Booster vaccination versus 2+1 primary immunization:

Does it matter?

28th September 2021

Dr. Tedros Adhanom Ghebreyesus, DG WHO

8th September 2021:

“There has been little change in the global situation since then, so today I am calling for an extension of the moratorium until at least the end of the year to enable every country to vaccinate at least 40% of its population”

Booster Doses: Better Immune Response / Increased VE?

- Improve immune response
  - Increase Ab titre
  - Ab maturation
  - …
- Prolong immune response
  - Delayed drop of Ab titres below detection limit
  - Immune memory
- Broaden immune response
  - Cross-neutralization to SARS-CoV-2 variants

COVID-19 Booster Doses: Increasing Complexity

- Public Health objective:
  - end the pandemic by having an **impact on incidences** (VE against infection and transmission) or
  - **prevent morbidity / mortality** (VE against severe disease, hospitalisation, death)?
- VOC: Boosting to broaden the immune response **in the context of VOCs** (and in absence of variant-adapted vaccines)?
- Interchangeability of vaccines: **Heterologous priming / boosting** with fractional doses
- Vaccine: **Which vaccine should be prioritised** for booster dose?
  - vaccines with highest immunogenicity (vaccine efficacy)? nAb *versus* CMI?
  - vaccines most widely available?
- **Target population**: all or selected populations at risk?
  - Immunocompromised patients
  - Older age groups
  - Chronic diseases
  - Only for specific (weakly immunogenic) vaccines?
  - HCW (at risk for infection)?

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Terminology: Booster *versus* Additional Doses of COVID Vaccines

- **Priming:**
  - 1 or 2 doses [given 3 weeks – 3 months apart (= dose 1 and 2)]

- **Additional Dose:**
  - 2+1 scheme requiring a 3rd (or 2nd) dose to complete primary immunization
    - for vaccines with a rapid initial decline in Ab-levels / with insufficient vaccine effectiveness post 2 doses
    - in special populations (e.g. elderly, immunocompromised)

- **Boosting:**
  - 1 dose given months (>6 months) or years after priming (= depending on scenarios above: dose 2, 3 or 4 ff.) To maintain / broaden immune response over time in the general healthy population

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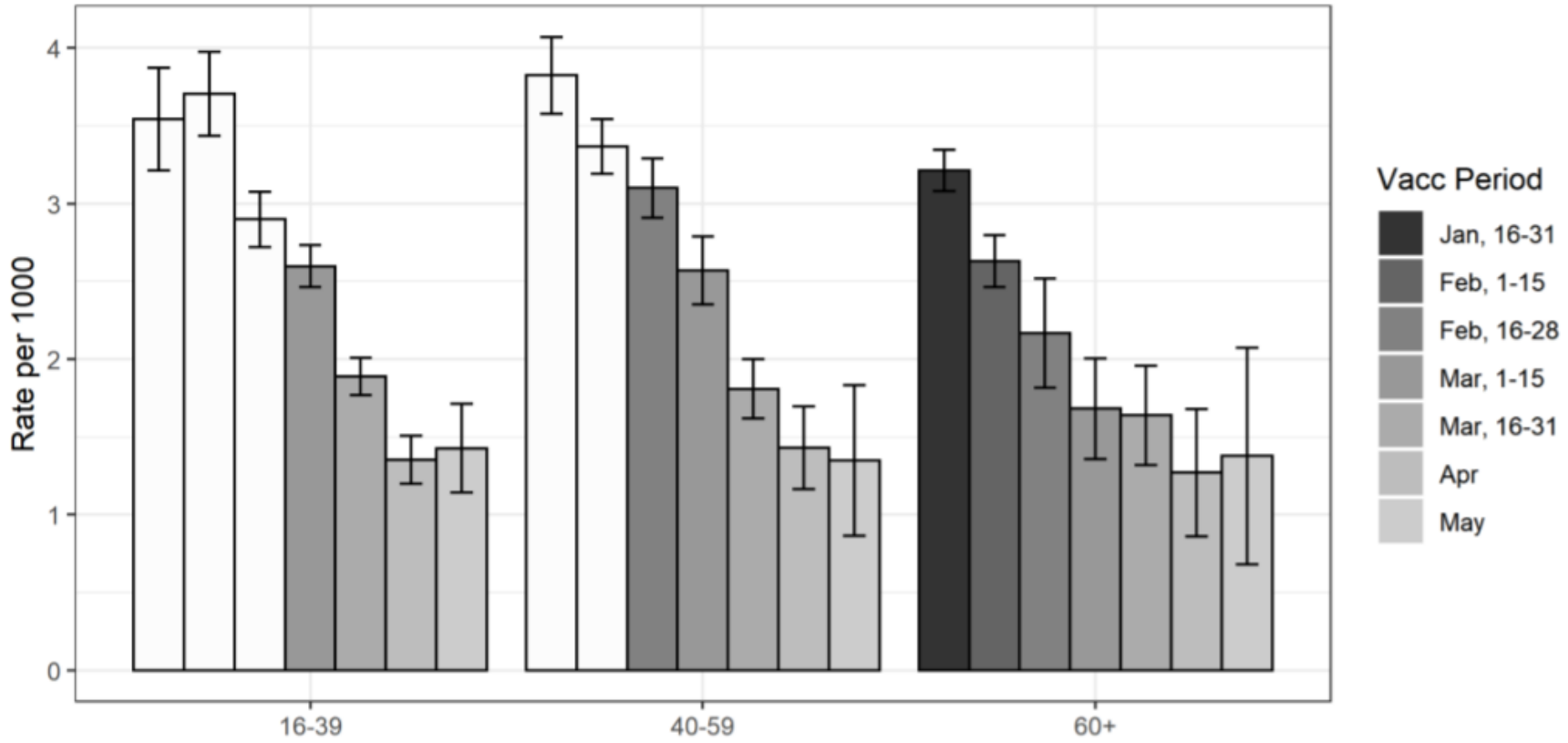
Waning Immunity of the BNT162b2 Vaccine: Data from Israel

