SARS-CoV-2 mRNA Vaccines

A Review of Pertinent Drug Information for SARS-CoV-2

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SARS-CoV-2 mRNA Vaccine Candidates

Candidate Name/Type	Sponsor	Clinical Trial Phase	Dosing	Clinical Trials
BNT162b2	Pfizer-BioNtech	FDA Approved 8/23/21	2 doses (d0, d21)	NCT04523571 (phase 1) NCT04588480 (phase 2) NCT04368728 (phase 2/3)** NCT04760132 (phase 4) NCT04844489 (immunocompromised)
mRNA-1273	Moderna	EUA Approval	2 doses (d0, d28)	NCT04283461 (phase 1 NCT04677660 (phase 1/2) NCT04649151 (phase 2/3) NCT04470427 (phase 3) NCT04760132 (phase 4) NCT04900467 (mix vaccine study)
CVnCoV Vaccine	CureVac AG	Phase 3	2 doses (d0, d28)	NCT04449276 (phase 1) NCT04515147 (phase 2) NCT04652102 (phase 2/3) NCT04674189 (phase 3)
SARS-CoV-2 mRNA vaccine	ARCoV	Phase 3	2 doses (d0, d14 or d28)	ChiCTR2000034112 (phase 1) ChiCTR2100041855 (phase2) NCT04847102 (phase 3)

All Information updated Aug 24, 2021
**Assessment of SARS-CoV-2 variants

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EUA: Emergency Use Authorization

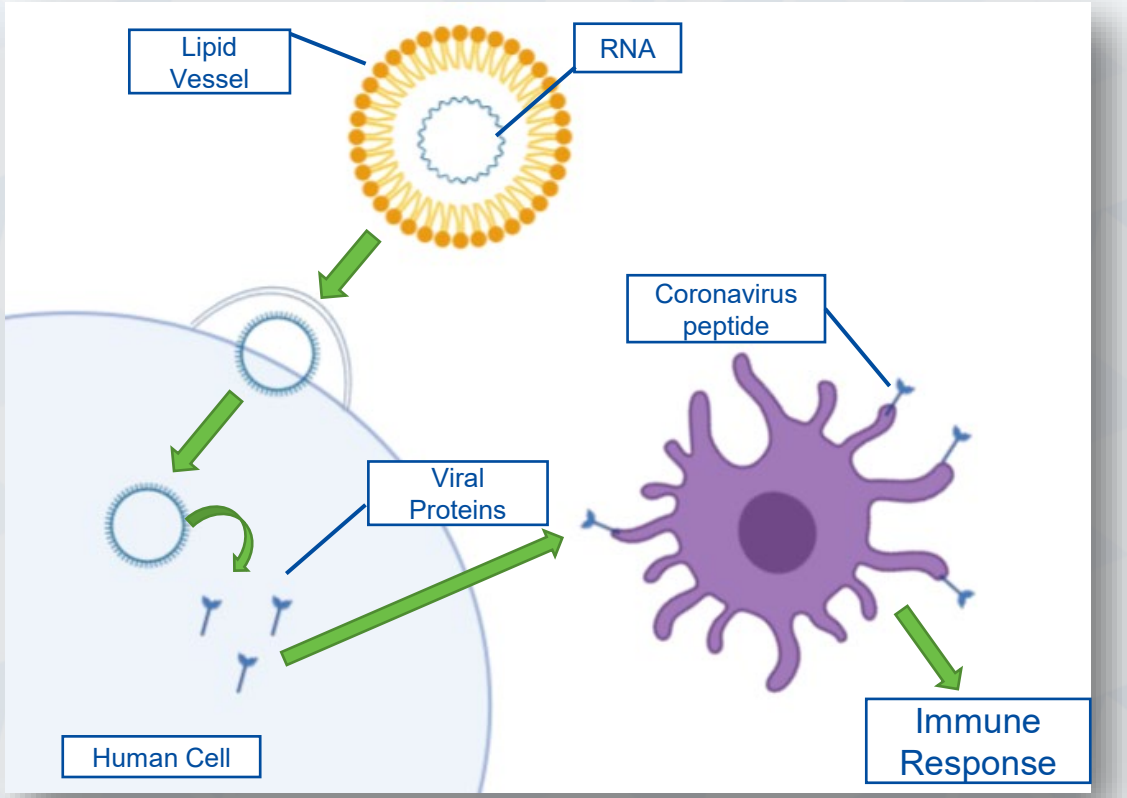
World Health Organization. Draft landscape of COVID-19 candidate vaccines. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. Accessed Aug, 24, 2021

Mechanism of Action mRNA Platform

- Previous concerns with mRNA technology
  - Instability
  - High innate immunogenicity
  - Inefficient *in vivo* delivery
- Benefits of mRNA technology
  - Non-infectious, non-integrating
  - More stable, highly translatable → administered repeatedly
  - Rapid, inexpensive production

At least 6 phase 1/2 clinical trials ongoing for mRNA vaccines against infectious diseases*

*Data from 2020, Wadhwa et al



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Callaway E. Nature. 2020. 580:576-577
Krammer F. Nature. 2020. 586:516-27
Pardi N, et al. Nature Reviews. 2018. 17:261-278
Wadhwa A. Pharmaceutics 2020. (12)102-27

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BNT162b1/b2 Preclinical and Phase I/II

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BNT162b Candidates

Safety and Immunogenicity

- Comparison of safety and immunogenicity of dose levels in two vaccine candidates
  - BNT162b1 → encodes SARS-CoV-2 RBD of the SARS-CoV-2 spike protein
  - BNT162b2 → encodes pre-fusion, membrane-anchored SARS-CoV-2 full-length, spike protein

- Two Primary Phase 1 studies
  - German Study: BNT162-01
  - US Study: C4591001

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RBD: receptor binding domain

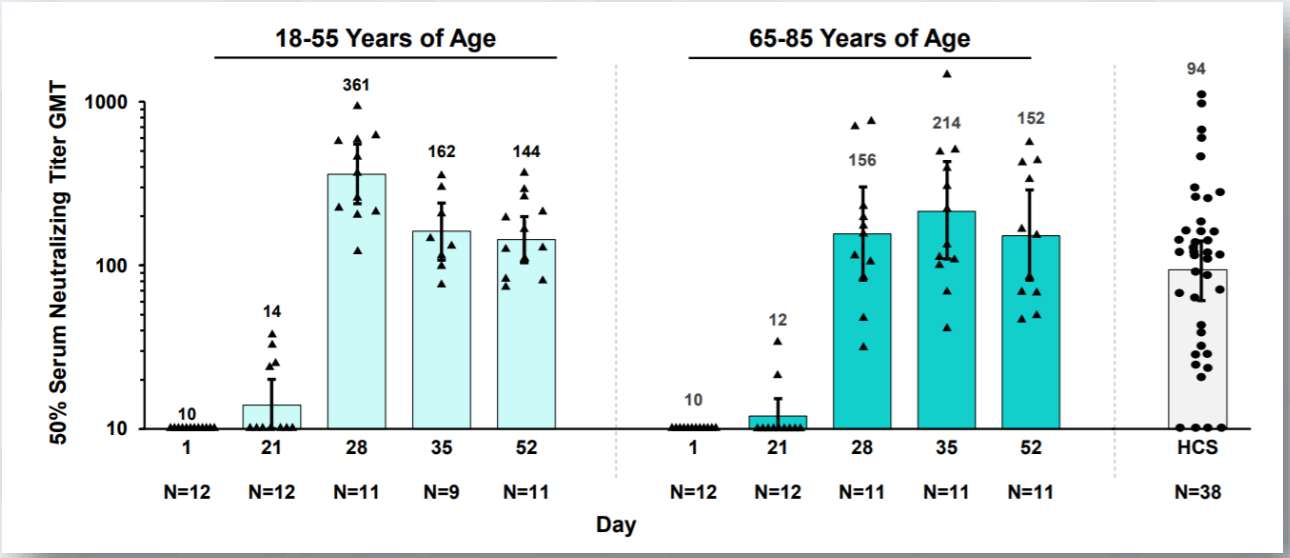
Walsh EE, et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2027906
Sahin U, et al. Nature. 2020. doi: 10.1038/s41586-020-2814-7
Mulligan MJ, et al. Nature. 2020. doi: 10.1038/s41586-020-2639-4

BNT162b Candidates

Safety and Immunogenicity

- Key Immunogenicity Findings
  - Serologic responses were similar between candidates
  - ↓ virus-neutralizing responses in 65-85 years of age
  - ↑ doses appeared to elicit higher antibody responses
  - Highest neutralizing titers on 7 and 14 days after dose 2

Two BNT162b2 30 mcg doses
Neutralizing Antibody Titers



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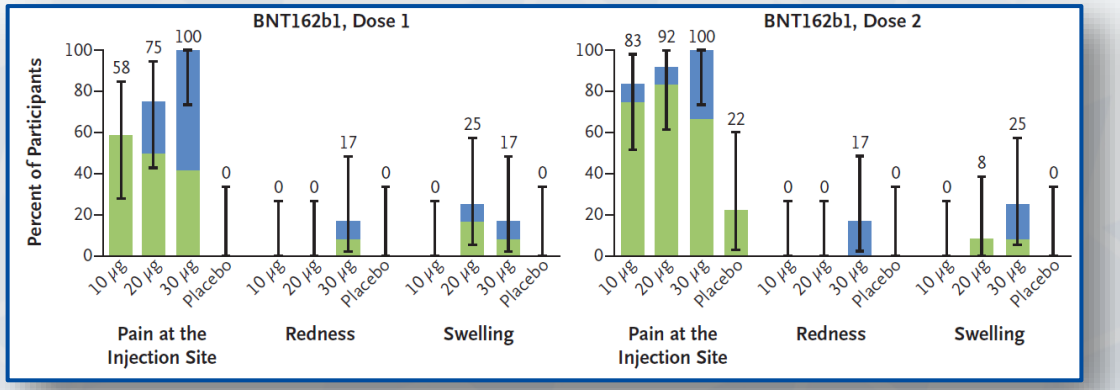
Walsh EE, et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2027906

BNT162b Candidates

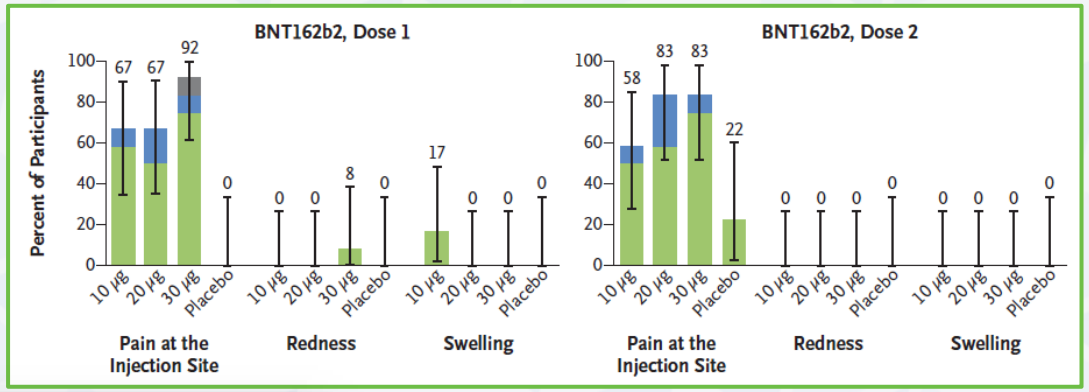
Safety and Immunogenicity

- Key Safety Findings
  - Local and systemic reactions were dose-dependent and transient
    - Peaked at day 2 and resolved by day 7
  - Fewer BNT162b2 recipients reported using pain medication

