The booster in your future: when, what, and why?

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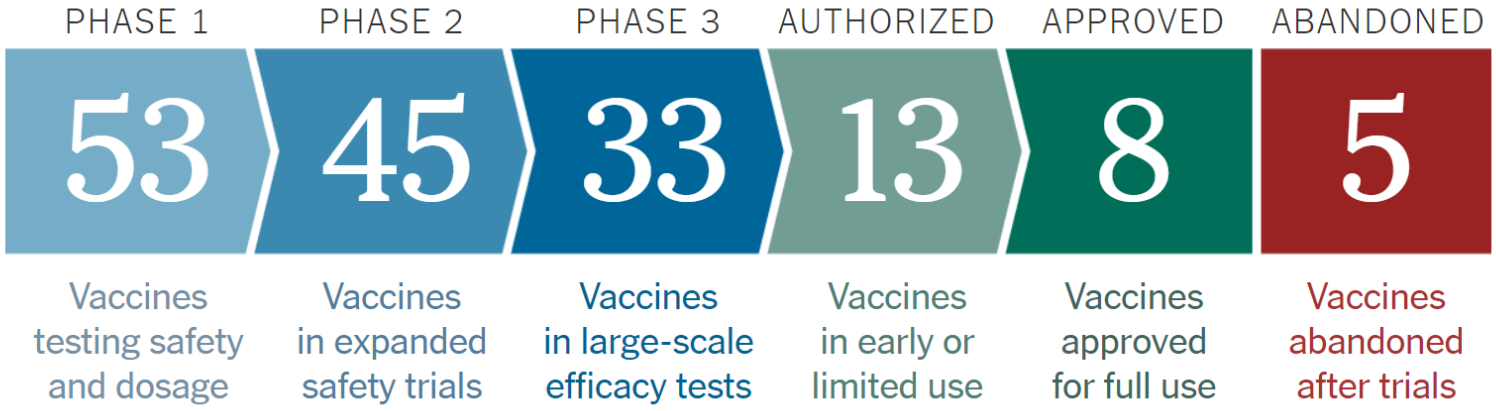
International Vaccine Institute

Disclosures:

- **Dr. Kim is a consultant for SK biosciences**
- **IVI works on the Inovio, Genexine, Cellid, Sanofi, SK bioscience, and Clover vaccines in human clinical trials**

The COVID-19 crisis has induced vaccine innovation



102 vaccines in human clinical testing
75 vaccines in pre-clinical testing

New York Times, 13 Sept 2021

Phase III vaccines, neutralizing antibody, efficacy

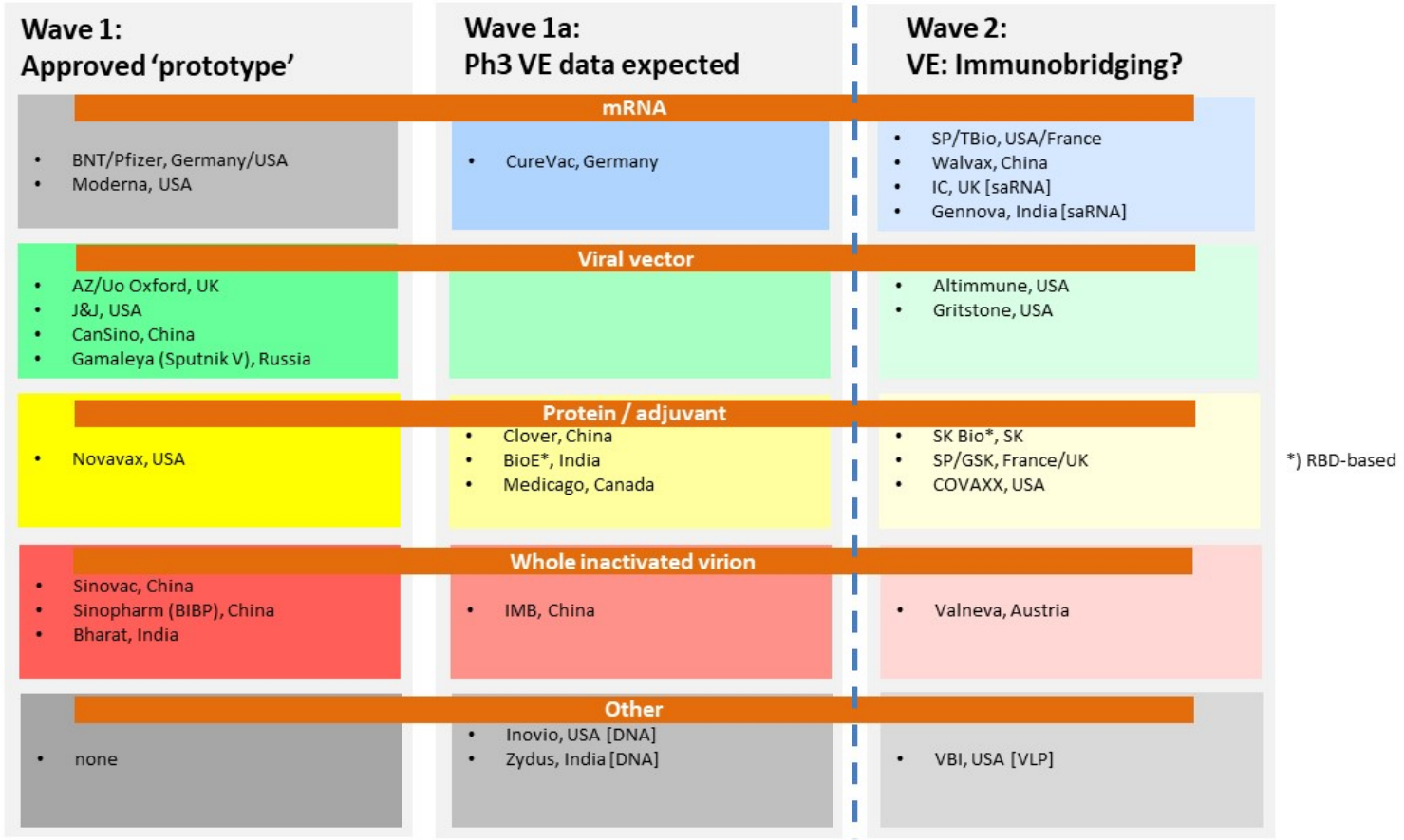
MANUFACTURER	Vaccine	Dose	seroconversion	ID_{50}	Efficacy	Regulatory approval	WHO approval
CANSINO	Ad5 spike	1 x 10^{11} VP 1.5 x 10^{11} VP	50% 75%	16 34	66%	China	
ZYDUS CADILA	DNA Spike	2 mg NFIS x3	80%	39	66%	India	
SINOVAC	WIV/alum	3 ug x2 (14d) 3 ug x 2 (28d) 6 ug x2 (14d) 6 ug x2 (28d)	>90% 97% >90% >90%	28 44 [1] 34 ~60	50% 65% 78% 91%	China Brazil Indonesia	WHO approved
GAMALEYA	Ad26 spike - Ad5 spike prime boost	10^{11} VP each	100%	49	92%	Russia	WHO review
Bharat	WIV/alum WIV/alum+IMDG (imidazoquinoline) WIV/alum+IMDG (imidazoquinoline)	6 ug x 2 (14d) 3 ug x 2 (14d) 6 ug x 2 (14d)	83% 88% 92%	62 66 48	81%	India	
Johnson & Johnson	stabilized Spike-Δfurin-S.PP	5 x 10^{10} VP 1x10^{11} VP	92% 92%	214 243	66% 72% (USA) 57% (RSA) 85% severe disease	US EU	WHO approved
SINOPHARM	WIV/alum	4 ug x 2 (0,14) 8 ug x 2 (0,28)	100% 100%	211 229	79%	China	WHO approved
PFIZER/BNT	prefusion Spike	30 ug x 2	100%	267	95%	US, UK, EU	WHO approved
AstraZeneca/ JENNER/ Serum Institute / SK bio	chimp ad Spike	5 x 10^{10} VP 5 x 10^{10} VP x2	100% 100%	201 372	62% full dose 90% split dose	UK, India, EU	WHO approved
Moderna	prefusion stabilized spike	25 ug x 2 100 ug x 2	100% 100%	340 $PRNT_{80}$ 654 $PRNT_{80}$	94.5%	US, EU	WHO approved
NOVAVAX	prefusion stabilized spike/ Matrix M	5 ug x 2	100%	3350 ID_{99+}	89.3% (UK) 60.1% (RSA)		