- SARS-CoV-2 infections:

Figure 3: Rate of documented SARS-CoV-2 infection (per 1,000 persons) from July 11, 2021 to July 31, 2021, stratified by period of second dose of COVID-19 vaccine and age group. White bars represent periods at which only persons at higher risk were allowed to receive vaccination.

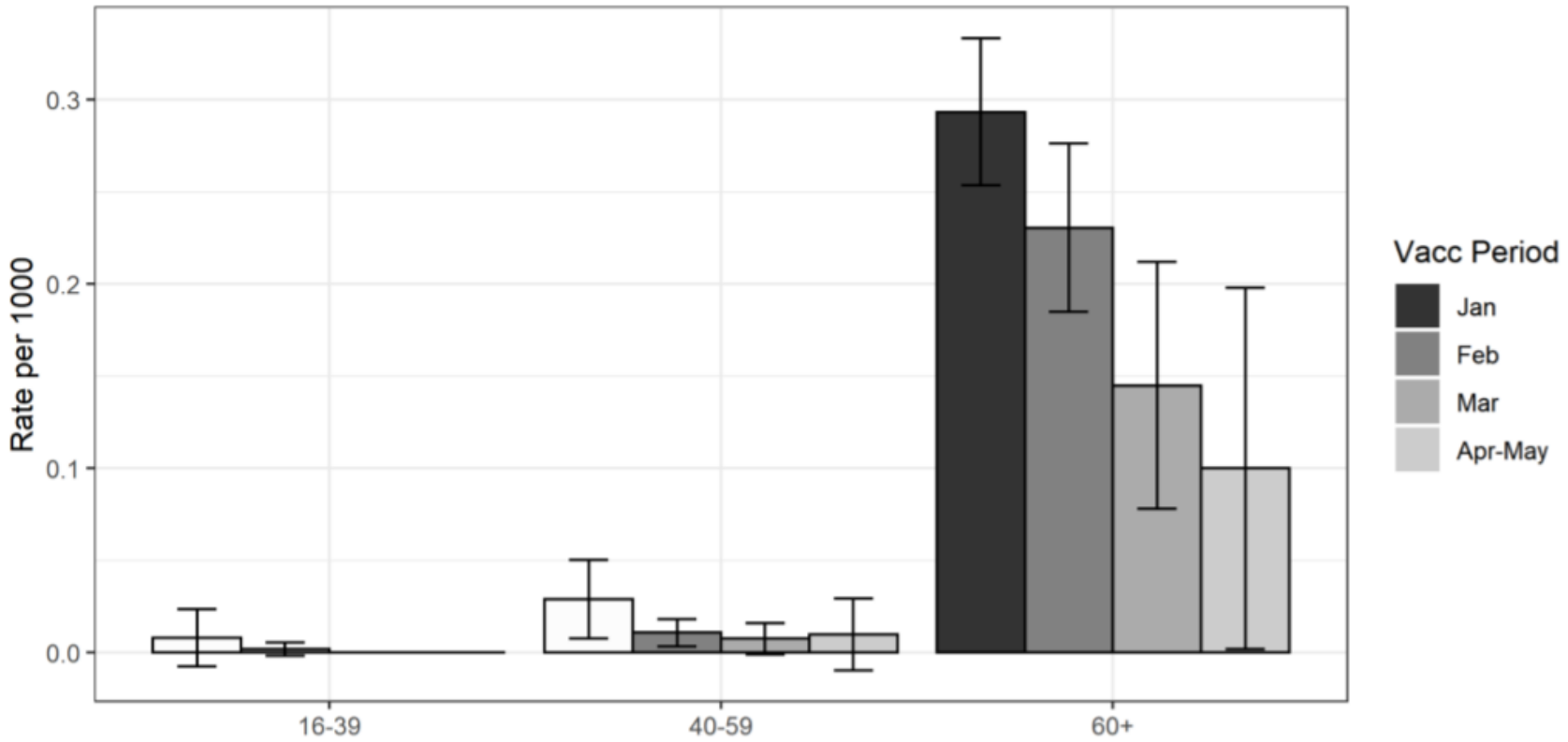


[Goldberg Y et al., 2021: https://www.medrxiv.org/content/10.1101/2021.08.24.21262423v1.full.pdf]