BNT162b1 18-55 yrs



BNT162b2 18-55 yrs



Mild Moderate Severe

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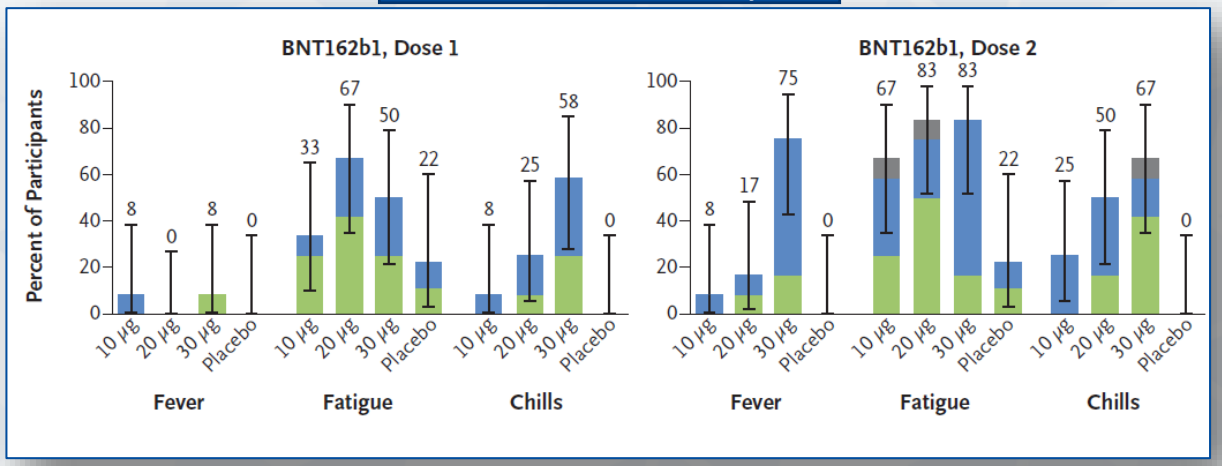
Walsh EE, et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2027906

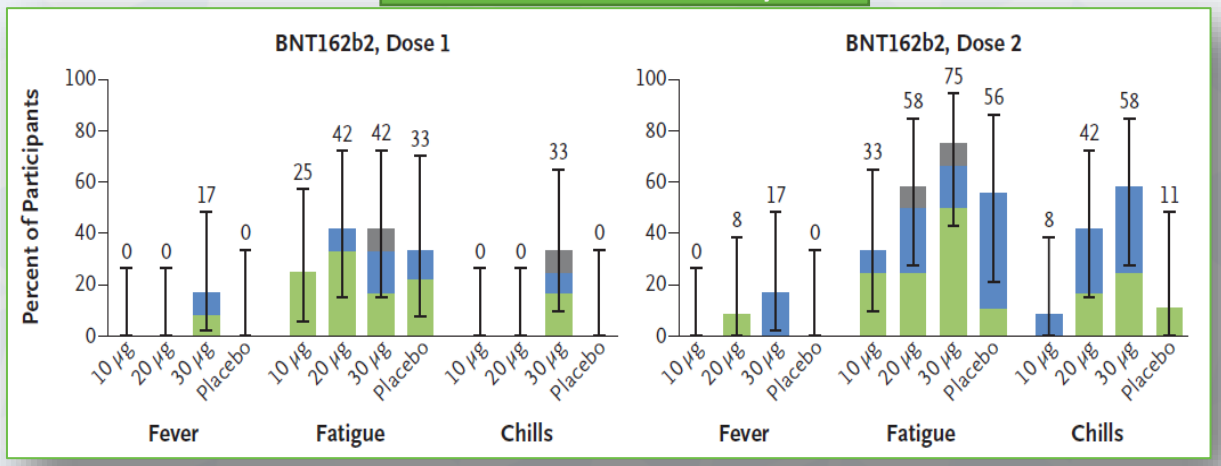
BNT162b Candidates

Safety and Immunogenicity

BNT162b1 18-55 yrs



BNT162b2 18-55 yrs



Mild Moderate Severe

- Systemic events in response to BNT162b2 milder than those with BNT162b1
- Transient decreases in lymphocyte count resolved in 1 week after vaccination

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Walsh EE, et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2027906

BNT162b2 Phase III

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BNT162b2 Vaccine

Polack et al.

Study Design

- Phase III, placebo-controlled, observer-blinded efficacy trial
- 1:1 randomization
- ≥16 years old, healthy or with stable chronic medical conditions*

Treatment Groups

- BNT162b2 30 mcg/dose, (0.3mL)
  - 2 doses
  - 21 days apart
- Placebo (0.3mL)
  - 2 doses
  - 21 days apart

Outcomes

- **Primary**: Efficacy of vaccine against symptomatic, lab-confirmed COVID-19 7 days after 2nd dose
- **Secondary**: Prevention of severe COVID-19 disease
- **Safety**: Local/systemic reactogenicity, all ADEs during specified time frames

*Excluded: pregnant or breastfeeding, medical history of COVID-19, immunocompromised, or treatment with immunosuppressive therapy

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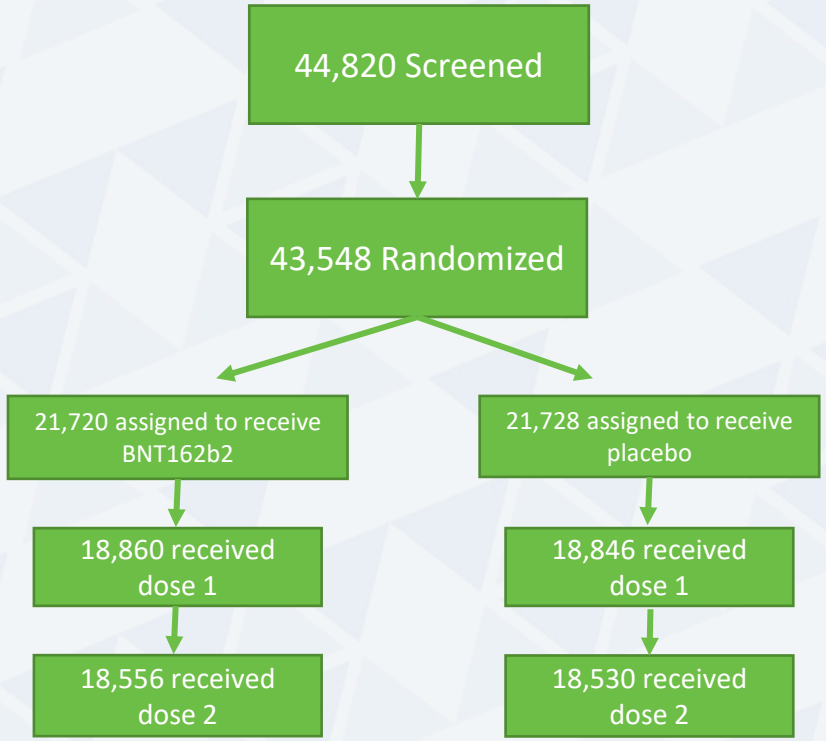
ADEs: Adverse Drug Events

Polack FP, et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2034577

BNT162b2 Vaccine

Polack et al.



Characteristic - no. (%)	BNT162b2 (N=18,860)	Placebo (N=18,846)	Total (N=37,706)
Sex			
Male	9,639 (51.1)	9,436 (50.1)	19,075 (50.6)
Female	9,221 (48.9)	9,410 (49.9)	18,631 (49.4)
Age group			
16-55 yr	10,889 (57.7)	10,896 (57.8)	21,785 (57.8)
>55 yr	7,971 (42.3)	7,950 (42.2)	15,921 (42.2)
Body Mass Index			
≥30 (kg/m^2)	6,556 (34.8)	6,662 (35.3)	13,218 (35.1)
Selected comorbidities			
Any Charlson Comorbidity	3,934 (20.9)	3,809 (20.2)	7,743 (20.5)
AIDS/HIV	59 (0.3)	62 (0.3)	121 (0.3)
COPD	1,478 (7.8)	1,453 (7.7)	2,931 (7.8)
DM	1,572 (8.3)	1,591 (8.4)	3,163 (8.4)
Any Malignancy	733 (3.9)	662 (3.5)	1,395 (3.7)

Ages 16-17 limited representation (N=153)

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Polack FP, et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2034577

BNT162b2 Vaccine

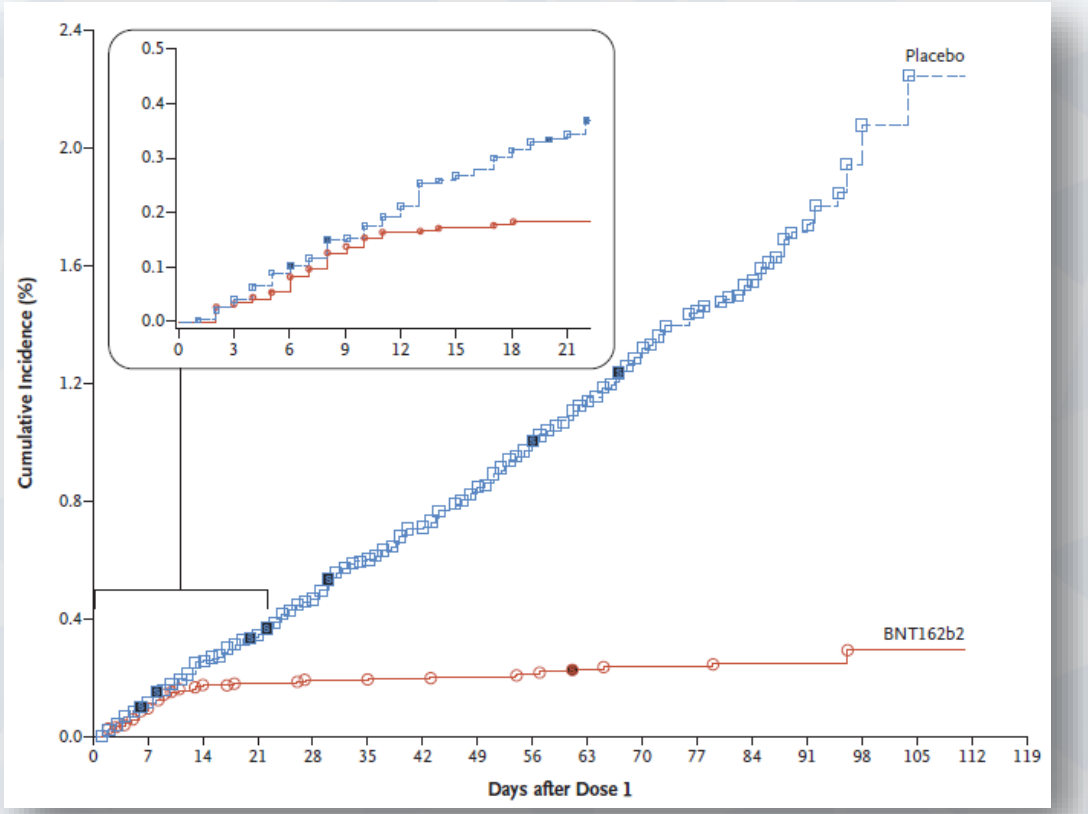
Polack et al.

