Covid-19 Vaccine Development

How 30,000 Nucleotides Changed the World

Update in Hospital Medicine
October 4, 2021

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Dana-Farber Cancer Institute
Brigham and Women's Hospital
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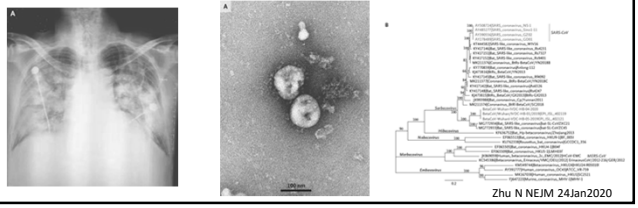
Disclosures

- Co-PI for the NIH-Moderna mRNA-1273 study
  - All funding for my activities from NIAID-NIH

The NEW ENGLAND JOURNAL of MEDICINE

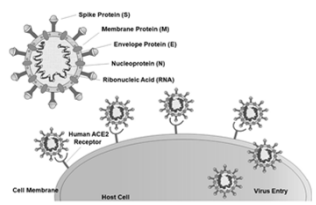
BRIEF REPORT

A Novel Coronavirus from Patients with Pneumonia in China, 2019



Zhu N NEJM 24Jan2020

Viral Genome



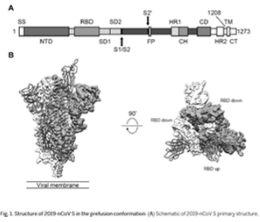


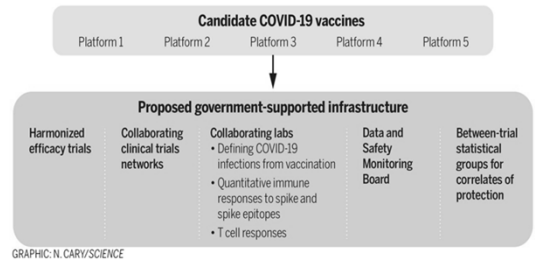
Fig. 1. Structure of 2019-nCoV S in the prefusion conformation. (A) Schematic of 2019-nCoV S primary structure.

Wrapp et al. Science 19 Feb 2020
Naqvi A et al. Vaccine 13Jun2020

US Advanced Development for COVID-19 Vaccine Candidates

Company	Platform	Product	Vaccination dose/schedule	Phase 3 Start
moderna	mRNA	mRNA: encodes 2P-stabilized Spike, TM, FI	2 doses at 100 μg (0, 28 days)	27July2020
BIONTECH	mRNA	mRNA: encodes stabilized SARS-CoV-2 Spike	2 doses at 30μg (0, 21 days)	27July2020
OXFORD AstraZeneca	Ad Vector	Replication incompetent ChAdOx1 wild type Spike; ΔF; TM	2 doses at 5×10^{10} vp, (0, 28 days)	28Aug2020
janssen	Ad Vector	Replication Incompetent Ad26; stabilized Spike; ΔF; TM	1 dose at 5×10^{10} vp	23Sept2020
NOVAVAX	Recombinant protein Adjuvanted	Baculovirus Expressed trimeric Stabilized Spike, ΔF; TM; trimerization domain; Matrix M	2 doses at 5 μg with Matrix M (0, 21 days)	27Dec2020
SANOFI	Recombinant protein Adjuvanted	Baculovirus Expressed trimeric Stabilized Spike, ΔF; TM; trimerization domain; AS03	5/15 μg +AS03 (0, 21 days)	2021

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) and COVID-19 Prevention Network (CoVPN)



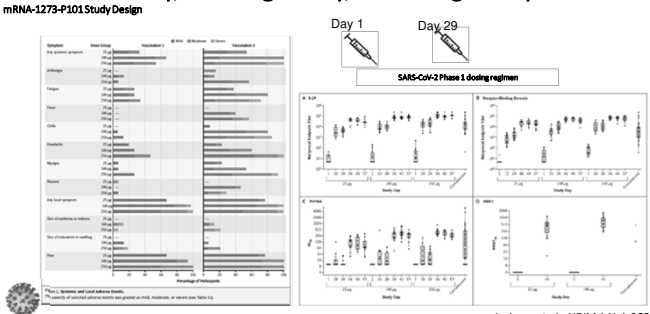
GRAPHIC: N. CARY/*SCIENCE*

Corey L et al. *Science* 2020;science.abc5312

Key mRNA-1273 Development Timeline

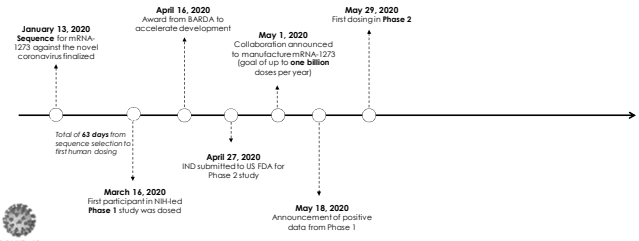
Phase 1: Safety, Reactogenicity, Immunogenicity

