Covid-19 Vaccine Development

How 30,000 Nucleotides Changed the World

Update in Hospital Medicine
October 4, 2021

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COVID-19 Prevention Network

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HARVARD MEDICAL SCHOOL

Disclosures

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

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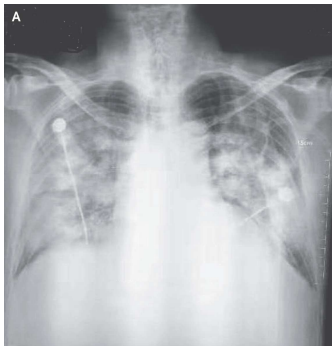
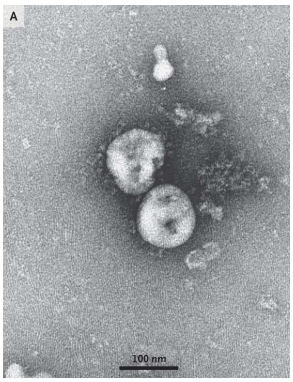
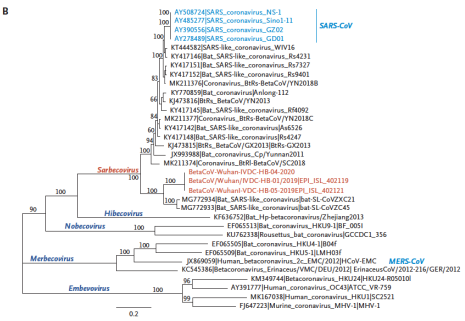
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

A Novel Coronavirus from Patients with Pneumonia in China, 2019

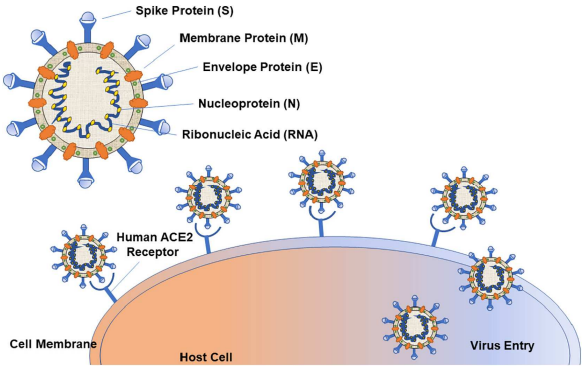






Zhu N NEJM 24Jan2020

Viral Genome



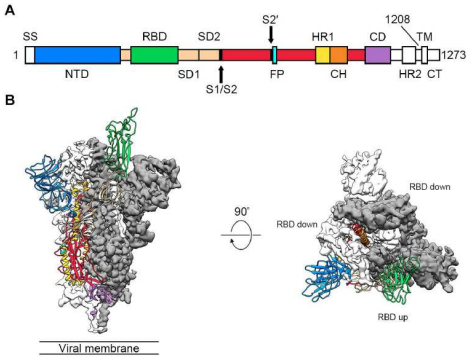


Fig. 1. Structure of 2019-nCoV S in the prefusion conformation. (A) Schematic of 2019-nCoV S primary structure.

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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; △F; TM	2 doses at 5×10^{10} vp, (0, 28 days)	28Aug2020
janssen	Ad Vector	Replication Incompetent Ad26; stabilized Spike; △F; TM	1 dose at 5×10^{10} vp	23Sept2020
NOVAVAX	Recombinant protein Adjuvanted	Baculovirus Expressed trimeric Stabilized Spike, △F; TM; trimerization domain; Matrix M	2 doses at 5 µg with Matrix M (0, 21 days)	27Dec2020
gsk SANOFI	Recombinant protein Adjuvanted	Baculovirus Expressed trimeric Stabilized Spike, △F; TM; trimerization domain; AS03	5/15 µg +AS03 (0, 21 days)	2021

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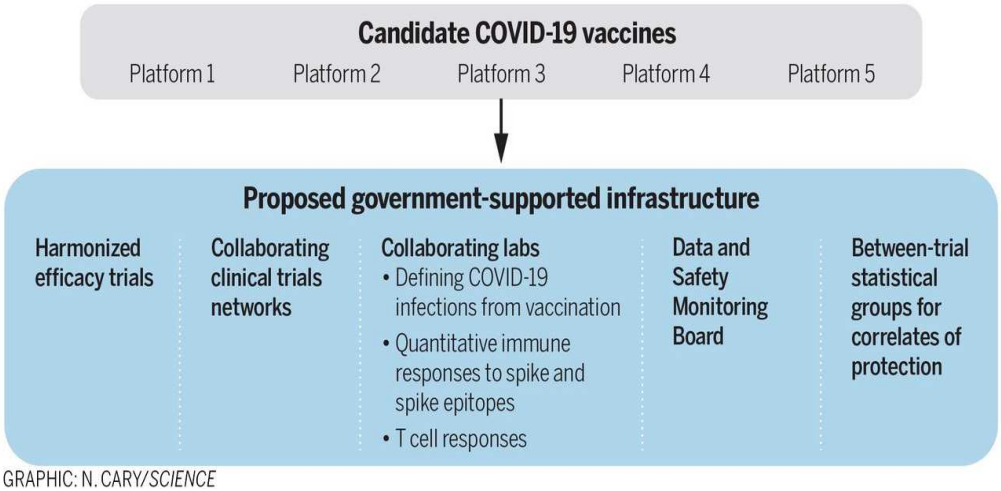
Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) and COVID-19 Prevention Network (CoVPN)



