster in individuals with prior SARS-CoV-2 infection?
  2. Could SARS-CoV-2 infection act as a *de facto* booster in individuals primed by a SD?
  3. Does the available evidence support the provision of SD without baseline testing (i.e. regardless of baseline serostatus) ?
  4. On a global level, what is the purpose of the clinical development of SD ”next generation” (e.g. adapted strain) COVID-19 vaccines? Boost-only vaccine development ??

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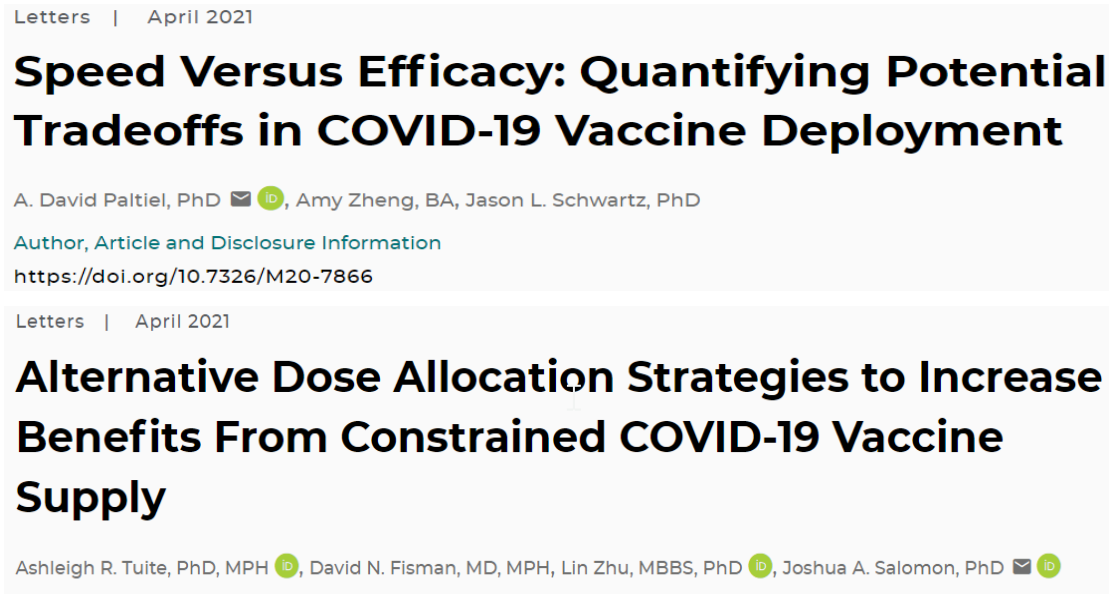
Outline

- SD effectiveness modelling
- SD in individuals primed by natural infection
- SD in individuals “primed by vaccination” (delayed 2nd “booster” dose)
- SD in unprimed individuals
- General immunologic considerations

Single dose effectiveness modelling studies

- Cumulative mortality reduction by up to 48% compared two-dose regimen
- The threshold SDE for disease prevention is ~ 50%



Letters | April 2021

Speed Versus Efficacy: Quantifying Potential Tradeoffs in COVID-19 Vaccine Deployment

A. David Paltiel, PhD, Amy Zheng, BA, Jason L. Schwartz, PhD

Author, Article and Disclosure Information

https://doi.org/10.7326/M20-7866

Letters | April 2021

Alternative Dose Allocation Strategies to Increase Benefits From Constrained COVID-19 Vaccine Supply

Ashleigh R. Tuite, PhD, MPH, David N. Fisman, MD, MPH, Lin Zhu, MBBS, PhD, Joshua A. Salomon, PhD

Optimizing vaccine allocation for COVID-19 vaccines: critical role of single-dose vaccination.

Laura Matrajt,[1*] Julia Eaton,[2] Tiffany Leung,[1] Dobromir Dimitrov,[1,3] Joshua T. Schiffer,[1,4] David A. Swan,[1] Holly Janes[1]

Public health impact of delaying second dose of BNT162b2 or mRNA-1273 covid-19 vaccine: simulation agent based modeling study

Santiago Romero-Brufau,[1,2] Ayush Chopra,[3] Alex J Ryu,[1] Esma Gel,[4] Ramesh Raskar,[3] Walter Kremers,[5] Karen S Anderson,[4] Jayakumar Subramanian,[6] Balaji Krishnamurthy,[6] Abhishek Singh,[3] Kalyan Pasupathy,[5] Yue Dong,[7] John C O'Horo,[1] Walter R Wilson,[1] Oscar Mitchell,[8] Thomas C Kingsley[1]

1. Tuite AR et al. Alternative Dose Allocation Strategies to Increase Benefits From Constrained COVID-19 Vaccine Supply. Ann Intern Med.
2. Paltiel AD et al. Speed Versus Efficacy: Quantifying Potential Tradeoffs in COVID-19 Vaccine Deployment. Ann Intern Med.
3. Romero-Brufau S et al. Public health impact of delaying second dose of BNT162b2 or mRNA-1273 covid-19 vaccine: simulation agent based modeling study. BMJ.
4. Matrajt L et al. Optimizing vaccine allocation for COVID-19 vaccines: critical role of single-dose vaccination. MedRxiv.

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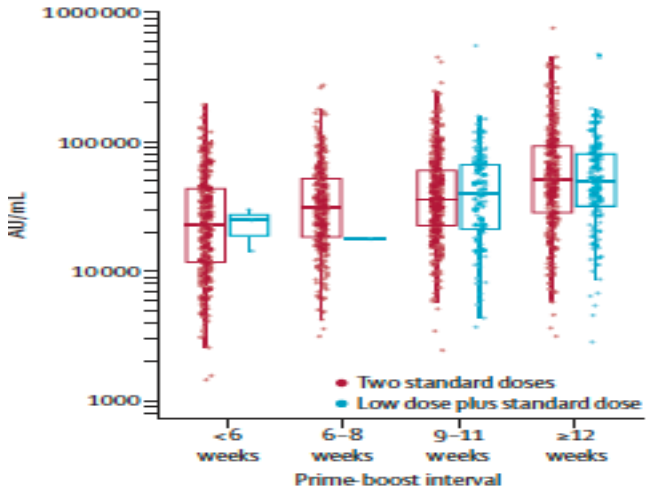
Single dose in individuals primed by natural infection

In individuals primed by natural infection, a SD should provide protection *at least* comparable to the level conferred by 2 doses in unprimed individuals:

- In HCW Cohorts, elicits Ab titres exceeding Ab titres after two doses in seronegatives
    - < 7 days after SD vaccination
- In the RECoVERED cohort (N=328), exceeding Ab titres after two doses in seronegative including in elderly (16%) & following severe (10%) and critical (12%) COVID-19 [1]
    - The infection-vaccination interval (3-15 months) did not affect post vaccination Ab titres
- Mounts robust B and T-cell responses, including against VOC [2, 3]
- Boosts cross-variant BAbs and NAbs elicited by prior infection, including against VOC [1, 3, 4]
- Prevents reinfection and transmission [5]

1. Van Gils et al. Single-dose SARS-CoV-2 vaccine in a prospective cohort of COVID-19 patients. MedXriv 25 May 2021
2. Prendecki et al. Effect of previous SARS-CoV-2 infection on humoral and T-cell responses to single-dose BNT162b2 vaccine. Lancet 2021; 397: 1178–81
3. Reynolds et al. Prior SARS-CoV-2 infection rescues B and T cell responses to variants after first vaccine dose. Science. 2021 Apr 30
4. Stamatos et al. mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection. Science (80-) 2021; 9175: eabg9175
5. Pritchard et.al. Impact of vaccination on SARS-CoV-2 cases in the community: a population-based study using the UK's COVID-19 Infection Survey. medRxiv. 2021 Apr 23;2021

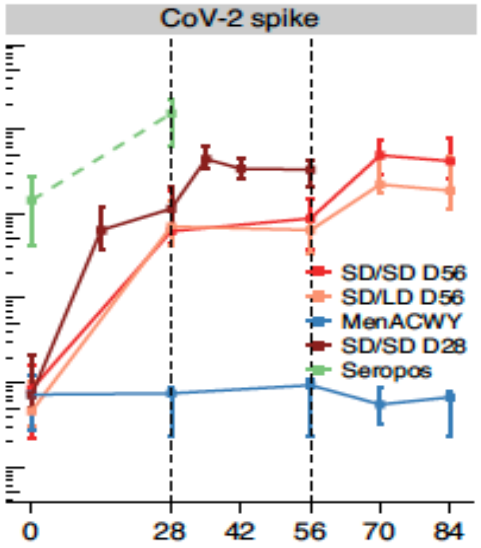
“Booster” dose in individuals “primed” by 1st dose



- Delaying the 2nd dose to 12 weeks (instead of 3-4 weeks)
  - ChAdOx-1: 2.5 -fold higher Ab responses [2]
  - BNT162b2: 3-fold higher Ab responses [3]

- Ab differences roughly in same order of magnitude when comparing
  - SD in primed versus naïve [1]
  - Booster after 4 versus 12 weeks [2]

- More data expected from COM-CoV trial as well other vaccine trials

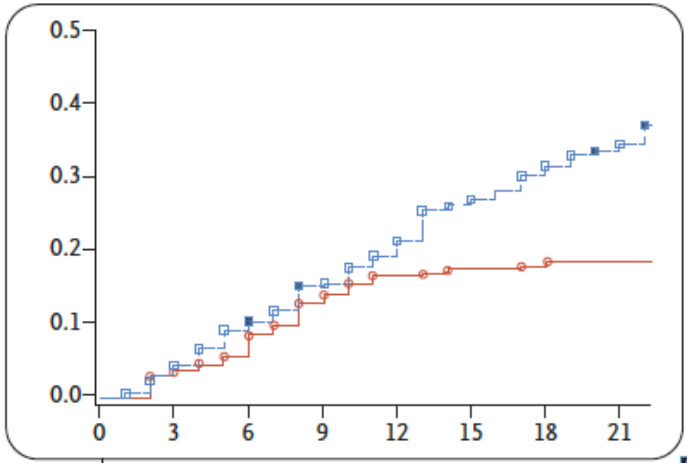


1. Barrett et.al. Phase 1/2 trial of SARS-CoV-2 vaccine ChAdOx1 nCoV-19 with a booster dose induces multifunctional antibody responses. Nat Med. 2021 Feb;27(2):279–88.
2. Voysey et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity…(….) Lancet 2021 Mar 6;397(10277):881–91.
3 Parry et.al. Extended interval BNT162b2 vaccination enhances peak antibody generation in older people. medRxiv. 2021 May 17;2021.05.15.21257017

Single dose vaccine efficacy (VE) in unprimed individuals

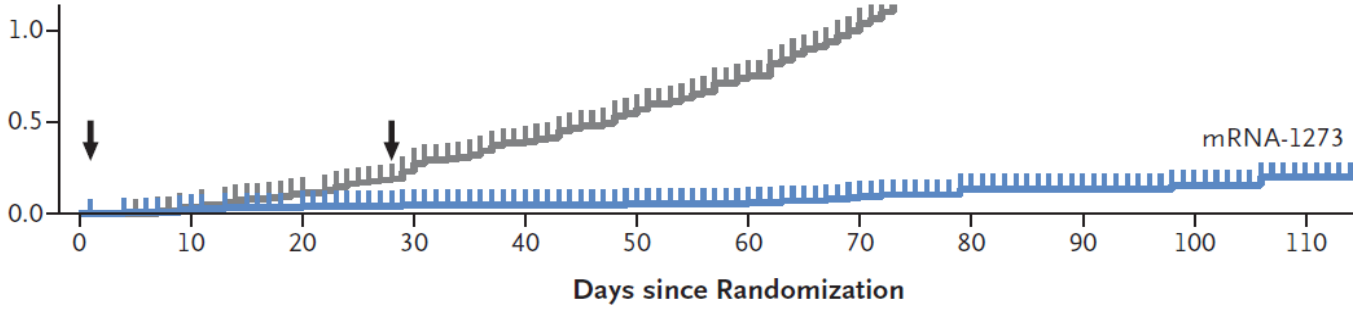
- Single dose VE, from 14 days post-dose 1 until 2nd dose in pivotal efficacy trials exceed 50%:
  - BNT162b2 (Pfizer): 92.6%
  - mRNA-1273 (Moderna): 91.2% [2]
  - NVX-CoV2373 (Novavax): 83% (press release)
  - Ad26.COV2 (Janssen): 67% (for moderate to severe disease); 77% for critical disease [3]

- Single Dose BNT162b2 overall efficacy: "VE 52%" [1]
  - PCR+ cases between the 1st and 2nd dose: 39 vs 82 cases (placebo) → VE 52.4% (29.5–68.4) [1]
  - PCR+ cases between Day 12 and 21: 4 vs 30 cases → VE 86.6% [4]
  - PCR+ cases between Day 14 and 21: 2 vs 27 cases → VE 92.6%
  - PCR+ cases between 2nd dose and 7 days post dose 2: 2 vs 21 cases → VE 90.5% [1]
  - PCR+ cases between Day 14 and 7 days post dose 2: 4 vs 48 cases → VE 91.7%



1. Polack et.al. N Engl J Med. 2020 Dec 31;383(27):2603–15.
2. VRBPAC mRNA-1273 December 17, 2020
3. Saadof et al. NEJM published April 21, 2021 on line ahead of print DOI: 10.1056/NEJMoa2101544
4. Romero-Brufau et al. BMJ 2021;373:n1087 http://dx.doi.org/10.1136/bmj.n1087

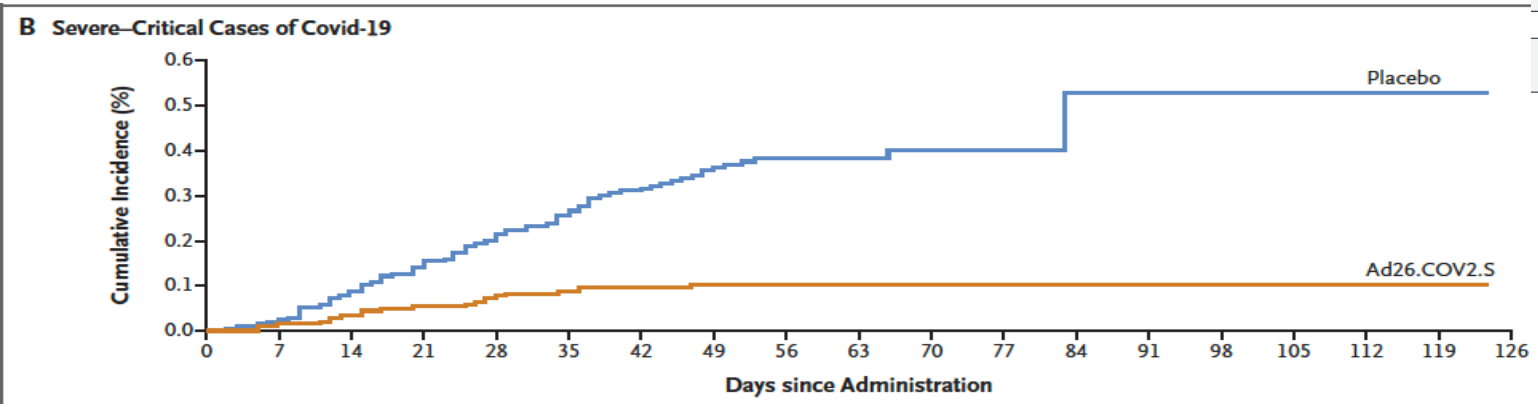
Early Onset of Protection after Single Dose



Study 301: Summary of COVID-19 Cases Within 6 Weeks After Randomization Based on CDC Case Definition[1]

mITT Population – Interim Analysis

	mRNA-1273 N=14,550 n	Placebo N=14,598 n
From randomization to 14 days post 1st dose	5	11
From 14 days post 1st dose to 2nd dose	3	34
From 2nd dose to 14 days post 2nd dose	0	17
Total	8	62



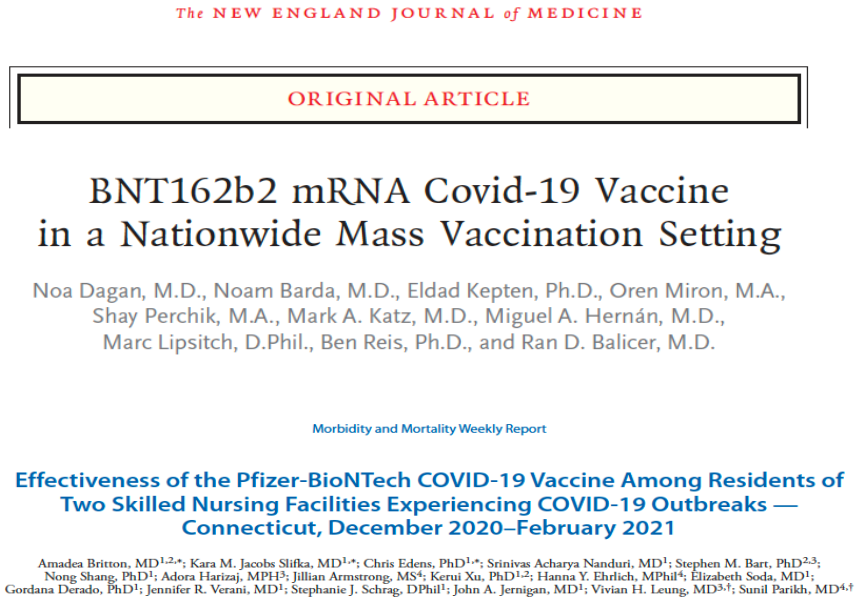
Trained Innate Immunity, Epigenetics, and Covid-19

Alberto Mantovani, M.D., and Mihai G. Netea, M.D.