mRNA-1273-P101 Study Design



Jackson et al. *NEJM* 14July2020
Anderson et al. *NEJM* 29Sept2020

Key mRNA-1273 Development Timeline



Key Design Considerations: Efficacy Trials

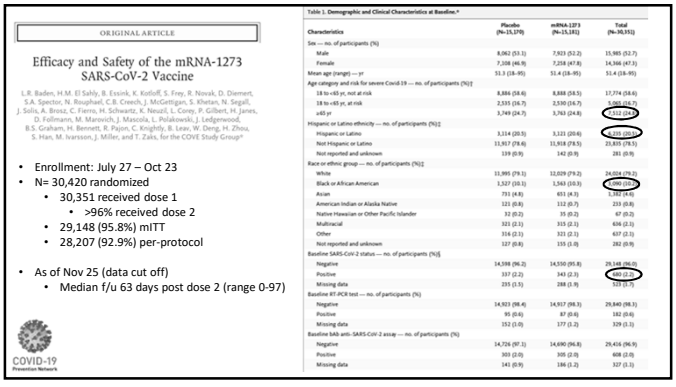
- Population Studied
  - Increased risk for SARS-CoV-2 **acquisition**
  - Increased risk for **complications** (>65yo), medical co-morbidities (DM, obesity, cardio-pulmonary dz)
- Primary End Point(s)
  - **CoV-Dis**
    - Prevention or reduction of severity of ≥moderate COVID illness
  - **CoV-Inf**
    - Reduction in mild COVID illness and asymptomatic infection
  - **CoV-Trans**
    - Reduce shedding of SARS-CoV-2 and acquisition
  - **Safety**
- Key Study Populations
  - mITT
  - Safety
  - **Per protocol**
    - Complete vaccination series (+2weeks), SARS-Cov-2 uninfected
- Statistical considerations
  - VE at least 50% with lower bound of VE >30%

FDA Briefing Document: VRBPAC 22Oct20
FDA Guidance Oct20: https://www.fda.gov/media/142749/download

Phase 3: Evaluate Efficacy, Safety, and Immunogenicity of mRNA-1273 Vaccine in Adults to Prevent COVID-19

- N= 30,000
  - 1:1 vaccine: Placebo
    - Double blind, placebo controlled
    - 2 vaccinations (d1 and d29), follow-up 2 years
  - High risk for SARS-CoV-2 infection and increased risk for complications from infection
  - Population studied needs to represent the country and those disproportionately impacted
- Primary Outcomes
  - Efficacy
    - COVID-19 starting 14 days after second dose (d42)
  - Safety
- Key Statistical Assumptions
  - COVID-19 incidence rate over 6 months 0.75% in placebo group
  - Target Vaccine Efficacy (VE) 60% with lower bound 95% CI >30%

CoVPN 3001, NIH-Moderna mRNA-1273-P301, NCT04470427



ORIGINAL ARTICLE

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

- Enrollment: July 27 – Oct 23
- N= 30,420 randomized
  - 30,351 received dose 1
    - >96% received dose 2
  - 29,148 (95.8%) mITT
  - 28,207 (92.9%) per-protocol
- As of Nov 25 (data cut off)
  - Median f/u 63 days post dose 2 (range 0-97)

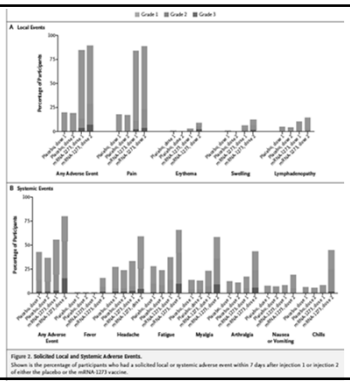
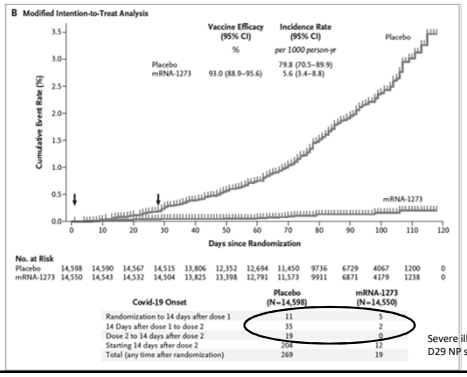