GRAPHIC: N. CARY/*SCIENCE*

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

Key mRNA-1273 Development Timeline

January 13, 2020
Sequence for mRNA-1273 against the novel coronavirus finalized

*Total of **63 days** from sequence selection to first human dosing*

March 16, 2020
First participant in NIH-led **Phase 1** study was dosed

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Phase 1: Safety, Reactogenicity, Immunogenicity

mRNA-1273-P101 Study Design

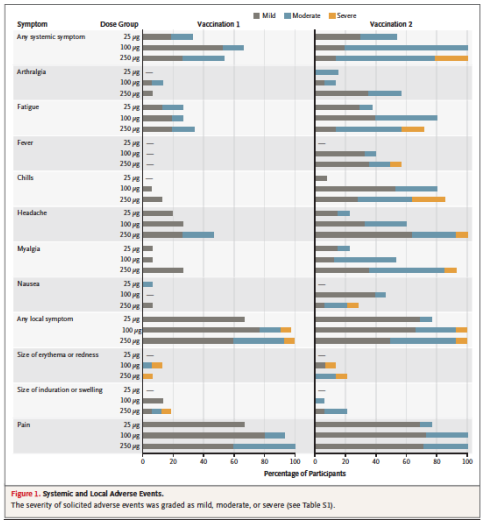
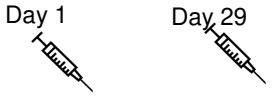
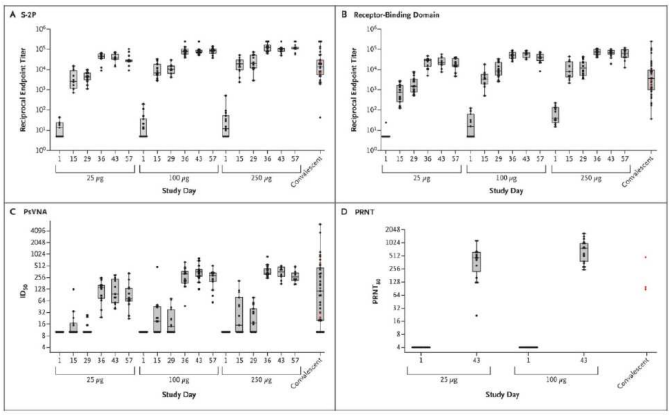


Figure 1. Systemic and Local Adverse Events.
The severity of solicited adverse events was graded as mild, moderate, or severe (see Table S1).



SARS-CoV-2 Phase 1 dosing regimen



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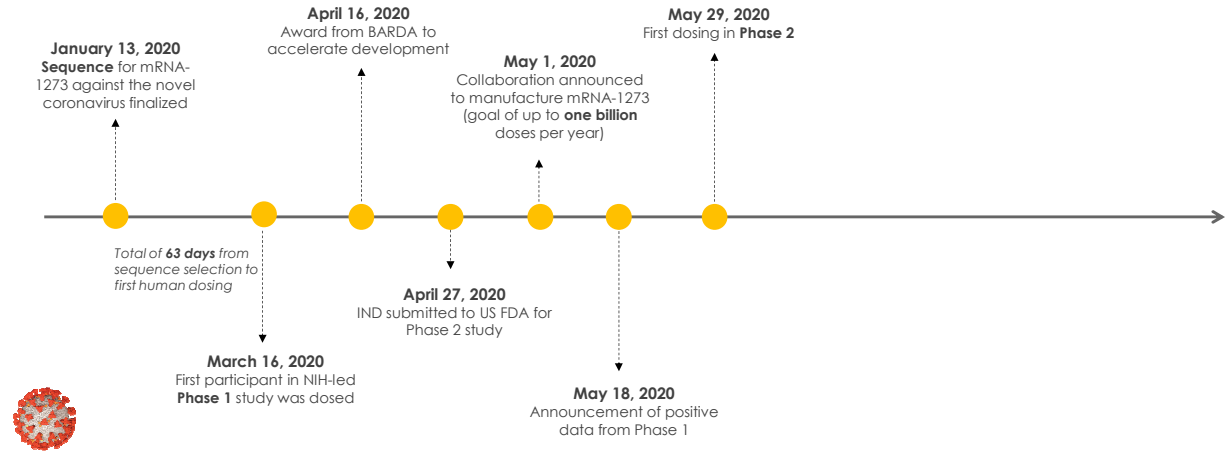
Jackson et al. *NEJM* 14July2020
Anderson et al. *NEJM* 29Sept2020

Key mRNA-1273 Development Timeline



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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%

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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%

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

ORIGINAL ARTICLE

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

L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, D. Diemert, S.A. Spector, N. Rouphael, C.B. Creech, J. McGettigan, S. Khetan, N. Segall, J. Solis, A. Brosz, C. Fierro, H. Schwartz, K. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, J. Mascola, L. Polakowski, J. Ledgerwood, B.S. Graham, H. Bennett, R. Pajon, C. Knightly, B. Leav, W. Deng, H. Zhou, S. Han, M. Ivarsson, J. Miller, and T. Zaks, for the COVE Study Group*

- 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)