	< 100
	100-500
	> 1000

ID50 groupings
CAVEAT: assays not standardized

New Platforms
- mRNA
- Adenoviral vectors
- DNA

Current and future COVID-19 vaccines



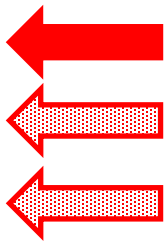
[Assumptions made based on publicly available data:
https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

- Curevac (mRNA): 48% against COVID-19 of any severity; 53% vs disease of any severity 18-60 yo; 73% VE for moderate-severe disease
- Zydus Cadila (DNA): 67% VE (delta); 100% VE for moderate-severe disease

We have 13 vaccines showing short term efficacy & safety: what's next for vaccines?

The other big questions:

- Optimization of dose, schedule, boosts
- Correlates of protection
- Effectiveness – Herd immunity?
- Surveillance for mutations or new emerging coronaviruses
- Longer term safety follow-up / post-licensure safety monitoring
- Opposition to vaccination

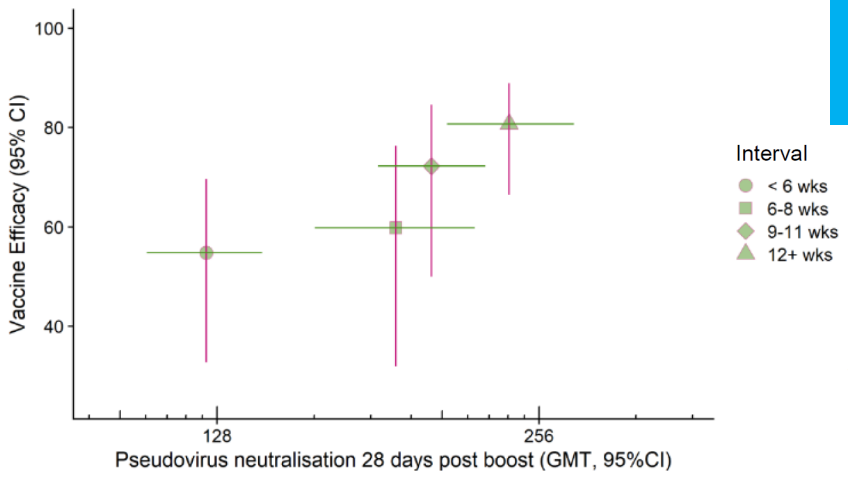


We need to optimize schedule, dose, boosting (AZ)

Voysey et al. Lancet 2020

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0·5%)	44·1 (248 299)	101/5829 (1·7%)	149·2 (247 228)	70·4% (54·8 to 80·6)†
COV002 (UK)	86	18/3744 (0·5%)	38·6 (170 369)	68/3804 (1·8%)	145·7 (170 448)	73·5% (55·5 to 84·2)
LD/SD recipients	33	3/1367 (0·2%)	14·9 (73 313)	30/1374 (2·2%)	150·2 (72 949)	90·0% (67·4 to 97·0)‡§
SD/SD recipients	53	15/2377 (0·6%)	56·4 (97 056)	38/2430 (1·6%)	142·4 (97 499)	60·3% (28·0 to 78·2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0·6%)	56·2 (77 930)	33/2025 (1·6%)	157·0 (76 780)	64·2% (30·7 to 81·5)‡
All SD/SD recipients	98	27/4440 (0·6%)	56·4 (174 986)	71/4455 (1·6%)	148·8 (174 279)	62·1% (41·0 to 75·7)