Waning Immunity of the BNT162b2 Vaccine: Data from Israel

- Severe COVID-19:

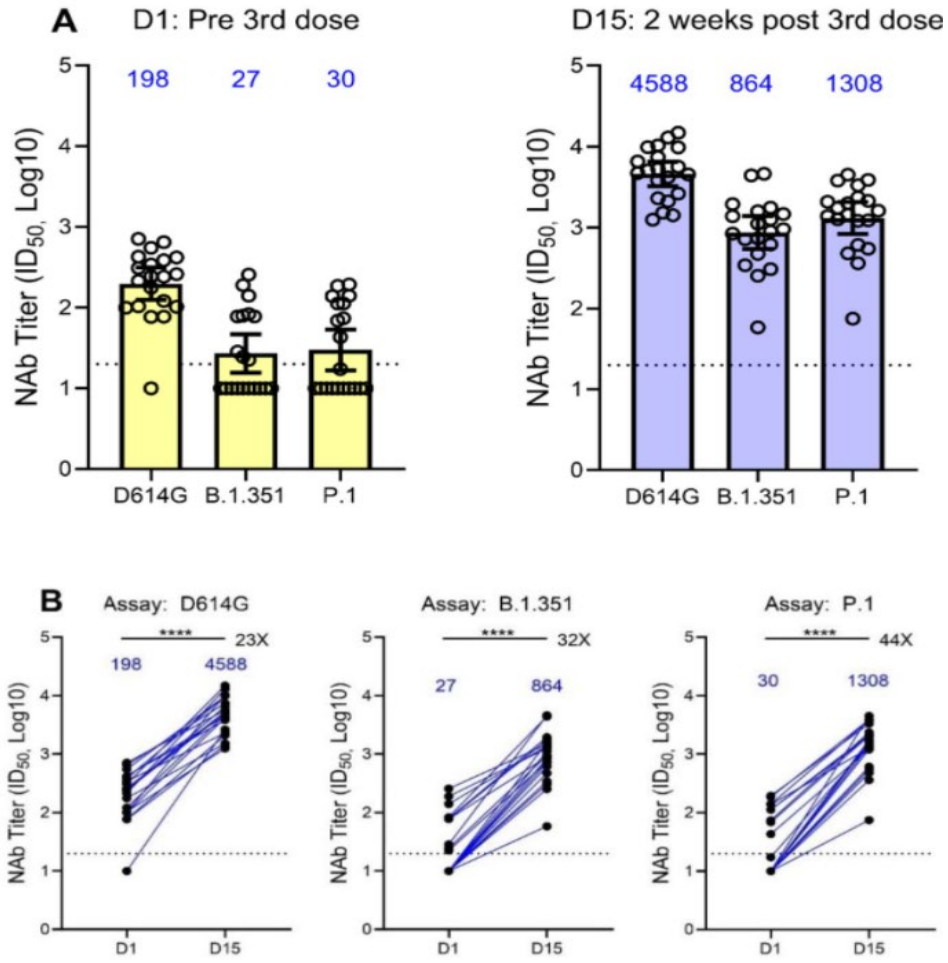
Figure 4: Rate of severe COVID-19 (per 1,000 persons) from July 11, 2021 to July 31, 2021, stratified by period of second dose of COVID-19 vaccine and age group. White bars represent periods at which only persons at higher risk were allowed to receive vaccination.