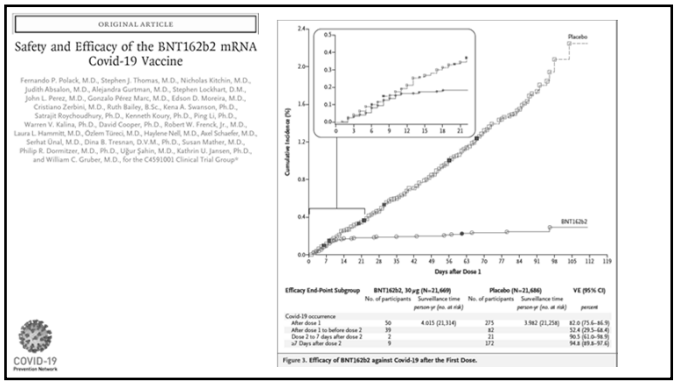
Figure 2. Solicited Local and Systemic Adverse Events.

Shown is the percentage of participants who had a solicited local or systemic adverse event within 7 days after injection 1 or injection 2 of either the placebo or the mRNA-1273 vaccine.



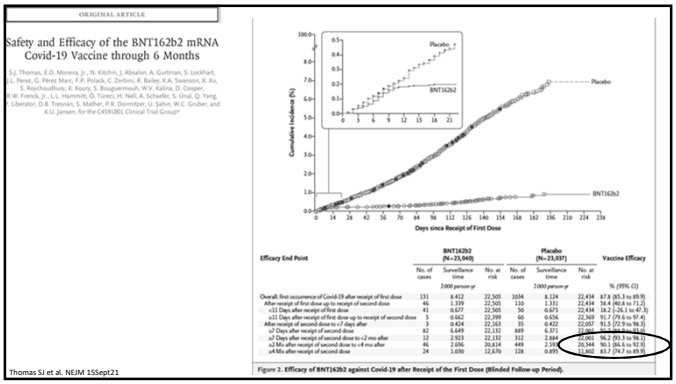
Covid-19 Onset	Placebo (N=14,598)	mRNA-1273 (N=14,550)
Randomization to 14 days after dose 1	11	5
14 Days after dose 1 to dose 2	35	2
Dose 2 to 14 days after dose 2	19	0
Starting 14 days after dose 2	204	12
Total (any time after randomization)	269	19

Severe illness 30 vs 0 cases
D29 NP swab+ 39 vs 15 cases



Efficacy End-Point Subgroup	BNT162b2, 30 µg (N=21,669) No. of participants	Surveillance time person-yr (no. at risk)	Placebo (N=21,686) No. of participants	Surveillance time person-yr (no. at risk)	VE (95% CI) percent
Covid-19 occurrence					
After dose 1	50	4,615 (21,314)	275	3,962 (21,256)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

Figure 3. Efficacy of BNT162b2 against Covid-19 after the First Dose.

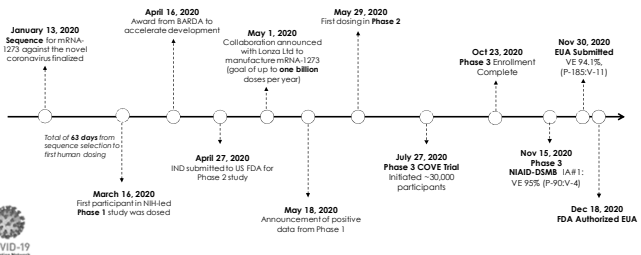


Efficacy End Point	BNT162b2 (N=23,040) No. of cases	Surveillance time 1000 person-yr	No. at risk	Placebo (N=23,037) No. of cases	Surveillance time 1000 person-yr	No. at risk	Vaccine Efficacy % (95% CI)
Overall: first occurrence of Covid-19 after receipt of first dose	131	8.412	22,505	1034	8.124	22,434	87.8 (83.3 to 89.9)
After receipt of first dose up to receipt of second dose	46	1.339	22,505	110	1.331	22,434	58.4 (40.8 to 71.2)
≥12 Days after receipt of first dose	41	0.677	22,505	50	0.675	22,434	18.2 (–26.1 to 47.3)
≥13 Days after receipt of first dose up to receipt of second dose	5	0.662	22,399	60	0.656	22,369	91.7 (79.6 to 97.4)
After receipt of second dose to <7 days after	3	0.424	22,163	35	0.422	22,057	91.5 (72.9 to 98.1)
≥7 Days after receipt of second dose	82	6.649	22,132	889	6.371	22,006	91.3 (89.1 to 93.1)
≥7 Days after receipt of second dose to <2 mo after	12	2.923	22,132	312	2.849	22,006	96.2 (91.3 to 98.7)
≥2 Mo after receipt of second dose to <4 mo after	46	2.696	20,814	449	2.595	20,344	90.1 (86.6 to 92.9)
≥4 Mo after receipt of second dose	24	1.030	12,676	126	0.895	11,402	83.7 (74.7 to 89.9)

Thomas SJ et al. NEJM 15Sept21

Figure 2. Efficacy of BNT162b2 against Covid-19 after Receipt of the First Dose (Blinded Follow-up Period).