1. Baden et.al. N Engl J Med 2021;384:403-16.
2. VRBPAC mRNA-1273 December 17, 2020
3. Saadof et al. NEJM published April 21, 2021 on line ahead of print DOI: 10.1056/NEJMoa2101544
4. Mantovani A, Netea MG. Trained Innate Immunity, Epigenetics, and Covid-19. N Engl J Med. 2020 Sep 10;383(11):1078–80

Single dose vaccine effectiveness in unprimed individuals

- Israel: SD BNT162b2 effectiveness 14-20 days post 1st dose [1]
  - 46% for infection,
  - 57% for symptomatic COVID-19,
  - 62% for severe disease
  - 74% for hospitalization
- US: SD BNT162b2 effectiveness in care home residents [2]
  - 60% (without past infection)
  - 63% (with past infection)
- UK: SD vaccine effectiveness in preventing hospitalization
  - 70 – 79 years: 82% (combined ChAdOx-1 & BNT162b2)
  - > 80 years: 80% (combined ChAdOx-1 & BNT162b2)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting

Noa Dagan, M.D., Noam Barda, M.D., Eldad Kepten, Ph.D., Oren Miron, M.A., Shay Perchik, M.A., Mark A. Katz, M.D., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Ben Reis, Ph.D., and Ran D. Balicer, M.D.

Morbidity and Mortality Weekly Report

Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine Among Residents of Two Skilled Nursing Facilities Experiencing COVID-19 Outbreaks — Connecticut, December 2020–February 2021

Amadea Britton, MD[1,2,*]; Kara M. Jacobs Slifka, MD[1,*]; Chris Edens, PhD[1,*]; Srinivas Acharya Nanduri, MD[1]; Stephen M. Bart, PhD[2,3]; Nong Shang, PhD[1]; Adora Harizaj, MPH[3]; Jillian Armstrong, MS[4]; Kerui Xu, PhD[1,2]; Hanna Y. Ehrlich, MPhil[4]; Elizabeth Soda, MD[1]; Gordana Derado, PhD[1]; Jennifer R. Verani, MD[1]; Stephanie J. Schrag, DPhil[1]; John A. Jernigan, MD[1]; Vivian H. Leung, MD[3,†]; Sunil Parikh, MD[4,†]

Effectiveness of BNT162b2 mRNA and ChAdOx1 adenovirus vector COVID-19 vaccines on risk of hospitalisation among older adults in England: an observational study using surveillance data

Sharif A. Ismail[1,2], Tatiana Garcia Vilaplana[1], Suzanne Elgohari[1], Julia Stowe[1,3], Elise Tessier[1], Nick Andrews[1,3], Amoolya Vusirikala[1], Mary Ramsay[1,3], Sema Mandal[1,3*], Jamie Lopez Bernal[1,3,4*]

1. Dagan et.al. N Engl J Med. 2021 Apr 15;384(15):1412–23
2. Britton et al. MMWR Morb Mortal Wkly Rep. 2021 Mar 19;70(11):396–401
3. Ismail preprint

Protective mechanisms, incubation time, and severe disease

- Prospective mechanisms against SARS-CoV-2
  - Neutralizing antibodies prevent against infection.
  - Memory B and T cells are expected to work post exposure thereby moderating disease severity;
    - cell immunity half-life : 3-5 months [1]
    - SARS-CoC-2 induces Long-lived (Quiescent) Spike-specific Bone Marrow Plasma Cells and Memory B Cells [2]
  - Innate trained monocytes may contribute to this mechanism, and in combination with B and T cells protect against severe disease despite waning antibody titres.

- SARS-CoV-2 incubation period up 3-14 days; median 6-7 days; time to hospitalisation (9-12 days),
  - Allows for activation of pre-existing immune responses upon reinfection prior to progression to severe disease
    - 5-7 days for humoral immunity
    - 7-10 days for cellular immunity
  - Can breakthrough SARS-CoV-2 infections following a SD act as a *de facto* booster and avert severe disease?

1. Dan et.al Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science. 2021 Feb 5;371(6529).
2. Turner et.al. SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans. Science. 2021 published on-line, ahead of print, May 24, 2021; https://doi.org/10.1038/s41586-021-03647-4

Summary

- SD effectiveness modelling studies:
  - Modelling suggests that SD saves lives and represents optimum vaccine allocation
  - If SDE exceeds 50% mortality can be reduced by up to 48% compared to 2-dose VE exceeding 90%
- SD in individuals primed by natural infection is an efficacious booster, enhancing humoral and cellular immune responses responses including against VOC and revents reinfection and transmission
- SD in individuals “primed by vaccination”: significantly better if 2nd dose is delayed to 12 weeks after 1st dose
- In unprimed people, high SD efficacy and effectiveness against severe disease / hospitalization
  - No data yet on boostability of SD immune responses by SARS breakthrough infection

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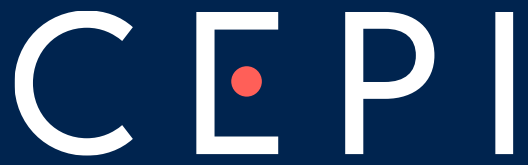
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Panel: Discussion of regulatory pathway for product as boost-only vaccination

Moderated By:

Peter Dull, MD

Deputy Director,

Integrated Clinical Vaccine Development,

Bill & Melinda Gates Foundation (BMGF)

Panel: Discussion of regulatory pathway for product as boost-only vaccination

Panel Members

- **Niranjan Kanesa-thasan – CMO, Icosavax**
- **Daniel Brasseur – Independent Consultant (ex-chair CHMP-PDCO-VWP at EMA)**
- **Marco Cavaleri – EMA**
- **Michel De Wilde – Independent Consultant (ex- Vaccines Research & Development professional)**

Discussion Questions

- *Presuming generating clinical efficacy is not feasible as a booster vaccination, will comparative immune analysis be supported for licensure of booster vaccines?*
- *Would success criteria be necessarily similar to those proposed for primary vaccination comparative analyses?*
- *Will a booster indication be linked to specific licensed SARS-CoV-2 vaccines or is a universal booster indication feasible? Universal boost to a vaccine platform?*
- *What challenges or opportunities for procurement might be envisioned for a "boost-only" product? What features would make such a product interesting to a country?*

ICOSAVAX

COVAX CLINICAL SWAT WORKSHOP - BOOSTER AND MIX & MATCH COVID-19 VACCINE STRATEGIES

Niranjan Kanesa-thasan, CMO

June 3, 2021

- **Icosavax Proposed Approach to Booster Vaccine Indication**
- **Overview of IVX-411, Icosavax RBD VLP candidate vaccine, and preclinical boost data**
- **Icosavax booster clinical program in previously SARS-CoV-2 vaccinated and/or infected subjects**
- **Proposed regulatory strategy for heterologous boost indication**

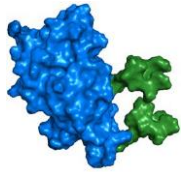
Icosavax Proposed Approach to Booster Vaccine Indication

- Icosavax plans to focus on development of a single-dose booster vaccine able to broadly protect against emerging variant strains in SARS-CoV-2 primed adults, and not intended for primary vaccination of SARS-CoV-2 naïve individuals. The target indication is: 'Booster vaccination against COVID-19 in previously SARS-CoV-2 vaccinated or previously SARS-CoV-2 infected individuals'.

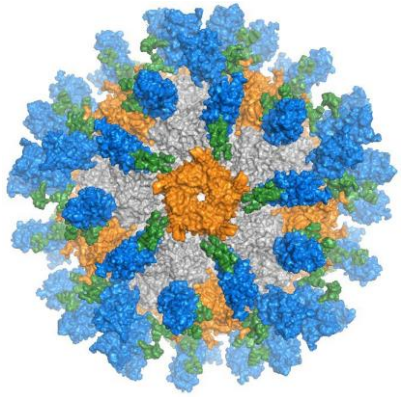
- There is no clear regulatory guidance at this time for licensure of booster "second wave" vaccines which lack placebo-controlled efficacy studies. The MHRA recently approved the potential use of cross-platform (heterologous) immuno-bridging for licensure of Valneva's inactivated vaccine. We intend to use immuno-bridging to support heterologous boosting with IVX-411 in SARS-CoV-2 primed individuals.
    - *Will a booster indication be linked to specific licensed SARS-CoV-2 vaccines or is a universal booster indication feasible across multiple platforms?*
    - *Immunologic endpoints include neutralizing antibody titers to B.1 and variant strains (VoC) using either live virus or pseudovirion standardized assays. Will comparative immune analysis be supported for licensure of booster vaccines?*

IVX-411 utilizes the Icosavax platform 2-component VLP technology to display receptor binding protein (RBD) antigens

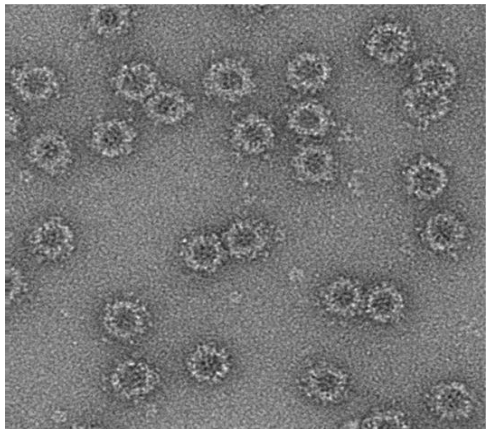
Monomeric RBD protein



Designed RBD VLP Candidate



Assembled RBD VLPs



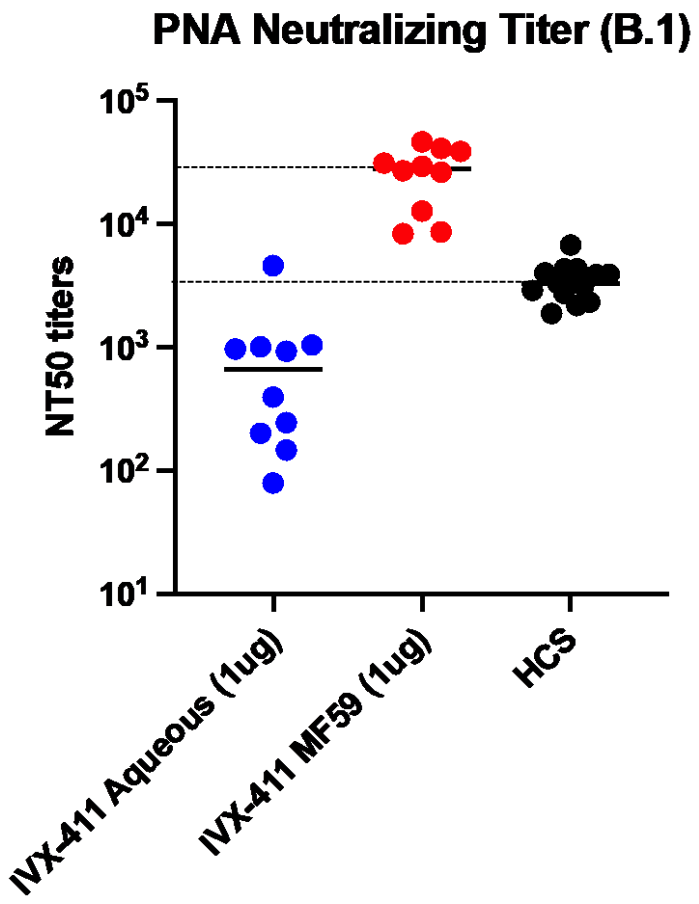
- RBD VLP vaccine candidates are high-yielding and stable
- Electron microscopy and dynamic light scattering indicate monodisperse nanoparticles
- Receptor (ACE2) and mAb (CR3022) binding indicate RBD is antigenically intact

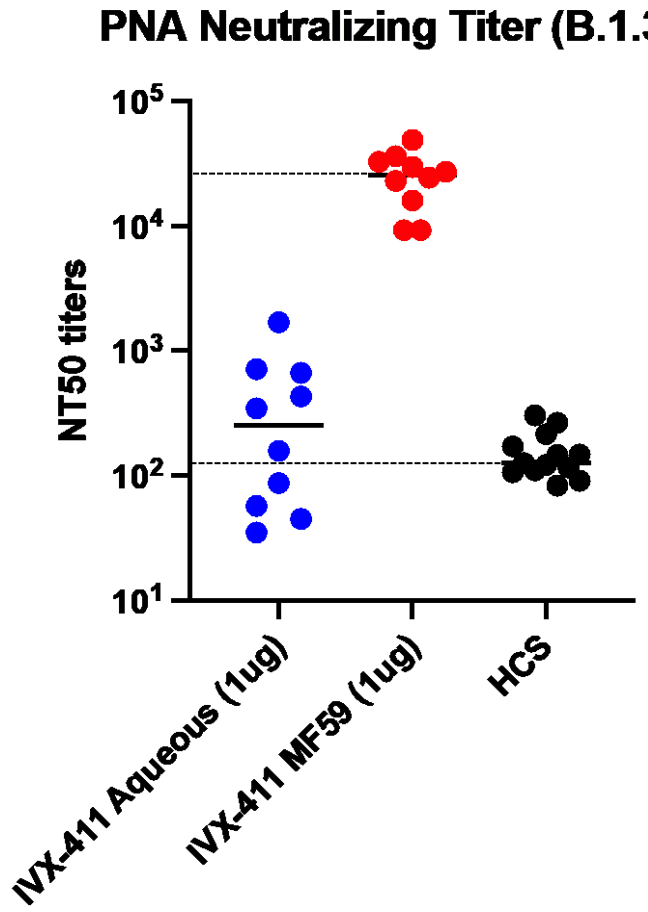
Two-component VLP platform enables use of the RBD as a vaccine antigen:

- Focuses immune response on function domain, reducing generation of binding, non-neutralizing antibodies and concerns about possible vaccine-enhanced disease
- Eliminates concerns about the stability of the spike trimeric antigen
- Increased yield (relative to spike VLPs) to facilitate large-scale manufacturing