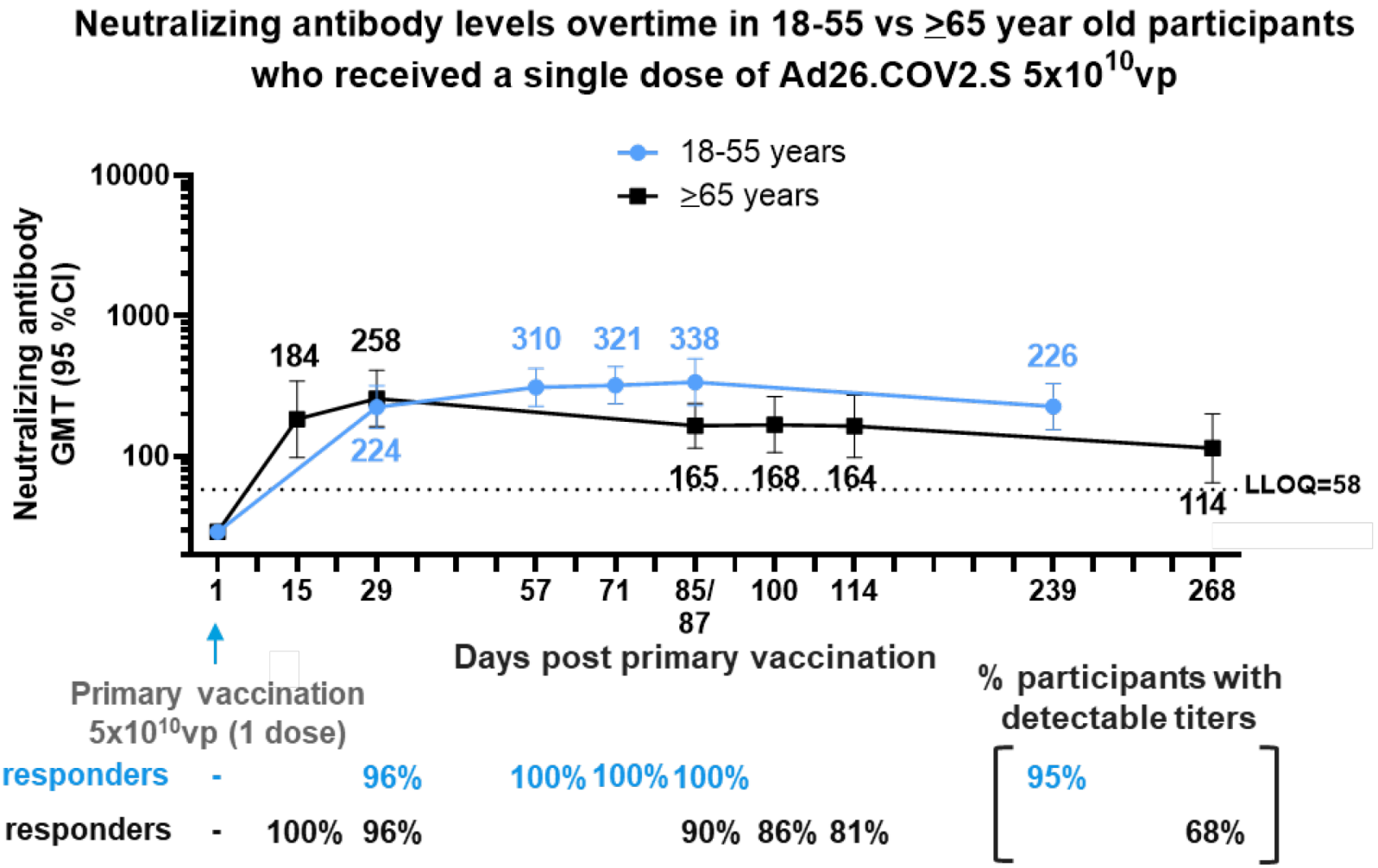
Low dose / Standard dose efficacy was 90% vs 62% fo Standard Dose / Standard Dose



- Efficacy increases as dosing interval increases
- Note correlation between efficacy and Nab titer

As interval between doses **increases**:
- Neutralizing titers **increase**
- Efficacy point estimates **increase**

