Homologous booster doses: immunogenicity data

David C. Kaslow, MD | PATH

SAGE Meeting

7th December 2021

Context and key assumptions

- Booster dose(s) are administered to *restore* a (previously) sufficient protective immune response rate in a vaccinated population that achieved an initial sufficient immune response rate but with time (e.g., through waning immunity and/or new variants) has fallen below a rate deemed sufficient in the vaccinated population.

- While accumulating evidence support the use of specific immunoassays as correlate(s) of *initial protection*, insufficient evidence exists to determine whether those or other immunoassays are correlate(s) of *durability of protection*

- Immunogenicity readouts provide a *potential* early signal of the likelihood for cross-protection of an immune response against new variants and *supplementary* data to vaccine effectiveness evidence

Immunogenicity from company-sponsored clinical studies

(data from regulatory presentations)

Response to a 50-µg booster dose of mRNA 1273

nature medicine ARTICLES
https://doi.org/10.1038/s41591-021-01527-y
Check for updates

OPEN

Safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in healthy adults: an interim analysis

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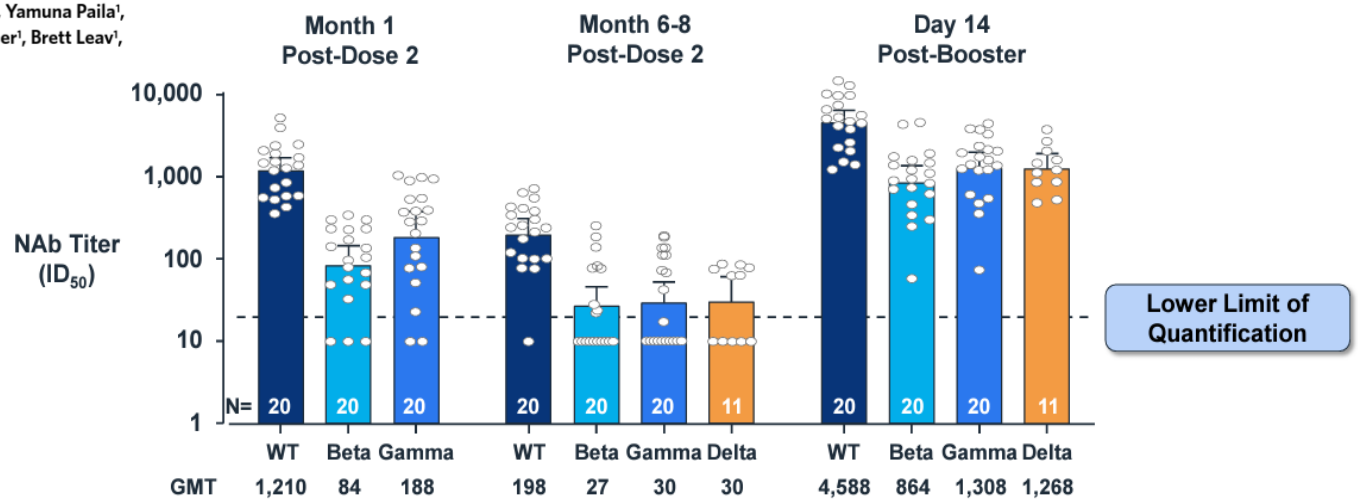
Overview

Study	Choi et al, Nat. Med. 2021
Trial ID	NCT04405076
Country	USA
Vaccine	mRNA-1273 (50 µg)
Population	Phase 3 COVE, Healthy adults, 27-79y
N	60 (20 per group)
D2–D3 interval	5.4 – 7.5 mo

Exploratory Analysis Against Variants of Concern



WT: original strain (D614G)
Research VSV pseudoneutralization assay used

Source: https://www.fda.gov/media/153089/download

Conclusions:

- **Waning:** statistically significant decline in nAb (psVNA; ID_{50}) titer across all strains studied (original D614G, Beta, Gamma, and Delta)
- **Boost:** induced strong anamnestic responses (up to 4.4-fold higher than peak titers post-primary series), with a 23- to 44-fold increase from titers 6-8 months after primary series, including for variants of concern studied