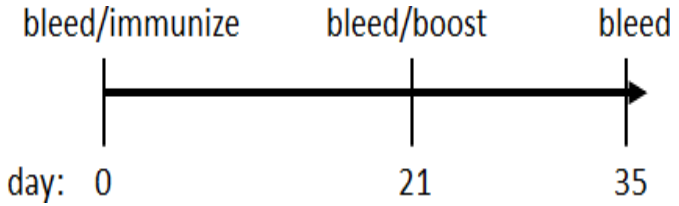
The receptor binding domain antigen appears to have both manufacturing and immunogenicity advantages over the Spike (S) antigen; advantages that should be further enhanced by expression on a VLP

Nonclinical data supports IVX-411 formulated with and without the Seqirus, Inc. proprietary MF59® oil-in-water adjuvant as vaccine against SARS-Cov-2 B.1 and VoC





Sera	B.1 pseudo-neuts	B.1.351 pseudo-neuts	Fold drop (B.1 / B.1.351)
IVX-411 + MF59	~27,000	~26,000	1.0
HCS	3,491	154	22.7



- Pseudovirion neutralizing titer assays (Day 35) performed at Nexelis
- 1872 Nexelis PNA units = 1000 WHO IU

IVX-411 demonstrating breadth of response - sera shows high titers against both B.1 and B.1.351
Human convalescent sera drops ~20X when tested against B.1.351

Icosavax IVX-411 booster clinical program

FIH Phase 1/2 study

Part 1: Primary immunization

- Candidate: IVX-411 (VLP with B.1 RBD antigen)
- Subjects: 84 Adults (18-69 years of age); seronegative
- Regimen: 2 doses on Days 0 and 28
- Formulation: aqueous or MF59-adjuvanted; 3 dose levels assessed

Part 2: Booster in previously vaccinated

- Candidate: IVX-411
- Subjects: 84 Adults (18-69 years of age); SARS-CoV-2 seropositive due to prior vaccination with licensed SARS-CoV-2 vaccines
- Regimen: 2 doses on Days 0 and 28
- Formulation: aqueous or MF59-adjuvanted; 3 dose levels assessed

Phase 2 studies (*designs in-progress*)

Boost previously vaccinated adults

- *Subjects: Up to 150 adults (18 - 75 years of age); Sero+ due to prior SARS-CoV-2 vaccination*
- *Regimen: Likely 1 dose, based on Phase 1/2 interim data*
- *Formulation: Two dose formulations (aqueous and/ or MF59-adjuvanted) down-selected from Phase 1/2*

Boost previously infected adults with IVX-411

- *Candidate: IVX-411*
- *Subjects: ~150 adults (18 - 75 years of age); Sero+ due to prior SARS-CoV-2 infection*
- *Regimen: 1 dose*
- *Formulation:*
  - *Aqueous and/ or MF59-adjuvanted*
  - *Dose levels assessed pending interim data*
- *Location: TBD – population w/ circulating VoC*

Objectives: to demonstrate that heterologous boosting with IVX-411 is tolerable and immunogenic against B.1 and VoC in subjects previously immunized with licensed SARS-CoV-2 vaccines or previously infected with SARS-CoV-2, and to identify the best IVX-411 candidate vaccine (aqueous or MF59-adjuvanted; dose) to move forward to scale-up and pivotal Phase 3 studies.

Regulatory strategy for potential licensure of IVX-411 as a booster vaccine to licensed primary vaccines

1. Engagement under CTN with TGA on early development of IVX-411 as booster vaccines
   - IVX-411 Phase 1/2 study received HREC approval and TGA acknowledgement, with FSI in early June
   - Aqueous and MF59-adjuvanted formulations in healthy SARS-CoV-2 naïve subjects and in subjects following primary immunization with licensed SARS-CoV-2 vaccines [adenoviral vectored, mRNA, and potentially protein subunit vaccines]
2. Lack of regulatory guidance on heterologous (cross-platform) boosting; therefore seek 'rapid scientific advice' (SA) from National Regulatory Authorities (NRAs) to obtain initial feedback on a heterologous boost indication
   - Will engage NRAs prior to Phase 1/2 interim data
   - Adequacy of proposed CMC, nonclinical and clinical development plan, including endpoints, to support MAA approval
3. Recent launch of the UK COV-Boost study (N=2886) validates our heterologous boost approach and will provide data on both homologous and heterologous boosting that could further inform regulatory approach for IVX-411
   - Evaluates immune response to single booster dose of 7 different B.1 vaccines in fully immunized (AZ or Pfizer) subjects
   - Precedent for comparative responses to homologous (AZ or Pfizer) or heterologous (other platforms) boost vs control
   - Potential for pivotal non-inferiority trial of homologous boost (eg AZ x 3 doses) vs IVX-411 boost after initial course (AZ x 2)

Plans to develop and refine regulatory strategy for heterologous boosting indication with early feedback from NRAs including support for immuno-bridging data from boosted individuals

Regulatory pathway for product as boost only vaccination

Daniel Brasseur

CEPI Consultant, Former CHMP-PDCO-VWP chair at EMA

Historical precedence for boost only regimen

- dTpa diphtheria Tetanus pertussis - boost/catch up
  - *Same antigens but different amounts to limit reactogenicity in adults*
- Monovalent oral polio - to achieve adequate response
  - *Same antigen to boost an insufficient (absent?) priming*
- Influenza vaccines - across seasons
  - *Same antigen to achieve cross protection if antigenic drift (not shift)*
  - *Same antigen using different routes (IM-nasal)*
- Hib-PRP conjugate vaccines
  - *Same antigen but formulated with different conjugates (Diphtheria carrier protein for booster only)*

Considerations / Questions

- ❑ Will a booster indication be linked to a specific licensed vaccine or a universal booster indication for use across multiple platforms?
- ❑ Will comparative immune analysis be supported for licensure of booster vaccines?

  - Can only compare formulations targeting the same antigen (e.g. Spike)
  - Can only compare the same type of immune response (ideally leveraging an acceptable CoP)

  - *Guideline on Clinical Evaluation of Vaccine**
    - Evaluation of cross-reactive antibody (e.g. antibody elicited by an antigen that cross-reacts with antigen[s] of one or more other species or subtypes within a species);
    - Evaluation of cross-priming (e.g. the ability of one antigen to induce immune memory to [an]other antigen[s]);
  - Inferring potential clinical protection to a broader 'spectrum' than the one having demonstrated clinical efficacy has been done (Pneumo, HPV…)

*EMA Guidance clinical evaluation, New Vaccines 2018: https://www.ema.europa.eu/en/clinical-evaluation-new-vaccines

Conclusions

- The concept of immune cross-reaction can convincingly lead to the conclusion of clinical cross-protection
- Implying the use, the demonstration of the same mechanism of action (type of immune response elicited)
- Not necessarily being achieved using the same platform (no matter the brand)
- But a similar magnitude of response (bridging) compared to a clinically demonstrated effective vaccine

Overview of Heterologous Vaccine Strategies

Jakob Cramer, MD

Head of Clinical Development
CEPI

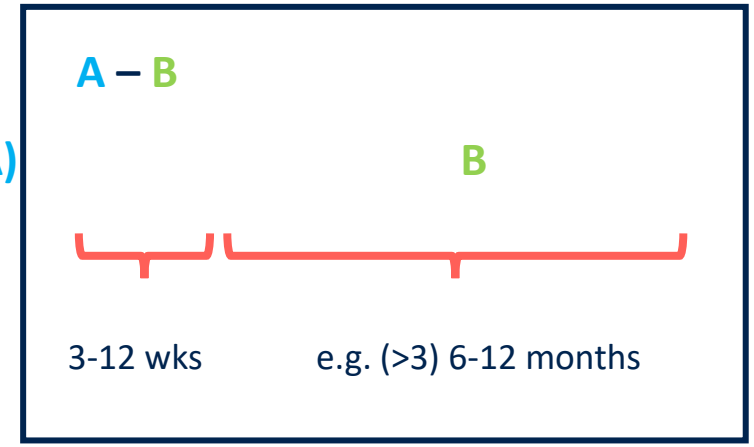
‘Mix & Match’
Overview of Heterologous COVID-19 Vaccine Strategies

June 3rd, 2021

“Mix & Match”

Concepts:

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



Aim:

- **Improve immune response***
  a) Breadth of IR
  b) Peak Ab response, duration, …
- **Address practical / operational aspects** (‘interchangeability’ of vaccines)
- **Adjuvant- / antigen-saving** strategy?
- **Anti-vector immunity**?
- Improve **tolerability** (of the 2nd dose)?

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

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

Points for Consideration: Specific Aspects

- **Heterologous priming:**
  - Trials initiated within the next months will not generate data before Oct / Nov
  - Interval (following local requirements): relevant from operational, timeline and immunologic point of view (currently 4-12 weeks)
  - Vaccine combinations:
    - Some studies covering HIC vaccines underway
    - Data on combinations relevant in LMICs
- **Heterologous boosting** (single dose): strategic thoughts (variant-adapted vaccines becoming available…)
  - Heterologous boosting against original variant
  - Heterologous priming against new variant
    - → original antigenic sin?
- **Both**
  - Improving the immune response: Which vaccines to select (1st / 2nd dose)?
  - Interchangeability: landscape analysis of most frequently used vaccines (by regions / LMICs)

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Points for Consideration: Operational Aspects

Heterologous vaccination regimen: Added complexity through differences in terms of….

- Shelf-life
- Shipment / storage conditions
- Contraindications
- Order of vaccination (A → B or also B → A)?

CEPI and BMGF funding M&M studies (heterologous priming and boosting) with vaccine combinations relevant in LMICs.

Registration of Zabdeno®, Mvabea® Vaccination for Ebola

The first licensed heterologous multidose vaccine regimen

Melinda, *Tree of Life*
Melinda's artwork reflects her journey living with HIV.

3 June 2021

Janssen Infectious Diseases & Vaccines
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

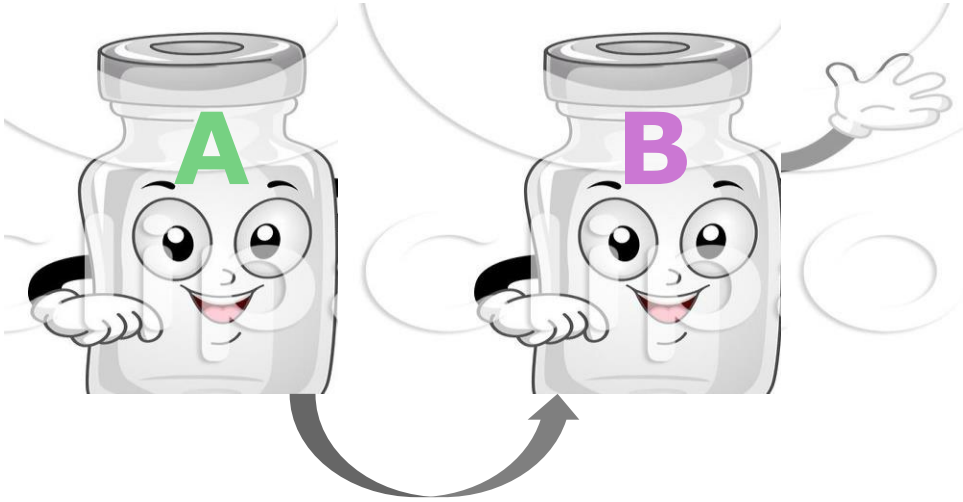
Rationale for heterologous vaccination regimens

- The goal of vaccination is to generate potent and long-term protection against diseases
- Heterologous vaccine regimens deliver antigens through different vaccine components or vector types at sequential time points. These regimens are developed as an avenue to prevent infectious diseases where protection and/or longer-lasting immunity has not been successfully achieved with other approaches
  - Among different vaccine modalities, heterologous strategies have been shown to enhance cellular and also humoral immunity in several animal models
  - These strategies have provided promising results in terms of safety and immunogenicity clinical trials. In many cases, heterologous regimens have been shown to be more immunogenic than homologous strategies
  - Several factors including selection of antigen, type of vector, delivery route, dose, adjuvant, boosting regimen, the order of vector injection, and the intervals between different vaccinations influence the outcome of heterologous immunization approaches
- Evidence is building on heterologous vaccination regarding improved immune responses regarding breadth, strength, persistence and functionality
- Potential application in a range of situations including public health emergencies, and use in special populations, such as the elderly and infants

Kardani, Vaccine 2016

Perceived potential implementation challenges for heterologous multidose vaccination

- **Logistics** - Transportation, storage and handling of each component of the regimen to ensure adequate supply and absence of error
- Population **acceptance** and **compliance** with both or more doses, in a specific order and interval
- Monitoring of the regimen, including the need for precise **tracking** of individuals, dates and doses administered
- **Regulatory** requirements complex



- Demonstrated for Ebola that obstacles can be overcome also under challenging conditions
- Some of those aspects don't apply for Covid Mix & Match vaccination scenarios

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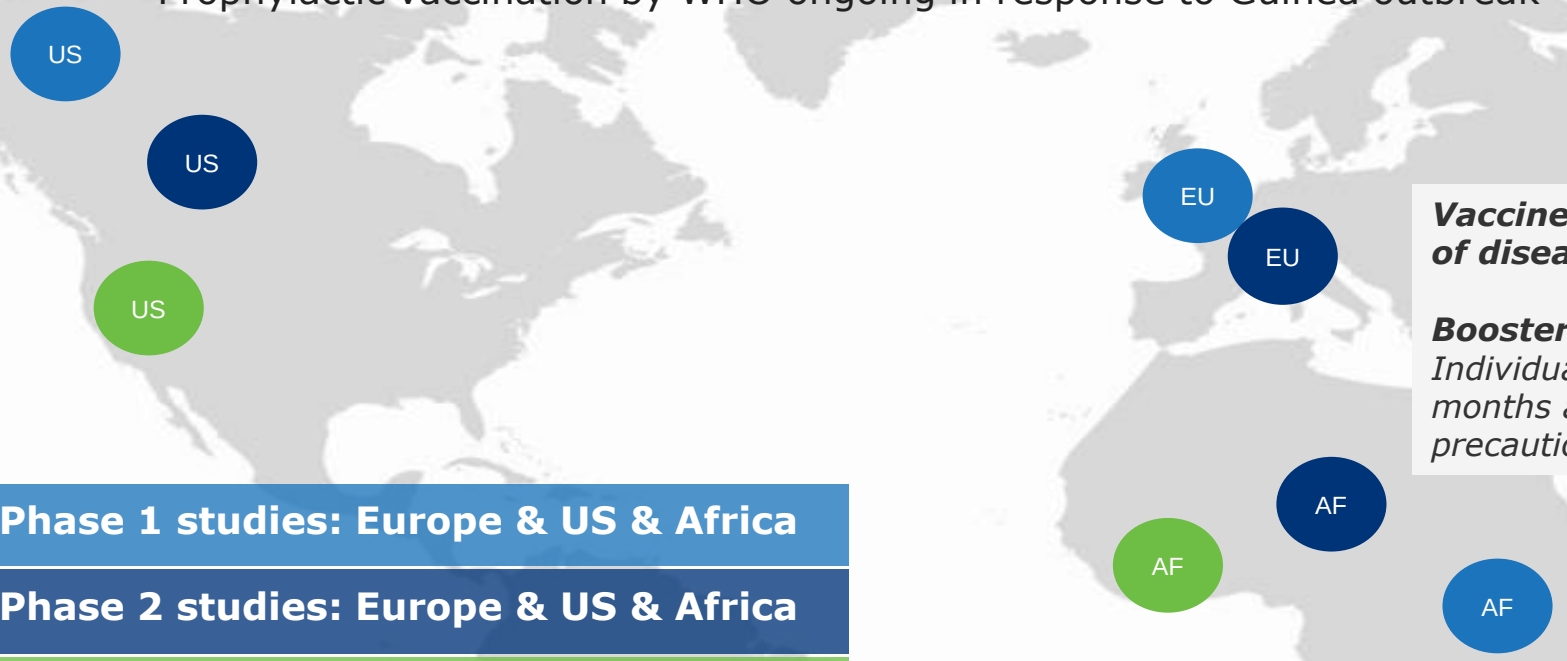
Ebola: broad development program with >230k vaccinated individuals

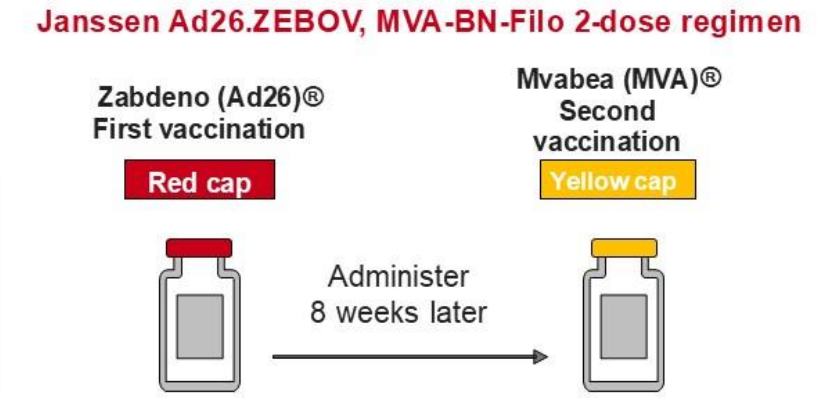
- **14 clinical trials sponsored by Janssen** (Phase 1/2/3) in Europe, US and Africa
- Participants include [**adults** (18-50yrs), **older adults** (>50-70yrs), **HIV+ adults**, **children** (1-17yrs)], **infants** (4-11 months)
- Janssen-sponsored phase 1 studies completed, *partner studies* ongoing
- 6 Phase 2 & 3 studies completed; 9 Phase 2&3 ongoing
- **Phase 3 study in pregnant women ongoing in Rwanda**
- Vaccination campaign ongoing in Rwanda
- Prophylactic vaccination by WHO ongoing in response to Guinea outbreak



Phase 1 studies: Europe & US & Africa

Phase 2 studies: Europe & US & Africa

Phase 3 studies: Africa & US



Storage and distribution **compatible with existing sub-Saharan African cold chain**.