Lower durability of Ad26.COV2.S in > 65 yo

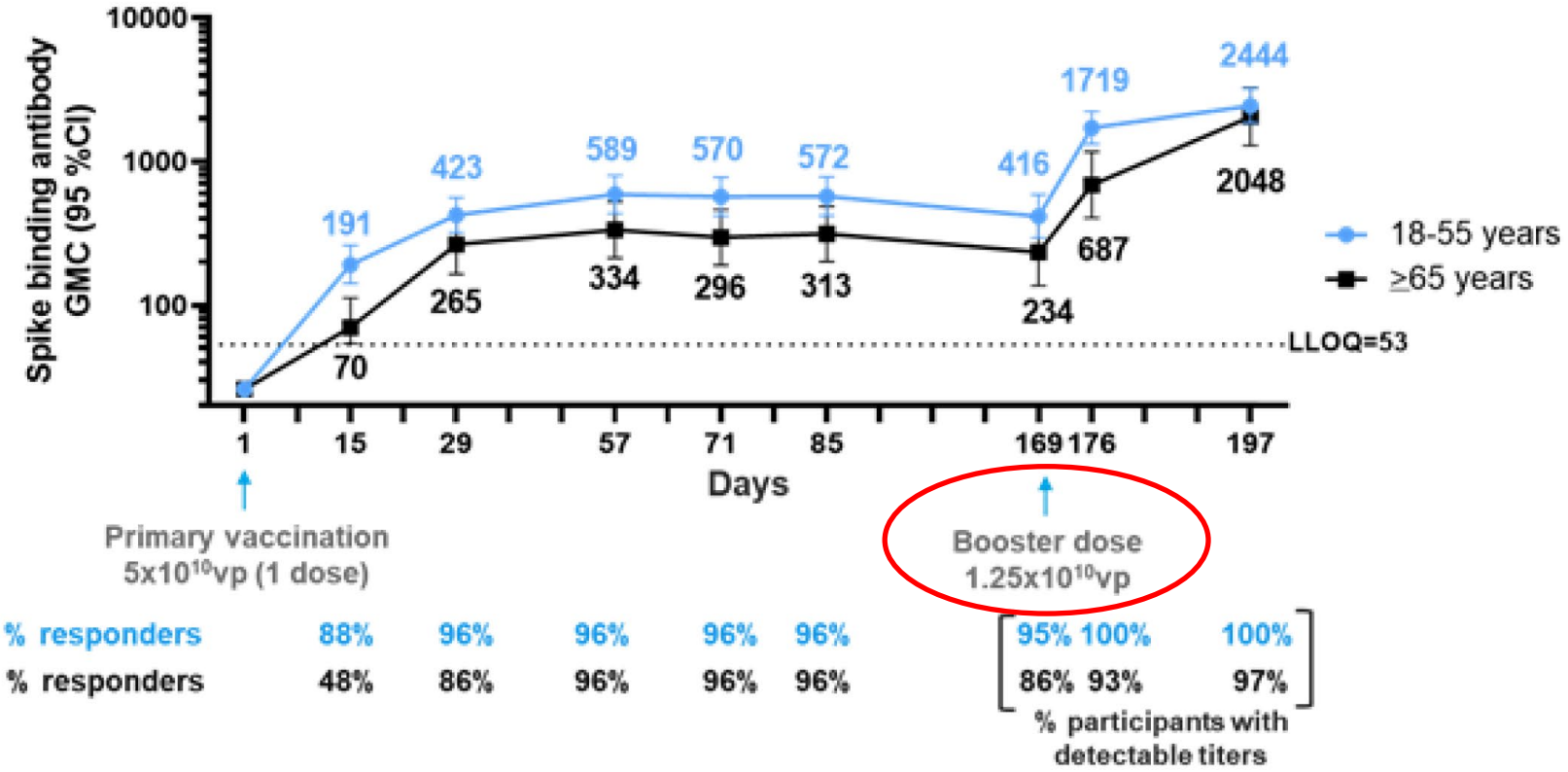


Participants > 65 yo have more rapid loss of Nab

Sadoff J, et al Medrxiv 2021

Homologous: Significant boosting after 2d dose of Ad26.COV2.S

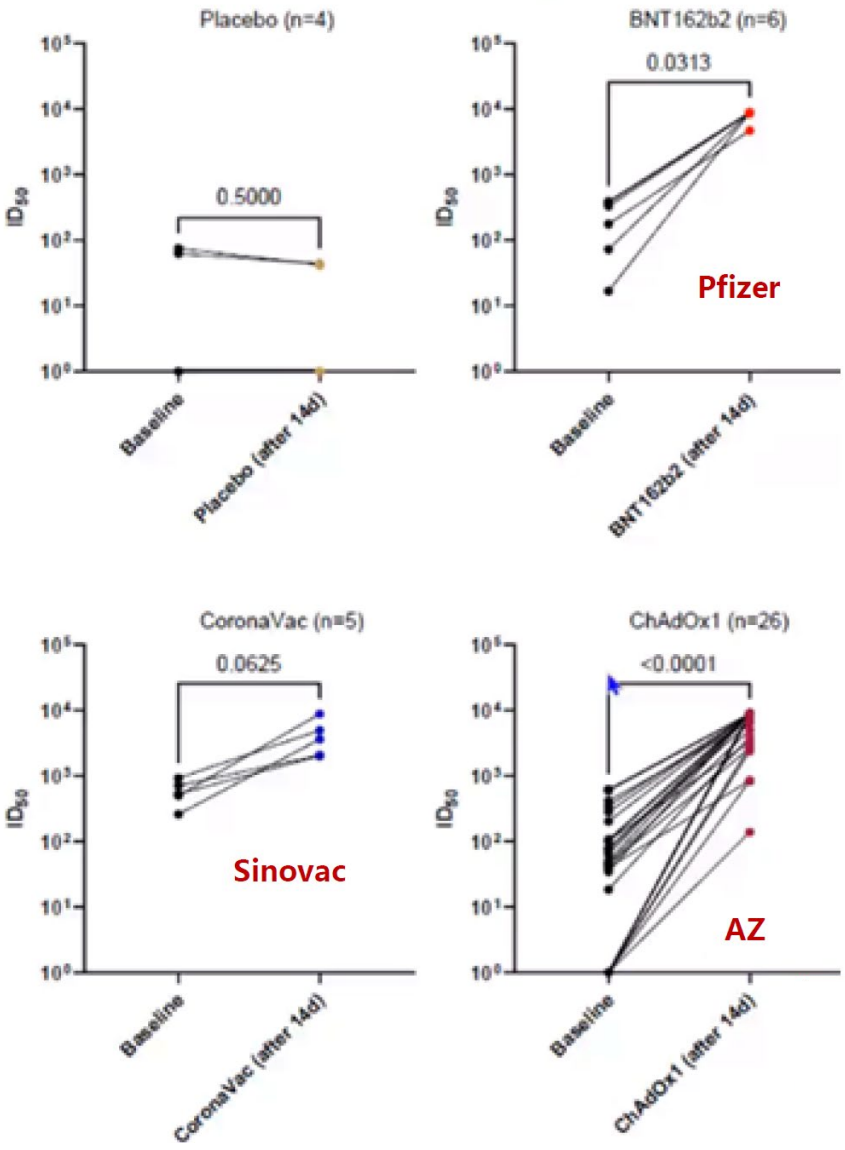
Spike binding antibody levels in 18-55 vs ≥65 year old participants who received one dose of $5x10^{10}$vp as primary regimen and a $1.25x10^{10}$vp booster dose at 6 months