Primary and Secondary Endpoints

	BNT162b2	Placebo	Efficacy (95% CI)
Symptomatic COVID-19 without evidence of infection	8 (N=18,198)	162 (N=18,325)	95.0% (95% CI, 90.3 to 97.6)
Symptomatic COVID-19 with and without evidence of infection	9 (N=19,965)	169 (N=20,172)	94.6% (95% CI, 89.9 to 97.3)
Severe COVID-19 *after dose 1	1 (N=21,314)	9 (N=21,259)	88.9% (95% CI, 20.1 to 99.7)

- Efficacy between 1st and 2nd dose: 52% (95% CI, 29.5 to 68.4)
  - 39 cases in BNT162b2
  - 82 cases in placebo

VE among subgroups consistent with overall primary outcome efficacy



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VE: Vaccine Efficacy
CI: confidence interval

Polack FP, et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2034577

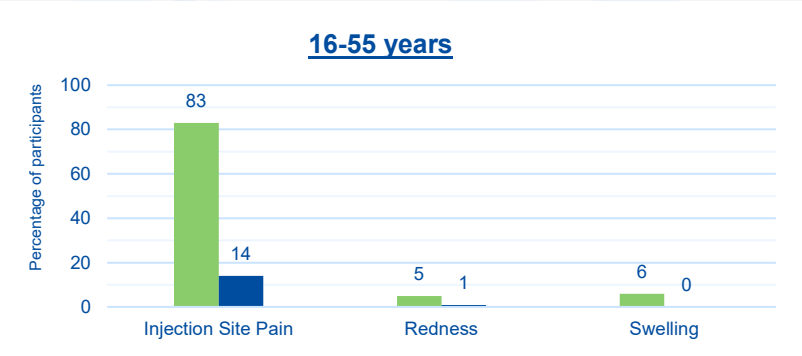
BNT162b2 Vaccine

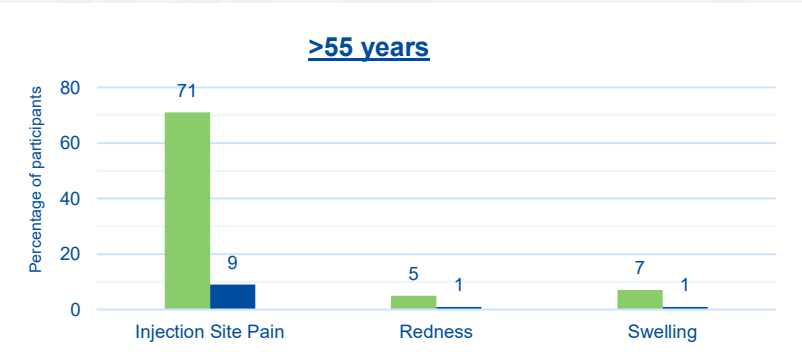
Polack et al.

Local Reactogenicity (n=8,183)

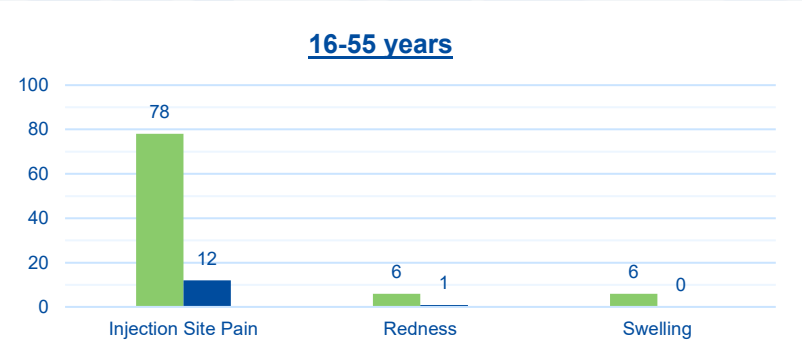
- ↑ local reactions in BNT162b2 than placebo
- Mild-moderate pain most commonly reported
- Older patients had lower rates of local reactions
- Most reactions resolved within 1-2 days

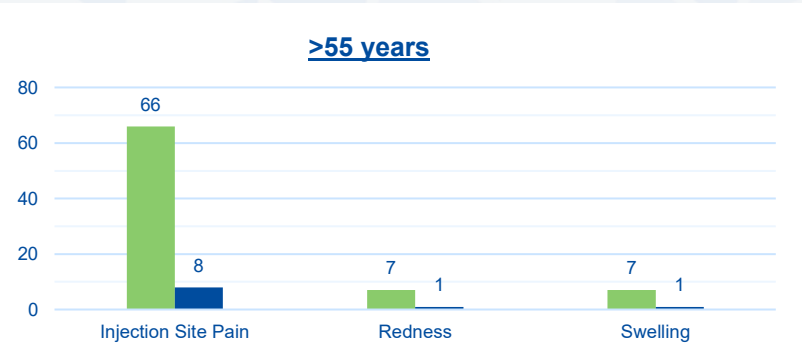
Dose 1





Dose 2





BNT162b2
Placebo

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Polack FP, et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2034577

BNT162b2 Vaccine

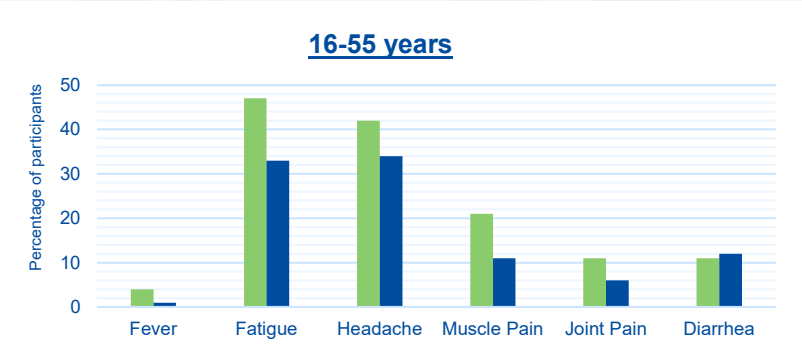
Polack et al.

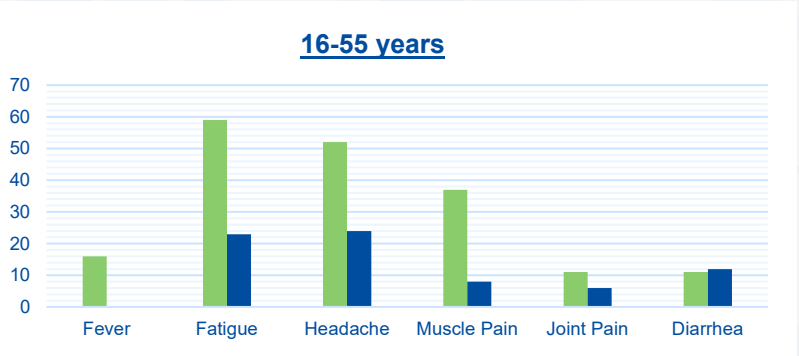
Systemic Reactogenicity (n=8,183)

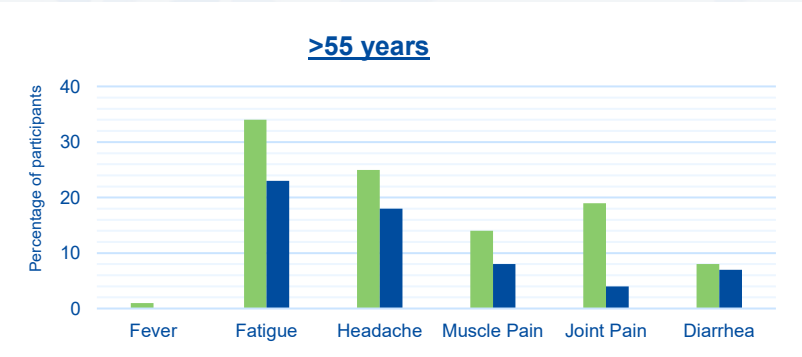
- Fatigue and headache most common overall
- Fever more common after dose 2
- Severe systemic events < 2% of vaccine recipients
- Older patients less likely to have systemic events
- Observed **within 1-2 days** and **resolved within a day**

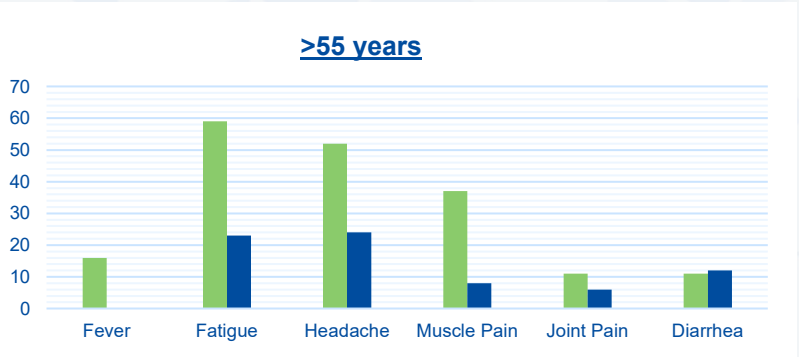
Dose 1

Dose 2









BNT162b2
Placebo

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Polack FP, et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2034577

BNT162b2 Vaccine

Polack et al.

Adverse Events (n=43,252)

- ↑ adverse events in BNT162b2 vs placebo (27% vs 12%)
- Lymphadenopathy occurred in 64 BNT162b2 vs 6 placebo
- No deaths were considered to be related to vaccine or placebo
- No COVID-19 related deaths were observed
- 4 reports of Bell's Palsy → consistent with expected background rate
  - Continued monitoring for this in future

Adverse Event – n(%)	BNT162b2 (N=21,621)	Placebo (N=21,631)
Any event	5,770 (26.7)	2,638 (12.2)
Related	4,484 (20.7)	1,095 (5.1)
Severe	240 (1.1)	139 (0.6)
Life-threatening	21 (0.1)	24 (0.1)
Any Serious Adverse Event	**126 (0.6)**	**111 (0.5)**
Related	4 (0)	0 (0)
Severe	71 (0.3)	68 (0.3)
Life-threatening	21 (0.1)	30 (0.1)
Any Adverse Event Leading to Withdrawal	**37 (0.2)**	**30 (0.1)**
Related	16 (0.1)	9 (0)
Severe	13 (0.1)	9 (0)
Life-threatening	3 (0)	6 (0)
Death	2 (0)	4 (0)

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Polack FP, et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2034577
Pfizer/FDA Briefing Document. Data updated Nov 14, 2020.