Vaccine regimen for active immunization for prevention of disease caused by Ebola virus in individuals ≥ 1year

Booster vaccination with Zabdeno
Individuals who previously completed the 2-dose regimen >4 months ago, at imminent risk of exposure to Ebola virus as a precautionary measure

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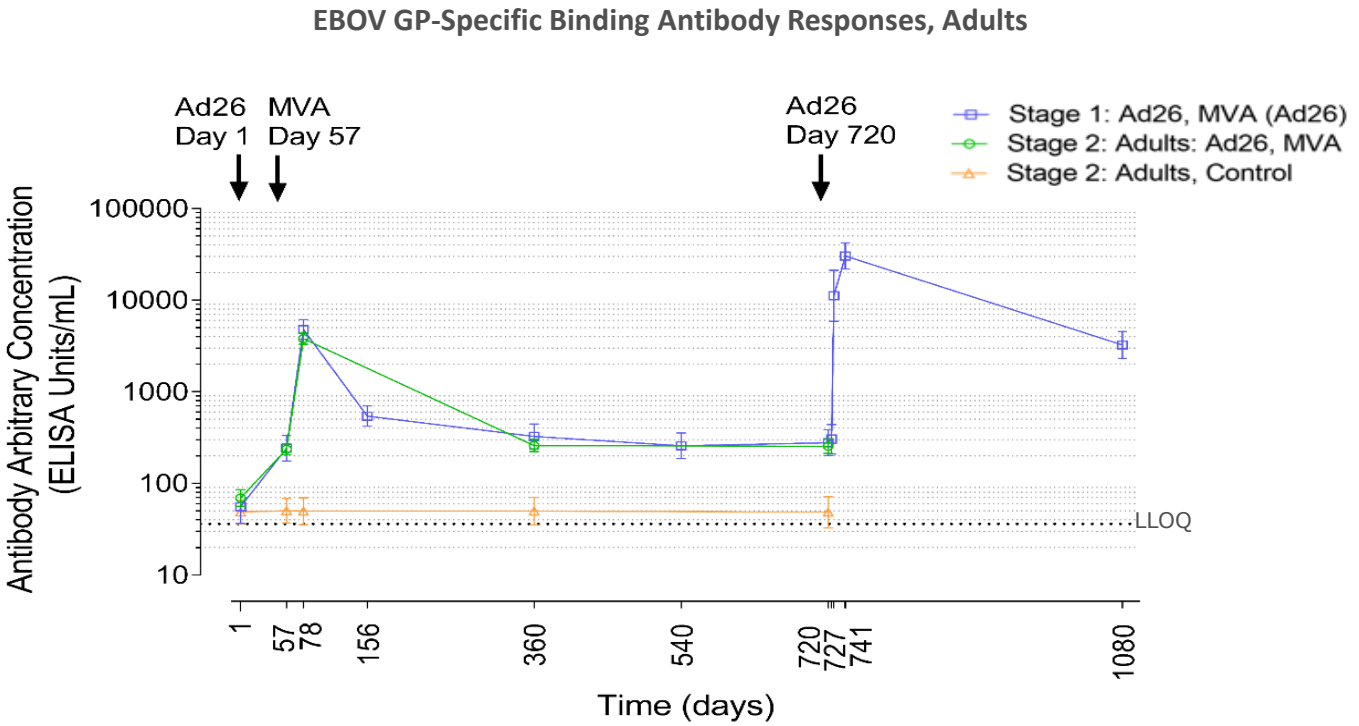
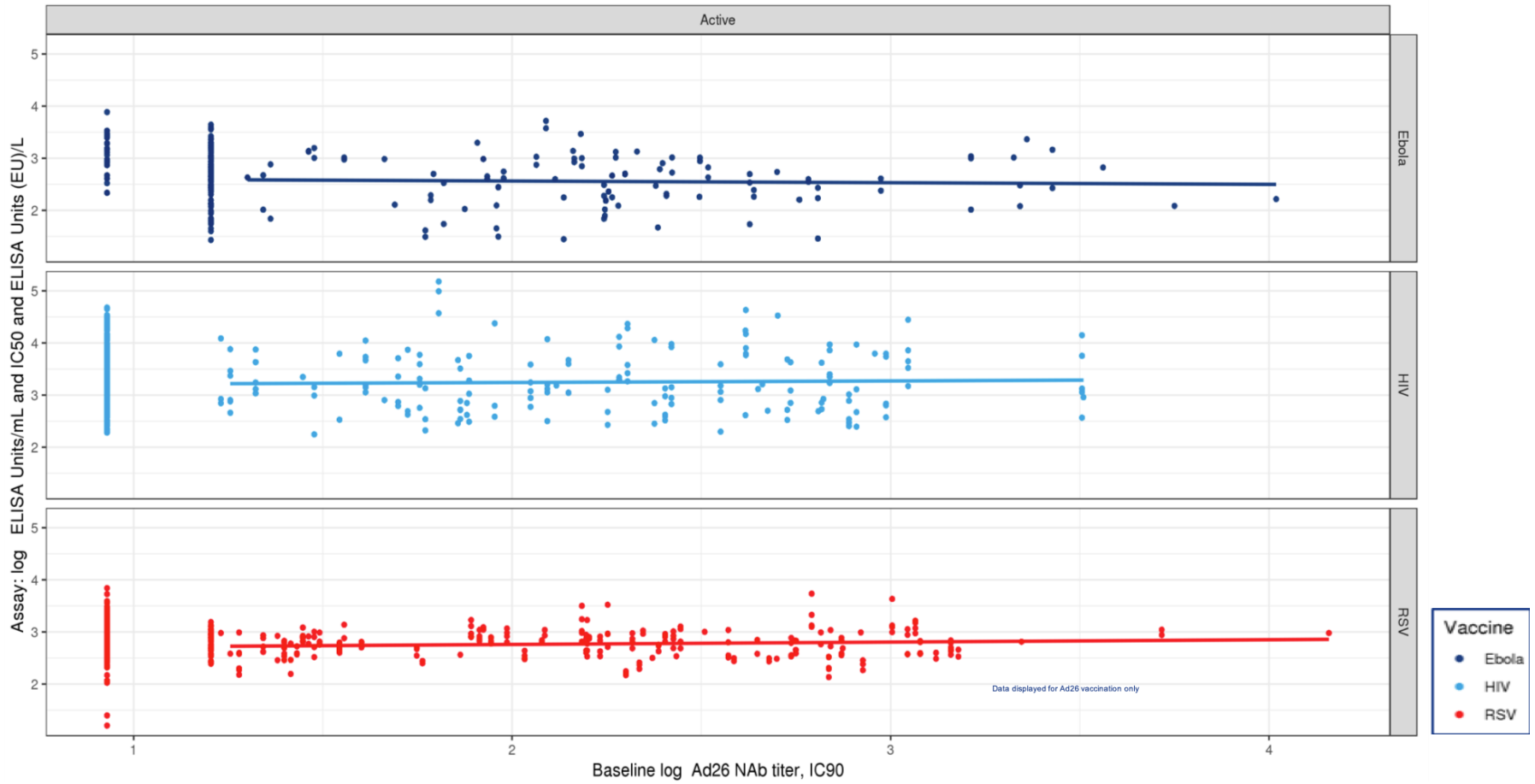
Anamnestic Response to Ad26.ZEBOV Booster Vaccination in Adults (EBL3001)



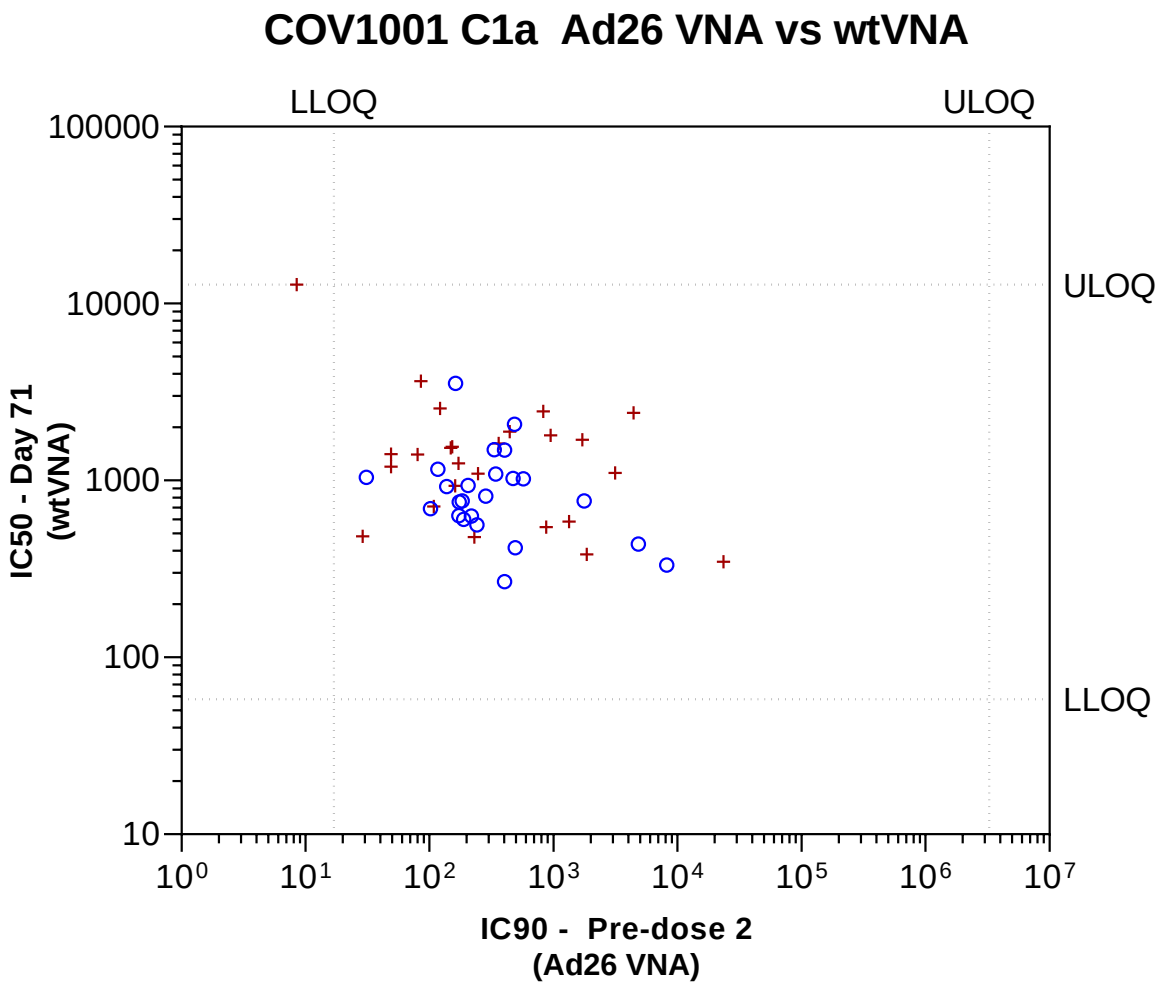
- **Strong anamnestic antibody response** within **7 days** post booster (± 40-fold increase)
- 21 days post-booster dose, antibody levels ± 10-fold greater than post-dose 2 levels
- In EBL3001 study, Ad26.ZEBOV, MVA-BN-Filo 56-day interval induces **humoral memory**
- Post-booster antibodies **persist at higher level** (10-fold difference)
- Similar results observed in studies EBL1002 (USA) and EBL2002 (KE, BF, C'I, UG)
- NHP are protected against Ebola virus challenge 3 days after the booster dose

No impact of pre-existing Ad26 immunity on vaccine humoral immunogenicity



Current analysis shows no impact of **naturally occurring** Ad26 neutralizing antibodies (Ebola, HIV, RSV)

Anti-Ad26 immunity does not hamper the response to a second dose of the same vaccine