Choi et al., Nat. Med. 2021; doi 10.1038/s41591-021-01527-y

Response to a 30-µg booster dose of BNT162b2

The NEW ENGLAND JOURNAL of MEDICINE

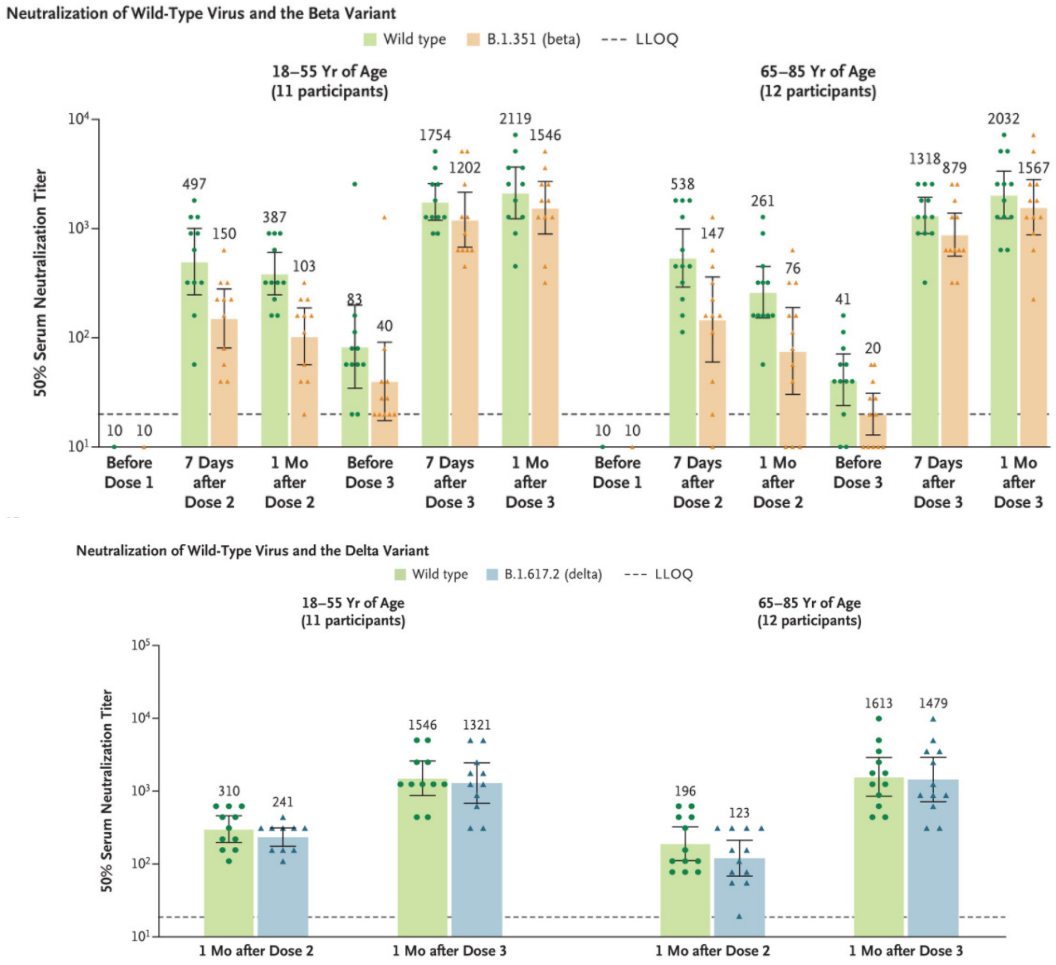
CORRESPONDENCE

SARS-CoV-2 Neutralization with BNT162b2 Vaccine Dose 3

October 21, 2021
N Engl J Med 2021; 385:1627-1629
DOI: 10.1056/NEJMc2113468

Overview

Study	Falsey et al, NEJM 2021
Trial ID	NCT04368728
Country	USA
Vaccine	BNT162b2 (30 µg)
Population	Part 1 Phase 1/2/3 , Healthy/disease stable adults, 18-85y
N	11 (24-55y); 12 (65-75y)
D2–D3 interval	7.9 to 8.8 mo



Source: https://www.nejm.org/doi/10.1056/NEJMc2113468

Conclusions:

- **Waning:** statistically significant decline in nAb titers (50% plaque-reduction neutralization test) against original D614G and Beta strain
- **Boost:** induced strong anamnestic responses (5 to 12-fold higher than peak titers post-primary series), with a 25 to 50-fold increase from titers 8-9 months after primary series, including for variants of concern studied