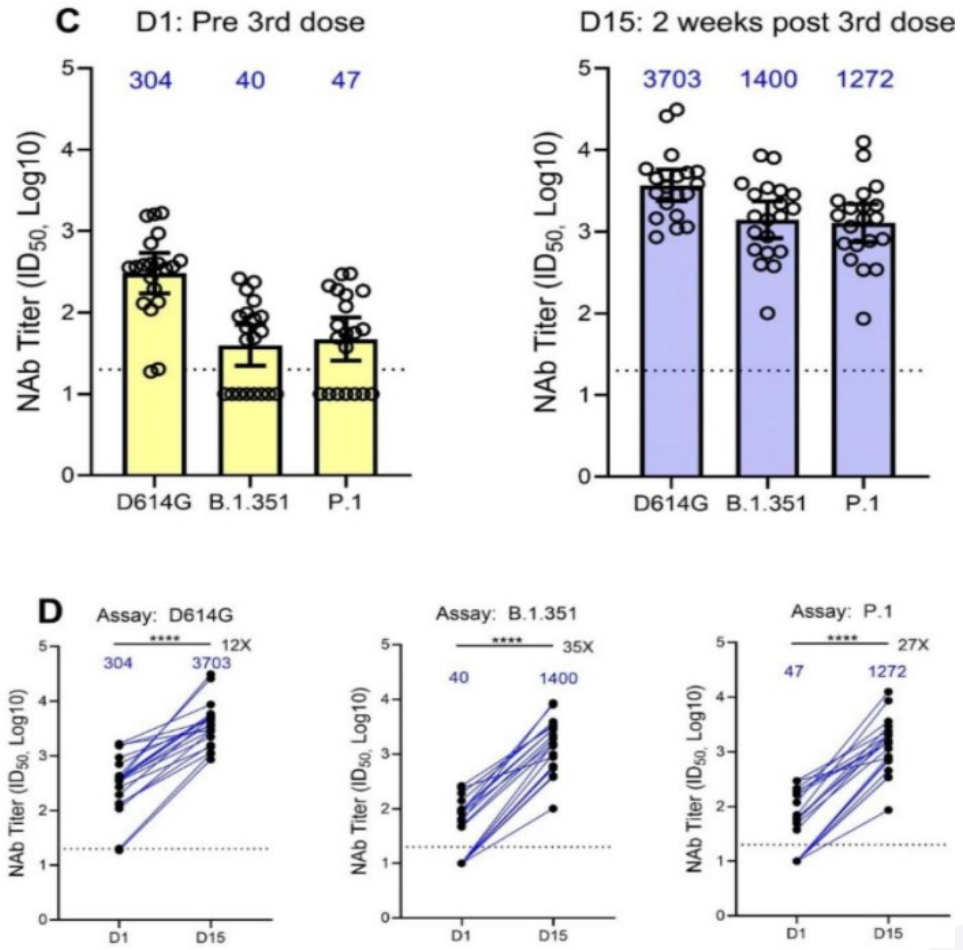
[Goldberg Y et al., 2021: https://www.medrxiv.org/content/10.1101/2021.08.24.21262423v1.full.pdf]

Moderna: PV Neutralisation (D614G, B.1.351 and P.1) by serum from participants before (D1) and 15 days after boosting @ 6 months (D15)*

50 µg of mRNA-1273



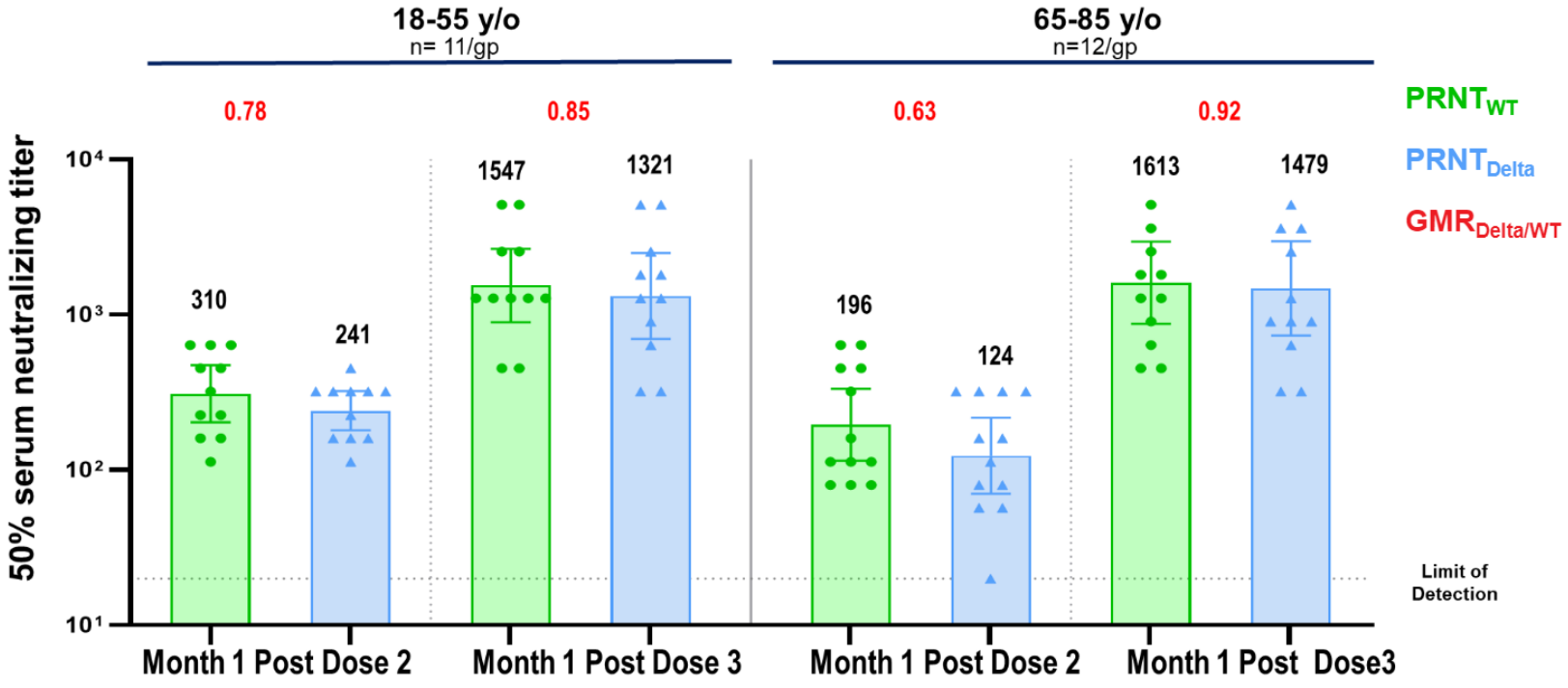
50 µg of mRNA-1273.351



*Wu, K. et al. Preliminary Analysis of Safety and Immunogenicity of a SARS-CoV-2 Variant Vaccine Booster, May 6, 2021, https://www.medrxiv.org/content/10.1101/2021.05.05.21256716v1.full-text