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Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristics	Placebo (N=15,170)	mRNA-1273 (N=15,181)	Total (N=30,351)
Sex — no. of participants (%)			
Male	8,062 (53.1)	7,923 (52.2)	15,985 (52.7)
Female	7,108 (46.9)	7,258 (47.8)	14,366 (47.3)
Mean age (range) — yr	51.3 (18–95)	51.4 (18–95)	51.4 (18–95)
Age category and risk for severe Covid-19 — no. of participants (%)†			
18 to <65 yr, not at risk	8,886 (58.6)	8,888 (58.5)	17,774 (58.6)
18 to <65 yr, at risk	2,535 (16.7)	2,530 (16.7)	5,065 (16.7)
≥65 yr	3,749 (24.7)	3,763 (24.8)	7,512 (24.8)
Hispanic or Latino ethnicity — no. of participants (%)‡			
Hispanic or Latino	3,114 (20.5)	3,121 (20.6)	6,235 (20.5)
Not Hispanic or Latino	11,917 (78.6)	11,918 (78.5)	23,835 (78.5)
Not reported and unknown	139 (0.9)	142 (0.9)	281 (0.9)
Race or ethnic group — no. of participants (%)‡			
White	11,995 (79.1)	12,029 (79.2)	24,024 (79.2)
Black or African American	1,527 (10.1)	1,563 (10.3)	3,090 (10.2)
Asian	731 (4.8)	651 (4.3)	1,382 (4.6)
American Indian or Alaska Native	121 (0.8)	112 (0.7)	233 (0.8)
Native Hawaiian or Other Pacific Islander	32 (0.2)	35 (0.2)	67 (0.2)
Multiracial	321 (2.1)	315 (2.1)	636 (2.1)
Other	316 (2.1)	321 (2.1)	637 (2.1)
Not reported and unknown	127 (0.8)	155 (1.0)	282 (0.9)
Baseline SARS-CoV-2 status — no. of participants (%)§			
Negative	14,598 (96.2)	14,550 (95.8)	29,148 (96.0)
Positive	337 (2.2)	343 (2.3)	680 (2.2)
Missing data	235 (1.5)	288 (1.9)	523 (1.7)
Baseline RT-PCR test — no. of participants (%)			
Negative	14,923 (98.4)	14,917 (98.3)	29,840 (98.3)
Positive	95 (0.6)	87 (0.6)	182 (0.6)
Missing data	152 (1.0)	177 (1.2)	329 (1.1)
Baseline bAb anti–SARS-CoV-2 assay — no. of participants (%)			
Negative	14,726 (97.1)	14,690 (96.8)	29,416 (96.9)
Positive	303 (2.0)	305 (2.0)	608 (2.0)
Missing data	141 (0.9)	186 (1.2)	327 (1.1)

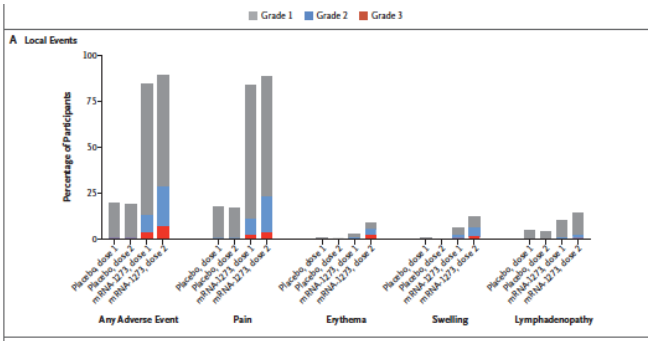

Figure 2. Solicited Local and Systemic Adverse Events.
Shown is the percentage of participants who had a solicited local or systemic adverse event within 7 days after injection 1 or injection 2 of either the placebo or the mRNA-1273 vaccine.

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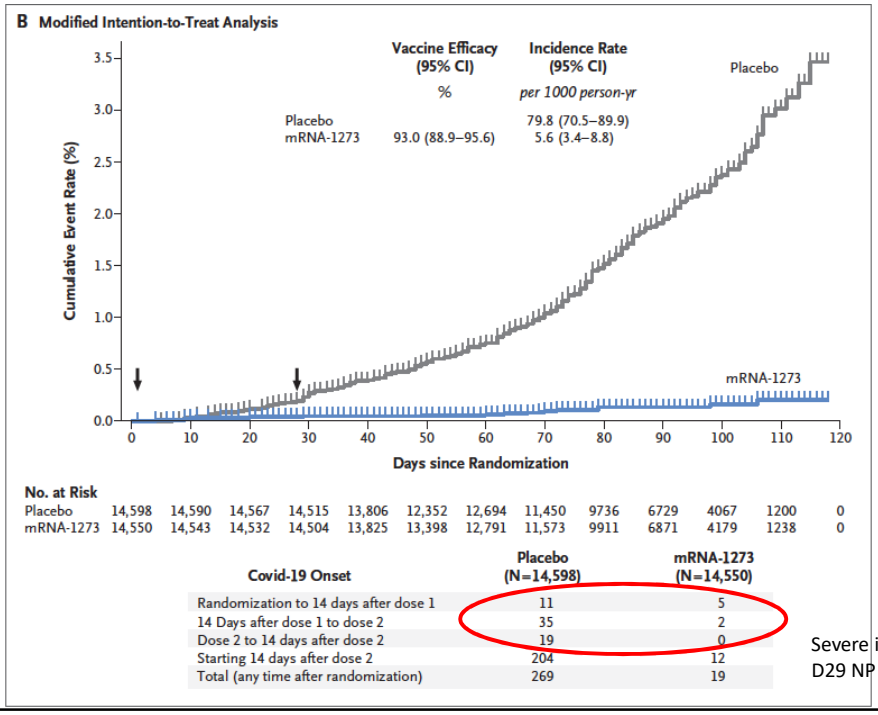

Covid-19 Onset	Placebo (N=14,598)	mRNA-1273 (N=14,550)
Randomization to 14 days after dose 1	11	5
14 Days after dose 1 to dose 2	35	2
Dose 2 to 14 days after dose 2	19	0
Starting 14 days after dose 2	204	12
Total (any time after randomization)	269	19

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

ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzalo Pérez Marc, M.D., Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D., Robert W. Frenck, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., Haylene Nell, M.D., Axel Schaefer, M.D., Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

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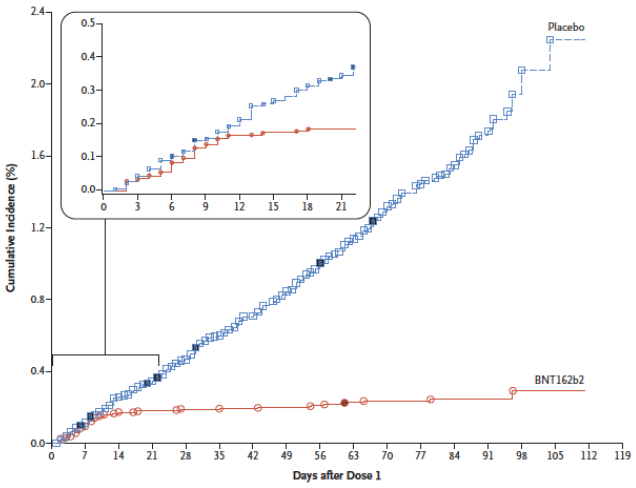