Key mRNA-1273 Development Timeline



US FDA: Emergency Use Authorization

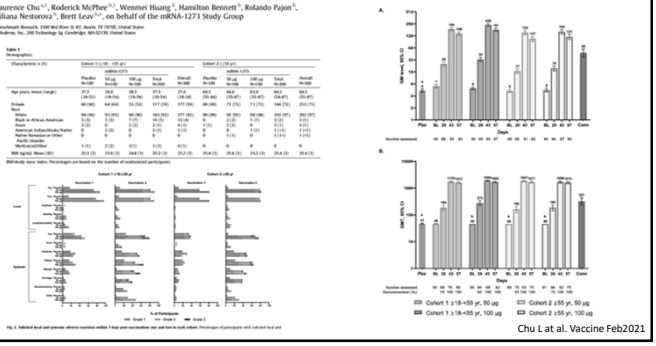
- Nov 15: NIAID DSMB meeting
- Nov 16: Press release
- Dec 18: VRBPAC meeting
- Dec 19: FDA action – EUA
- Dec 20: ACIP/CDC Guidance
- Dec 21: Vaccine shipped

Key question:
What to do with study volunteers
Study is NOT over (yet EUA/clinical vaccine available)
Asymptomatic infection, viral shedding/carriage, durability/waning immunity, protection in sub-groups

A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine

Laurence Chu[a,1], Roderick McPhee[b,1], Wenmei Huang[b], Hamilton Bennett[b], Rolando Pajon[b], Biliana Nestorova[b], Brett Leav[a,b], on behalf of the mRNA-1273 Study Group

[a]Benchmark Research, 3300 Red River St #2, Austin, TX 78705, United States
[b]Moderna, Inc., 200 Technology Sq, Cambridge, MA 02139, United States



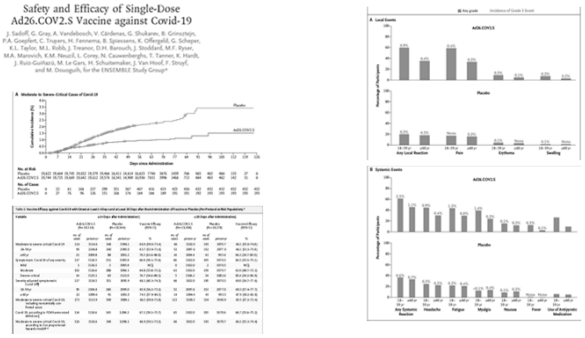
Cohort 1: ≥18–<55 yr, 50 µg
Cohort 2: ≥18–<55 yr, 100 µg
Cohort 3: ≥55 yr, 50 µg
Cohort 4: ≥55 yr, 100 µg

Chu L et al. Vaccine Feb2021

ORIGINAL ARTICLE

Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19

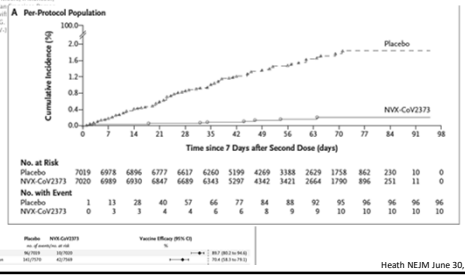
J. Sadoff, G. Gray, A. Vandebosch, V. Cárdenas, G. Shukarev, B. Grinsztejn, P.A. Goepfert, C. Truyers, H. Fennema, B. Spiessens, K. Offergeld, G. Scheper, K.L. Taylor, M.L. Robb, J. Treanor, D.H. Barouch, J. Stoddard, M.F. Ryser, M.A. Marovich, K.M. Neuzil, L. Corey, N. Cauwenberghs, T. Tanner, K. Hardt, J. Ruiz-Guiñazú, M. Le Gars, H. Schuitemaker, J. Van Hoof, F. Struyf, and M. Douoguih, for the ENSEMBLE Study Group*