Pfizer/BNT: Booster Data

COVID-19 Vaccine: 3rd Dose Strongly Boosts Neutralizing Titers Against Delta Strain[1,2]



- Post dose 3 titers vs. the Delta variant are **>5-fold post dose 2 titers** in 18-55 y/o & **>11-fold post dose 2 titers** in 65-85 y/o
- Estimated potential for up to **100-fold increase in Delta neutralization post-dose three** compared to **pre-dose three**

Pfizer/BNT Booster Vaccination in Israel: Real-World Data

- On July 30th, Israel approved booster vaccination with BNT162b2 in 60+ primed >5 months earlier
- Israeli MoH database n=1,137,804: data extracted from July 30 through August 31st

Table 2. Primary Outcomes of Confirmed Infection and Severe Illness.*

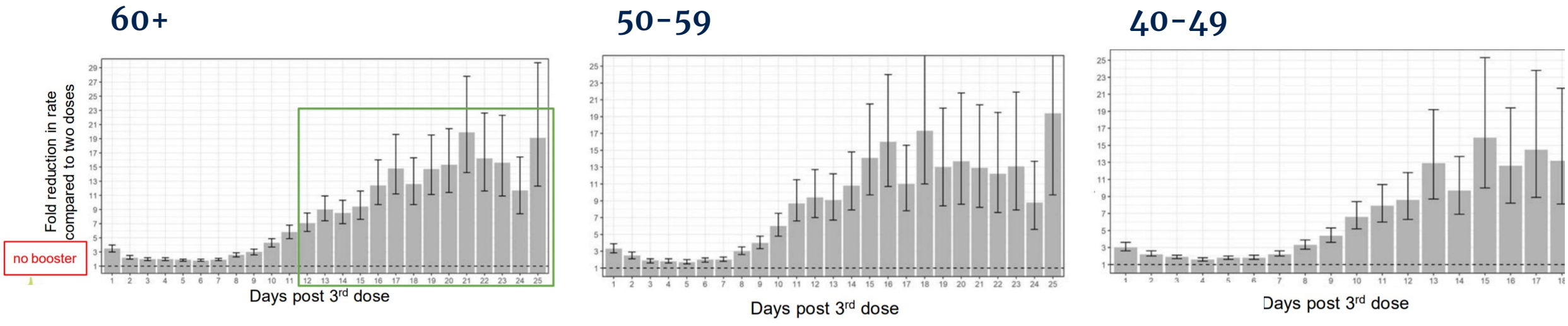
Outcome	Nonbooster Group	Booster Group	Adjusted Rate Ratio (95% CI)†
Confirmed infection			11.3 (10.4 to 12.3)
No. of cases	4439	934	
No. of person-days at risk	5,193,825	10,603,410	
Severe illness			19.5 (12.9 to 29.5)
No. of cases	294	29	
No. of person-days at risk	4,574,439	6,265,361	

* Listed are the results of the Poisson regression analysis in participants who received a booster vaccine and in those who did not receive a booster. The booster group includes data that were obtained at least 12 days after receipt of the booster dose.
† The rate ratio is the estimated factor reduction in the rate in the booster group as compared with the rate in the non-booster group.

[Bar-on et al., NEJM 2021]

Booster protection against confirmed infection as a function of time post vaccination

- Poisson regression adjusted for age, gender, demographic group, 2nd dose period and calendar day. Based on data from August 10 to August 31

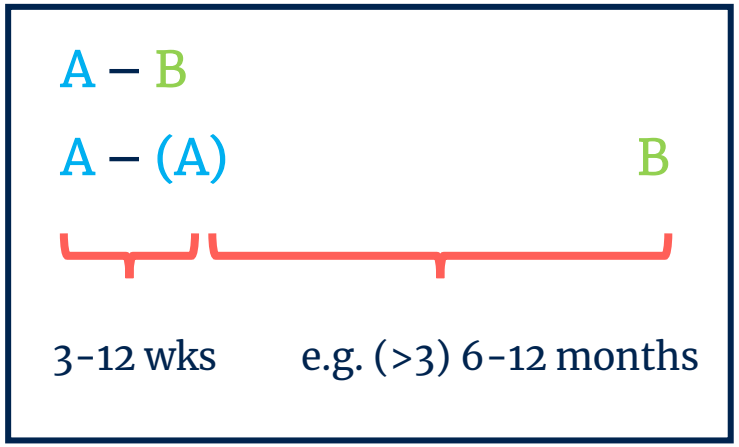


[Bar-on et al., NEJM 2021; https://www.fda.gov/media/152205/download]

“Mix & Match”

Concepts:

- Heterologous primary vaccination*:
- Heterologous boosting:



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)?