BNT162b2 Vaccine | Follow-up Data

- Phase 3 clinical trial updated with 6-month data (accrued up to March 13, 2021)
  - 927 confirmed symptomatic cases of COVID-19
  - 55% of vaccinated participants with at least 6-months of follow-up after 2nd dose

	BNT162b2	Placebo	Efficacy (95% CI)
Symptomatic COVID-19	77	850	**91.3% (89, 93.2)**
Severe COVID-19 (FDA)	1	21	95.7% (73.9, 99.9)

15 deaths in BNT162b2 and 14 deaths in placebo
Causes of death were balanced between groups

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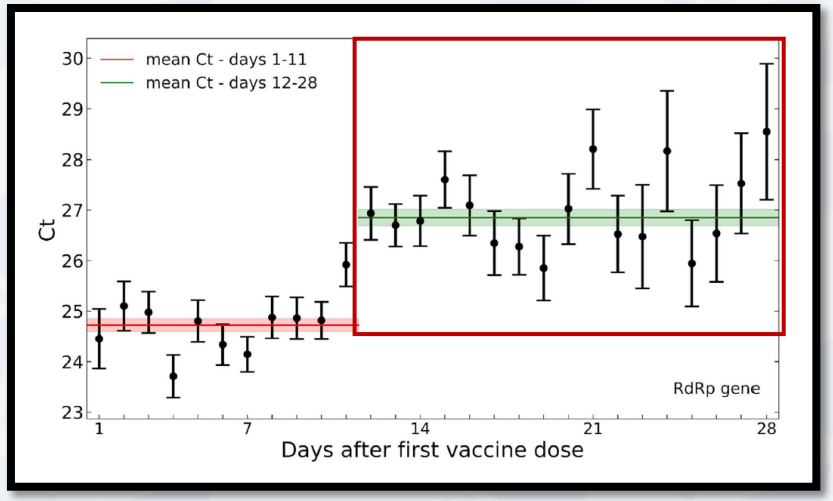
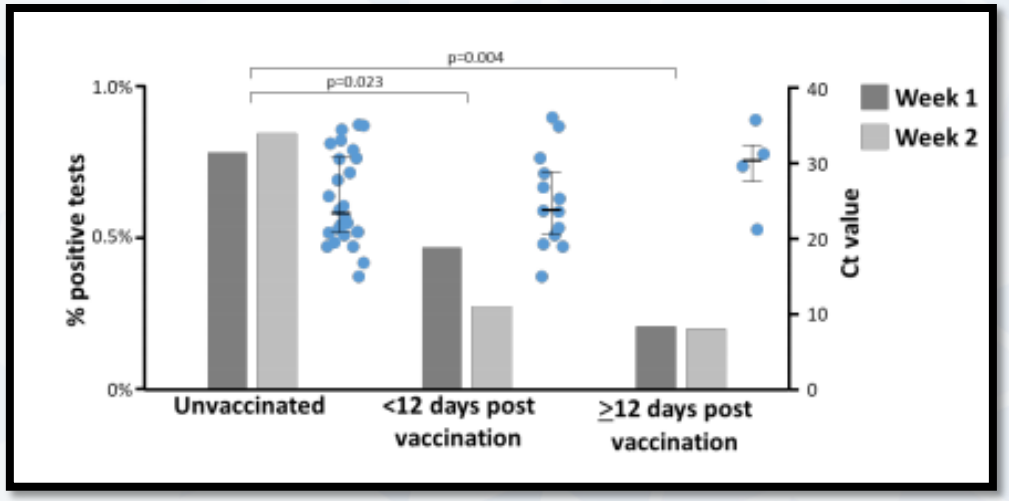
Thomas SJ, et al. MedRxiv [Preprint]. 2021. doi: 10.1101/2021.07.28.21261159

BNT162b2 Vaccine Asymptomatic Data



Decreased SARS-CoV-2 viral load after 12 days post-vaccination



Proportion testing positive for SARS-CoV-2 in asymptomatic screen

Study	Design	Endpoints	Asymptomatic Results
Dagan et al	Observational, ≥ 16 yrs old, healthcare worker	Documented SARS-CoV-2 infection by PCR (VE defined as 1-RR)	VE 7 days after 2nd dose for asymptomatic SARS-CoV-2: **90% (95%CI, 83 to 94)**
Tande et al	Retrospective cohort, ≥ 18 yrs old, pre-procedure SARS-CoV-2 testing	Relative risk of positive SARS-CoV-2 molecular test in asymptomatic persons	RR >0 days after 2nd dose: **0.27 (95%CI 0.12 to 0.60, p=0.001)**

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Levine-Tiefenbrun et al. MedRxiv [Preprint]. 2021. doi: 10.1101/201.02.06.21254283
Weekes et al. Authorea. February 24, 2021. doi: 10.22541/au.161420511.12987747/v1
Dagan et al. N Engl J Med 2021; 384:1412-1423
Tande et al. Clin Infect Dis. 2021;ciab229. doi:10.1093/cid/ciab229

BNT162b2 Vaccine | Pediatric Data

- 2,260 adolescents ages 12 to 15 years
  - 1,308 adolescents followed for >2 months after 2nd dose

Demographics	%
Female	49.9
White	85.9
Hispanic/Latino	11.7
Asian	6.4
Black or African American	4.6
American Indian/Alaskan Native	0.4

	Dose 1	Dose 2
Local Pain	86.2%	78.9%
Redness	5.8%	5%
Muscle Pain	24.1%	32.4%
Fatigue	60.1%	66.2%
Headache	55.3%	64.5%
Chills	27.6%	41.5%
Fever	10.1%	19.6%
Joint Pain	9.7%	15.8%

Serious adverse events reported in 0.4% BNT162b2 recipients and 0.1% of placebo

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Emergency Use Authorization of the Pfizer-Biontech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 [Healthcare Provider Fact Sheet]. U.S. FDA. Revised 10 May 2021

BNT162b2 Vaccine

Pediatric Data

Ages 12 through 15	BNT162b2 Cases	Placebo Cases	Vaccine Efficacy % (95% CI)
First COVID-19 Occurrence from 7 days after Dose 2 without prior SARS-CoV-2 infection	0 (N=1,005)	16 (N=978)	100 (75.3, 100)
First COVID-19 Occurrence from 7 days after Dose 2 with and without prior SARS-CoV-2 infection	0 (N=1,119)	18 (N=1,110)	100 (78.1, 100)

Assay	12 to 15 years (N=190) GMT (95% CI)	16 to 25 years (N=170) GMT (95% CI)	Met Noninferiority Objective
SARS-CoV-2 50% neutralizing titer – 1 mo. Post Dose 2	1239.5 (1095.5, 1402.5)	705.1 (621.4, 800.2)	Yes

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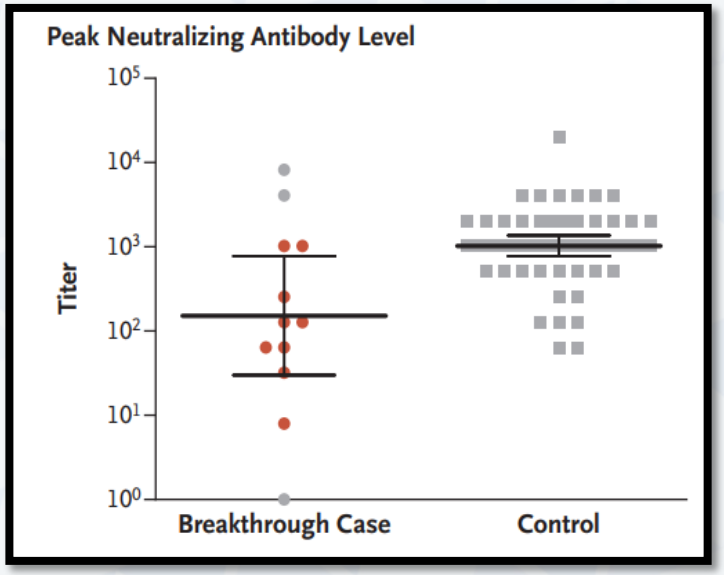
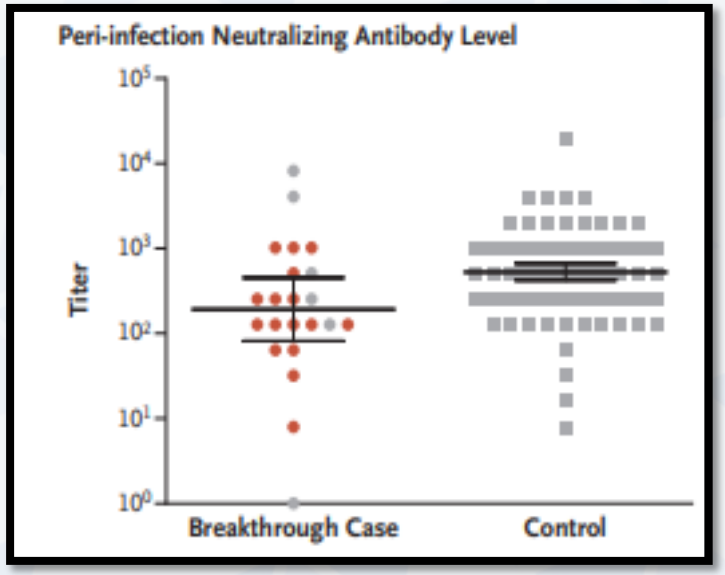
BNT162b2 Vaccine Immune Correlates





- Matched case-control analysis to identify correlates of breakthrough
- 1,497 vaccinated health care workers → 39 breakthrough infections over 14 weeks
- Neutralizing antibody titers in peri-infection period were lower in cases compared to matched controls
  - Case-control ratio 0.361; 95%CI 0.165 to 0.787

Limitations:

- Breakthrough infections in young, un-hospitalized
- Not matched based on testing and exposure, only availability of antibodies

Bergwerk et al. N Engl J Med. 2021 Jul 28:NEJMoa2109072.

BNT162b2 Vaccine

Polack et al.