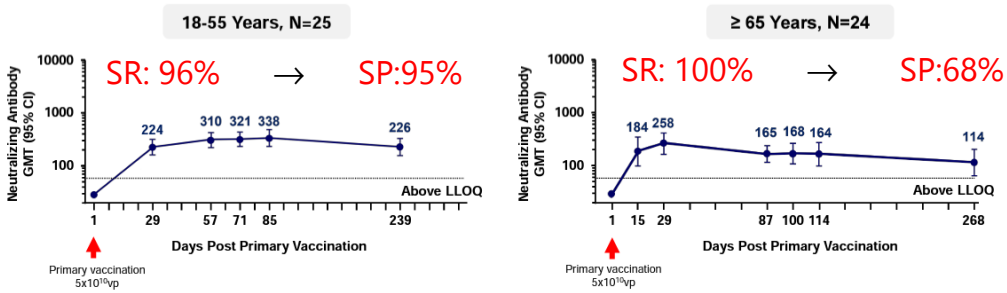
Falsey, et al., Nat. Med. 2021; doi 10.1056/NEJMc2113468

Response to a second dose of Ad26.COV2.S

Durability of antibody responses elicited by a single dose of Ad26.COV2.S and substantial increase following late boosting

Authors: Jerald Sadoff,[1#] Mathieu Le Gars,[1#] Vicky Cardenas,[2] Georgi Shukarev,[1] Nathalie Vaissiere,[3] Dirk Heerwegh,[3] Carla Truyers,[3] Anne Marit de Groot,[1] Gert Scheper,[1] Jenny Hendriks,[1] Javier Ruiz-Guiñazú,[3] Frank Struyf,[3] Johan Van Hoof,[1] Macaya Douoguih,[1] Hanneke Schuitemaker[1]

Janssen COV1001: Humoral Immune Responses Persist Over Time, Following a Single Dose (18-55 and ≥ 65 years)

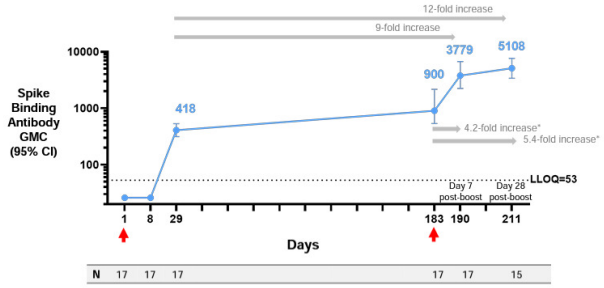


SR: % seroresponse
SP: % detectable Ab

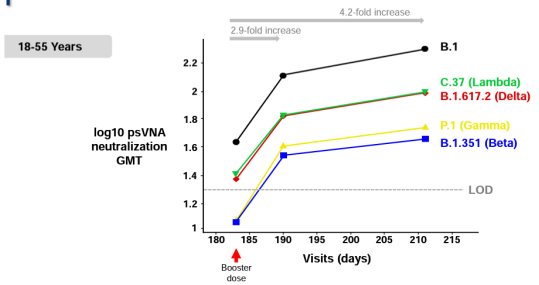
Overview

Study	Sadoff et al, medRxiv 2021
Trial ID	NCT04436276
Country	USA; Belgium
Vaccine	Ad26.COV2.S (5×10^{10} vp)
Population	COV1001 Healthy adults, 18-55;≥65y
N	17-25 per group
D1–D2 interval	6 mo

COV1001: Boost at 6 Months Increases Antibody Titers by 9- to 12-fold



COV1001: Booster 6 Months After Single-Dose Primary Regimen Proportionally Increases nAb Levels Against Variants of Concern



Source: https://www.fda.gov/media/153129/download

Conclusions:

- **Waning:** over >200d after single dose, nAb (wtVNA) GMT declined minimally in 18-55y and 2.3-fold in ≥65y
- **Boost:** induced strong anamnestic spike Ab GMT responses (9- to 12-fold higher than peak titers after single dose), with 2.9- to 4.2-fold increase in nAb (psVNA) GMT across all strains studied (original D614G, Beta, Gamma, Delta, and Lambda)

Sadoff et al., medRxiv 2021; doi 10.1101/2021.08.25.21262569

Immunogenicity from other clinical studies

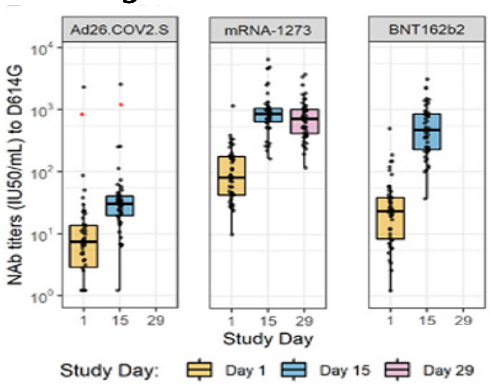
(today's heterologous booster presentation)

MixNMatch

Overview

Study	Atmar et al; medRxiv
Country	USA
Study type	Non-randomised CT
Population	Adults, 19–85y