Vaccine sequence

- Ad26.COV2.S 5e10 vp, Ad26.COV2.S 5e10 vp (n=24)
- Ad26.COV2.S 5e11 vp, Ad26.COV2.S 5e11 vp (n=25)

n = 49

Spearman correlation = -0.249

Adapted from Sadoff & Le Gars, NEJM, 2021

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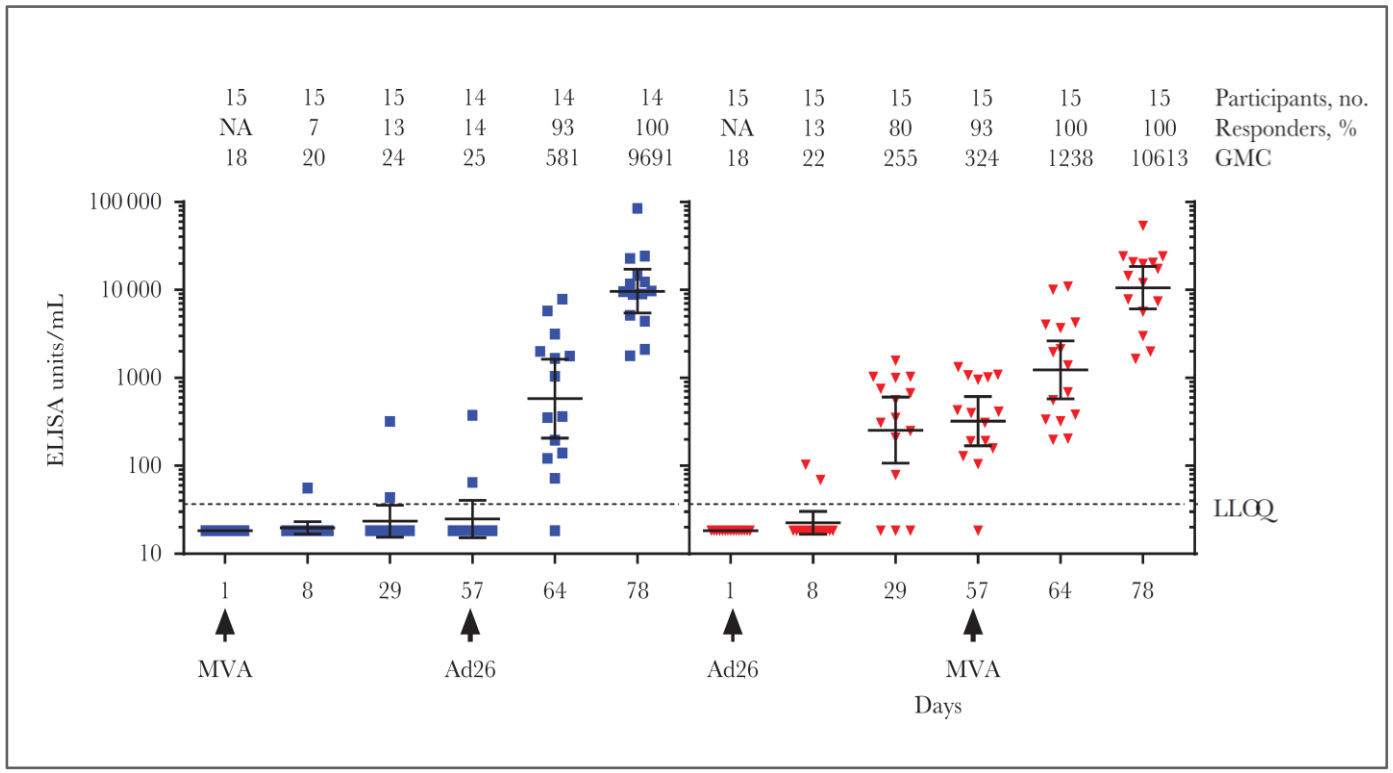
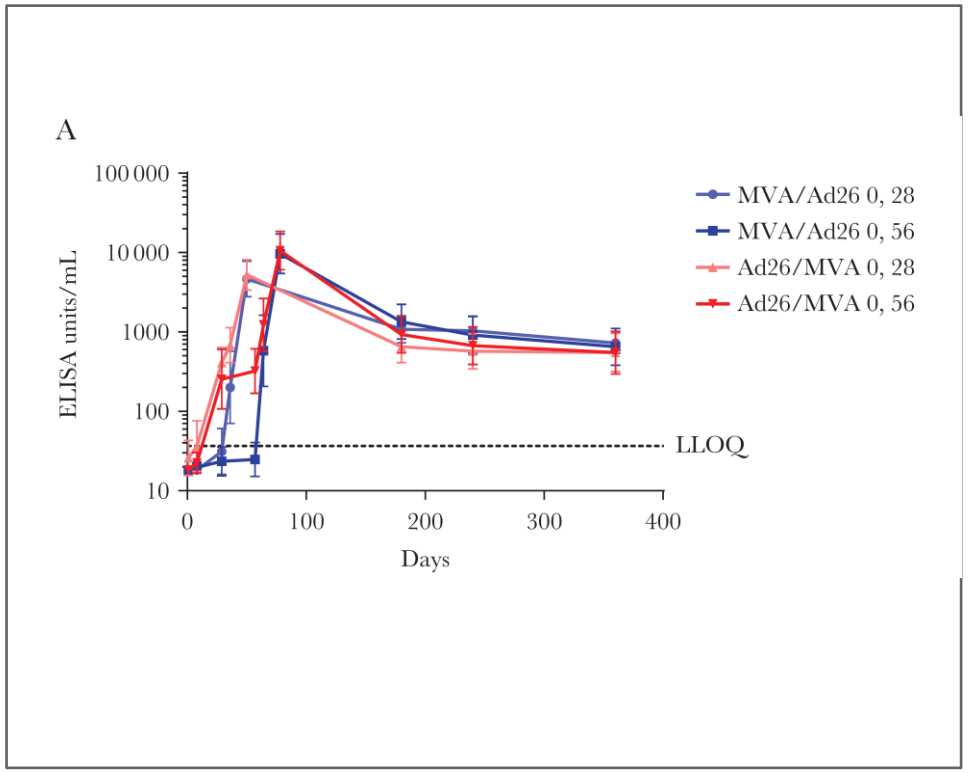
Sequence of different vaccines matters!!

EBL1004, Tanzania/Uganda*





- Earlier onset of antibody response after Ad26.ZEBOV as first dose
  - Different survival rates observed in NHP Ebola virus challenge model after various sequences of vaccine components
  - CDC recommends administration of pneumococcal vaccine PCV13 before use of PPSV23^
- Magnitudes of persisting antibody response induced by regimens with different sequence and interval in the same range

*Anywaine et al., JID 2019

^ Kobayashi et al., MMWR Morb Mortal Wkly Rep 2015

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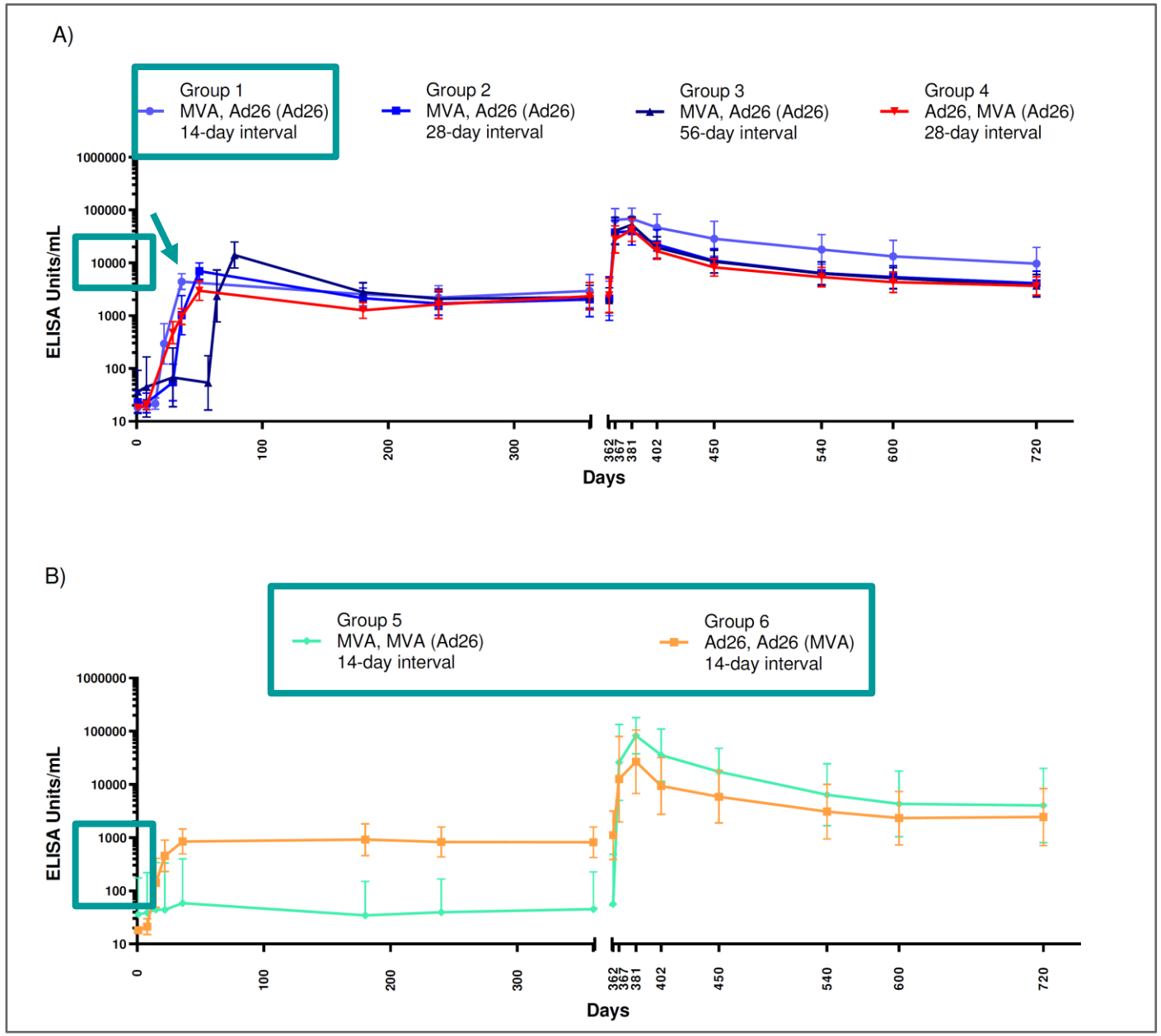
Heterologous regimen superior to homologous strategy

EBL1002, US



- Heterologous regimen is inducing higher antibody response magnitude in comparison to both homologous regimens

Goldstein et al., JID 2020

Implementation feasible under challenging conditions in SSA:

DRC and Rwanda: Completion rates superior to those reported in large-scale campaign reports**

Study Number Countries	Population (Actual N Active)	Overall % receiving Dose 2	Deployment context
EBL3008 *DRC, North Kivu* (before COVID interruption, 2 March 2020)	Healthy individuals (20,340) Adults 63% Pregnant women 4% 5-17y 25% 1-5y 8%	**78% received Dose 2** **(75% received dose within window)**	Rollout in a war zone Community engagement not started from beginning Mobile messaging
UMURINZI *Rwanda* (before COVID interruption, 31 Mar 2020)	Healthy individuals (32,190) Adults 72.4% 12-17 yrs 12.6% 6-11 yrs 9.6% 2-5 yrs 5.6%	**99% received Dose 2*** **(97% within window)**	Community engagement Mobile messaging Iris scanning

- **Current status** (June 2021)
- **Rwanda**: Campaign ongoing, 900-1,000 vaccinees per day; >200,000 doses of Zabdeno® administered, >170,000 received Mvabea®, 84% within window despite Covid interruption
- **DRC**: Study ended in Feb 2021, despite Covid impact vaccine regimen completion rate of 75% by study's end

Conclusions: **Even in uniquely challenging circumstances, it is feasible to administer a 2-dose vaccine regimen to adults in LMIC**. Community engagement is critical to success

*As verified by iris scanning

**Gallagher KE, Kadokura E, Eckert LO, et al. Factors influencing completion of multi-dose vaccine schedules in adolescents: a systematic review. BMC Public Health. 2016;16:172. Published 2016 Feb 19. doi:10.1186/s12889-016-2845-z

Janssen Infectious Diseases & Vaccines
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Lessons learned for future heterologous multidose vaccination implementation in deprived settings

Iris scans and fingerprints	• Feasible & well accepted to accurately record who has received which dose to avoid errors
Mobile phone reminders	• Can be developed based on an open-source technology, • Are feasible & well accepted
These technical solutions…	• **Scalable** in low resource settings, • Can be fully transferred to local staff for sustainable local ownership and data sharing/interface with other vaccination management system is possible

EBODAC technology using the biometric ID system and MOTECH demonstrated to offer the ability to capture & monitor the vaccination status in resource-poor communities in clinical study as well as large-scale deployment context

Janssen Infectious Diseases & Vaccines
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Regulatory requirements

2 MAA's were requested by EMA for licensure of the Ebola vaccine:

- EU regulation does not allow for 1 MAA if not co-formulated or co-packed
- Co-packaging only allowed in exceptional situations (indispensable public health reasons)
- Parts of MAA (including most Clinical and Non-Clinical documents) with identical elements
- **Each label** containing relevant **safety and efficacy information for the full regimen**

➢ **Labels of different Covid vaccines could be updated with relevant information for Mix & Match boosting**

COVID-19 Vaccines Mix & Match

Overview of pre-clinical and clinical mix & match activities

03 June 2021

Paul Oloo

Heterologous Priming Pre-Clinical Studies

Platforms	Vaccines	Animal	Dose Interval *(in days)*	Location	Status
VV- WIV VV- Protein WIV- Protein VV-mRNA	Cansino → Sinopharm Cansino → Zhifei ZF2001 Sinopharm → Zhifei ZF2001 Cansino → Walvax	Mice	21	China[1]	Published
Protein - Protein	S-protein → RBD protein	Mice and Macaques	21	Australia[2]	Published
VV-saRNA	AZ → saRNA	Mice	28	UK[3]	Published

VV-Viral Vector; saRNA-Self Amplifying mRNA; WIV-Whole Inactivated Virus

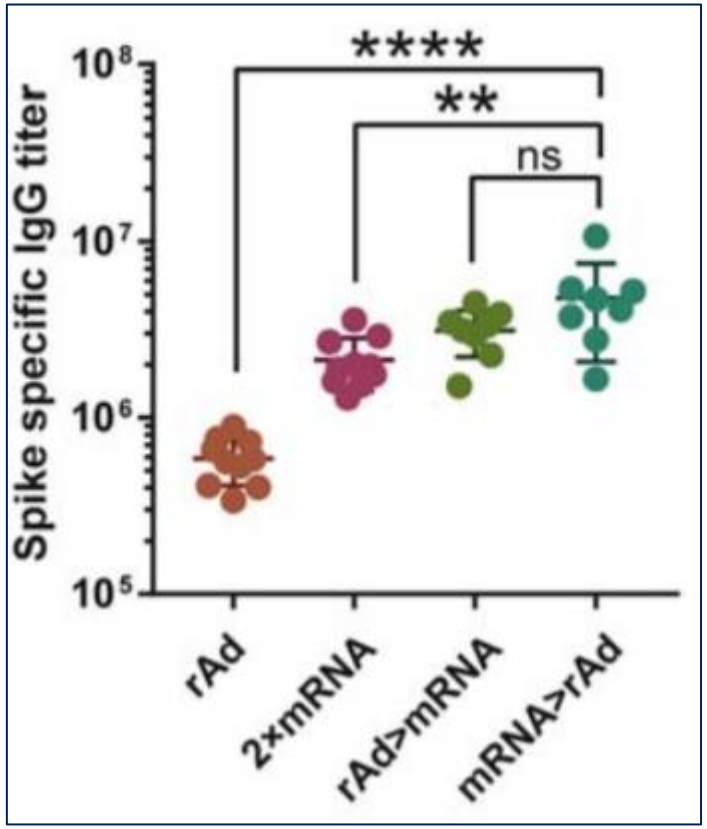
1. He et al. Emerging Microbes & Infections 2021, Vol 10
2. Tan et al. Nature Communications, 2021
3. Spencer et al. Nature Communications, 2021

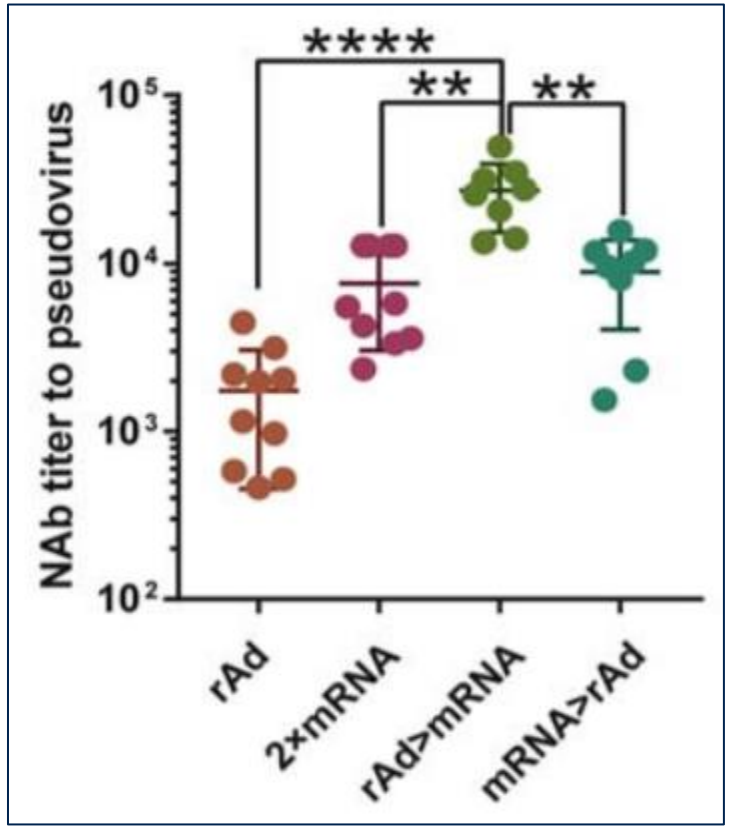
Heterologous Priming Pre-Clinical data

- Binding Ab induced by mRNA >rAd comparable to that induced by the rAd >mRNA1
- rAd (Cansino Ad5) prime, followed by mRNA (ArCoVax) boost induced higher NAb response than the 2 × mRNA vaccine