ORIGINAL ARTICLE

Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine

P.T. Heath, E.P. Galiza, D.N. Baxter, M. Boffito, D. Browne, F. Burns, D.R. Chadwick, R. Clark, C. Cosgrove, J. Galloway, A.L. Goodman, A. Heer, A. Higham, S. Iyengar, A. Jamal, C. Jeanes, P.A. Kalra, C. Kyriakidou, D.F. McAuley, A. Meyrick, A.M. Minassian, J. Minton, P. Moore, I. Munsoor, H. Nicholls, O. Osanlou, J. Packham, C.H. Pretswell, A. Saich, D. Saralaya, R.P. Sheridan, R. Smith, R.L. Soiza, P.A. Swift, J. Turner, M.E. Viljoen, G. Albert, I. Chu, F. Dubovsky, G. A. Robertson, K. Smith, and S. Toback, for the 2019nCoV-3



Heath NEJM June 30, 2021

ORIGINAL ARTICLE

Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile

Alejandro Jara, Ph.D., Eduardo A. Undurraga, Ph.D., Cecilia González, M.D., Fabio Paredes, M.Sc., Tomás Fontecilla, M.Sc., Gonzalo Jara, B.S.E., Alejandra Pizarro, M.D., Johanna Acevedo, M.S., Katherine Leo, B.S.E., Francisco Leon, M.B.A., Carlos Sans, B.S.E., Paulina Leighton, B.S.E., Pamela Suárez, B.S.E., Heriberto García-Escorza, M.S., and Rafael Araos, M.D.

Table 2. Effectiveness of CoronaVac Vaccine in Preventing Covid-19 Outcomes in Overall Study Cohort, According to Immunization Status.*

Outcome and Immunization Status	Study Cohort	Persons with Covid-19		Vaccine Effectiveness (95% CI)		
	No. of Person-Days	No. of Persons	Incidence Rate	Analysis Adjusted for Sex and Age	Analysis Adjusted for All Covariates†	Stratified Analysis‡
			no. of events/ 1000 person-days		*percent*	
Covid-19						
Unvaccinated	614,868,240	185,633	0.3019	—	—	—
Partially immunized	69,788,352	20,865	0.2990	8.0 (6.5–9.4)	15.5 (14.2–16.8)	17.2 (15.8–18.6)
Fully immunized	91,671,797	12,286	0.1340	61.2 (60.3–62.0)	65.9 (65.2–66.6)	63.7 (62.8–64.6)
Hospitalization						
Unvaccinated	620,894,706	18,034	0.0290	—	—	—
Partially immunized	70,690,796	3,370	0.0477	31.4 (28.6–34.0)	37.4 (34.9–39.9)	40.3 (37.6–42.8)
Fully immunized	92,445,333	1,462	0.0158	86.0 (85.1–86.8)	87.5 (86.7–88.2)	86.5 (85.6–87.4)

Jara NEJM July 7, 2021

ORIGINAL ARTICLE

Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents

Robert W. Frenck, Jr., M.D., Nicola P. Klein, M.D., Ph.D., Nicholas Kitchin, M.D., Alejandra Gurtman, M.D., Judith Absalon, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Emmanuel B. Walter, M.D., Shelly Sed[illegible], Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Hua Ma, Ph.D., Kenneth Koury, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Timothy Jennings, D.O., Donald M. Brandon, M.D., Stephen J. Cannon, Ozlem Türeci, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. and William C. Gruber, M.D., for the C4591001 Clinical T[illegible]

Table 2. SARS-CoV-2 Serum Neutralization Assay Results 1 Month after Dose 2 of BNT162b2 among Participants without Evidence of Infection.*

Age Group	No. of Participants	Geometric Mean 50% Neutralizing Titer (95% CI)†	Geometric Mean Ratio (95% CI), 12 to 15 Yr vs. 16 to 25 Yr‡
12–15 yr	190	1239.5 (1095.5–1402.5)	1.76 (1.47–2.10)
16–25 yr	170	705.1 (621.4–800.2)	—

Table 3. Vaccine Efficacy against Covid-19 in Participants 12 to 15 Years of Age.*

Efficacy End Point†	BNT162b2		Placebo		% Vaccine Efficacy (95% CI)‡
	No. of Participants with Event/Total No.§	Surveillance Time (No. at Risk)¶	No. of Participants with Event/Total No.§	Surveillance Time (No. at Risk)¶	
Covid-19 occurrence at least 7 days after dose 2 in participants without evidence of previous infection	0/1005	0.154 (1001)	16/978	0.147 (972)	100 (75.3–100)
Covid-19 occurrence at least 7 days after dose 2 in participants with or without evidence of previous infection	0/1119	0.170 (1109)	18/1110	0.163 (1094)	100 (78.1–100)