Homologous boost Ad26 & mRNA

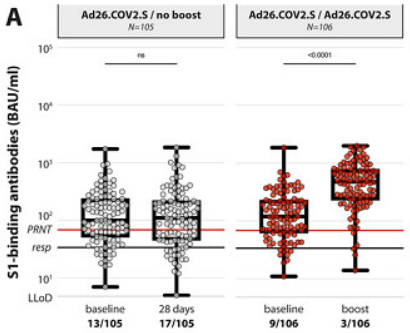


SWITCH

Overview

Study	Sablerolles et al; medRxiv
Country	Netherlands
Study type	Single-blind RCT
Population	Adults, 18–65y

Homologous boost Ad26

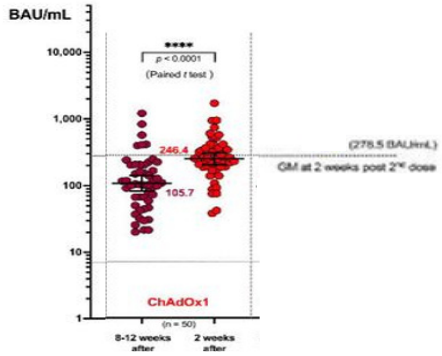


Thailand Cohort

Overview

Study	Angkasekwinai et al; medRxiv
Country	Thailand
Study type	Cohort
Population	Adults, 18–60y

Homologous boost ChAdOx1



COV-BOOST

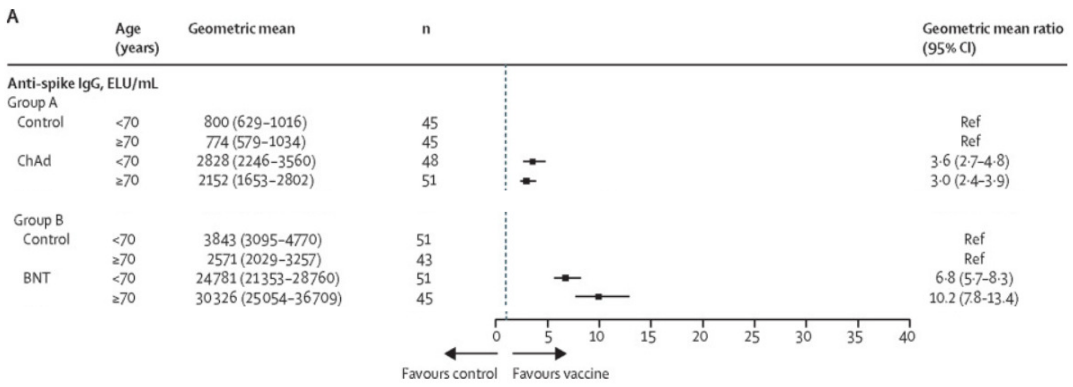
Overview

Study	Munro et al; Lancet
Country	UK
Study type	Observer-blind RCT
Population	Adults, 18–65y

Homologous boost

ChAdOx1

BNT162b2



Immunogenicity from other clinical studies

(inactivated virus vaccine booster presentation – 05 OCT 2021 SAGE meeting)

Inactivated vaccine homologous 2- and 3-dose schedules - Summary

- Antibodies induced by 2-dose primary series of CoronaVac and BIBP wane swiftly over 6 months, becoming undetectable in over two-thirds of study participants
- Antibodies binding to Alpha, Beta, and Delta variants were significantly lower by 3 months after Dose 2 (D2) of CoronaVac compared to 2-3 weeks after D2
- Dose 3 (D3) of CoronaVac/BIBP at 6 months elicits peak nAb titres 3–8-fold higher than those observed after D2; whereas D3 of CoronaVac given 1 month after D2 elicits peak nAb titres 1.3–2-fold higher than those observed after D2

Summary

- *Based on limited immunogenicity data*, neutralizing and/or binding assay titers:
  - variably decline over time for mRNA, viral vector (VV), and inactivated virus (IA) vaccines
  - rate of decline: IA > mRNA > VV
  - greater decline in older adults

- A homologous booster dose restores neutralizing and/or binding assay titers to at least peak post-primary series and frequently several fold higher (i.e., anamnestic response)

- As vaccine effectiveness evidence accumulates and models are refined, immunoassays may be found to be reliable predictors of restored protective immunity

Booster Dose Vaccine Effectiveness

December 7, 2021

Minal K. Patel, MD

Daniel R. Feikin, MD

Definitions

	Efficacy	Effectiveness
Absolute	RCT comparing vaccinated to unvaccinated	Real world (observational) studies comparing vaccinated to unvaccinated
Relative	RCT comparing boosted to non-boosted	Real world (observational) studies comparing boosted to non-boosted