Key Messages

- Enhanced NAb titres attributed to the heterologous prime-boost strategy
- Order of heterologous priming possibly matters (animal model)





CEPI

1. He et al. Emerging Microbes & Infections 2021, Vol 10

Heterologous Priming Studies

Platforms	Vaccines	Dose Interval *(in weeks)*	Location	Status	Trial number
VV-mRNA	AZ → Pfizer *(CombivacS study)*	4	Spain	Ongoing	NCT04860739
VV-mRNA	AZ → Pfizer Pfizer → AZ *(Com-CoV study)*	4 & 12	UK	Ongoing	ISRCTN69254139
VV-mRNA	AZ → Pfizer	10-12	Germany	Ongoing	EudraCT_2021-001512-28
VV-mRNA VV-Protein mRNA-mRNA mRNA-Protein	AZ/AZ→ D3 (Moderna/Novavax) Pfizer/Pfizer → D3 (Moderna/Novavax) *(Com-CoV2 study)*	8-12	UK	Recruiting	ISRCTN27841311
VV-mRNA	AZ → Pfizer	12	Austria	Recruiting	NCT04907331
VV-SAM	Gritstone ChAdV68 → saRNA	4 & 8-12	USA	Recruiting	NCT04776317
VV-VV	AZ → GamAd26	4	Belarus Russia	Not yet recruiting	NCT04684446
VV-VV	AZ → GamAd26	4	Azerbaijan	Not yet recruiting	NCT04686773
VV-VV	AZ → GamAd26	4	UAE	Not yet recruiting	NCT04760730
VV-Protein	Cansino Ad5 → Zhifei Zf2001	4 & 8	China	Not yet recruiting	NCT04833101
mRNA-mRNA	Pfizer → Moderna	4-6	France	Not yet recruiting	NCT04900467
WIV-VV	Sinovac → Cansino Ad 5	4-12	China	Not yet recruiting	NCT04892459
mRNA-mRNA VV-mRNA	Moderna → Pfizer Pfizer → Moderna AZ → Moderna AZ → Pfizer *(MOSAIC study)*	4	Canada	Not yet recruiting	NCT04894435

VV-Viral Vector; saRNA-Self Amplifying mRNA

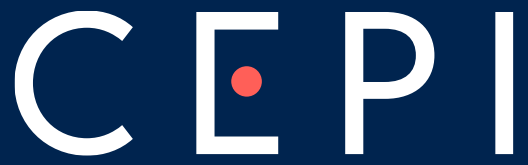
Heterologous Boosting Studies

Platforms	Vaccines	Dose Interval *(in months)*	Location	Status	Trial number
mRNA-VV mRNA-Protein VV-Protein mRNA- WIV mRNA –VV2 VV-mRNA VV-WIV VV-VV2 mRNA-mRNA2 mRNA-mRNA3 VV-mRNA2 VV-mRNA 3	Pfizer/Pfizer → AZ Pfizer/Pfizer → Novavax (full & ½ dose) AZ/AZ → Novavax (full & ½ dose) Pfizer/Pfizer → Valneva (full & ½ dose) Pfizer/Pfizer → Janssen AZ/AZ → Pfizer AZ/AZ → Valneva (full & ½ dose) AZ/AZ → Janssen Pfizer/Pfizer → Moderna Pfizer/Pfizer → Curevac (full & ½ dose) AZ/AZ → Moderna AZ/AZ → Curevac (full & ½ dose) *(CoV-Boost study)*	>3 after 2nd dose	UK	Recruiting	
VV-mRNA mRNA-mRNA2 mRNA-variant /platform boost/VV/Protein	Janssen (1 dose) → Moderna Pfizer/Pfizer → Moderna Moderna → Homologous/heterologous variant or platform boost or Janssen /Novavax	3- 5	USA (NIAID)	Not yet recruiting	NCT04889209
WIV-VV	Sinovac/Sinovac → D3 (Cansino Ad 5)	3-6	China	Not yet recruiting	NCT04892459

CEPI

Conclusion

- Animal data do not always translate to humans; similar trials in humans needed for further evidence
- Durability of immune responses may vary depending on the specific combination
- Challenge figuring out vaccines to combine, and which should be the prime and the boost
- Trials covering HIC vaccines are underway
- Relevant combinations for LMICs need to be assessed
- CEPI and BMGF to fund separate heterologous priming and heterologous boosting studies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Emerging data and lessons being learnt from NISEC heterologous prime/boost studies

(Com-COV, Com-COV2, Cov-Boost)

Matthew Snape
Director of NISEC
Associate Professor in Paediatrics and Vaccinology
Oxford Vaccine Group

Comparing COVID-19 Vaccine Schedule Combinations

Evaluating COVID-19 vaccine boosters

COM-COV

Comparing COVID-19 Vaccine Schedule Combinations

oxford vaccine group

- Randomised Controlled Trial, single blind
- Funded by Vaccine Task Force
- Non-inferiority of immunogenicity of heterologous with homologous prime/boost schedules

1st dose	2nd dose
ChAdOx1 nCOV-19 (AZ)	ChAdOx1 nCOV-19 (AZ)
ChAdOx1 nCOV-19 (AZ)	BNT162b2 (P)
BNT162b2 (P)	BNT162b2 (P)
BNT162b2 (P)	ChAdOx1 nCOV-19 (AZ)

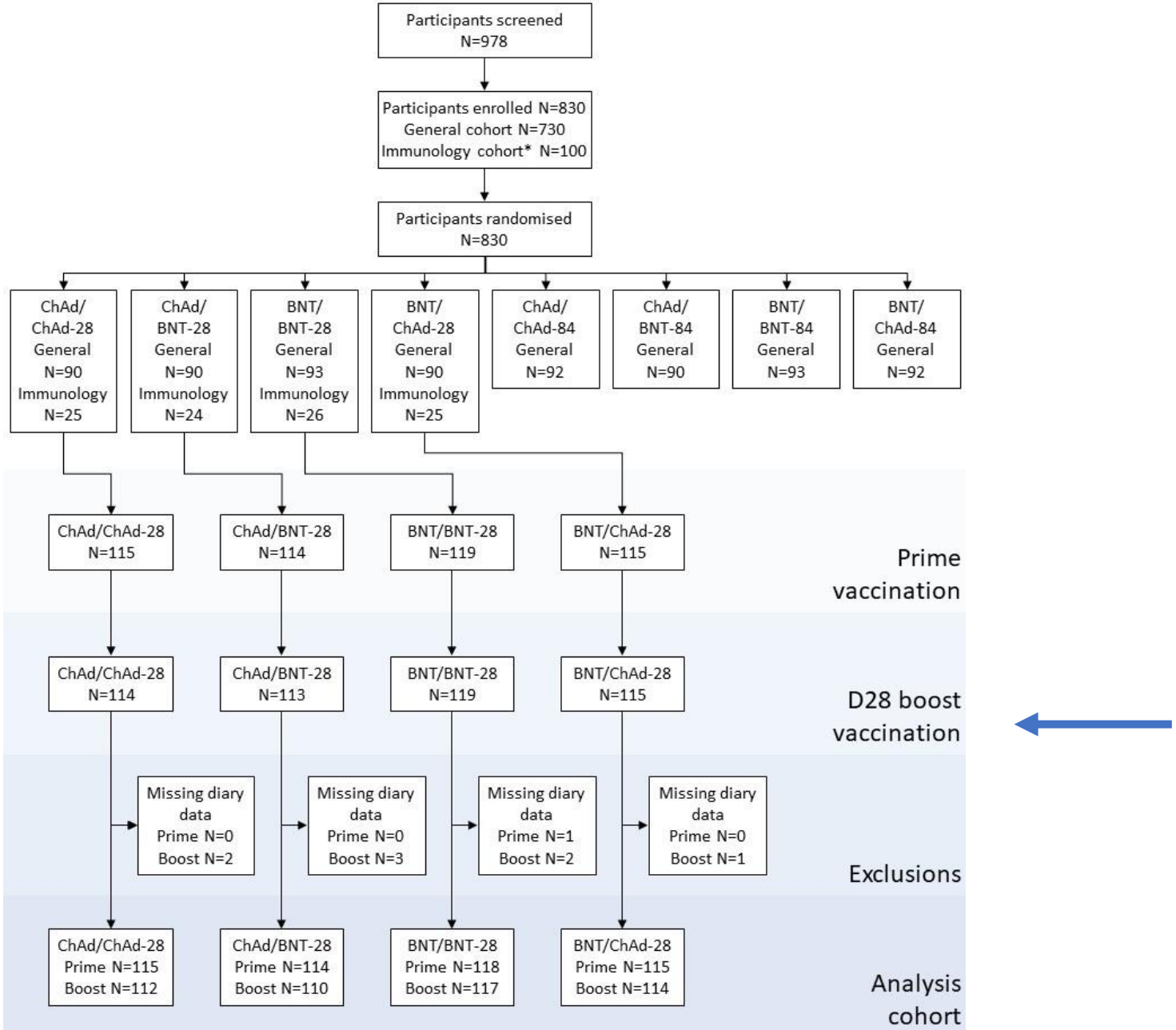
- Brief to increase flexibility and resilience of vaccine delivery in the UK
- Incorporates both 4 and 12 week dosing interval

COM-COV

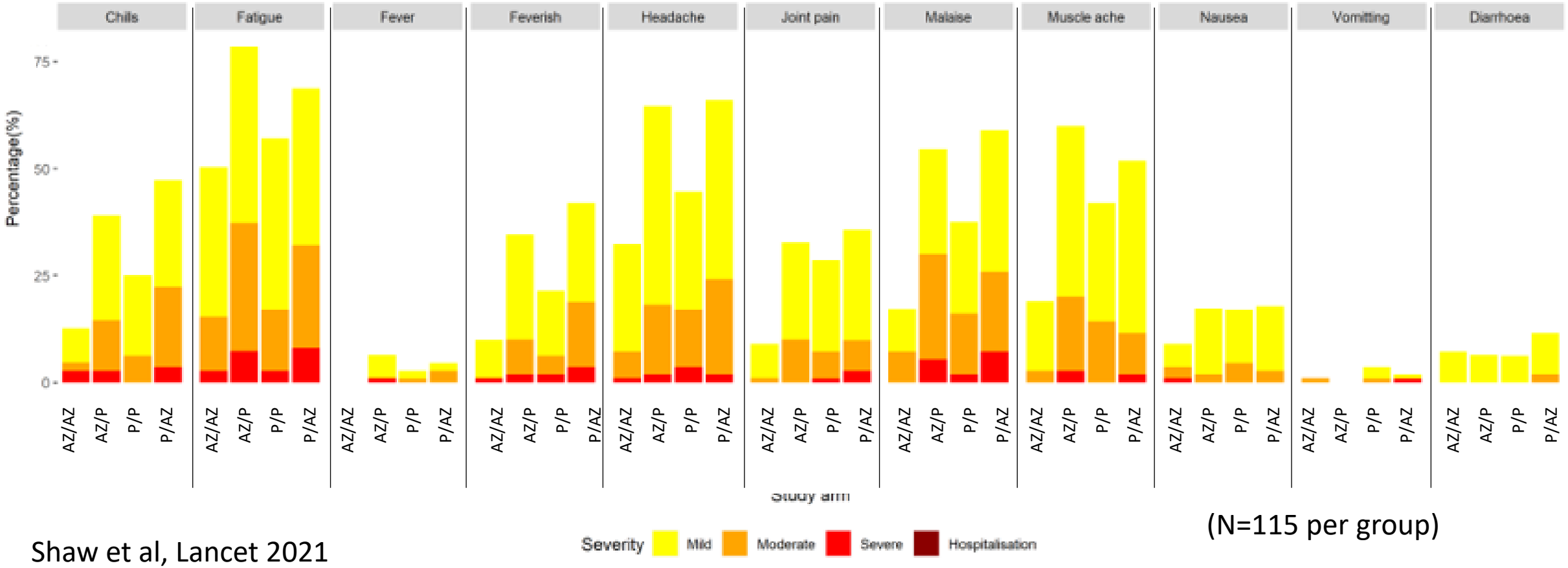
Comparing COVID-19 Vaccine Schedule Combinations

Male/Female	56/44
BAME	23%
1 or more comorbidity	55%

Age range	
50-55	39.2%
56-60	34.2%
61-65	20.5%
66-70	5.9%
71-75	0.2%



Solicited systemic reactions after boost vaccination



(N=115 per group)

Shaw et al, Lancet 2021

Immunogenicity Assays:

COM-COV
Comparing COVID-19 Vaccine Schedule Combinations

Assay	Laboratory/Assay
Anti-spike IgG	Nexelis
Neutralising antibodies against SARS-CoV-2	Porton Down
Anti-nucleocapsid immunoglobulins	Roche (Porton Down)
Pseudo virion 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

COM-COV

Comparing COVID-19 Vaccine Schedule Combinations

‘COM-COV 2’

New study

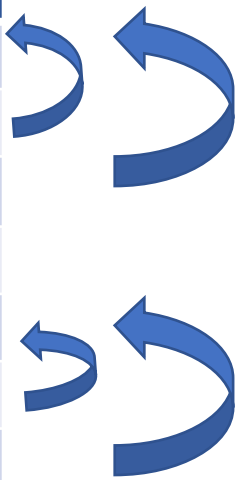
Enrols those

- 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

Blood tests for main immune readout – May/June

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	



Lessons being learnt (1)

Study design

- Designed as non-inferiority for immunogenicity ('no worse than usual schedule')
  - Emerging data suggesting robust immune response in mixed schedules…if confirmed in RCT then suggests need to switch to superiority, e.g. against variants of interest ('better than usual schedule?')

- Interval
  - Balance between matching local policy, and providing data as quickly as possible…ideally include arms with both

- Randomisation at 1st, 2nd dose
  - Randomisation at baseline facilitates comparisons between whole schedules (prime and boost), without confounders of differences for populations receiving different prime
  - Randomisation at 2nd dose
    - Still allows comparisons between homologous vs heterologous schedules
    - More rapid data
  - Choice may be influenced by the proportion of general population already immunized with one dose
- Single blind
  - Has been important to ensure credibility of reactogenicity results

Lessons being learnt (2)

Age group

- 50 years and over recruited to obtain data in those at greatest risk of disease
- Does not include those at greatest risk of vaccine reactions…therefore may be better to include
  - > 60 years
  - < 40 years
- May be determined by what cohort suits study design

Reactogenicity

- Increased systemic reactogenicity in adenovirus/mRNA schedule, leading to addition of
  - Randomisation to advise for routine vs prophylactic paracetamol to see if tolerability can be improved
  - Questionnaire about impact on daily life
    - Time off work
    - Need for extra care
    - Seeking medical attention
    - Potential to also ask about ‘acceptability’

Given emerging data suggesting increased immunogenicity for Adenovirus followed by RNA, compared with AD/AD, then consider testing ‘half dose’ RNA boost arms

- Potentially dose sparing
- ? Maintain immunogenicity benefits while reducing reactogenicity?

Lessons being learnt (3)

Immunogenicity

- Capacity issues for VNA are real
- Pragmatic solution of binding ELISA, with confirmation of trend by live VNA on subset, appears to be practical solution

- Standard deviation on Nexelis ELISA at day 28 post immunisation in adults 50 years and older is 0.3 to 0.4

Looking ahead….