9x increase in Nab after 2d dose of Janssen

Sadoff J, et al Medrxiv 2021

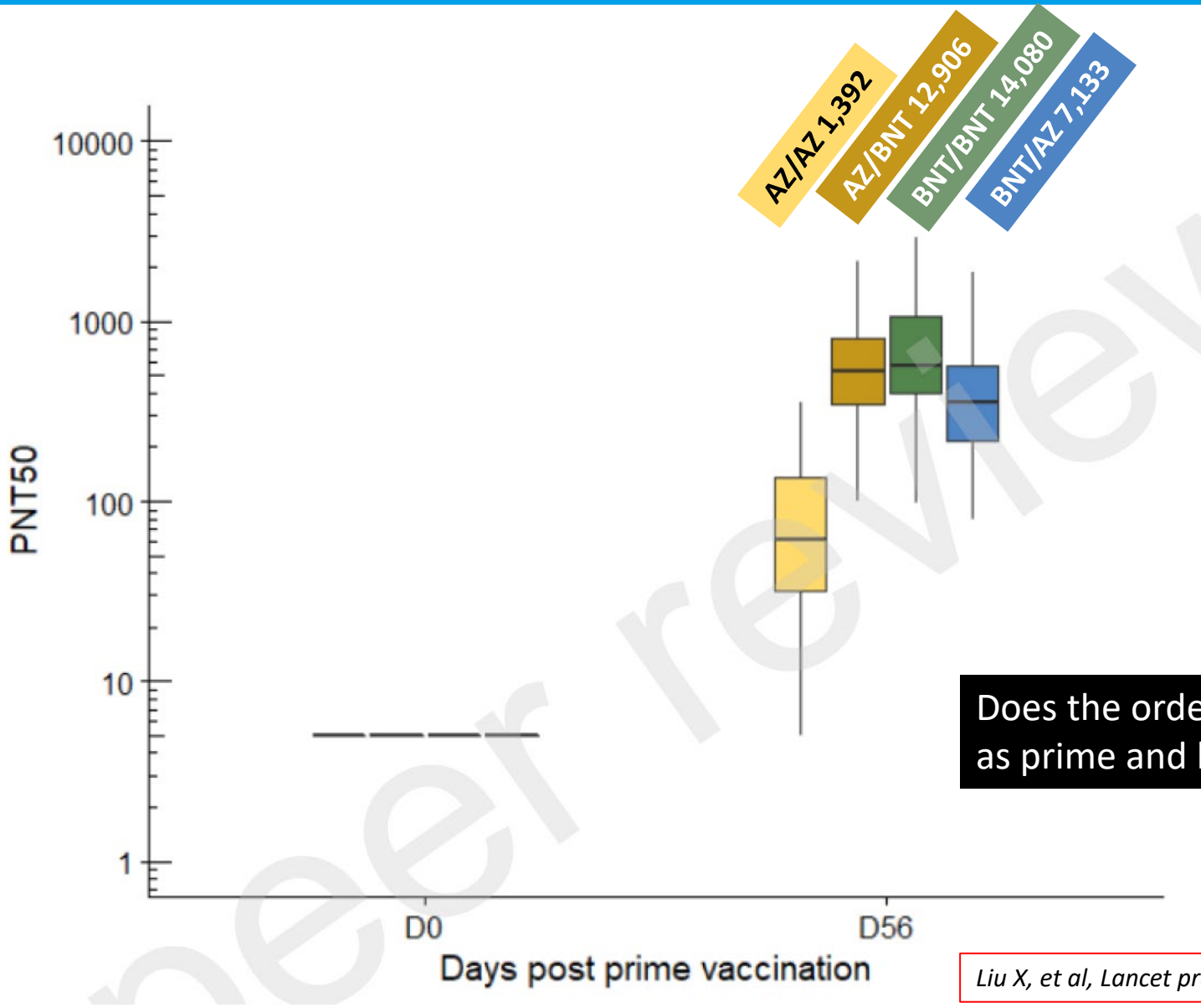
Homologous vs heterologous boosting: Sinovac