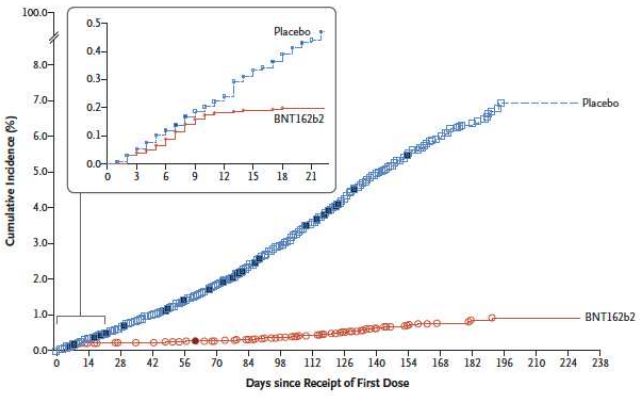
Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669) No. of participants	Surveillance time person-yr (no. at risk)	Placebo (N=21,686) No. of participants	Surveillance time person-yr (no. at risk)	VE (95% CI) percent
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
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.

ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months

S.J. Thomas, E.D. Moreira, Jr., N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, J.L. Perez, G. Pérez Marc, F.P. Polack, C. Zerbini, R. Bailey, K.A. Swanson, X. Xu, S. Roychoudhury, K. Koury, S. Bouguermouh, W.V. Kalina, D. Cooper, R.W. Frenck, Jr., L.L. Hammitt, Ö. Türeci, H. Nell, A. Schaefer, S. Ünal, Q. Yang, P. Liberator, D.B. Tresnan, S. Mather, P.R. Dormitzer, U. Şahin, W.C. Gruber, and K.U. Jansen, for the C4591001 Clinical Trial Group*

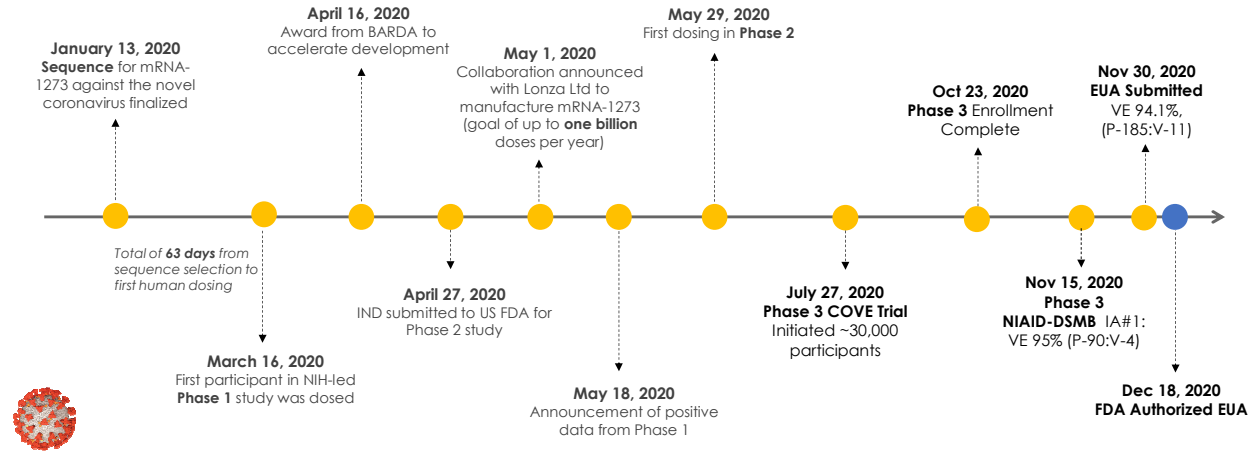


Efficacy End Point	BNT162b2 (N=23,040) No. of cases	Surveillance time 1000 person-yr	No. at risk	Placebo (N=23,037) No. of cases	Surveillance time 1000 person-yr	No. at risk	Vaccine Efficacy % (95% CI)
Overall: first occurrence of Covid-19 after receipt of first dose	131	8.412	22,505	1034	8.124	22,434	87.8 (85.3 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)
<11 Days after receipt of first dose	41	0.677	22,505	50	0.675	22,434	18.2 (−26.1 to 47.3)
≥11 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 98.3)
≥7 Days after receipt of second dose	82	6.649	22,132	889	6.371	22,001	91.7 (88.9 to 93.9)
≥7 Days after receipt of second dose to <2 mo after	12	2.923	22,132	312	2.884	22,001	96.2 (93.3 to 98.1)
≥2 Mo after receipt of second dose to <4 mo after	46	2.696	20,814	449	2.593	20,344	90.1 (86.6 to 92.9)
≥4 Mo after receipt of second dose	24	1.030	12,670	128	0.895	11,802	83.7 (74.7 to 89.9)

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

Thomas SJ et al. NEJM 15Sept21

Key mRNA-1273 Development Timeline



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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

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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 [b,*], on behalf of the mRNA-1273 Study Group

[a] Benchmark Research, 3100 Red River St #2, Austin, TX 78705, United States
[b] Moderna, Inc., 200 Technology Sq, Cambridge, MA 02139, United States

Table 1
Demographics.