- Absolute Efficacy/Effectiveness will always be higher than relative as the non-boosted still have some protection resulting in a lower estimate
- The difference between the relative and absolute efficacy/effectiveness is dependent on the non-boosted efficacy/effectiveness compared to the unvaccinated

Vaccine Efficacy

Janssen-Ad26.COV 2.S ENSEMBLE 2 RCT

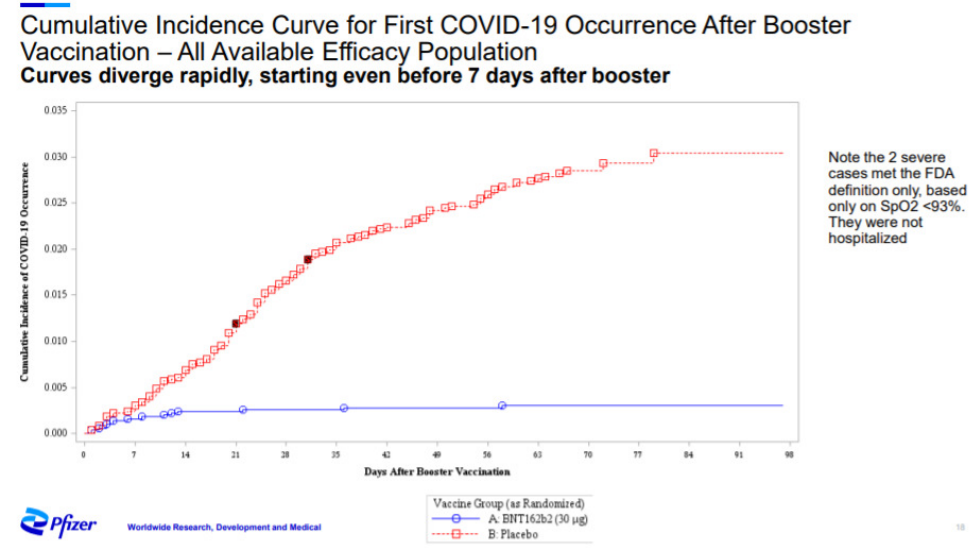
- Global RCT designed to measure 2 dose absolute vaccine efficacy with 56 day interval
  - 31,300 participants randomized to 2 doses or 0 doses
    - Due to availability of other vaccines/unblinding, only 4,245 (29%) were in per protocol analysis, with median follow up of 36 days post dose 2 (range 0-172 days)
    - 38% Alpha, 4% Delta

	1 dose efficacy 15-56 days post dose 1	2 dose efficacy 14+ days post dose 2
Infection		51 (30-66%)
Asymptomatic Infection		34 (-6-60%)
Moderate-severe/critical	68% (58-76%)	75% (55-87%)
Severe critical	92% (76-98%)	100% (33-100%)

Janssen Biotech. (2021). *Vaccines and Related Biological Products Advisory Committee October 14-15, 2021 Briefing Document - Sponsor (Janssen).* https://www.fda.gov/media/152954/download

Pfizer BioNTech-Comirnaty (BNT162b2) Booster RCT C4591031

- 10,000 persons ≥16 years who had already received 2 doses of BNT162b2
  - Randomized with age stratification to receive either placebo or 3rd dose at least 6 months after the 2nd dose
    - 65% of 3rd/placebo administered 10-12 months after dose 2
- Results
  - Relative VE against disease in those without prior infection (7 days-<2 months post boost): 95.3% (89.5-98.3)
  - No difference by age group, sex, race, ethnicity, comorbidity



Vaccine Effectiveness

Israel: Relative VE of Pfizer BioNTech-Comirnaty -Clalit

- Methods
  - July 30-Sept 23
  - Cohort study with 1:1 matching of persons with 3rd dose versus those who received 2nd dose 5+ months ago
  - Outcome: infection, disease, hospitalization, severe, death 7+ days post dose 3
- Results
  - 728,321 in each arm
  - Median follow up: 13 days (IQR 6-21, max 55 days)
- Risk of bias: Moderate

	# of events in 3 dose	# of events in 2 dose	Relative VE of 3 vs 2 dose
Infection	1135	6131	88 (87-90)
Disease	514	3345	91 (89-92)
Hospitalization	29	231	93 (88-97)
Severe disease*	17	157	92 (82-97)
Death	7	44	81 (59-97)