Boosting after Sinovac primary series

WHO SAGE July 2021

Homologous v heterologous: Pfizer and AZ

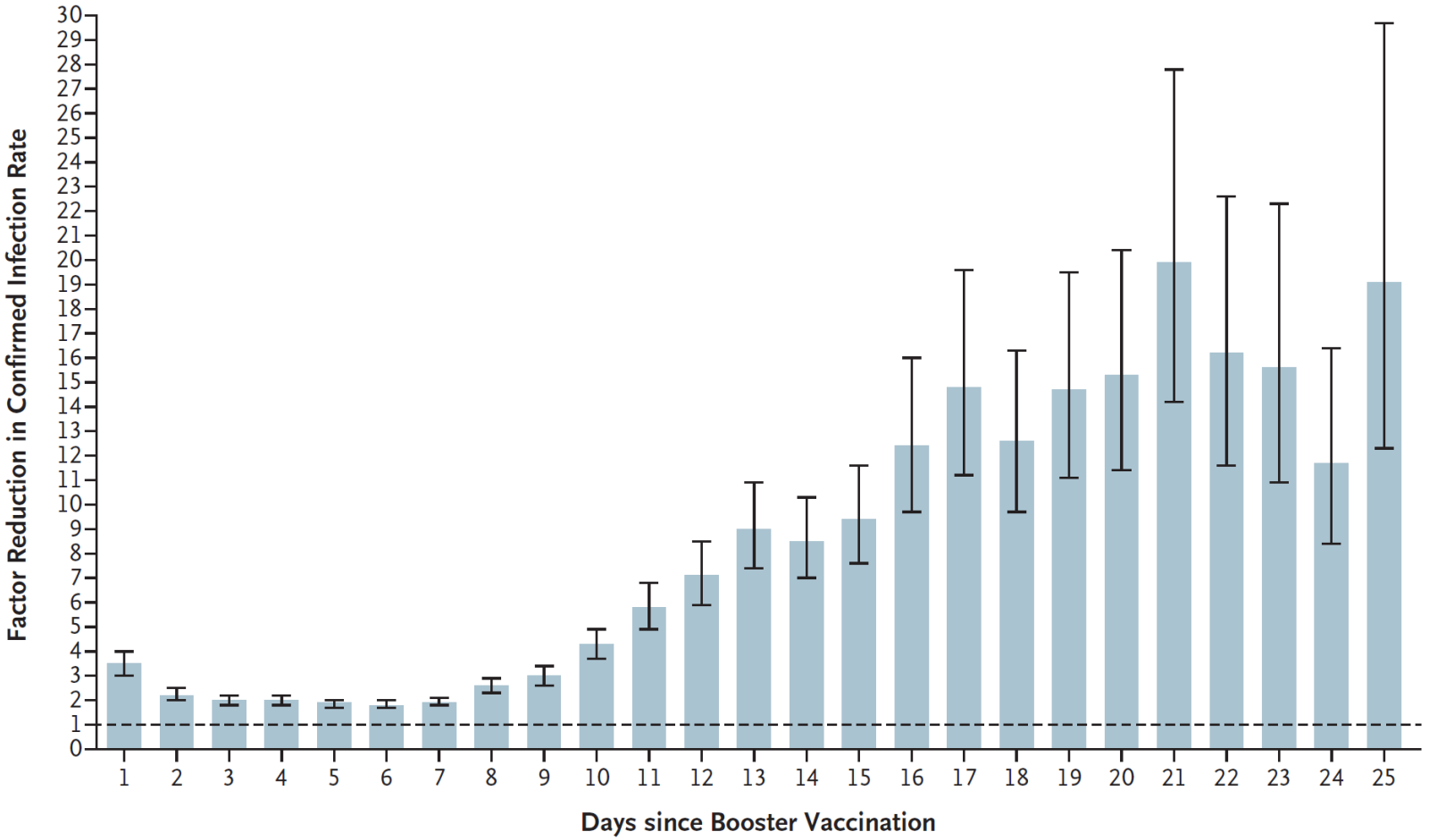


Does the order of vaccines as prime and boost matter?

Liu X, et al, Lancet preprint 2021

peer review

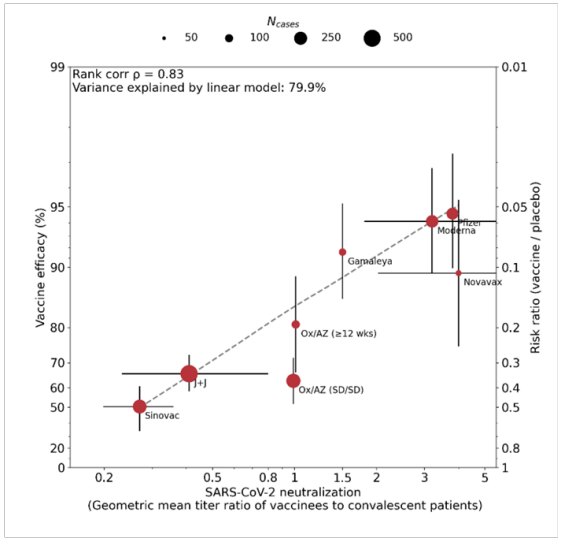
Booster vaccination with BNT162b2 reduces infection



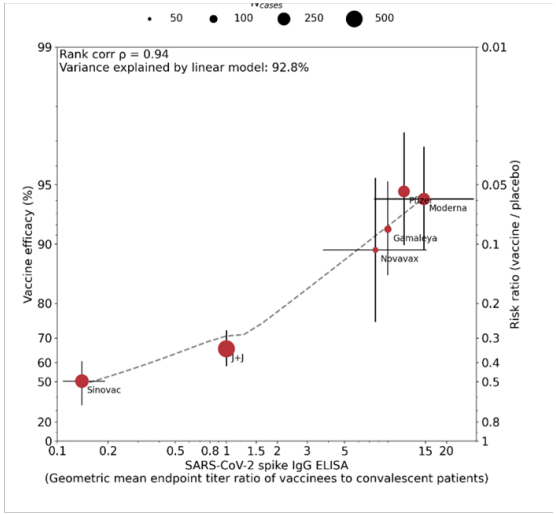
Bar-on et al, NEJM 2021

Immune correlates of protection (ICP): NAb or BAb?

COMPARISON OF GMT RATIO FROM PHASE I/II STUDIES / CONVALESCENT PLASMA

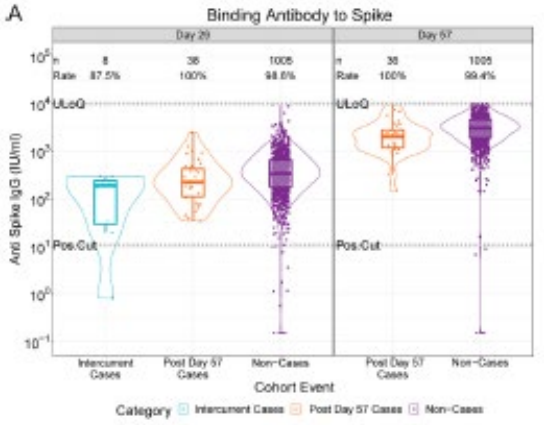


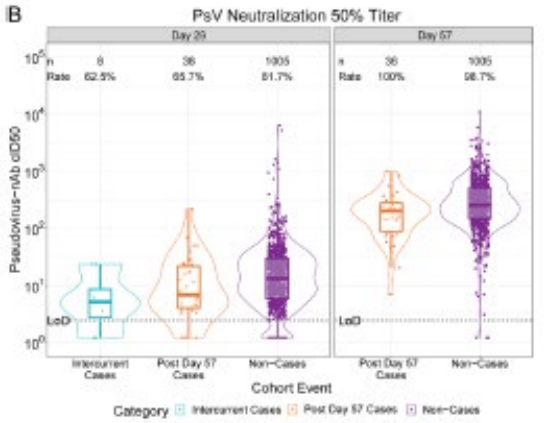
Correlation with neutralizing antibody (Nab)