Frenk NEJM May 27, 2021

Where Are We Today

- mRNA (?Booster doses)
  - Pfizer – FDA EUA 12/11
    - DSMB review: Efficacy data 11/9
    - Cold chain considerations
    - Up to 1.3 billion by end 2021
  - Moderna – FDA EUA 12/18
    - DSMB review: efficacy data 11/16
    - Cold chain less challenging – ok at 2-8C for 30 days
    - Up to 1 billion doses by end 2021
- Viral Vector
  - AstraZeneca
    - DSMB review: efficacy data 11/23
    - Use in UK and elsewhere
  - Janssen – FDA EUA Feb 27
    - Phase 3 trial ongoing
    - Single and multiple doses regimens being studied

COVID-19 Prevention Network

ORIGINAL ARTICLE

Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings

M.G. Thompson, E. Stenehjem, S. Grannis, S.W. Ball, A.L. Naleway, T.C. Ong, M.B. DeSilva, K. Natarajan, C.H. Bozio, N. Lewis, K. Dascomb, B.E. Dixon, R.J. Birch, S.A. Irving, S. Rao, E. Kharbanda, J. Han, S. Reynolds, K. Goddard, N. Grisel, W.F. Fadel, M.E. Levy, J. Ferdinands, B. Fireman, J. Arndorfer, N.R. Valvi, E.A. Rowley, P. Patel, O. Zerbo, E.P. Griggs, R.M. Porter, M. Demarco, L. Blanton, A. Steffens, Y. Zhuang, N. Olson, M. Barron, P. Shifflett, S.J. Schrag, J.R. Verani, A. Fry, M. Gaglani, E. Azziz-Baumgartner, and N.P. Klein

- CoV-Inf
  - Asymptomatic+
- CoV-Dis
  - Mild/mod
  - Severe – hospitalization, death
- CoV-Trans
  - Surveillance – PCR, serology

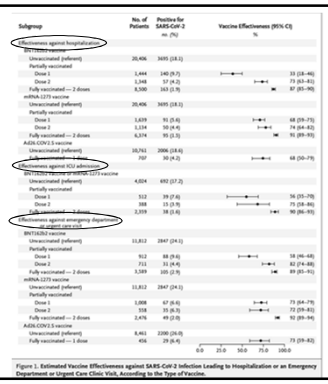
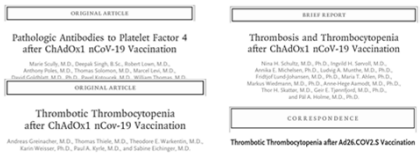


Figure 1. Estimated Vaccine Effectiveness against SARS-CoV-2 Infection Leading to Hospitalization or an Emergency Department or Urgent Care Clinic Visit, According to the Type of Vaccine.

Thompson MG et al., NEJM 8Sept21

Emerging Safety Considerations

- mRNA
  - Delayed local site reactions
  - Anaphylaxis
  - Myocarditis, anaphylaxis
- Viral Vectors
  - Thrombosis (CVST, splanchnic), GBS


ORIGINAL ARTICLE

Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination

ORIGINAL ARTICLE

Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination

BRIEF REPORT

Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination

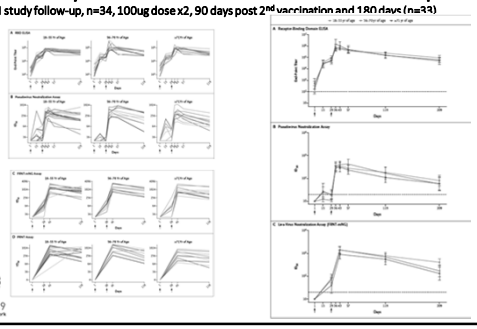
CORRESPONDENCE

Thrombotic Thrombocytopenia after Ad26.COV2.S Vaccination

NEJM 09Apr21 and 14Apr21

Durability of mRNA-1273 Immune Response

Phase I study follow-up, n=34, 100ug dose x2, 90 days post 2nd vaccination and 180 days (n=33)



COVID-19 Prevention Network

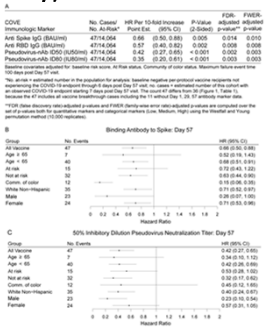
Widge A et al. 07Jan2021 NEJM 384
Doria-Rose N et al, 06Apr21 NEJM

Understanding VE (Vaccine Efficacy)

- CoR – Correlate of Risk
- CoP – Correlate of Protection
- Sieve Analysis

- Mechanism(s) of protection
- Immunologic bridging
  - Key populations,
  - Future generation vaccines