Characteristic n (%)	Cohort 1 (≥18 - <55 yr)					Cohort 2 (≥55 yr)				
		mRNA-1273					mRNA-1273			
	Placebo N=100	50 µg N=100	100 µg N=100	Total N=200	Overall N=300	Placebo N=100	50 µg N=100	100 µg N=100	Total N=200	Overall N=300
Age years, mean (range)	37.3 (18-53)	36.6 (18-54)	38.3 (18-54)	37.5 (18-54)	37.4 (18-54)	64.3 (55-84)	64.6 (55-87)	63.9 (55-87)	64.3 (58-87)	64.3 (55-87)
Female	60 (60)	64 (64)	53 (53)	117 (59)	177 (59)	69 (69)	73 (73)	71 (71)	144 (72)	213 (71)
Race										
White	94 (94)	93 (93)	90 (90)	183 (92)	277 (92)	99 (99)	95 (95)	98 (98)	193 (97)	292 (97)
Black or African American	3 (3)	3 (3)	7 (7)	10 (5)	13 (4)	0	2 (2)	1 (1)	3 (2)	3 (1)
Asian	2 (2)	0	2 (2)	2 (1)	4 (1)	1 (1)	2 (2)	0	2 (1)	3 (1)
American Indian/Alaska Native	0	2 (2)	0	2 (1)	2 (1)	0	0	1 (1)	1 (<1)	1 (<1)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	1 (1)	0	1 (1<)	1 (<1)
Multiracial/Other	1 (1)	2 (2)	1(1)	3 (2)	4 (1)	0	0	0	0	0
BMI kg/m2, Mean (SD)	25.3 (3)	25.6 (3)	24.8 (3)	25.2 (3)	25.2 (3)	25.4 (3)	25.6 (3)	25.2 (3)	25.4 (3)	25.4 (3)

BMI=body mass index; Percentages are based on the number of randomized participants.

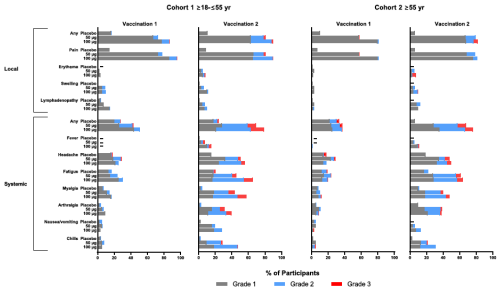
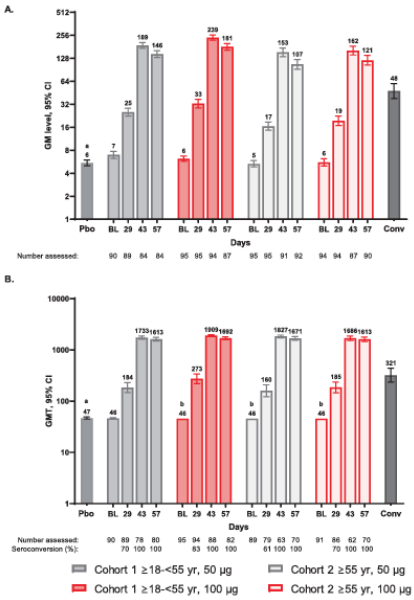


Fig. 2. Solicited local and systemic adverse reactions within 7 days post-vaccinations one and two in each cohort. Percentages of participants with solicited local and

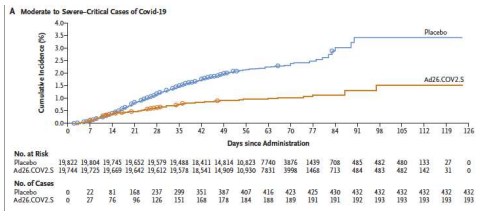


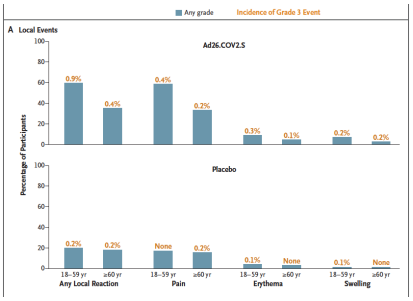
Chu L at al. Vaccine Feb2021

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*





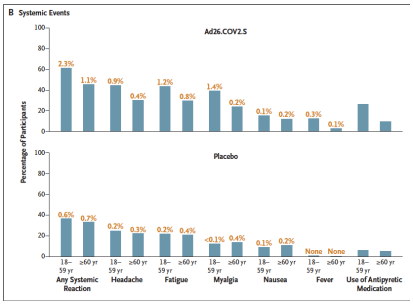


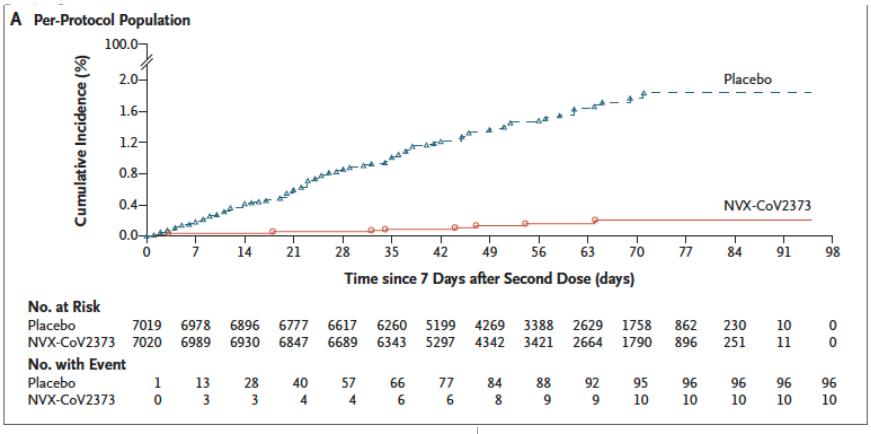
Table 2. Vaccine Efficacy against Covid-19 with Onset at Least 14 Days and at Least 28 Days after the Administration of Vaccine or Placebo (Per-Protocol at-Risk Population).*