FDA Approved on 8/23/2021 for prevention of COVID-19 disease in individuals 16 years of age and older

The Good

- Serious adverse events low and consistent between groups
- RNA-vaccines proof of concept and promising
- Rapid delivery of results, large patient population
- **Pediatric data**
- **Protection against severe disease**
- **Limited data for asymptomatic infection prevention**
- **Clinical efficacy against variants**
- **EUA approved in patients 12 through 15**

The Gap

- Long-term safety outcomes
- **Duration of efficacy (current data out to 6-months)**
- Lacks data in pregnancy and immunocompromised

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The Ugly

-70°C cold storage requirement

BNT162b2 Vaccine

Looking Forward

Pregnant Women
Feb 2021 first participant in Phase 2/3

Children Under 12
March 2021 first participant in Phase 1/2/3

Booster
Feb 2021 evaluation of 3rd dose as booster

Lyophilized Formulation
Phase 3 evaluating refrigerator stable formulation

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Pfizer-BioNtech. Vaccine Efforts. https://www.pfizer.com/science/coronavirus/vaccine-efforts. Accessed May 17, 2021

mRNA-1273 Preclinical and Phase I/II

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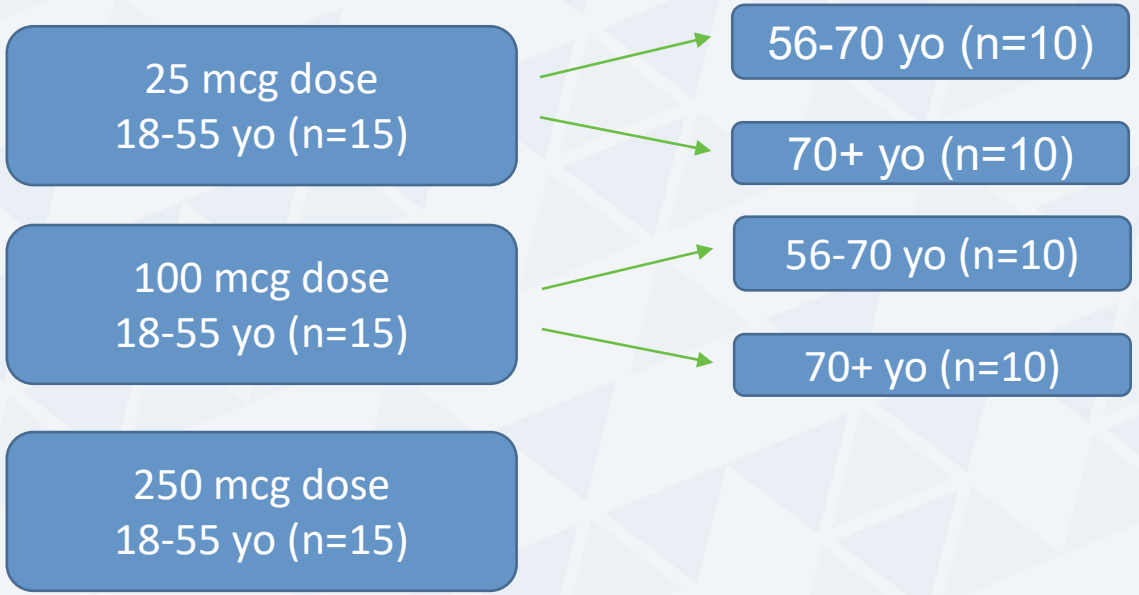
mRNA-1273 Vaccine

Safety and Immunogenicity

- Phase I studies to evaluate safety and immunogenicity a 2-dose vaccine given 28 days apart



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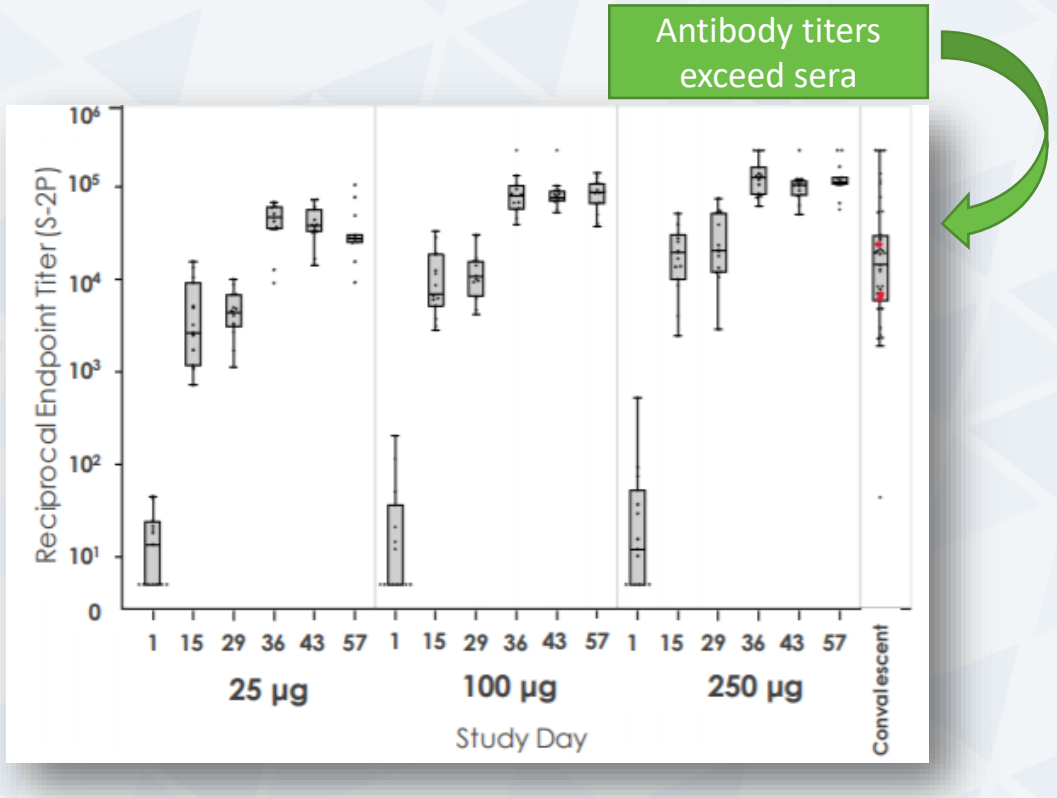
Jackson LA, et al. N Engl J Med. 2020;383:1920-31
Anderson EJ, et al. N Engl J Med. 2020;383:2427-38

mRNA-1273 Vaccine

Safety and Immunogenicity

- Key Immunogenicity Findings: <56 years
  - Day 57 pseudovirus neutralization geometric mean titers at 100 mcg dose →2.1-fold higher than convalescent sera
  - Neutralizing antibody titers observed in 100% of patients
  - Predominant Th1 T cell responses, with minimal Th2 T cell response
  - 100 mcg dose elicited favorable neutralization response over 25 mcg



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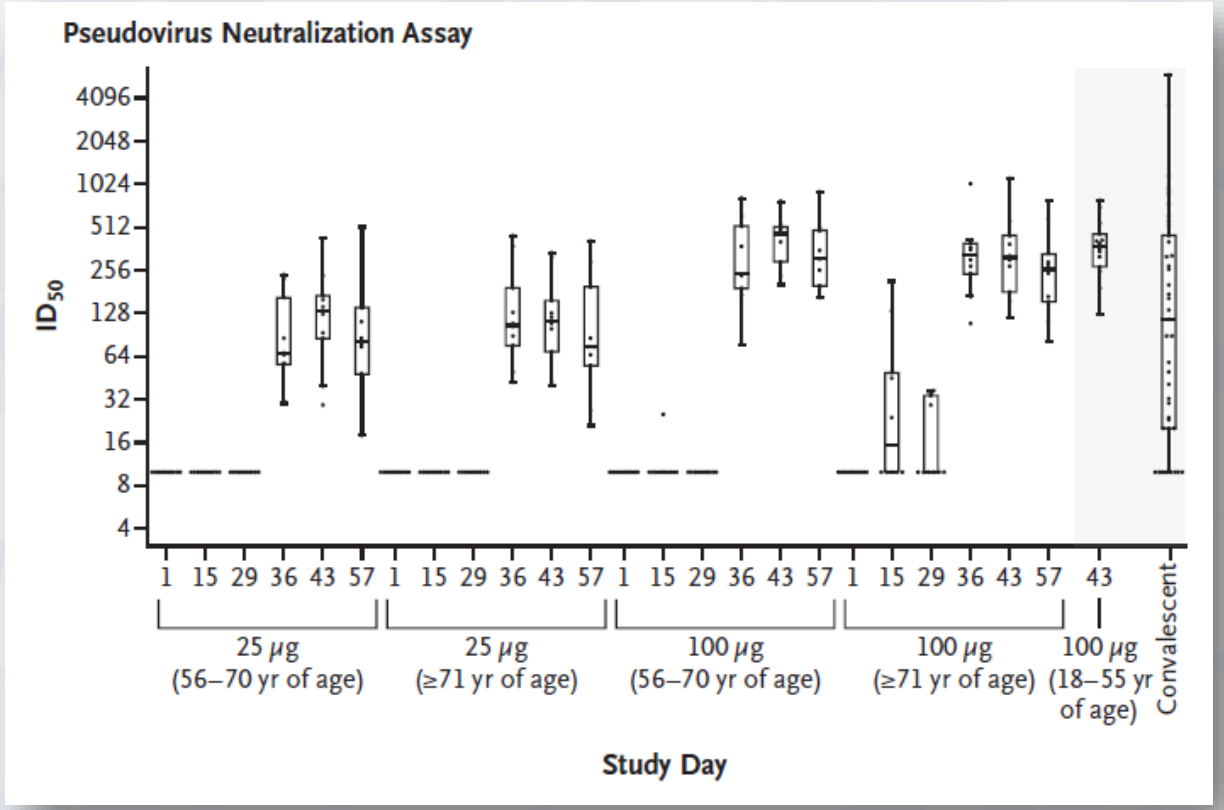
Jackson LA, et al. N Engl J Med. 2020;383:1920-31

mRNA-1273 Vaccine

Safety and Immunogenicity

- Key Immunogenicity Findings: ≥56 years
  - Induced high-level of binding and neutralizing-antibody levels in older cohorts
  - Antibody responses similar to younger patients
  - Titers rapidly increased after booster dose
    - Importance of 2nd dose in older patients
  - Based on small number of patients (n=10 per age and dose group)



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Anderson EJ, et al. N Engl J Med. 2020;383:2427-38

mRNA-1273 Phase III

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mRNA-1273 Vaccine

Baden et al.

Study Design

- Phase III, placebo-controlled, observer-blinded efficacy trial
- 1:1 randomization
- ≥18 years old and at high risk of SARS-CoV-2 infection

Treatment Groups

- mRNA-1273 100 mcg (0.5 mL)
  - 2 doses
  - 28 days apart
- Placebo (0.5 mL)
  - 2 doses
  - 28 days apart

Outcomes

- **Primary**: efficacy of vaccine against symptomatic, lab-confirmed COVID-19, 14 days after dose 2
- **Secondary**: prevention of severe COVID-19 disease
- **Safety**: local/systemic reactogenicity, all ADEs during specified time frames

*Excluded: pregnant or breastfeeding, known history of SARS-CoV-2 infection, immunosuppressed, asplenia, recurrent severe infections

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ADEs: Adverse Drug Reactions

Baden, et al. N Eng J Med. 2020. doi: 10.1056/NEJMoa2035389
Moderna/FDA Briefing Document. Data Updated Nov 25, 2020.

mRNA-1273 Vaccine

Baden et al.