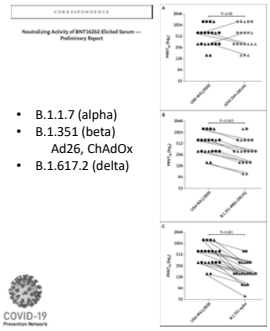
- Strain Variation



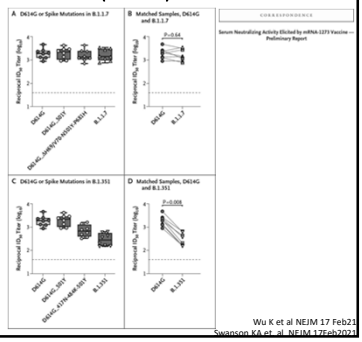
COVID-19 Prevention Network

Gilbert PB et al, medRxiv 15Aug21

Viral Variants and Neutralization (B.1.351)



- B.1.1.7 (alpha)
- B.1.351 (beta)
  Ad26, ChAdOx
- B.1.617.2 (delta)



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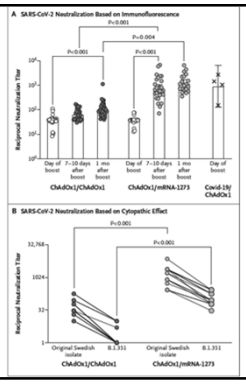
Wu K et al NEJM 17 Feb21
Swanson KA et al, NEJM 17Feb2021

CORRESPONDENCE

Heterologous ChAdOx1 nCoV-19 and mRNA-1273 Vaccination



Normark NEJM July 14, 2021

CORRESPONDENCE

Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients

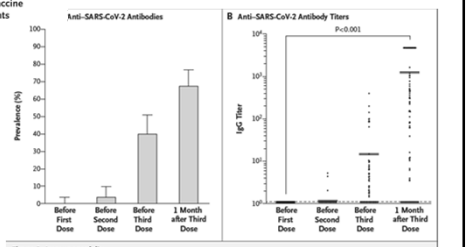


Figure 1. Immunogenicity.
Panel A shows the prevalence of anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies before and after vaccination in the study population. Panel B shows anti–SARS-CoV-2 antibody titers before and after vaccination in the study population.

Kamar NEJM June 23, 2021

Comparing SARS-CoV-2 Serologic Assays

3 commercial and 2 laboratory assays
n=251 PCR+ Covid-19 cases

Table 4. Assay sensitivities by days post symptom onset.

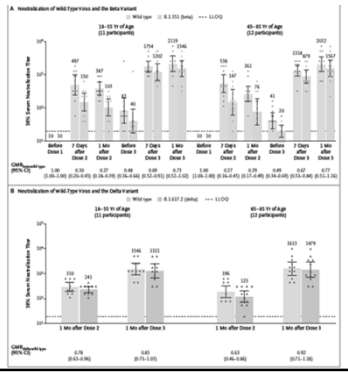
Assay	Days PSO	Total No. of PCR-positive samples	No. testing positive	Percentage	95% CI
Epitope IgG	<8 days	26	11	42.31	25.54-61.05
	8-14 days	77	65	84.42	74.71-90.85
	15-21 days	65	60	92.31	83.22-96.67
	>21 days	83	71	85.54	76.41-91.53
	Overall	251	207	82.47	77.29-86.67
Epitope IgM	<8 days	26	8	30.77	16.50-49.99
	8-14 days	77	43	55.84	44.74-66.39
	15-21 days	65	41	63.08	50.92-73.77
	>21 days	83	26	31.33	22.36-41.94
	Overall	251	118	47.01	40.93-53.18
Ragon/MGH IgG*	<8 days	26	5	19.23	8.51-37.88
	8-14 days	77	44	57.14	46.01-67.60
	15-21 days	65	52	80.00	68.73-87.92
	>21 days	83	61	73.49	63.11-81.80
	Overall	251	162	64.54	58.45-70.20
Roche†	<8 days	26	13	50.00	32.06-67.94
	8-14 days	77	62	80.52	70.31-87.82
	15-21 days	65	59	90.77	81.29-95.70
	>21 days	83	74	89.16	80.66-94.19
	Overall	251	208	82.87	77.72-87.03
Simoa (Early)‡	<8 days	26	15	57.69	38.95-74.46
	8-14 days	77	72	93.51	85.68-97.19
	15-21 days	65	65	100.00	94.42-100.00
	>21 days	83	79	95.18	88.25-98.11
	Overall	251	231	92.03	88.01-94.78

*For sensitivity of Ragon/MGH IgM and IgA see Supplemental Materials.
†The Roche Elecsys Anti-SARS-CoV-2 immunoassay detects IgG and likely IgM and IgA; details of other isotypes are not provided by the manufacturer.
‡Sensitivity of the Simoa multiplex assay Early Model. For sensitivities of the Late and 12-Parameter Models, see Supplementary Materials.