COV-BOOST
Evaluating COVID-19 vaccine boosters

- Study to inform optimal use of '3rd dose' booster, if required
- Enrols those primed with 2 doses of
  - Pfizer/Pfizer
  - AZ/AZ
- > 3 months after 2nd dose enrolled and randomized to receive one of 7 potential booster doses

COV-BOOST
Evaluating COVID-19 vaccine boosters

Stage 1 SITE GROUP A

6 sites

Enrol 111 per arm, 888 in total per site group.

Allows 25% baseline seropositive/exclusion

90% power to show 1.75 fold higher GMC over control group at 1 month post vaccine

	V1	V2	V3	V4
	0	1 month	approx. 3 months	12 months
Time Line	June '21	July '21	Sept - Oct '21	Aug '22
	Blood	Blood	If routine boosting recommended = unblind control group only* Blood test	Blood
Pfizer/ Pfizer (2nd dose at least 84 days prior to enrolment)	ChAdOx		Continue in study	
	Novavax			
	Novavax half dose			
	MenACWY		Offer booster dose as per NHS recommendations, with blood test before and 1 month after (acts as a randomised group to late rather than early boost)	
ChAdOx/ ChAdOx (2nd dose at least 84 days prior to enrolment)	ChAdOx		Continue in study	
	Novavax			
	Novavax half dose			
	MenACWY		Offer booster dose as per NHS recommendations, with blood test before and after (acts as a randomised group to late rather than early boost)	

* Unblinding and Booster doses could also be offered to any group with sub-optimal response to booster

COV-BOOST
Evaluating COVID-19 vaccine boosters

Stage 1 SITE GROUP B

6 sites

Enrol 111 per arm, 1110 in total per site group.

Allows 25% baseline seropositive/exclusion

90% power to show 1.75 fold higher GMC over control group at 1 month post vaccine

	V1	V2	V3	V4	V5
	0	1 month	approx. 3 months	6 months	12 months
Time Line	June '21	July '21	Sept - Oct '21	Dec '21	Aug '22
	Blood	Blood	If routine boosting recommended = unblind control group only* Blood test	Blood	Blood
Pfizer/ Pfizer (2nd dose at least 84 days prior to enrolment)	Pfizer		Continue in study		
	Valneeva				
	Valneeva half dose				
	Janssen				
	MenACWY		Offer booster dose as per NHS recommendations, with blood test before and 1 month after (acts as a randomised group to late rather than early boost)		
ChAdOx/ ChAdOx (2nd dose at least 84 days prior to enrolment)	Pfizer		Continue in study		
	Valneeva				
	Valneeva half dose				
	Janssen				
	MenACWY		Offer booster dose as per NHS recommendations, with blood test before and after (acts as a randomised group to late rather than early boost)		

* Unblinding and Booster doses could also be offered to any group with sub-optimal response to booster

COV-BOOST
Evaluating COVID-19 vaccine boosters

Stage 1 SITE GROUP C

6 sites

Enrol 111 per arm, 888 in total per site group.

Allows 25% baseline seropositive/exclusion

90% power to show 1.75 fold higher GMC over control group at 1 month post vaccine

	V1	V2	V3	V4	V5
	0	1 month	approx. 3 months	6 months	12 months
Time Line	June '21	July '21	Sept - Oct '21	Dec '21	Aug '22
	Blood	Blood	If routine boosting recommended = unblind control group only* Blood test	Blood	Blood
Pfizer/ Pfizer (2nd dose at least 84 days prior to enrolment)	Moderna		Continue in study		
	Curevac				
	Curevac half dose				
	MenACWY		Offer booster dose as per NHS recommendations, with blood test before and 1 month after (acts as a randomised group to late rather than early boost)		
ChAdOx/ ChAdOx (2nd dose at least 84 days prior to enrolment)	Moderna		Continue in study		
	Curevac				
	Curevac half dose				
	MenACWY		Offer booster dose as per NHS recommendations, with blood test before and after (acts as a randomised group to late rather than early boost)		

* Unblinding and Booster doses could also be offered to any group with sub-optimal response to booster

EICOV / COVIM Studies

Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1-nCoV19 and BNT162b2: a prospective cohort study

David Hillus, Tatjana Schwarz, Pinkus Tober-Lau, Hana Hastor, Charlotte Thibeault, Stefanie Kasper, Elisa T Helbig, Lena J Lippert, Patricia Tscheak, Marie Luisa Schmidt, Johanna Riege, Andr Solarek, Christof von Kalle, Chantip Dang-Heine, Piotr Kopankiewicz, Norbert Suttorp, Christian Drosten, Harald Bias, Joachim Seybold, COVIM/EICOV Study Group, Florian Kurth, Victor M Corman, Leif Erik Sander

doi: https://doi.org/10.1101/2021.05.19.21257334

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Leif Erik Sander

06/03/2021

Study design and baseline characteristics

Vaccine group	BNT/BNT[1] homologous boost		ChAdOx[2]/BNT heterologous boost	
Prime to boost interval , median days (IQR)	21 (21-21)		71 (70-73)	
Prime and boost vaccination	1st BNT, n=179	1st BNT / 2nd BNT n=189	1st ChAdOx n=151	1st ChAdOx / 2nd BNT n=110
Reactogenicity data, n	178	159	148	99
Age, median years (IQR)	34 (29-44)	34 (29-43)	35 (28-47)	37 (29-51)
Female, n (%)	98 (55.0%)	87 (54.7%)	101 (68.2%)	77 (77.8%)
Serology data measured, n	94	101	57	61
Δvaccination to sampling, median days (IQR)	21 (21-21)	28 (27-30.5)	26 (22-28)	21 (I21-21)
Age, median years (IQR)	35 (30.75-48)	35 (30.5-47.5)	38 (31-52.5)	38 (30.5-51.5)
Female, n (%)	66 (70.2%)	73 (72.3%)	46 (80.7%)	47 (77.1%)

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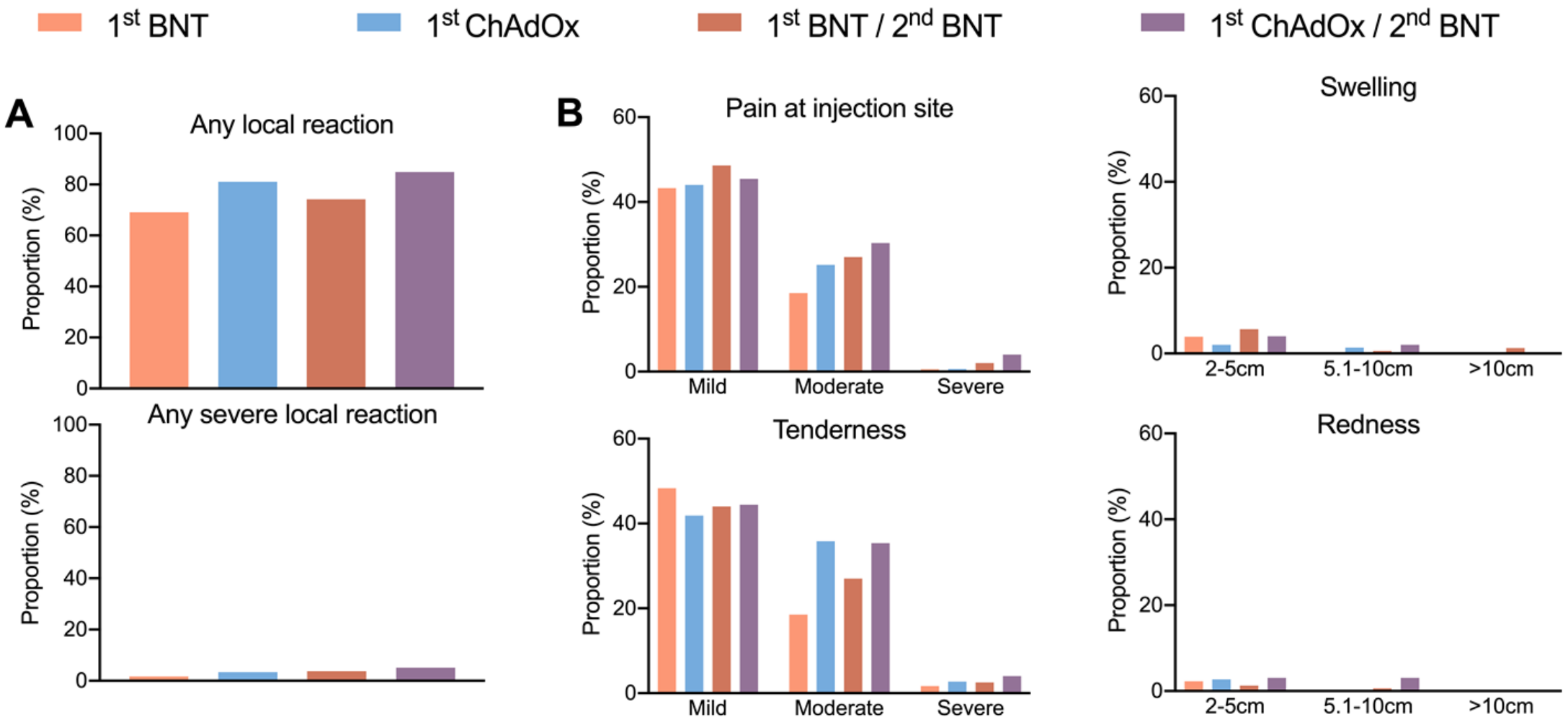
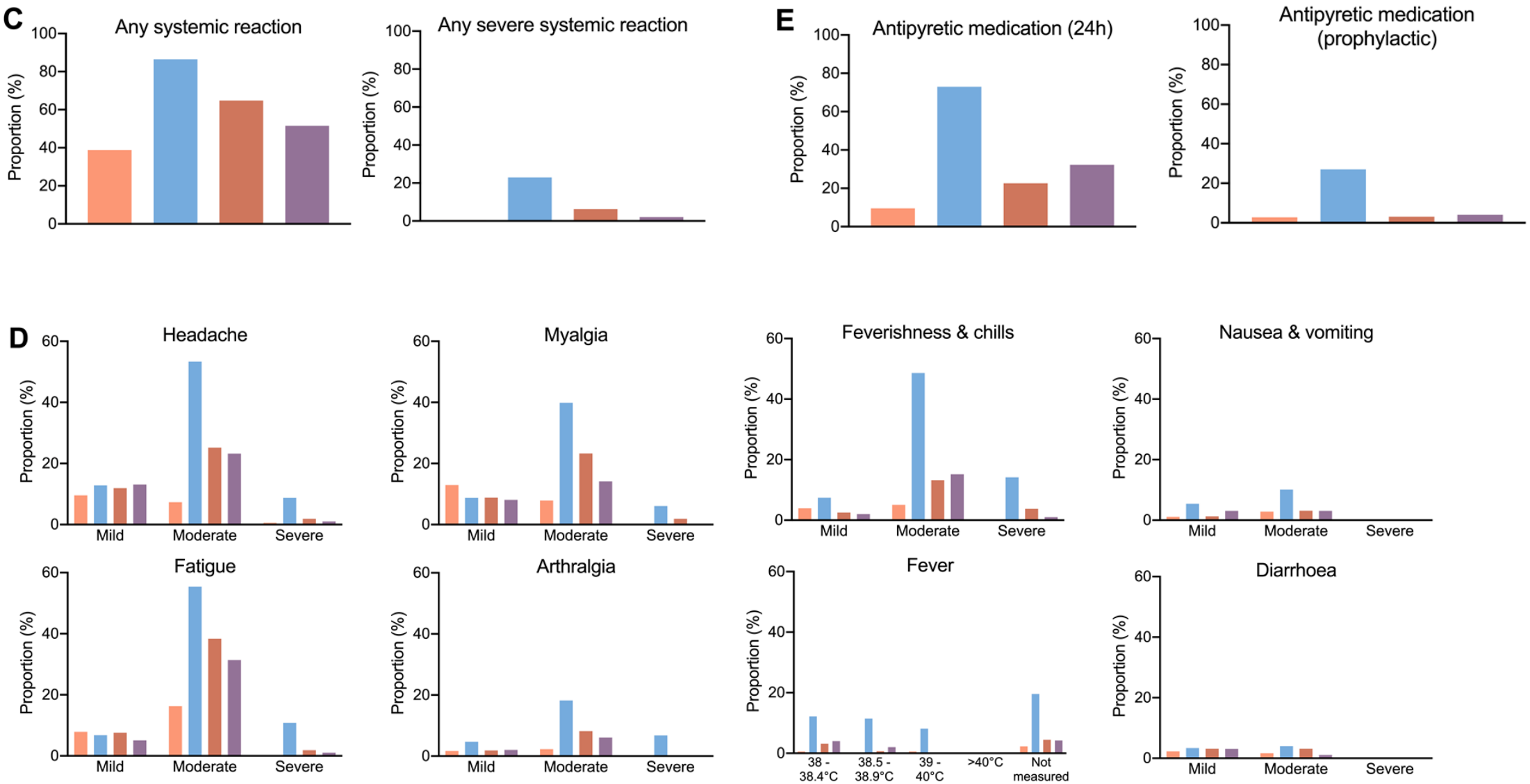
https://www.medrxiv.org/content/10.1101/2021.05.19.21257334v2