Variable	≥14 Days after Administration†			≥28 Days after Administration‡		
	Ad26.COV2.S (N=19,514)	Placebo (N=19,544)	Vaccine Efficacy (95% CI)	Ad26.COV2.S (N=19,306)	Placebo (N=19,378)	Vaccine Efficacy (95% CI)
	no. of cases	person-yr	%	no. of cases	person-yr	%
Moderate to severe–critical Covid-19	116	3116.6	66.9 (59.0-73.4)	66	3102.0	66.1 (55.0-74.8)
18–59 yr	95	2106.8	63.7 (53.9-71.6)	52	2097.6	66.1 (53.3-75.8)
≥60 yr	21	1009.8	76.3 (61.6-86.0)	14	1004.4	66.2 (36.7-82.0)
Symptomatic Covid-19 of any severity	117	3116.5	66.9 (59.1-73.4)	66	3102.0	66.5 (55.5-75.1)
Mild	1	3116.3	3	3095.9	NC‖	0	3102.0	2	3070.3	NC‖
Moderate	102	3116.6	288	3096.1	64.8 (53.8-72.2)	61	3102.0	159	3070.7	62.0 (48.7-72.2)
Severe–critical	14	3120.1	60	3122.0	76.7 (54.6-89.1)	5	3106.2	34	3082.6	85.4 (54.2-96.9)
Severity-adjusted symptomatic Covid-19¶	117	3116.5	351	3095.9	68.1 (60.3-74.3)	66	3102.0	195	3070.5	69.0 (56.7-77.9)
18–59 yr	95	2106.8	260	2095.0	65.8 (56.2-73.1)	52	2097.6	152	2077.0	69.3 (57.4-77.7)
≥60 yr	22	1009.6	91	1001.0	74.5 (57.9-84.3)	14	1004.4	43	993.5	67.9 (38.2-82.8)
Moderate to severe–critical Covid-19, including noncentrally confirmed cases	173	3113.9	509	3089.1	66.3 (59.9-71.8)	113	3100.3	324	3048.9	65.5 (57.2-72.4)
Covid-19, according to FDA-humanized definition‖	114	3116.6	345	3,096.3	67.3 (59.3-73.7)	65	3102.0	193	3070.6	66.7 (55.6-75.1)
Moderate to severe–critical Covid-19, according to Cox proportional-hazards model**	116	3116.6	348	3096.1	66.9 (59.1-73.2)	66	3102.0	193	3070.7	66.2 (55.3-74.4)

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. San D. Saralaya, R.P. Sheridan, R. Smith, R.L. Soiza, P.A. Swift J. Turner, M.E. Viljoen, G. Albert, I. Cho, 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., Katherinne 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.

ble 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 Se Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Hua Ma, Ph.D., Kenneth Koury, Ph.D., Warren V. Kalina, Ph.D., David Co Timothy Jennings, D.O., Donald M. Brandon, M.D., Stephen J Özlem 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

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

Thompson MG et al., NEJM 8Sept21

Subgroup	No. of Patients	Positive for SARS-CoV-2 no. (%)	Vaccine Effectiveness (95% CI) %
Effectiveness against hospitalization			
BNT162b2 vaccine			
Unvaccinated (referent)	20,406	3695 (18.1)	
Partially vaccinated			
Dose 1	1,444	140 (9.7)	33 (18–46)
Dose 2	1,348	57 (4.2)	73 (63–81)
Fully vaccinated — 2 doses	8,500	163 (1.9)	87 (85–90)
mRNA-1273 vaccine			
Unvaccinated (referent)	20,406	3695 (18.1)	
Partially vaccinated			
Dose 1	1,639	91 (5.6)	68 (59–75)
Dose 2	1,134	50 (4.4)	74 (64–82)
Fully vaccinated — 2 doses	6,374	95 (1.5)	91 (89–93)
Ad26.COV2.S vaccine			
Unvaccinated (referent)	10,761	2006 (18.6)	
Fully vaccinated — 1 dose	707	30 (4.2)	68 (50–79)
Effectiveness against ICU admission			
BNT162b2 vaccine or mRNA-1273 vaccine			
Unvaccinated (referent)	4,024	692 (17.2)	
Partially vaccinated			
Dose 1	512	39 (7.6)	56 (35–70)
Dose 2	388	15 (3.9)	75 (58–86)
Fully vaccinated — 2 doses	2,359	38 (1.6)	90 (86–93)
Effectiveness against emergency department or urgent care visit			
BNT162b2 vaccine			
Unvaccinated (referent)	11,812	2847 (24.1)	
Partially vaccinated			
Dose 1	912	88 (9.6)	58 (46–68)
Dose 2	711	31 (4.4)	82 (74–88)
Fully vaccinated — 2 doses	3,589	105 (2.9)	89 (85–91)
mRNA-1273 vaccine			
Unvaccinated (referent)	11,812	2847 (24.1)	
Partially vaccinated			
Dose 1	1,008	67 (6.6)	73 (64–79)
Dose 2	558	35 (6.3)	72 (59–81)
Fully vaccinated — 2 doses	2,476	49 (2.0)	92 (89–94)
Ad26.COV2.S vaccine			
Unvaccinated (referent)	8,461	2200 (26.0)	
Fully vaccinated — 1 dose	456	29 (6.4)	73 (59–82)

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.

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

Marie Scully, M.D., Deepak Singh, B.Sc., Robert Lown, M.D., Anthony Poles, M.D., Thomas Solomon, M.D., Marcel Levi, M.D.,

ORIGINAL ARTICLE

Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination

Andreas Greinacher, M.D., Thomas Thiele, M.D., Theodore E. Warkentin, M.D., Karin Weisser, Ph.D., Paul A. Kyrle, M.D., and Sabine Eichinger, M.D.

BRIEF REPORT

Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination

Nina H. Schultz, M.D., Ph.D., Ingvild H. Sørvoll, M.D., Annika E. Michelsen, Ph.D., Ludvig A. Munthe, M.D., Ph.D., Fridtjof Lund-Johansen, M.D., Ph.D., Maria T. Ahlen, Ph.D., Markus Wiedmann, M.D., Ph.D., Anne-Hege Aamodt, M.D., Ph.D., Thor H. Skattør, M.D., Geir E. Tjønnfjord, M.D., Ph.D., and Pål A. Holme, M.D., Ph.D.