Demographic and Clinical Characteristics at Baseline		
Characteristic - no. (%)	mRNA-1273 (N=15,181)	Placebo (N=15,170)
Sex		
Male	7,923 (52.2)	8,062 (53.1)
Female	7,258 (47.8)	7,108 (46.9)
Age group		
18-65 yr	11,413 (75.2)	11,418 (75.3)
>65 yr	3,768 (24.8)	3,752 (24.7)
Age and health risk for severe COVID-19		
≥18 and <65 years and **not at risk**	8,888 (58.5)	886 (58.6)
≥18 and < 65 years and **at risk**	2,530 (16.7)	2,535 (16.7)
≥65 years	3,763 (24.8)	3,739 (24.7)
Baseline SARS-CoV-2 Status		
Negative	14,550 (95.8)	14,598 (96.2)
Positive	343 (2.3)	337 (2.2)
Missing	288 (1.9)	235 (1.5)

"At Risk" population:

- Chronic lung disease
- Significant cardiac disease
- Severe obesity
- Diabetes
- Liver disease
- Controlled HIV

Disease Acquisition Risk Factor:
82.1% Occupational Risk
25.1% Healthcare Worker

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Baden, et al. N Eng J Med. 2020. doi: 10.1056/NEJMoa2035389
Moderna/FDA Briefing Document. Data Updated Nov 25, 2020.

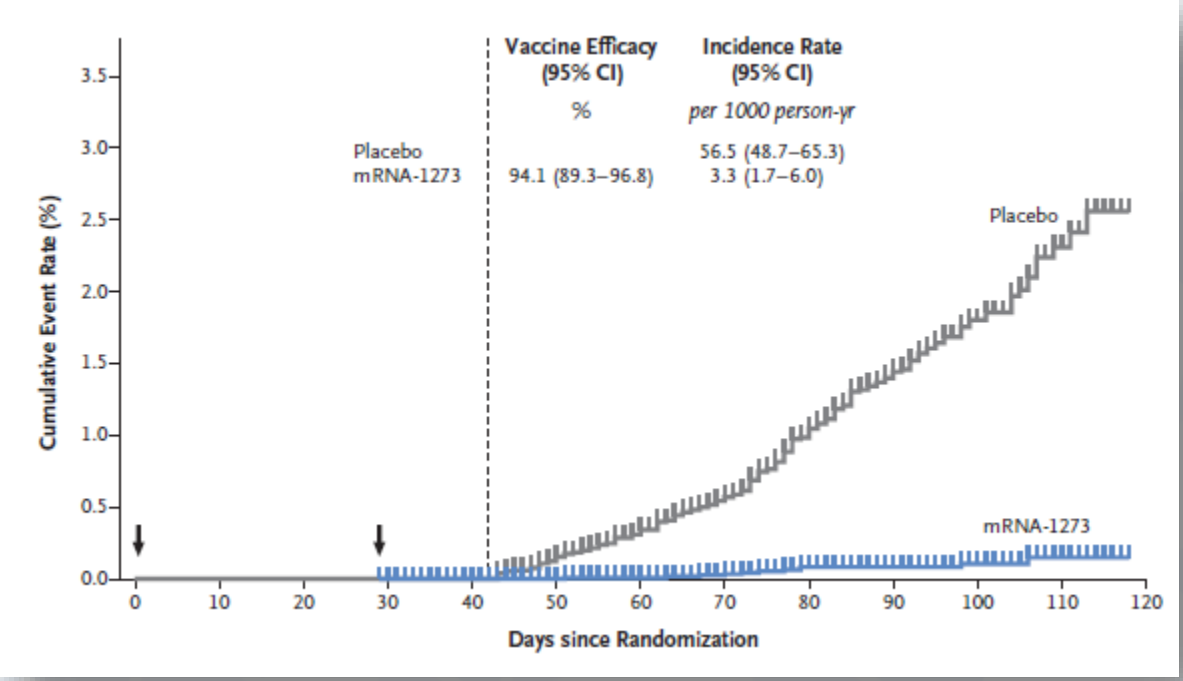
mRNA-1273 Vaccine

Baden et al.

Primary and Secondary Endpoints

Per-Protocol Analysis	mRNA-1273	Placebo	Efficacy (95% CI)
Symptomatic COVID-19 without evidence of infection	11 (N=14,134)	185 (N=14,073)	**94.1%** (95% CI, 89.3 to 96.8)
Symptomatic COVID-19 with and without evidence of infection	12 (N=15,181)	187 (N=15,170)	**93.6%** (95% CI, 88.6 to 96.5)
Severe COVID-19 *14 days after 2nd dose	0 (N=14,134)	30 (N=14,073)	**100%**

- Efficacy after 1st dose in mITT Set: 80.2% (95% CI, 55.2 to 92.5) → **median follow-up time: 28 days**
  - 7 cases in mRNA-1273 (N=996)
  - 39 cases in placebo (N=1070)
- Severe COVID-19 cases after dose 1 in mITT Set: 42.6% (95% CI, -300.8 to 94.8)
  - 2 cases in mRNA-1273 (N=996)
  - 4 cases in placebo (N=1079)



Cumulative Incidence of COVID-19 events in the primary analysis in the per-protocol population

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VE: Vaccine Efficacy

Baden, et al. N Eng J Med. 2020. doi: 10.1056/NEJMoa2035389
Moderna/FDA Briefing Document. Data Updated Nov 25, 2020.

mRNA-1273 Vaccine

Baden et al.

Preliminary Analysis of Infection from Randomization, Modified Intent to Treat Population

COVID-19 Onset	mRNA-1273 (N=14,550)	Placebo (N=14,598)
Randomization to 14 days after dose 1	5	11
14 days after dose 1 to dose 2	2	35
Dose 2 to 14 days after dose 2	0	19
Starting 14 days after dose 2	12	204
Total (any time after randomization)	19	269
Total with Secondary COVID-19 Definition	1	24
Positive RT-PCR at pre-dose 2 visit	**15**	**39**
Total Infection (all COVID-19 definitions)	**35**	**332**

Vaccine Efficacy: 89.5% (95% CI 85.2% to 92.6%)

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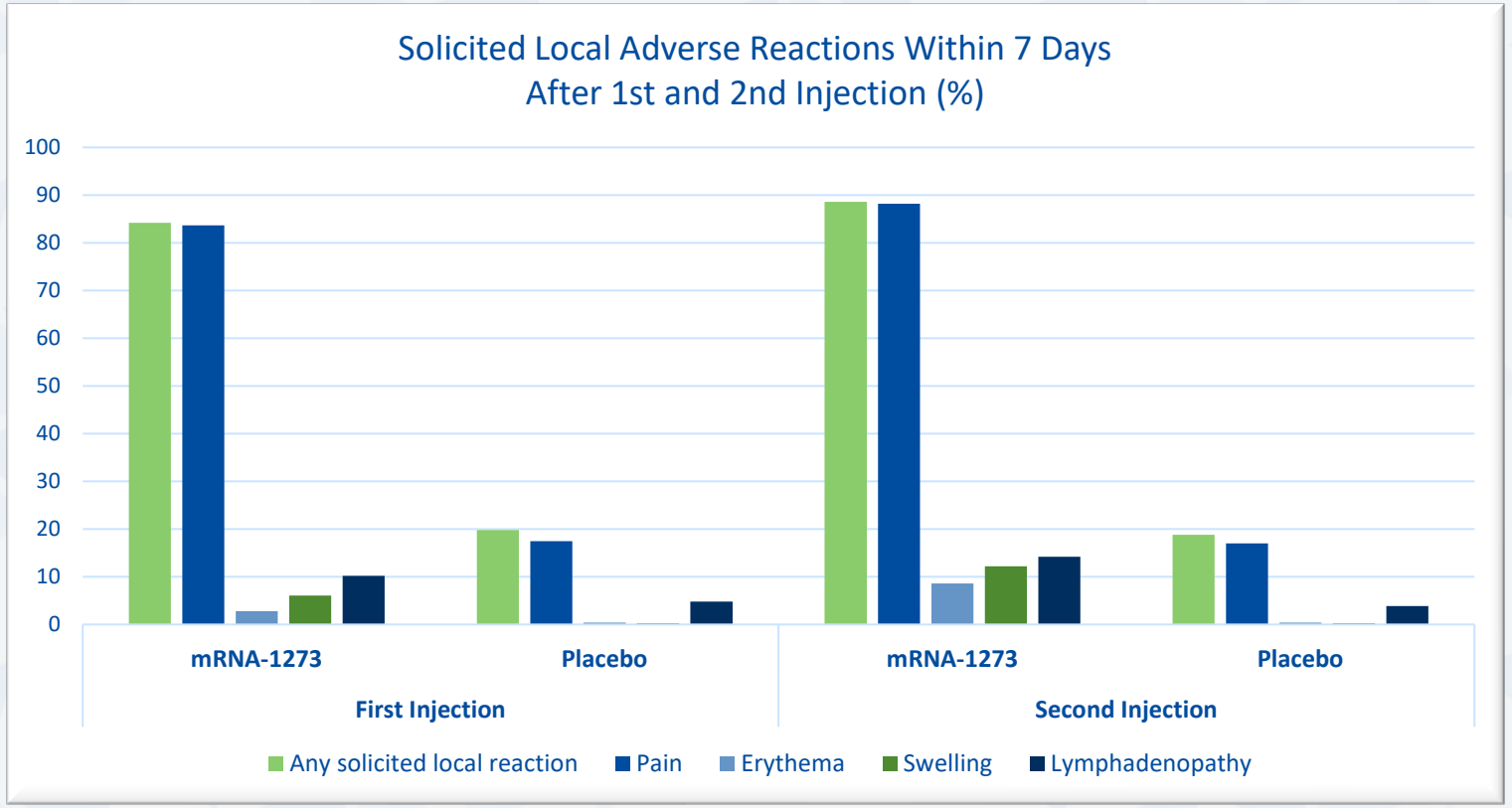
Baden, et al. N Eng J Med. 2020. doi: 10.1056/NEJMoa2035389
Moderna/FDA Briefing Document. Data Updated Nov 25, 2020.

mRNA-1273 Vaccine

Baden et al.