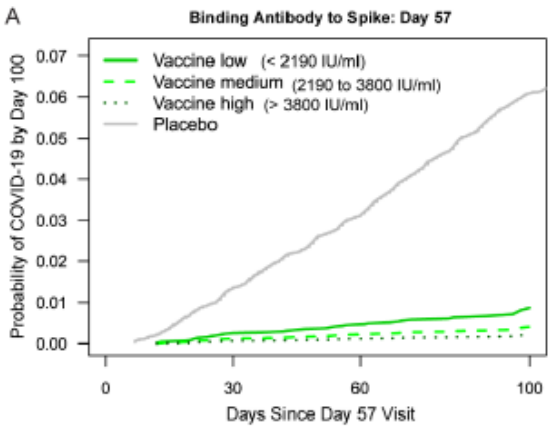


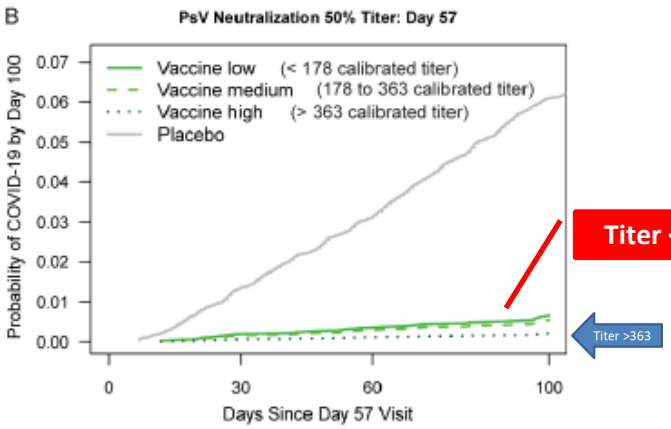
Correlation with binding antibody (Bab)

COVAX Clinical Development and Operations SWAT team, 25 Feb 2021









Gilbert et al, Medrxiv 2021. BAb and PsV Ab among vaccinated, infected cases and vaccinated uninfected controls

What does an immune correlate of protection tell us about long-term protection?

Efficacy, effectiveness, herd immunity

Approximate Basic Reproduction Numbers (in Developed Countries) and Implied Crude Herd Immunity Thresholds (*H*, Calculated as *1-1*/R_0), VE, E for Selected Diseases

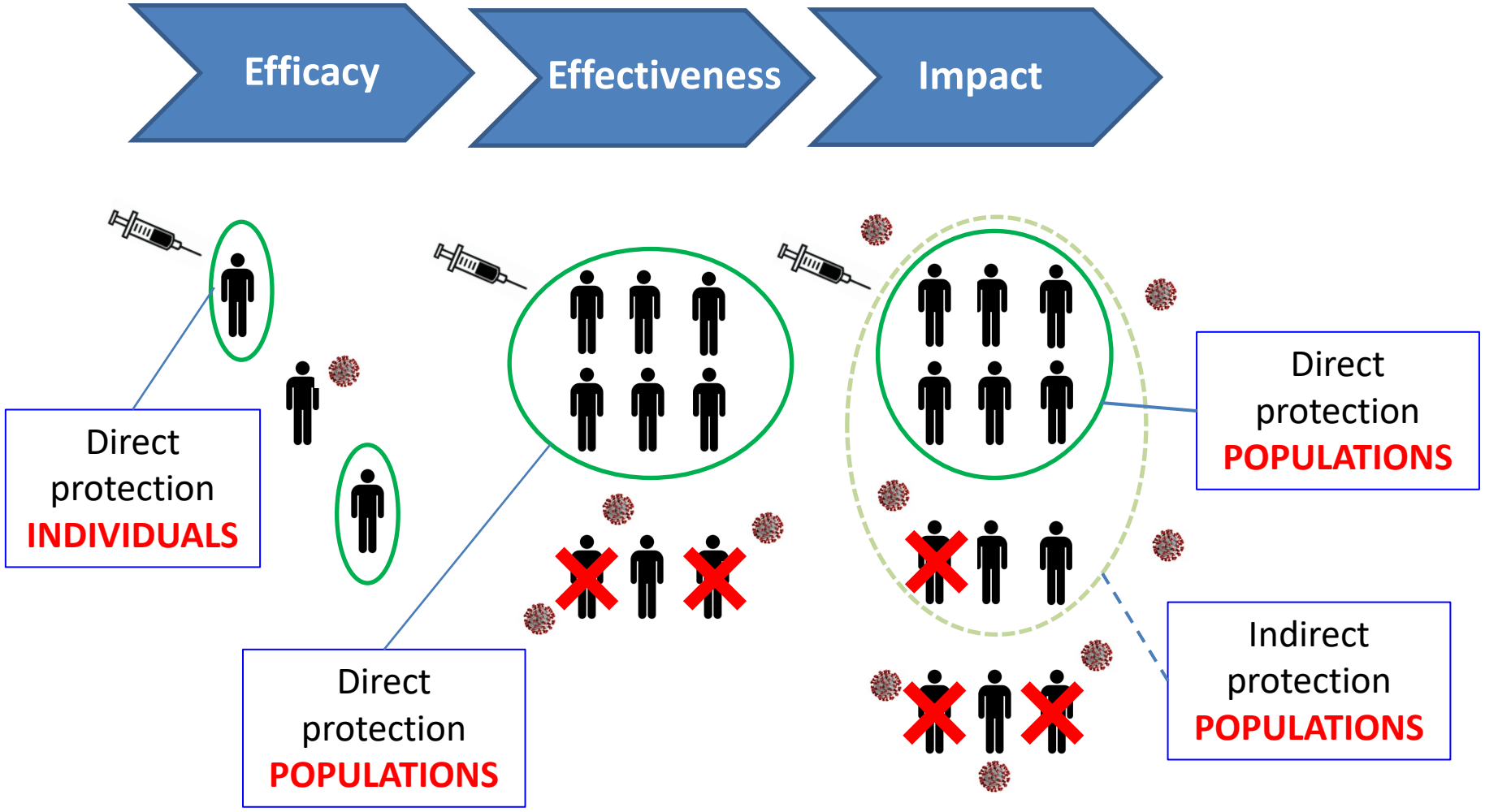
Infection	Basic Reproduction Number (R_0)	Herd Immunity Threshold (%)	Vaccine Efficacy (%)	Effectiveness	References
Diphtheria	6-7	85	97	>95	70,71
Measles	12-18	55-94	94	90-95	71
Mumps	4-7	75-86	95	78	71
Pertussis	12-17	92-94	70-90	75-85	71
Polio	12-15	50-93	80-90	>90	71
Rubella	6-7	83-85	94-95	>95	71
Smallpox	5-7	80-85	90-97	?	71
Ebola	1.5-2.5	33-60	95-100	70	65
Varicella	8-10	87-90	90-98	>95	71
Spanish flu 1918	2-3	50-67	NA	NA	72
Cholera	1-2	50%	42-66%	86%	73-75
SARS-CoV-2	2.5 – 5.8	60-83	60-95%	?	72,76

The vaccines have been shown to prevent disease, not infection or transmission. Herd immunity is about protection from transmission.