*US FDA definition

Barda, N., Dagan, N., Cohen, C., Hernán, M. A., Lipsitch, M., Kohane, I. S., Reis, B. Y., & Balicer, R. D. (2021). Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *The Lancet*. https://doi.org/10.1016/S0140-6736(21)02249-2

Israel: Relative VE against infection of Pfizer BioNTech-Comirnaty —Maccabi Study 1

- Methods
  - ≥40 year olds with 2nd or 3rd dose between January 2021-August 21, 2021
  - Tested between August 1-August 21
  - Different types of analyses
    - Test-negative design
    - Matched case-control
- Results (n=182,076 tests in 153,753 persons)

Time after booster	Test-negative analysis	Matched case-control (conditional)
7-13 days	48% (42-54%)	68% (64-72%)
14-20 days	79% (72-84%)	84% (79-88%)

- Risk of Bias: Moderate
- Conclusion: Relative vaccine effectiveness against infection of Pfizer BioNTech-Comirnaty booster dose is high

Patalon, T., Gazit, S., Pitzer, V. E., Prunas, O., Warren, J. L., & Weinberger, D. M. (2021). Short Term Reduction in the Odds of Testing Positive for SARS-CoV-2; a Comparison Between Two Doses and Three doses of the BNT162b2 Vaccine. *MedRxiv*, 2021.08.29.21262792. https://doi.org/10.1101/2021.08.29.21262792

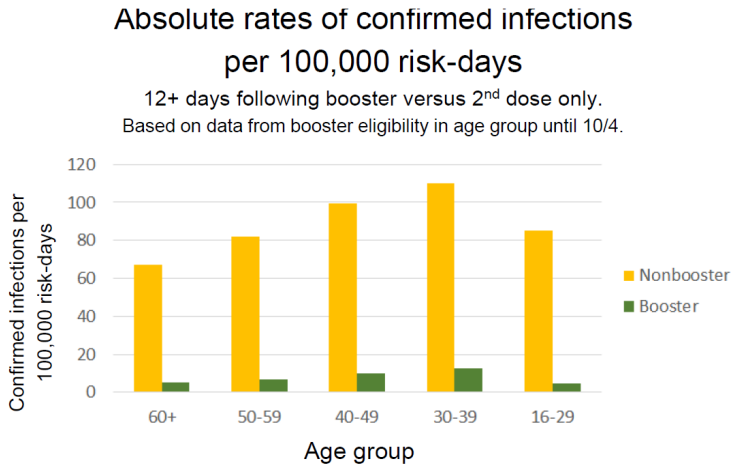
Israel: Relative VE against infection of Pfizer BioNTech-Comirnaty —Maccabi Study 2

- Methods
  - August 7-October 15
  - Retrospective cohort study with matching
  - Comparing those 2-dose vaccinated in January-February to 3 dose vaccinated (>7 days)
- Results
  - n=141,437 3 dose; n=724,540 2→3 dose; 81,244 only 2 dose
  - Relative VE against infection: 89.1% (87.5-90.5)
    - <60 years: 88.4% (87.7-89.1)
    - ≥60 years: 87.7% (86.4-88.8)
- Risk of bias: Serious

Saciuk, Y., Kertes, J., Shamir Stein, N., & Ekka Zohar, A. (2021). Effectiveness of a third dose of BNT162b2 mRNA vaccine. *The Journal of Infectious Diseases*. https://doi.org/10.1093/infdis/jiab556

Israel: Relative VE against infection and severe disease, and death—MOH

- Methods
  - July 30-October 6
  - Persons who had 2 doses of Pfizer BioNTech-Comirnaty ≥5 months earlier
    - Compared rates boosted (≥12 days) to non-boosted
  - Unlike HMO analyses, based on rates in national surveillance data
- Results
  - 4,621,836 persons
- Risk of Bias: Serious



Outcome	Age Group	Relative VE (95% CI)
Infection	16-29	94% (94-95)
	30-39	89% (88-89)
	40-49	90% (89-90)
	50-59	92% (91-92)
	≥60	92% (92-92)
Severe Disease	40-59	95% (90-98)
	≥60	95% (94-96)
Death	≥60	93% (89-96)

Bar-On, Y. M., Goldberg, Y., Mandel, M., Bodenheimer, O., Freedman, L., Kalkstein, N., Mizrahi, B., Alroy-Preis, S., Ash, N., Milo, R., & Huppert, A. (2021). Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. *New England Journal of Medicine*, *385*(15), 1393–1400. https://doi.org/10.1056/NEJMoa2114255
Bar-On, Y. M., Goldberg, Y., Mandel, M., Bodenheimer, O., Freedman, L., Alroy-Preis, S., Ash, N., Huppert, A., & Milo, R. (2021). Protection Across Age Groups of BNT162b2 Vaccine Booster against Covid-19. *MedRxiv*, 2021.10.07.21264626. https://doi.org/10.1101/2021.10.07.21264626