Local Reactogenicity (n=29,243)

- ↑ local reactions in mRNA-1273 than placebo
- Mild-moderate pain most commonly reported
- Most reactions occurred in 1-2 days and persisted for 1-3 days
    - mRNA-1273 group had higher ARs that persisted beyond 7 days compared to placebo



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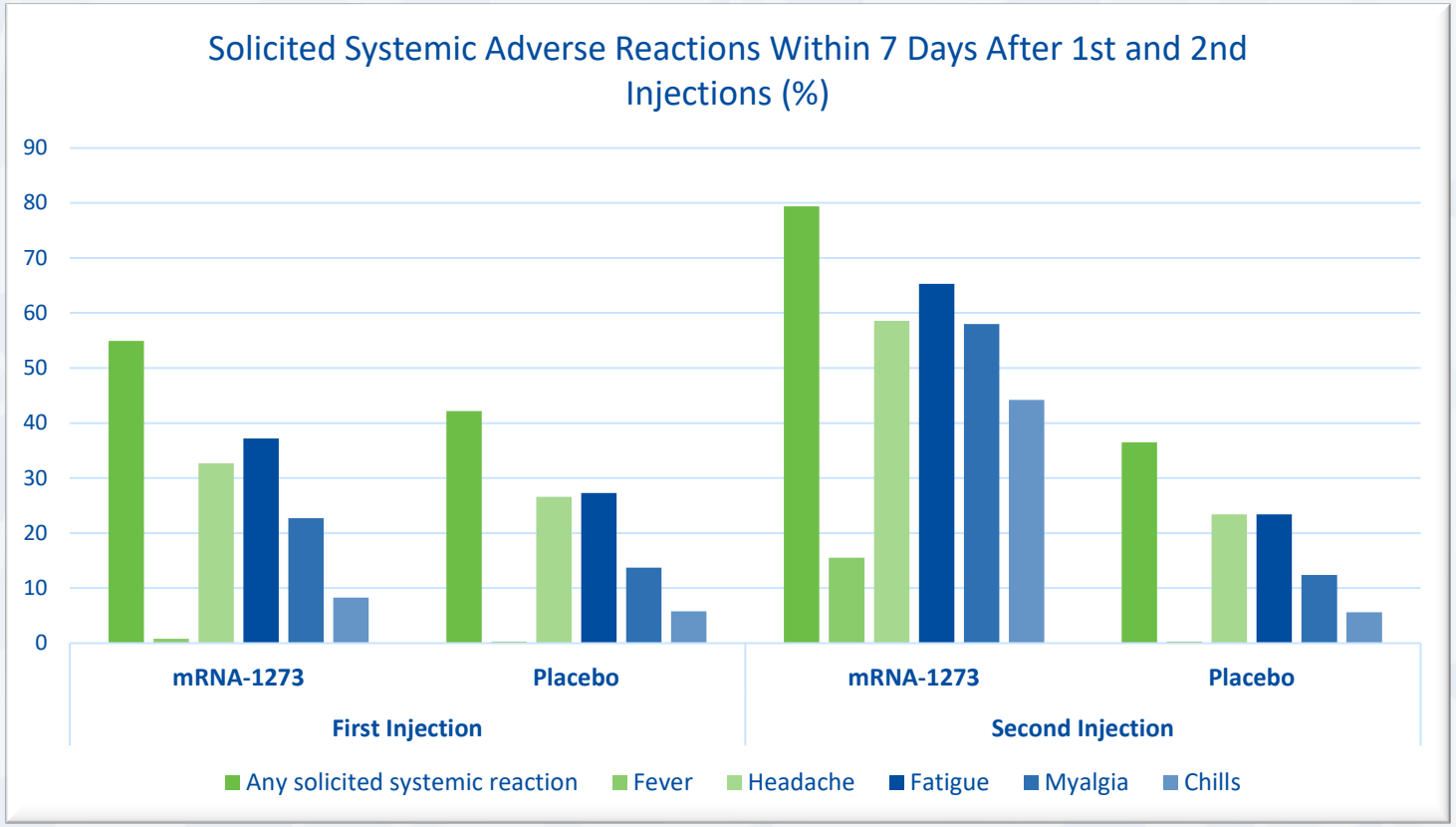
Baden, et al. N Eng J Med. 2020. doi: 10.1056/NEJMoa2035389
Moderna/FDA Briefing Document. Data Updated Nov 25, 2020.

mRNA-1273 Vaccine

Baden et al.

Systemic Reactogenicity (N=29,243)

- More prevalent in mRNA-1273 group than placebo
- Severity of ARs increased after the 2nd injection
- Most common severity grades were 1 and 2
- **Onset of 1-2 days and persisted for median of 1-2 days**



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Baden, et al. N Eng J Med. 2020. doi: 10.1056/NEJMoa2035389
Moderna/FDA Briefing Document. Data Updated Nov 25, 2020.

mRNA-1273 Vaccine

Baden et al.

Unsolicited Adverse Events (n=30,351)

- Severe AEs reported more in mRNA-1273 arm for headache, myalgia, arthralgia, and injection site pain
- 5 deaths reported, **NONE** were considered to be related to vaccine or placebo
- 1 COVID-19 related death in placebo group
- 3 reports of Bell's Palsy in treatment arm and 1 in placebo arm

Adverse Event – n(%)	mRNA-1273 (N=15,185)	Placebo (N=15,166)
All	3,632 (23.9)	3,277 (21.6)
Severe	234 (1.5)	202 (1.3)
Fatal	2 (<0.1)	3 (<0.1)
Leading to discontinuation from study vaccine	50 (0.3)	80 (0.5)
Leading to discontinuation from participation in the study	2 (<0.1)	2 (<0.1)
Serious	93 (0.6)	89 (0.6)
Medically-attended AEs	1,372 (9)	1,465 (9.7)

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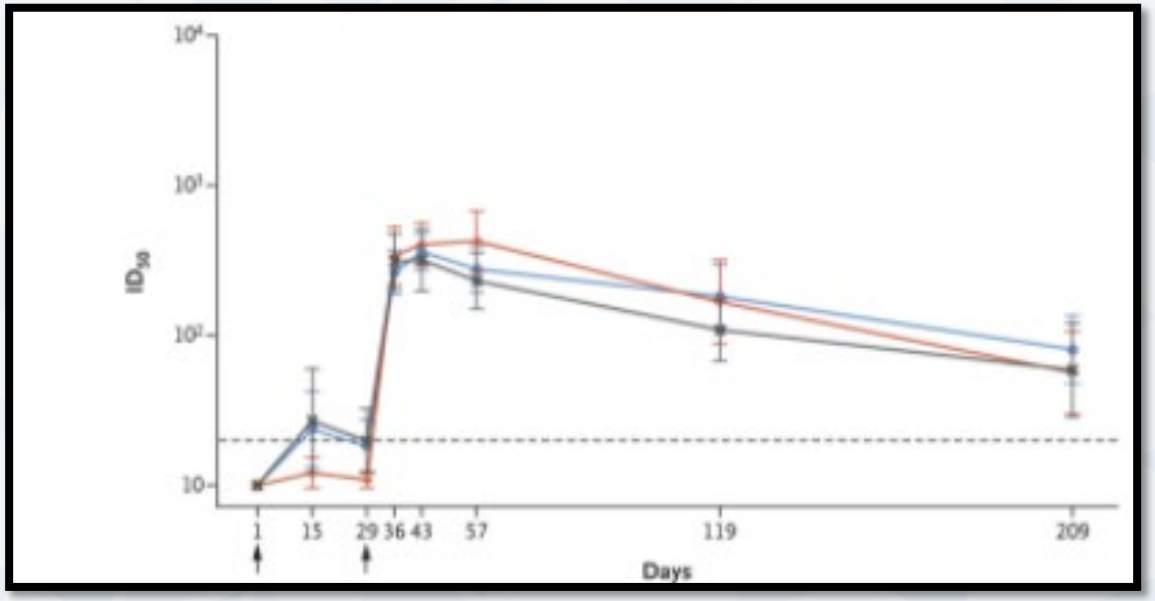
Baden, et al. N Eng J Med. 2020. doi: 10.1056/NEJMoa2035389
Moderna/FDA Briefing Document. Data Updated Nov 25, 2020.

mRNA-1273 Vaccine Follow-up Data

- 33 healthy adult participants in ongoing phase 1 trial
  - 180 days after 2nd dose (day 209)
- Detectable pseudo virus neutralization with 50% inhibitory dilutions GMTs
- Half-life binding of antibodies was 52-109 days (model dependent)
- Antibodies persisted for 6 months, ongoing studies to determine booster effects



Pseudo virus neutralization assay

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Doria-Rose et al. N Eng J Med. 2021. doi: 10.1056/NEJMc2103916

mRNA-1273 Vaccine | Pediatric Data

- Teen COVE → 3,732 adolescents ages 12 to 17 years; 2,489 100 mcg mRNA-1273 and 1,243 placebo
  - Median duration of follow-up from second injection was 53 days

Demographics	%
Female	49
White	84
Hispanic/Latino	12
Asian	6
Black or African American	3
American Indian/Alaskan Native	1

	Dose 1	Dose 2
Local Pain	93%	92%
Redness	13.5%	19.5%
Muscle Pain	27%	47%
Fatigue	48%	68%
Headache	45%	70%
Chills	18%	43%
Fever	2.5%	12%
Joint Pain	15%	29%

No cases of myocarditis or pericarditis reported at time of publication

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Ali et al. N Engl J Med. 2021. doi: 10.1056/NEJMoa2109522

mRNA-1273 Vaccine

Pediatric Data

Ages 12 through 17	mRNA-1273 Cases	Placebo Cases	Vaccine Efficacy % (95% CI)
COVID-19 Occurrence from 14 days after Dose 2, PP	0	4	100 (28.9, NE)
COVID-19 Occurrence (secondary definition) from 14 days after Dose 2, PP	1	7	93.3 (47.9 to 99.9)
Asymptomatic SARS-CoV-2 14 days after Dose 2, PP	21	16	39.2 (-24.7, 69.7)
Asymptomatic SARS-CoV-2 14 days after Dose 2, mITT	25	29	59.5 (28.4, 77.3)

Assay	12 to 17 years (N=340) GMT (95% CI)	18 to 25 years (N=296) GMT (95% CI)	Met Noninferiority Objective
SARS-CoV-2 50% neutralizing titer – 1 mo. Post Dose 2	1401.7 (1276.3, 1539.4)	1301.3 (1177.0, 1438.8)	Yes