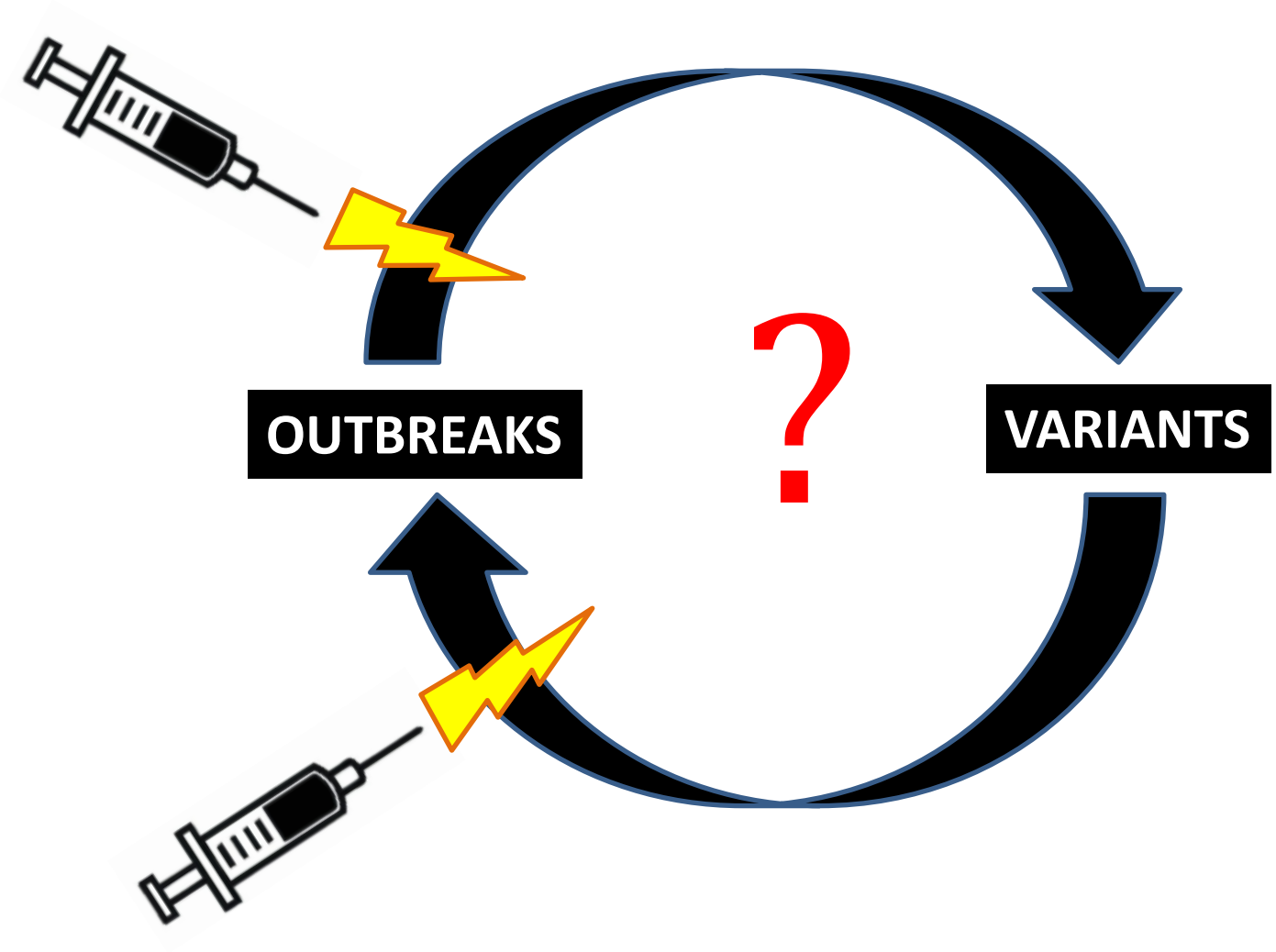
[1]Petersen et al, Lancet, 2020 & Ke et al, MedRxiv, 2020
[2]Plotkin SE, et al. Vaccines, 6th ed
[3]US CDC Pink Book, but no formal controlled trials

Will boosters affect infection or transmission?

That is, do they prevent acquisition and lower viral load in vaccinees post infection?



Can boosters break the outbreak – variants cycle?



Is there a booster in your future: probably, but what & when?

Boosts/Mix & Match

- **Homologous: it does increase Nab levels**
- **Heterologous: give the AZ first not Pfizer**
- **Does increasing Nab increase protection after boosting: vs infection or severity of disease?**
- **Does decreased effectiveness imply waning immune response or changing variants?**
- **Could random mixing and matching hurt?**

➢ **Boosters should be subject to systematic not empirical testing**

Should we vaccinate everyone before we give boosters to those who are not elderly or immune compromised or present particular risk of acquisition or transmission?

IVI is an International Organization dedicated to Global Health

Global Vaccine Research Institute

- **HQ and labs at Seoul National University**
- **Field programs in 28+ countries: Asia, Africa, Latin America**
- **23 nationalities in workforce of 184**

OECD-recognized International Organization (not for profit)

- **UNDP initiative**
- **First international organization in Korea (1997)**
- **36 countries and WHO as state parties (Madagascar, Argentina, Colombia, UAE, and Spain pending final submission to UN)**

Thank you for your attention!