Niles EJ et al, JALM, in press

CORRESPONDENCE

SARS-CoV-2 Neutralization with BNT162b2 Vaccine Dose 3



Falsey AR NEJM 15Sept21

Breakthrough (delta) Covid-19 Infections: COVE Trial

Covid-19 Cases and Incidence Rates After mRNA-1273 Vaccination
During July 1st to August 27, 2021 in the Modified Intent-to-Treat Population

	mRNA-1273e N=14746			mRNA-1273p* N=11431			mRNA-1273p vs mRNA-1273e
Covid-19 Cases†	Cases n	Person-yr	Rate/1000 Person-yr	Cases n	Person-yr	Rate/1000 Person-yr	Reduction of observed incidence rate % (95% CI)
All cases	162	2102	77.1	88	1796	49.0	36.4 (17.1-51.5)
≥18–<65 yr	136	1558	87.3	68	1289	52.8	39.6 (18.6-55.5)
≥65 yr	26	544	47.8	20	507	39.5	17.4 (-53.9-56.3)
Severe	13	2102	6.2	6	1796	3.3	46.0 (-52.4-83.2)
≥18–<65 yr	7	1558	4.5	4	1289	3.1	30.9 (-171.7-85.2)
≥65 yr	6	544	11.0	2	507	3.9	64.2 (-100.2-96.5)

Baden LR et al, medRxiv Sept21

ORIGINAL ARTICLE

Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel

Yinon M. Bar-On, M.Sc., Yair Goldberg, Ph.D., Micha Mandel, Ph.D., Omri Bodenheimer, M.Sc., Laurence Freedman, Ph.D., Nir Kalkstein, B.Sc., Barak Mizrahi, M.Sc., Sharon Alroy-Preis, M.D., Nachman Ash, M.D., Ron Milo, Ph.D., and Amit Huppert, Ph.D.

- Fully vaccinated by March 1, 2021
- >60yo, Israel, no prior Covid +PCR
- Covid-19 infection in August21

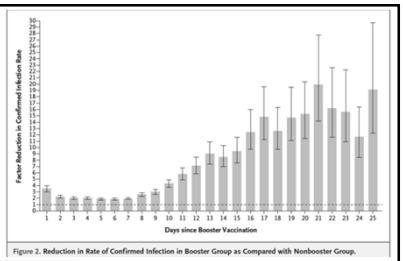


Figure 2. Reduction in Rate of Confirmed Infection in Booster Group as Compared with Nonbooster Group.

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	4419	914	
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	

NEJM 15Sept 2021

Boosters

- Goal
  - Infection, illness, severe illness/death
  - Use CoP for a 'protective immunologic level'?
    - Vary by vaccine platform?
- Variants
  - Beta, delta, mu,…
- Scenarios
  - Initial vaccine:
    - Dose
    - Heterologous/homologous delivery system
    - Heterologous/homologous insert
  - Time interval
- Benefit
  - CoV-Inf, CoV-Dis, Cov-Dis-severe, CoV-Trans
  - By risk group
    - Illness – age, co-morbidities
    - Risk of acquisition – healthcare workers

Questions Before US

- **Efficacy shown in under a year!**
  - ~95% for molecularly confirmed symptomatic Covid-19
  - What about: acquisition, transmission
- **How much data do we need to judge safety?**
  - Phase 3 trials (~38,000 participants), median follow-up > 6 months post receipt full vaccination regimen
  - Less common (e.g., allergy) and longer term safety (>1 year, etc.)
- **What about?**
  - Special populations: children, pregnancy, immunocompromised patients
  - Those with prior SARS-CoV-2 infection
  - Immunity – duration, development CoR/CoP (approval for next generation vaccines)
  - Impact of viral evolution – variants of concern (VOCs): alpha, beta, delta….
- **How do we prioritize distribution?**
  - Increase supply
  - At risk for acquisition, for severe disease
  - Global equity
- **How do we compare EUA vaccines and impact on vaccine development?**
  - As more vaccines are shown to be efficacious - how do we choose; and timing of availability
  - Can vaccines be interchanged
- **Where do booster doses fit in?**
  - Define benefit
  - Primary series, dose, interval/timing, insert
- **Community acceptance/ Vaccine Hesitancy**
  - How do we gain trust

COVID-19 Prevention Network

Acknowledgements

- Many, many partners
  - Study teams across the nation/globe
  - NIH-NIAID, CoVPN, BARDA, OWS
  - Industry: Moderna, Pfizer, AZ, J+J, Novavax, Sanofi
  - Regulators, safety oversight process: FDA, DSMB, IRBs
  - Investigators and associated teams
- Community
  - Local and global
- Volunteers
  - >>100,000

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