UK: VE against disease of Pfizer BioNTech-Comirnaty booster

- TND study of ≥50 years evaluating VE against symptomatic disease
  - September 13-November 1, 2021
  - 2 doses of AstraZeneca-Vaxzevria+1 Pfizer BioNTech-Comirnaty or 3 doses of Pfizer BioNTech-Comirnaty compared to
    - 2 dose recipients >140 days post dose 2 but no dose 3
    - Unvaccinated

Comparison group	2 AstraZeneca-Vaxzevria+ 1 Pfizer BioNTech-Comirnaty (14+ days)	3 Pfizer BioNTech-Comirnaty (14+ days)
Relative VE comparing to 2 dose recipients >140 days post dose 2	87.4% (84.9-89.4)	84.4% (82.8-85.8)
Absolute VE comparing to unvaccinated	93.1% (91.7-94.3)	94.0 (93.4-94.6)

- Risk of bias: Moderate

Andrews, N., Stowe, J., Kirsebom, F., Gower, C., Ramsay, M., & Lopez Bernal, J. (2021). Effectiveness of BNT162b2 (Comirnaty, Pfizer-BioNTech) COVID-19 booster vaccine against covid-19 related symptoms in England: test negative case-control study. *MedRxiv*, 2021.11.15.21266341. https://doi.org/10.1101/2021.11.15.21266341

Chile: Absolute VE against infection, disease, hospitalization, ICU admission of 3 vs 2 vs 0

- Cohort administrative database study
  - In cohort 2 dose Sinovac-CoronaVac+ booster
    - 1.7 million AstraZeneca-Vaxzevria
    - 966,000+ Pfizer BioNTech-Comirnaty
    - 165,000+ Sinovac-CoronaVac
  - Risk of Bias: None (presentation, no preprint)

	Infection	Disease	Hospitalization	ICU admission
2 doses of Sinovac-CoronaVac	52 (52-53)	55 (55-56)	84 (83-84)	87 (86-88)
3 doses of Sinovac-CoronaVac	68 (61-73)	71 (64-76)	75 (65-82)	79 (59-89)
2 doses Sinovac-CoronaVac+AstraZeneca-Vaxzevria	90 (89-91)	93 (92-94)	96 (95-97)	98 (96-99)
2 doses of Sinovac-CoronaVac+Pfizer BioNTech-Comirnaty	93 (91-94)	95 (93-96)	89 (84-93)	90 (78-95)

Araos, R and Jara, A. https://cdn.who.int/media/docs/default-source/blue-print/chile_rafael-araos_who-vr-call_25oct2021.pdf?sfvrsn=7a7ca72a_7

USA: Relative VE in Veterans against Infection and Hospitalization

- Match cohort study from September 23-November 25, 2021

	Pfizer BioNTech-Comirnaty	Moderna-mRNA-1273
Number of matched pairs	74,032	55,098
Median age (IQR)	72 (64-75)	72 (66-77)
% Males	94%	95%
Median follow up time (IQR)	30 days (14-44)	16 days (8-25)
Relative VE against Infection (95% CI)	45.7% (37.9 -52.5)	46.6% (36.4 - 55.3)
Relative VE against Hospitalization (95% CI)	44.8% (26.6 – 58.4)	50.0% (26.2 - 66.1)

IQR=Interquartile Range VE=Vaccine Effectiveness CI=Confidence Intervals

- Risk of Bias: pending

Sharma, A., Oda, G., & Holodniy, M. (2021). Effectiveness of a third dose of BNT162b2 or mRNA-1273 vaccine for preventing post-vaccination COVID-19 infection: an observational study. *MedRxiv*, 2021.11.29.21266777. https://doi.org/10.1101/2021.11.29.21266777

Summary

	# of Studies	Infection	Disease	Hospitalization/ Severe disease/death
2 doses of Janssen-Ad26.COV 2.S	1	51% efficacy	75% efficacy	100% efficacy
3 doses of Pfizer BioNTech-Comirnaty	5	46-94% rVE	95% relative efficacy 84-91% rVE 94% aVE	45-95% rVE
2 doses AstraZeneca-Vaxzevria+3rd Pfizer BioNTech-Comirnaty	1		87% rVE 93% aVE	
2 doses Sinovac-CoronaVac+3rd Pfizer BioNTech-Comirnaty	1	93% aVE	95% aVE	89-90% aVE
2-dose Sinovac-CoronaVac+3rd AstraZeneca-Vaxzevria	1	90% aVE	93% aVE	96-98% aVE
3 doses of Sinovac-CoronaVac	1	68% aVE	71% aVE	75-79% aVE
3 doses of Moderna-mRNA-1273	1	47% rVE		50% rVE