Intervals: dosing interval relevant as priming evolves over months (nAbs versus CMI)

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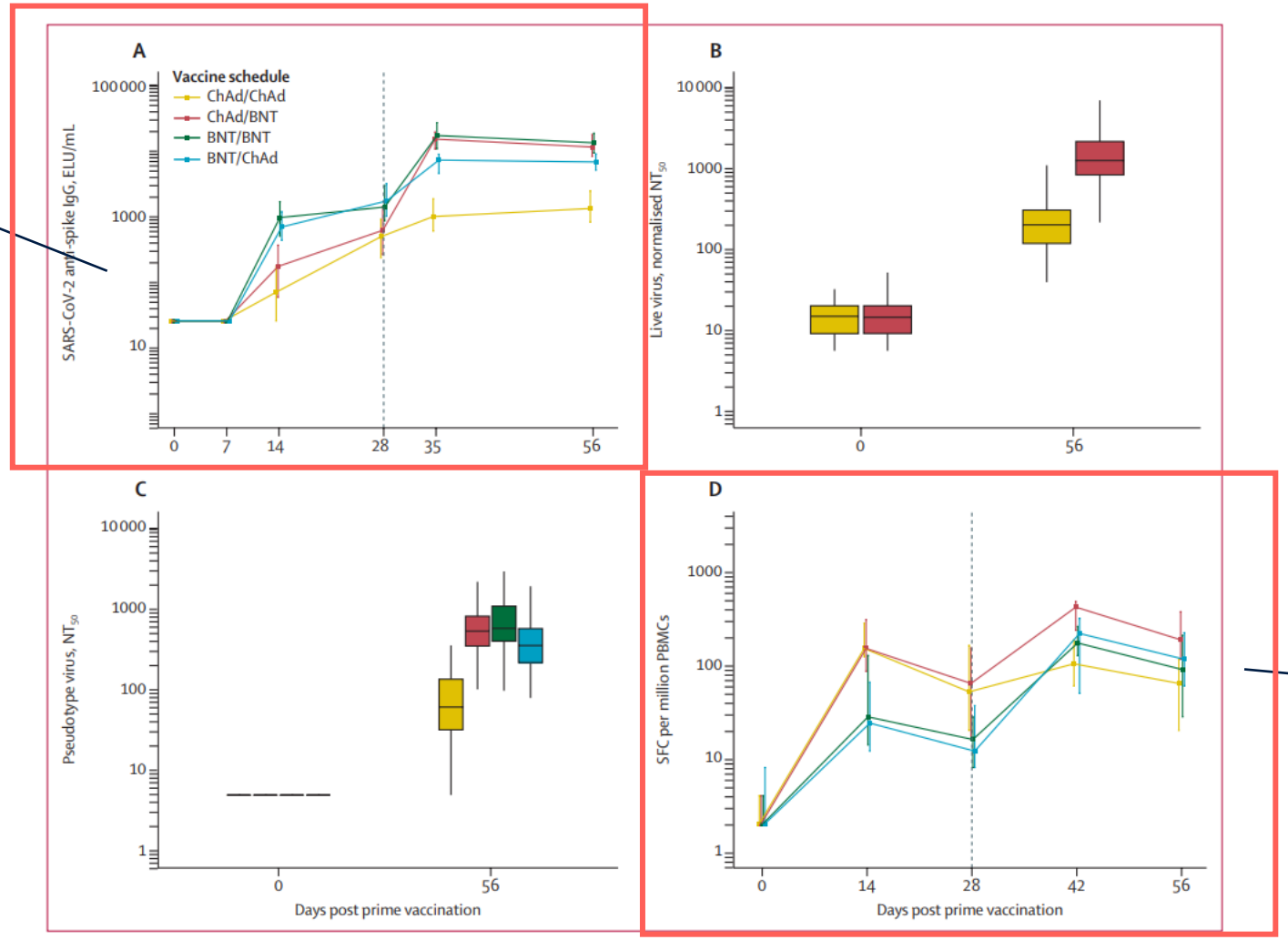
Heterlogous Primary Immunisation: ChAdOx-1/AZ *versus* Pfizer/BNT

COM-CoV, UK: n=463; adults 50+ yoa, interval 28 days

IgG (bAb)



CMI

[Liu X. et al., Lancet 2021: https://doi.org/10.1016/ S0140-6736(21)01694-9]

Fractional Doses?