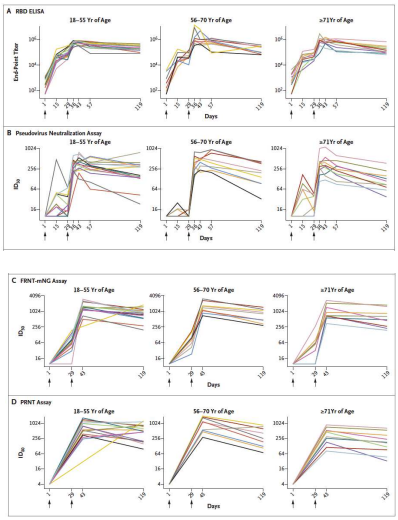
CORRESPONDENCE

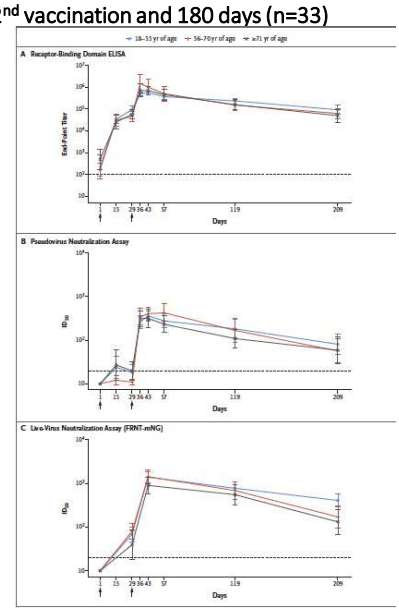
Thrombotic Thrombocytopenia after Ad26.COV2.S Vaccination

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

A

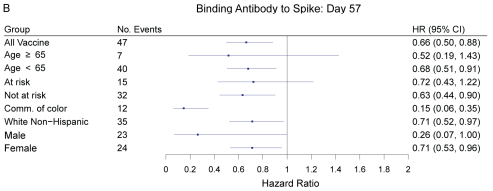
COVE Immunologic Marker	No. Cases/ No. At-Risk*	HR Per 10-fold Increase Point Est.	(95% CI)	P-Value (2-Sided)	FDR-adjusted p-value**	FWER-adjusted p-value
Anti Spike IgG (BAU/ml)	47/14,064	0.66	(0.50, 0.88)	0.005	0.014	0.010
Anti RBD IgG (BAU/ml)	47/14,064	0.57	(0.40, 0.82)	0.002	0.008	0.008
Pseudovirus-nAb ID50 (IU50/ml)	47/14,064	0.42	(0.27, 0.65)	< 0.001	0.002	0.003
Pseudovirus-nAb ID80 (IU80/ml)	47/14,064	0.35	(0.20, 0.61)	< 0.001	0.003	0.003

Baseline covariates adjusted for: baseline risk score, At Risk status, Community of color status. Maximum failure event time 100 days post Day 57 visit.

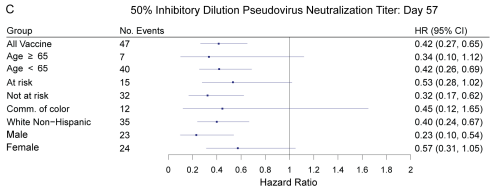
*No. at-risk = estimated number in the population for analysis: baseline negative per-protocol vaccine recipients not experiencing the COVID-19 endpoint through 6 days post Day 57 visit; no. cases = estimated number of this cohort with an observed COVID-19 endpoint starting 7 days post Day 57 visit. The count 47 differs from 36 (Figure 1, Table 1), because the 47 includes all vaccine breakthrough cases including the 11 without Day 1, 29, 57 antibody marker data.

**FDR (false discovery rate)-adjusted p-values and FWER (family-wise error rate)-adjusted p-values are computed over the set of p-values both for quantitative markers and categorical markers (Low, Medium, High) using the Westfall and Young permutation method (10,000 replicates).

B



C



COVID-19 Prevention Network

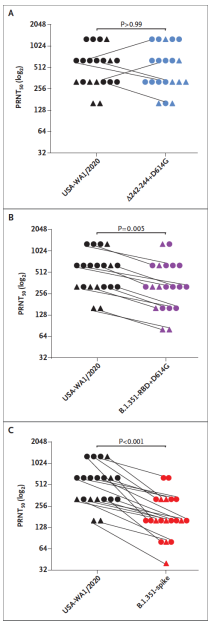
Gilbert PB et al, medRxiv 15Aug21

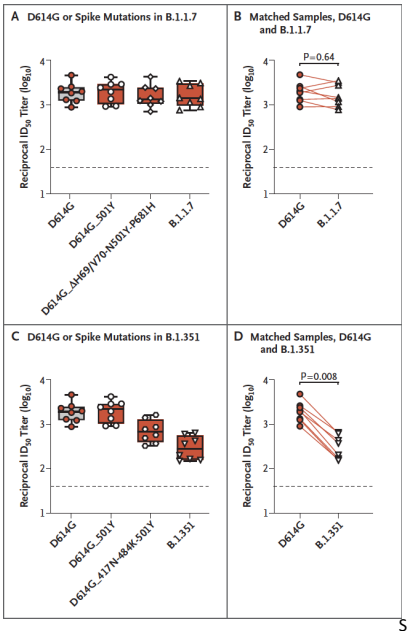
Viral Variants and Neutralization (B.1.351)