- Limited data
- Additional dose increases efficacy/effectiveness
  - No difference by age
  - Absolute gain dependent on vaccine and starting point
- Need to consider biases: first to get boosted might be different—more health seekers, lower risk of exposure or maybe higher risk of exposure
- Duration of boost—unknown as most studies short term (<2 months)

rVE=relative vaccine effectiveness; aVE=absolute vaccine effectiveness

Safety of booster vaccination

Sonali Kochhar

SAGE meeting 7 December 2021

Heterologous Booster Doses: Preliminary Safety/Reactogenicity Data

Study	Priming vaccine	Booster vaccine	N	Interval pre-boost
Moghnieh et al; Vaccine	2 x Sinopharm (SP)	Pfizer (BNT)	50	<3m
Angkasekwinai et al; medRxiv	2 x Sinovac (SV)	Astrazeneca (AZ)	65	8-12w
	2 x SV	BNT	100	8-12w
	2 x AZ	SP	23	8-12w
	2 x AZ	RNA	100	8-12w
Patamatamkul et al; medRxiv	2 x SV	AZ	18	~4m
	2 x SV	BNT	23	~4m
Pun Mok et al; medRxiv	2 x SV	BNT	40	>1m
Munro et al, Lancet	2 x AZ 2 x BNT	BNT (full, half dose), JNJ, Moderna (MOD), AZ	2878	>2-3m
Atmar; medRxiv	1 x JNJ	MOD/BNT	106	≥3m
	2 x MOD 2 x BNT	JNJ	201	≥3m
Sablerolles; medRxiv	1 x JNJ	MOD/BNT	223	3m

- No safety concerns identified across the studies
- Reactogenicity profiles similar to primary series of vaccines
- Modest sample size for most studies

Homologous Booster Doses: Preliminary Safety/Reactogenicity Data

RCT extensions

Study	Priming vaccine	Booster vaccine	N	Interval pre-boost
Pfizer unpublished data	2 x BNT	BNT	>10,000	>6m
Choi et al; Nat Med	2 x MOD	MOD/ MOD (VOC)	79	6-7m
Sadoff et al; medRxiv	1 x JNJ	JNJ (5×10^{10},1.2×10^{10})	98	6m
Flaxman et al; Lancet	2 x AZ	AZ	80	5-10m
Pan et al; medRxiv	2 x SV	SV (3/6 µg)	540	1/6m
Li et al; medRxiv	2 x SV	SV (1.5,3,6 µg)	256	≥8m
Gilboa et al, J Infect Dis	2 x BNT	BNT	208	>5m

- No major safety concerns identified across the studies
- Reactogenicity profiles consistent with primary series of vaccine in question

DMID 21-0012 - Heterologous Platform Boost Study (Mix and Match)

Group	Sample Size	EUL Vaccine	Interval (weeks)	Booster vaccination
1	53	JNJ	≥12 (mean 13.7)	MOD (100 mcg)
2	51	2 x MOD	≥12 (mean 16.4)	
3	50	2 x BNT	≥12 (mean 16.8)	
4	50	JNJ	≥12 (mean 17.7)	JNJ ($5x10^{10}$ vp)
5	49	2 x MOD	≥12 (mean 19.3)	
6	51	2x BNT	≥12 (mean 20.6)	
7	53	JNJ	≥12 (mean 19.9)	BNT (30 mcg)
8	51	2 x MOD	≥12 (mean 22.9)	
9	50	2 x BNT	≥12 (mean 24.1)	

- Safety and reactogenicity seen on study days 15 and 29
- Groups matched for age, sex, race, ethnicity
- Reactogenicity similar to that reported for the primary series. Injection site pain, malaise, headache, and myalgia occurred in more than half the participants
- Most related AEs were Grade 1 or 2 severity
- No safety concerns identified

Conclusion

- Vaccine effectiveness reported following heterologous booster doses e.g Chile (SV-SV-AZ, *n* = 1.7M; SV-SV-BNT, *n* = ~1M) but without safety data
- Homologous and heterologous booster well-tolerated
- Reactogenicity profiles similar to the primary series
- Most AEs mild to moderate and transient