- Optimal dose: Full dose versus reduced dose?
- If reduced dose:
  - While **half dose** might be easiest from a practical perspective – is this the way forward (why not 1/3 or 3/4 or 1/10 dose)?
  - Formulation: **Currently licensed vaccine formulations may not be suitable for fractional dose administration** – e.g. small dose volume, for other vaccines (formulated as multi-dose) impossible to double diluent volume

A platform trial approach to assess the immunogenicity and safety / reactogenicity of fractional COVID-19 vaccine(s) given as a single additional dose in selected primed populations

→ Platform approach: to define core elements and design features

→ individual trials / projects addressing specific needs / gaps / objectives with the following scope:

- **Improve immune response (and vaccine effectiveness)** against SARS-CoV-infection / transmission and COVID-19 illness in the context of increasing numbers of VOCs in selected / special populations
- Limit impact on **vaccine supply:** accelerate vaccination coverage (without compromising VE / public health impact)
- **Improve reactogenicity (and safety?) profile**

A platform trial approach to assess the immunogenicity and safety / reactogenicity of fractional COVID-19 vaccine(s) given as a single additional dose in selected primed populations

Aim: Data are primarily expected to support pragmatic recommendation by e.g. NITAGs / WHO SAGE (but may also serve to support regulatory approval of additional label claims)

- Focus on needs in LMICs
- It is not the intention to duplicate other programmes / trials generating similar evidence (e.g. on the general need for a booster dose in fully vaccinated healthy populations)

Platform Trial Concept: Prospective randomised trial to assess the immunogenicity of fractional *versus* full dose given as a single 'booster' vaccination in previously primed subjects

Additional blood draw for long term immuno?

Study Arm	Study Population	Visit #1	Visit #2	… F/U
	'Primed' populations, as defined by individual project with hx of …	Day 1	Day 29 (week 4)	1, 2 years… ?
A	• One dose (single dose regimen / incomplete 2-dose regimen) or • 2 doses (any vaccine, different intervals) • Evidence of nat. infection	1		
B		½ b)		
(C) a)		1		

a) Should a different vaccine be tested for full versus fractional dose for 'booster' it is recommended to include one comparator arm assessing a full dose of the vaccine used for primary vaccination
b) Fractional dose (not necessarily half dose)

'Rescue strategy' → Offer full vaccination with locally registered / available vaccine to those with insufficient immune response

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Platform Trial Approach: Core and Flexible Elements

Defined trial populations, e.g.

- Immunocompromised / SOT
- Immunocompromised / HIV
- Elderly / immunosenescense
- Primed via natural infection
- Other chronic conditions / risk groups
- 2 → 3 dose regimen (2+1)
- Post single dose

Selected vaccines*

Immunocompromised / SOT → **Fractional single dose**

1:1

Immunocompromised / SOT → **Full single dose**

Immun response read-out

Day 1: Day 29:

Immune response (core assay + additional assays defined by project (incl. e.g. CMI, cross-reactivity etc.):

<u>Primary comparison:</u>
→ Individual trial population

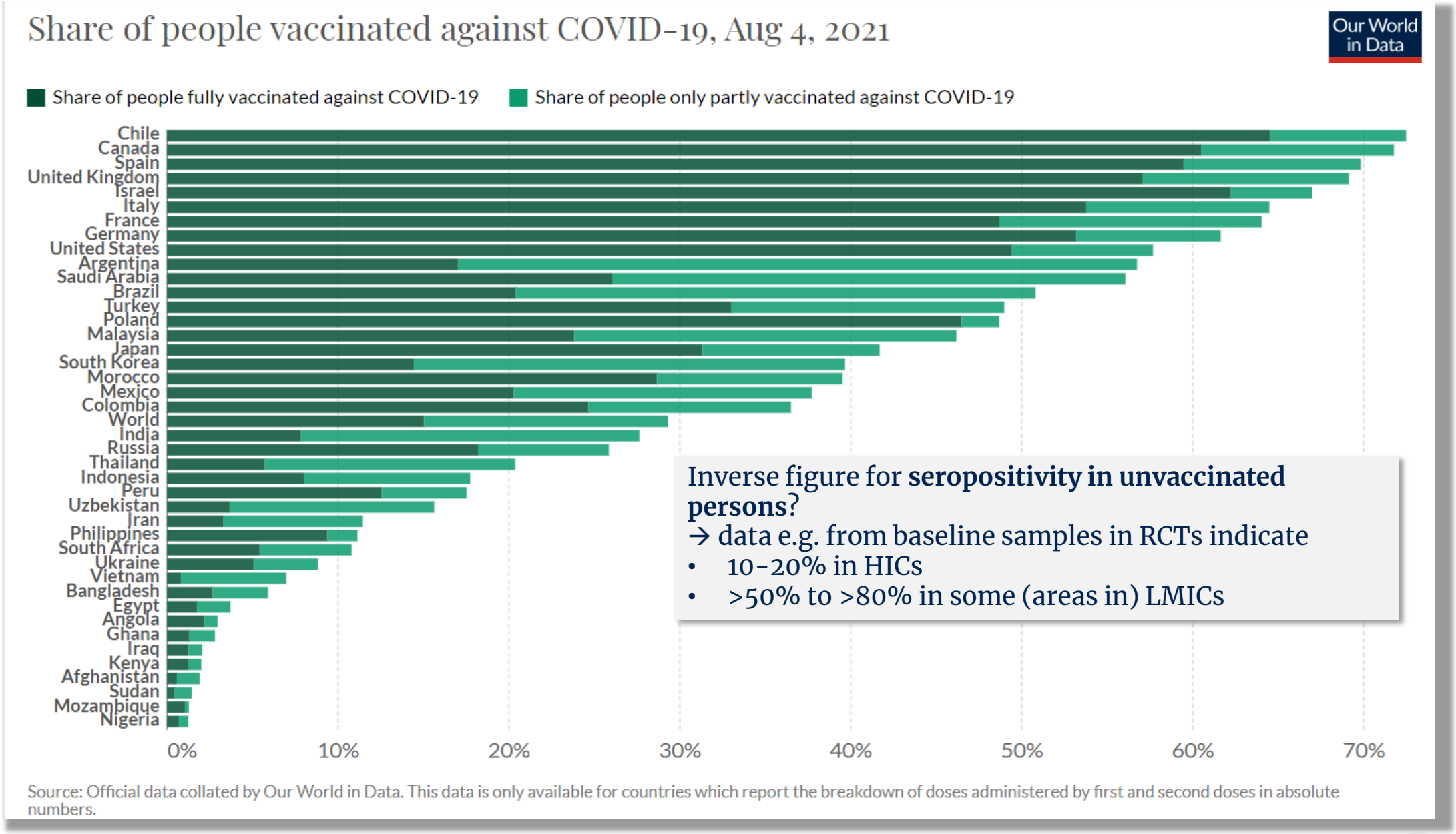
<u>Secondary comparisons</u>
→ in subgroups, e.g.
- Within each individual trial
- Across all trials