CORRESPONDENCE

Neutralizing Activity of BNT162b2-Elicited Serum — Preliminary Report

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





CORRESPONDENCE

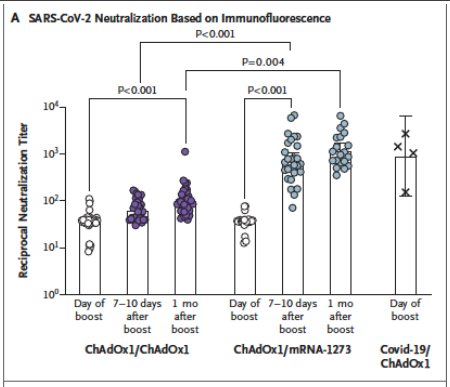
Serum Neutralizing Activity Elicited by mRNA-1273 Vaccine — Preliminary Report

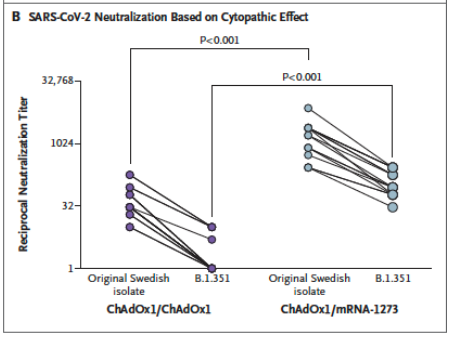
COVID-19 Prevention Network

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

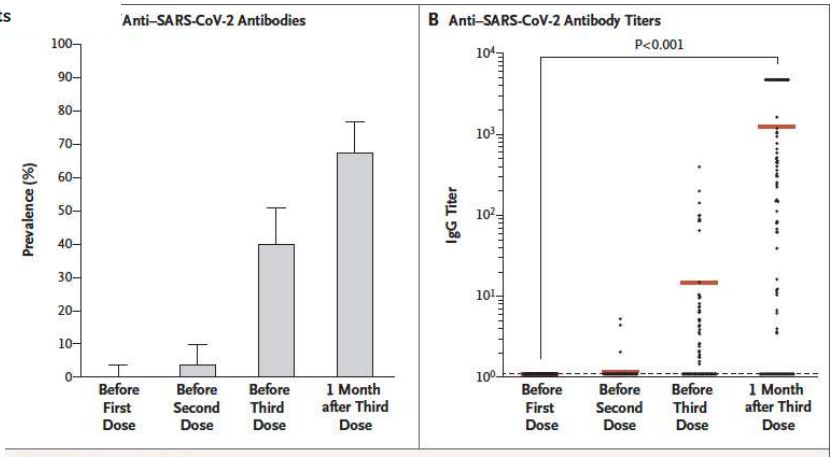


Figure 1. Immunogenicity.

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.

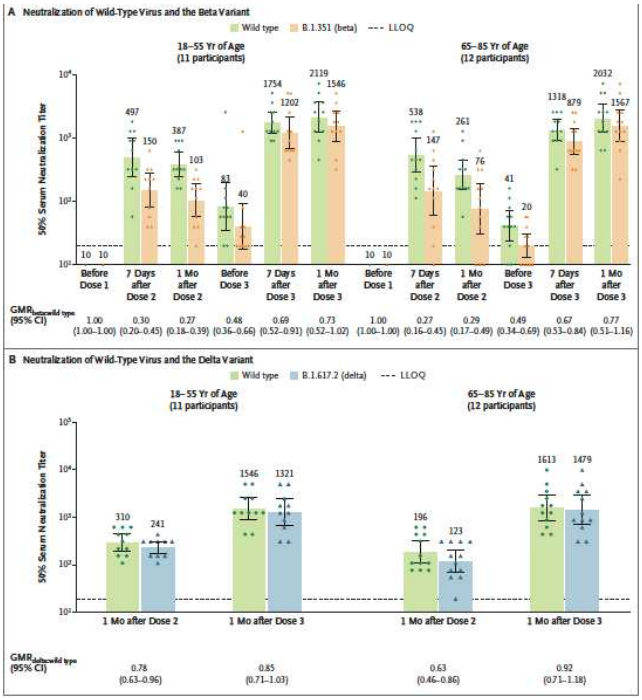
Assay	Days PSO	Total No. of PCR-positive samples	No. testing positive	Percentage	95% CI
Epitope IgG	<8 days	26	11	42.31	25.54–61.05
	8–14 days	77	65	84.42	74.71–90.85
	15–21 days	65	60	92.31	83.22–96.67
	>21 days	83	71	85.54	76.41–91.53
	Overall	251	207	82.47	77.29–86.67
Epitope IgM	<8 days	26	8	30.77	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[a]	<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[b]	<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)[c]	<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

[a] For sensitivity of Ragon/MGH IgM and IgA see Supplemental Materials.
[b] 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.
[c] 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

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

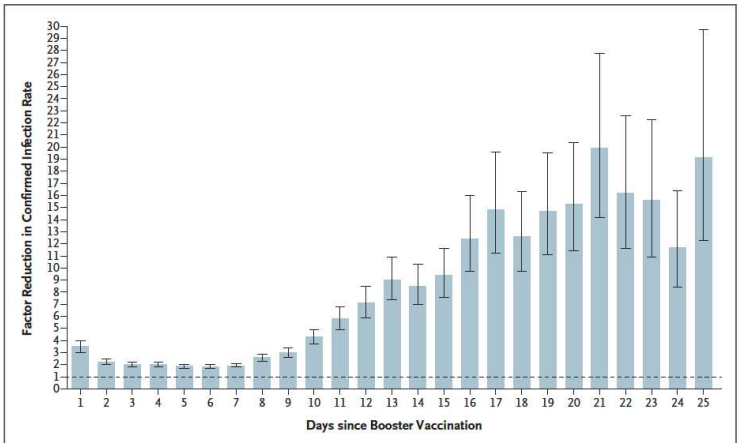

Figure 2. Reduction in Rate of Confirmed Infection in Booster Group as Compared with Nonbooster Group.

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	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	

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
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  - Regulators, safety oversight process: FDA, DSMB, IRBs
  - Investigators and associated teams
- Community
  - Local and global
- Volunteers
  - >>100,000

COVID-19 Prevention Network