Reactogenicity: Local reactions



https://www.medrxiv.org/content/10.1101/2021.05.19.21257334v2

Reactogenicity: Systemic reactions



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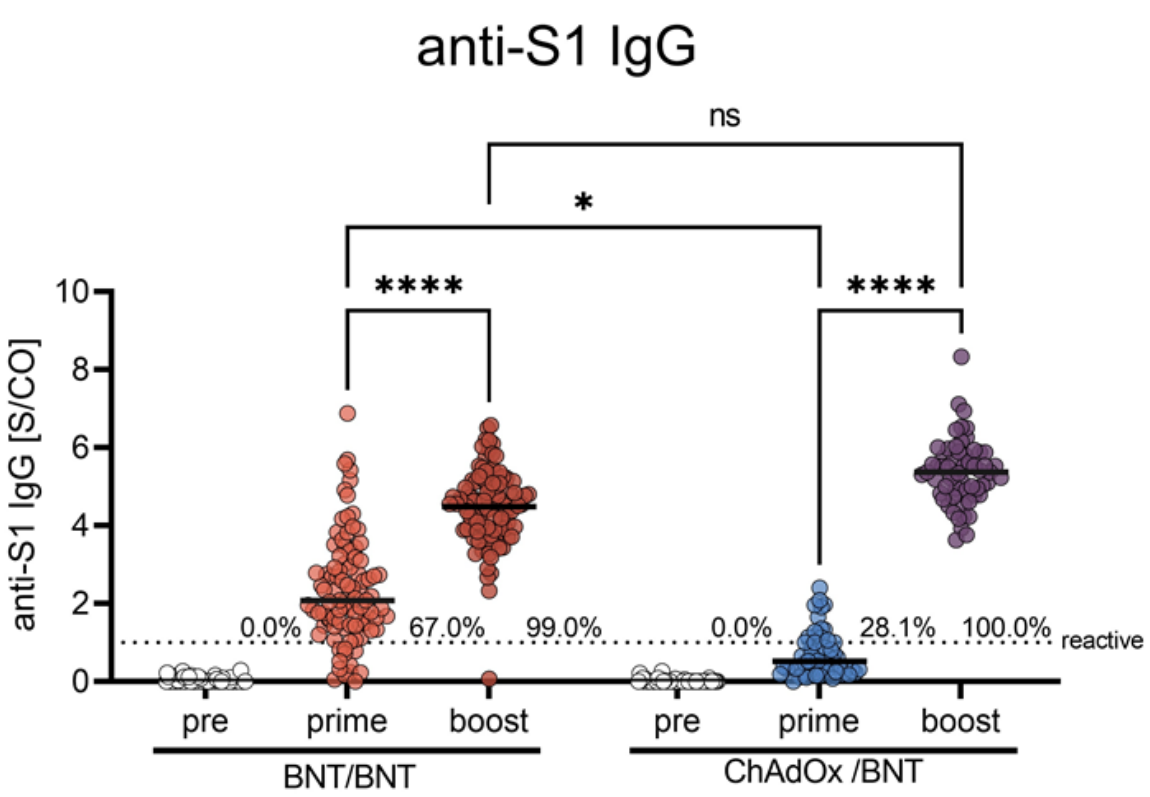
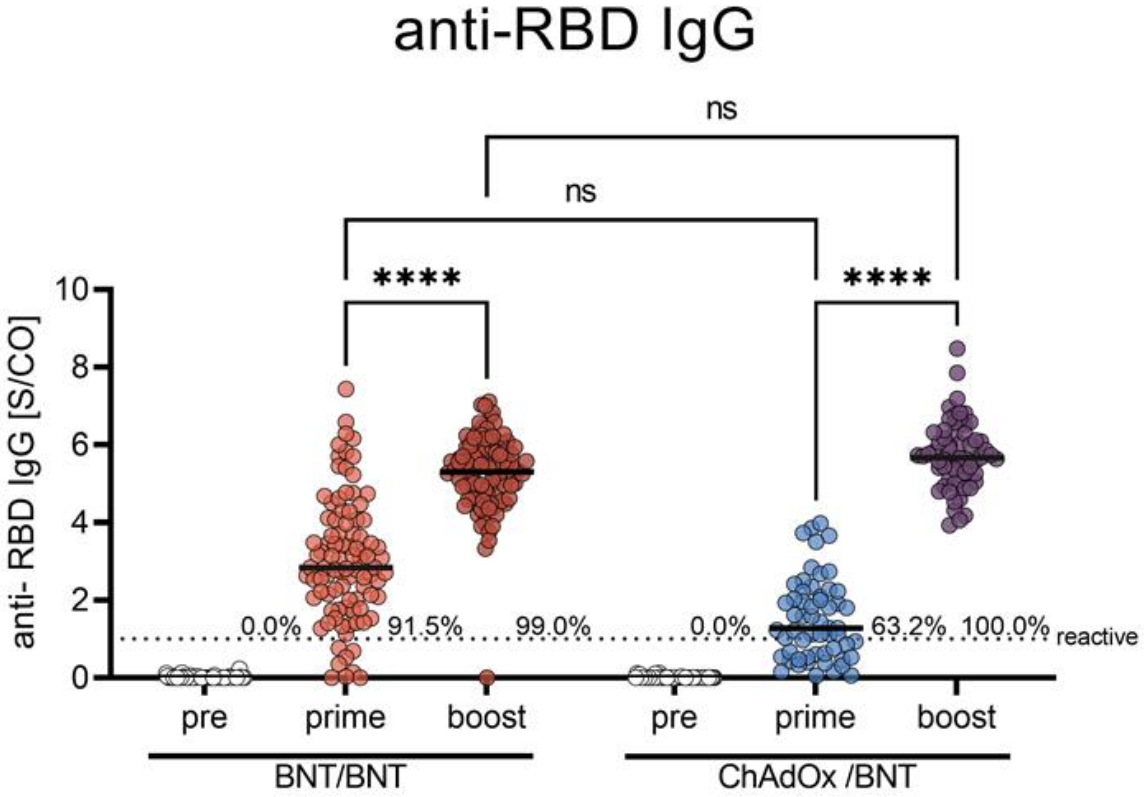
Immunogenicity: Serum antibody response to SARS-CoV-2 S1 and RBD





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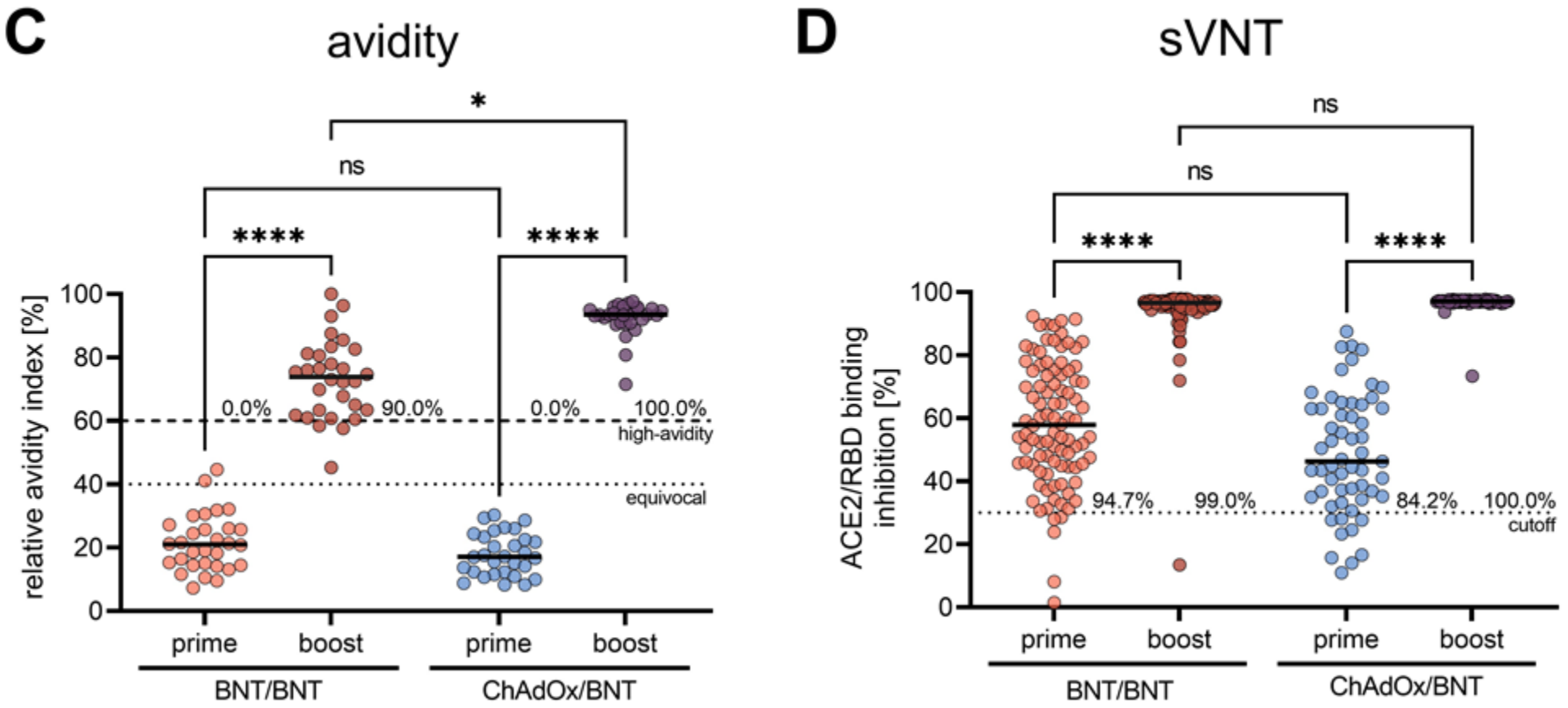
Immunogenicity: Serum IgG avidity and surrogate neutralisation capacity



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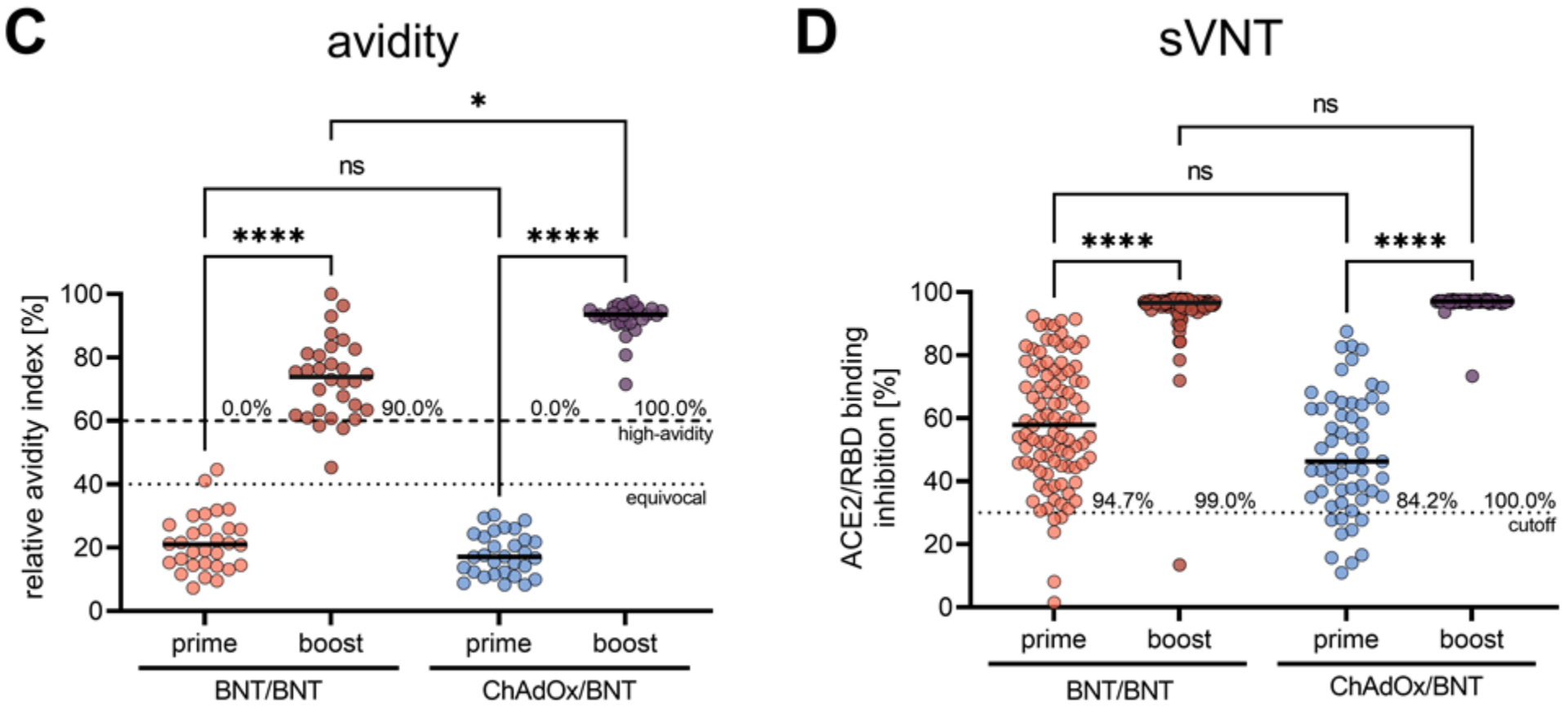
https://www.medrxiv.org/content/10.1101/2021.05.19.21257334v2

Immunogenicity: Serum IgG avidity and surrogate neutralisation capacity



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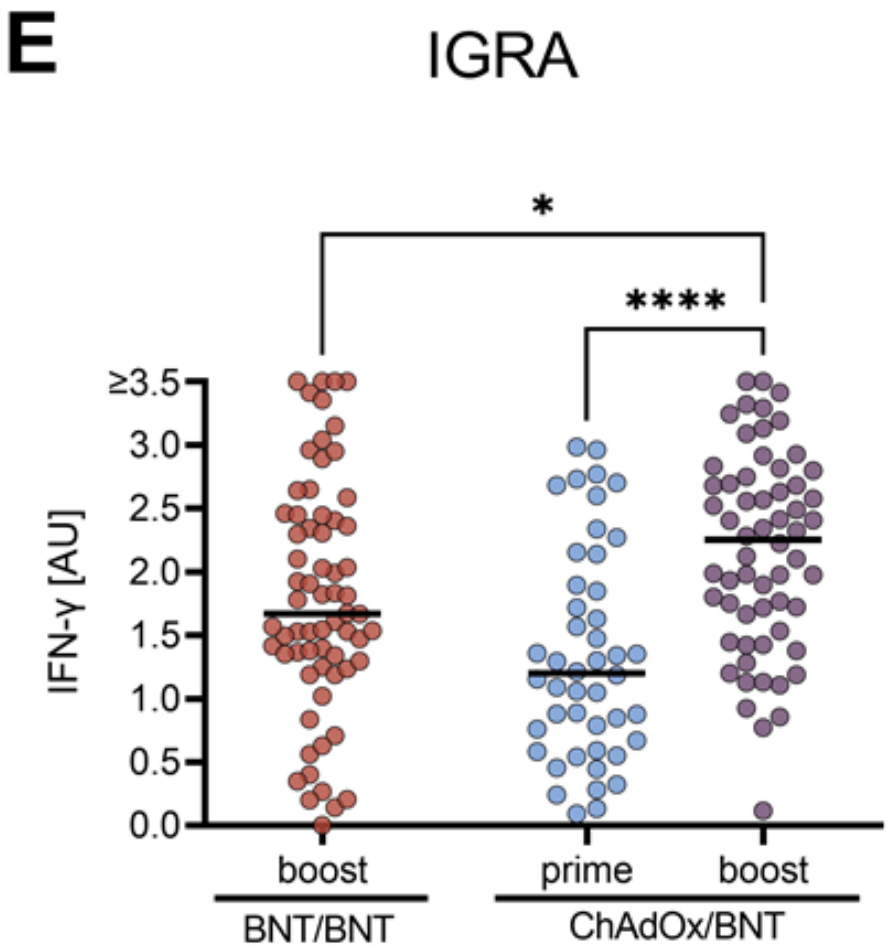
https://www.medrxiv.org/content/10.1101/2021.05.19.21257334v2

Immunogenicity: T cell reactivity, IFN-gamma release assay (IGRA)



https://www.medrxiv.org/content/10.1101/2021.05.19.21257334v2

Conclusions

- Homologous BNT/BNT and heterologous ChAdOx/BNT prime-boost vaccination is **well-tolerated** with 10-12 week intervals between ChAdOx and BNT
- Reactogenicity of homologous BNT/BNT and heterologous ChAdOx/BNT is **comparable**
- Homologous BNT/BNT and heterologous ChAdOx/BNT prime-boost vaccination is **highly immunogenic**
- **Immunogenicity** of homologous BNT/BNT and heterologous ChAdOx/BNT is **comparable**
- Heterologous ChAdOx/BNT vaccination slightly increases T cell reactivity and antibody avidity

This study provides real-world evidence that supports heterologous ChAdOx/BNT immunisation with 10-12 week intervals, as it is currently recommended in several countries

Acknowledgements

This study was supported by

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BIH Berlin Institute of Health @Charité

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GEFÖRDERT VOM Bundesministerium für Bildung und Forschung

COVIm Bestimmung und Nutzung von SARS-CoV-2 Immunität

We thank all study participants

Panel: Vaccine Policy Implications

Moderated By:

Jakob Cramer, MD

Head of Clinical Development

Coalition for Epidemic Preparedness Innovations (CEPI)

Peter Dull, MD

Deputy Director,

Integrated Clinical Vaccine Development,

Bill & Melinda Gates Foundation (BMGF)

Panel: Vaccine Policy Implications

Panel Members

- **Willis Akhwale, Chair of the COVID-19 Taskforce in Kenya**
- **Rudzani Muloiwa, University of Cape Town**
- **Thomas Mertens, Chairman of STIKO, Former director of the Institute of Virology, University of Ulm**
- **Kari Johansen, SAGE**

Potential Discussion Questions

- *From a NITAG perspective, can you please comment on the (minimum / optimal) evidence level required to recommend heterologous priming regimens without formal licensure?*
- *Evidence for homologous and heterologous vaccinations is still limited on special populations / age groups. Could you please comment from a NITAG perspective?*
- *Heterologous boosting: From your country perspective, will documentation of vaccination status support the selection of a vaccine platform which is different from the one used for primary immunization?*
- *What are your thoughts with regards to (heterologous) boosting with (single dose) variant-adapted vaccine e.g. 9-12 months after primary immunization?*

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/
- Please consider sharing your thoughts and suggestions on this and/or future workshop in our Discussion Forum https://epi.tghn.org/community/groups/group/cwsg/
- Next workshops: TBD
- 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

Clinical Development & Operations SWAT Team

CEPI

Gavi The Vaccine Alliance

World Health Organization

unicef