→ overall, across all trials

*) E.g., as available in the country. Vaccine developers may want to contribute to specific trials / projects.

Follo-up

- At least 3 months for safety F/U
- May include an additional blood draw e.g. at 6 months to assess long-term immune response post booster



Inverse figure for **seropositivity in unvaccinated persons**?

→ data e.g. from baseline samples in RCTs indicate

- 10-20% in HICs
- >50% to >80% in some (areas in) LMICs

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Additional (2+1) *versus* Booster Dose: Special Populations / VOC

- The world needs more
  - **Vaccine** (= supply of those products already approved / authorized)
  - **Vaccines** (= products yet to be approved / authorized)
- There is a shift from **vaccinating immune-naïves** towards **vaccinating primed populations** (when will e.g. >50% of the world's population be primed – with / without vaccination?):

2020 / 2021:
- Primary vaccination in unprimed (seronegatives)

⇨

2022 ff.
- Primary vaccination in unprimed
- Primary vaccination in primed (seropositives = post natural infection)
- Booster vaccination in previously vaccinated

- SARS-CoV-2 variants: Will we eventually need a (seasonal) VOC-adapted vaccine given irrespective of previous vaccination / infection (influenza)?
- For approved / authorized vaccines, are there dose-sparing options?
  - **Increase vaccine supply:** accelerate vaccination coverage (without compromising VE / public health impact)
  - **Improve reactogenicity (and safety?) profile**

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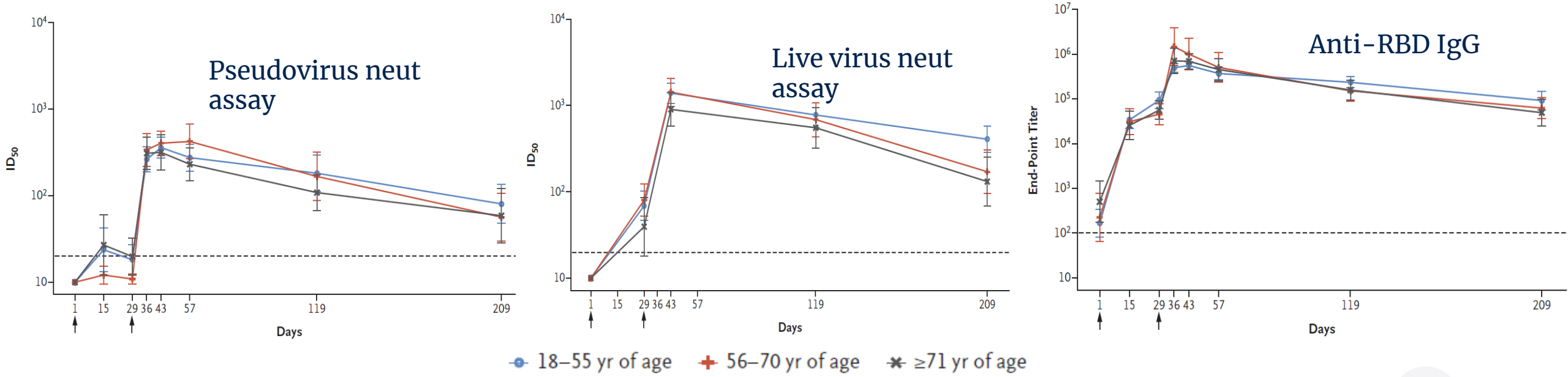
Immune Persistence Following Vaccination: Moderna

- 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.*