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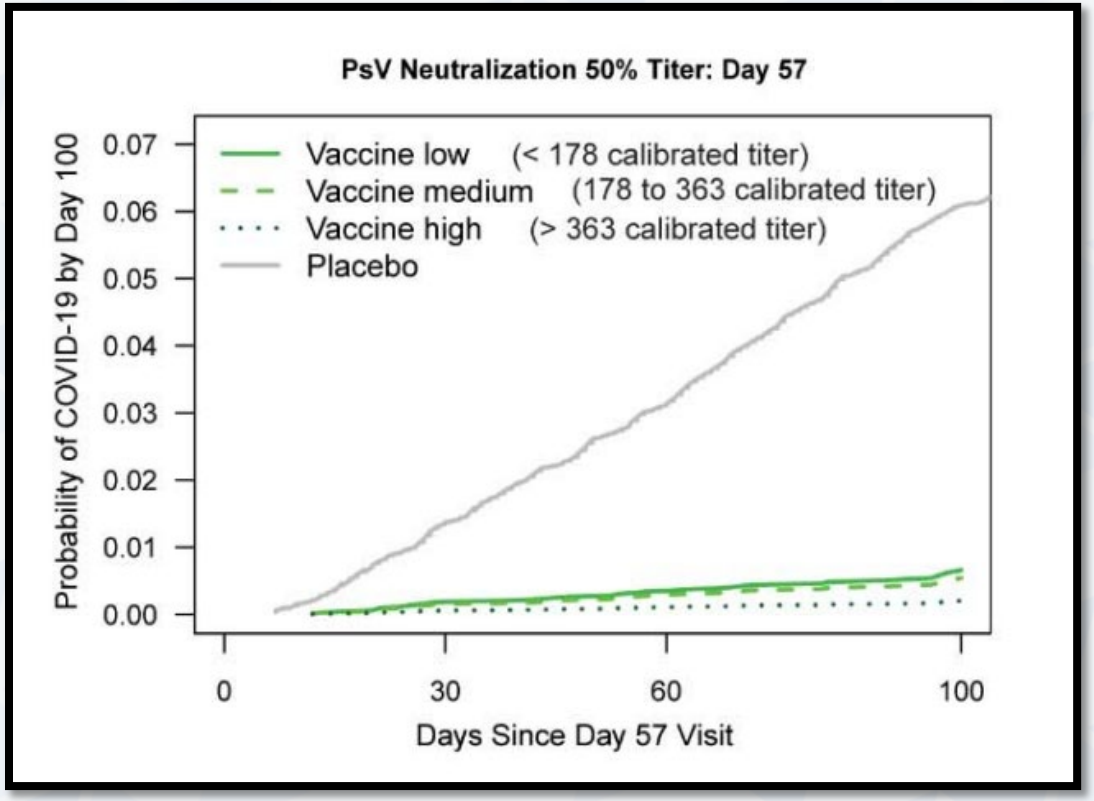
Ali et al. N Engl J Med. 2021. doi: 10.1056/NEJMoa2109522

mRNA-1273 Vaccine Immune Correlates



- IgG bAbs to Spike, IgG bAbs to Spike RBD, ID50 nAb titer, and ID80 nAb titer assessed as correlates of risk and protection
- All 4 markers at day 29 and 57 → inverse correlates of risk through 4 months post dose 2
- Positive vaccine efficacy in subgroup with undetectable antibody level
  - Implies vaccine efficacy not fully mediated through antibody markers
- Limitations → no data for correlates of COVID-19 outcomes, COVID-19 due to variants not assessed, low number of cases and persons with undetectable titers

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bAbs: binding antibodies
nAbs: neutralizing antibodies
RBD: receptor binding domain

Gilbert et al. medRXiv [PREPRINT]. Doi: 10.1101/2021.08.09.21261290

mRNA-1273 Vaccine

Phase III Data

2-dose regimen of mRNA-1273 is safe and effective against COVID-19

94.1% Vaccine Efficacy in primary outcome group

The Good

- Serious adverse events low and consistent between groups
- Some protection after 1st dose → 2 doses is the best!
- RNA-vaccines proof of concept and promising
- Rapid delivery of results, large patient population
- **Prevention of asymptomatic infection**
- **Clinical efficacy against variants (booster trials pending)**

The Gap

- Long-term safety outcomes
- **Duration of efficacy (current data out to 6-months)**
- Lacks data in pregnancy, immunocompromised and patients <18 years old

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The Kinda Ugly

-20°C cold storage requirement

Most expensive

Moderna/FDA Briefing Document. Data Updated Nov 25, 2020.
Baden, et al. N Eng J Med. 2020. doi: 10.1056/NEJMoa2035389
Jackson LA, et al. N Engl J Med. 2020;383:1920-31

mRNA-1273 Vaccine

Looking Forward

Children Under 12
NCT04796896

Heme/Onc
Hematologic malignancies and solid tumors
NCT04847050

Transplant
Adult organ transplant recipients
NCT04860297

Variant Booster
mRNA-1273.351
NCT04785144

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Information obtained from Clinicaltrials.gov on May 17, 2021.

mRNA Vaccine Comparison

Comirnaty

	BNT162b2 (Pfizer-BioNTech)	mRNA-1273 (Moderna)
Dose	• Ages ≥ 12: 30 mcg (0.3 mL) IM	• Ages ≥18: 100 mcg (0.5 mL) IM
Schedule	• 2 doses (21 days apart) • 3rd dose in immunocompromised (28 days after 2nd dose)	• 2 doses (28 days apart) • 3rd dose in immunocompromised (28 days after 2nd dose)
EUA Age Req.	• ≥ 12 years old	• ≥ 18 years old
Undiluted/Unpunctured Storage Requirements	• -80°C and -60°C until specified date on vial • -25 and -15 °C for up to 2 weeks • 2°C and 8°C for up to 31 days • DO NOT REFREEZE	• -25°C and -15°C until specified date on QR code • 2°C and 8°C for up to 30 days • 8°C and 25°C for **up to 24 hours** • DO NOT REFREEZE
BUD Once Punctured	• 2°C to 25°C for up to 6 hours • Do not refreeze	• Store between 2°C and 25°C for up to 12 hours • Do not refreeze
Preservative	• No preservatives	• No preservatives

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Moderna/FDA Briefing Document. Data Updated Nov 25, 2020.
CDC. Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the US. Accessed Dec. 22 2020.
Emergency Use Authorization of the Pfizer-Biontech COVID-19 Vaccine to Prevent Coronavirus Disease 2019 [Healthcare Provider Fact Sheet]. U.S. FDA. Revised 12/2020
Emergency Use Authorization of the Moderna COVID-19 Vaccine to Prevent Coronavirus Disease 2019 [Healthcare Provider Fact Sheet]. U.S. FDA. Revised 12/2020

Side Effect Comparison

- 71 cases of anaphylaxis reported to VAERS
- Most cases of anaphylaxis were within 30 minutes
  - 90% of cases within 30 minutes
- Most were female (68, 95.7%) with hx of allergies or allergic reactions (58, 81.7%)
- Most were with 1st dose

	BNT162b2	mRNA-1273
Clinical Trial Data		
Bell's Palsy (n)		
Treatment	4	3
Placebo	0	1
Anaphylaxis (n)		
Treatment	1	0
Placebo	0	0
Real World Data		
Anaphylaxis*	5 per million doses	2.8 per million doses

*From Dec 14, 2020 to Jan 18, 2021

Previously reported rates:

- Pfizer: 11.1 per million doses admin (Dec 14, 2020 to Dec 23, 2020)
- Moderna: 2.5 per million doses admin (Dec 21, 2020 to Jan 10, 2021)

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Moderna/FDA Briefing Document. Data Updated Nov 25, 2020.
Polack FP, et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2034577
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-01/06-COVID-Shimabukuro.pdf
Bohlke et al. Pediatrics. 2003. 112(4):815-820.

mRNA Vaccines

Myocarditis

ACIP recommendations → benefits of mRNA COVID-19 vaccines clearly outweigh the risks in all populations (including adolescents and young adults)

- Retrospective multicenter study in US patients <21 yrs
  - 63 patients, mean age 15.6 years, 92% male, all but one had 1 dose
  - 88% met diagnostic criteria for myocarditis
  - Follow-up data for 86% of patients should resolution of symptoms, arrhythmias, and ventricular dysfunction at mean of 35 days
- Case series of children with hospitalized myocarditis within 30 days of BNT162b2
  - Mostly male, median age 15 years following 2nd dose of vaccine, 73% of patients had resolution of symptoms by day 13 post-discharge
  - Short term → mild; Long term → longer follow-up needed

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Gargano et al. MMWR Morb Mortal Wkly Rep 2021;70:977–982
Jain et al. Pediatrics. 2021 Aug 13:e2021053427
Dionne et al. JAMA Cardiol. 2021 Aug 10:e213471

Pregnancy and Lactation Data

- Data from Dec. 2020 to February 2021 in V-safe data base for total of 35,691 patients identified as pregnant
  - No obvious safety signals among pregnant patients
- 2 Immunogenicity evaluations:
  - 1: 30 pregnant and 16 were lactating women 2 to 8 weeks after 2nd mRNA dose
  - 2: 84 pregnant and 31 lactating women 2 to 6 weeks after 2nd mRNA dose
- Vaccine-induced antibody titers were equivalent in pregnant and non-pregnant
  - Antibodies also observed in infant cord blood and breast milk

ACOG Recommendations:

- Pregnant individuals should be free to make their own decision in conjunction with their clinical care team
- Lactating individuals should be offered vaccine once eligible
  - No need to avoid breastfeeding if received SARS-CoV-2 vaccine

CDC Recommendations:

- Pregnant individuals may choose to get vaccinated once eligible
- Lactating individuals may choose to get vaccinated once eligible
- No not need to avoid pregnancy after receiving SARS-CoV-2 vaccine

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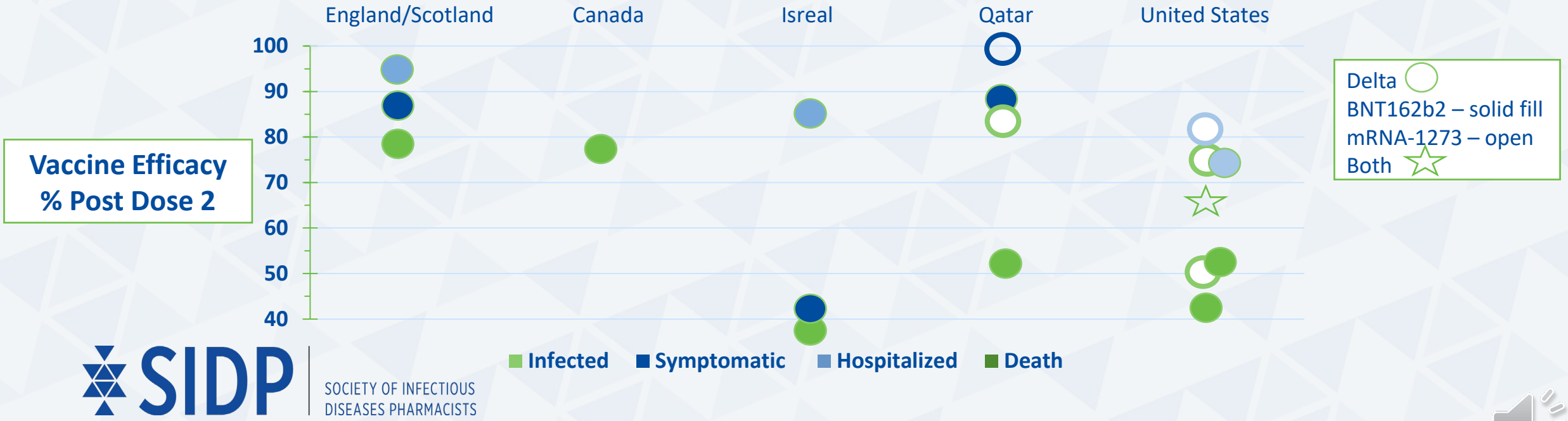
Shimabukuro TT, et al. N Engl J Med. 2021. doi: 10.1056/NEJMoa2104983
Collier AY, et al. JAMA. 201. doi: 10.1001/jama.2021.7563
Gray KJ, et al. Am J Obstet Gynecol. 2021. doi: 10.1016/j.ajog.2021.03.023
CDC. Interim Clinical Considerations for Use of mRNA COVID-19 Vaccines Currently Authorized in the US. Accessed May 17, 2021
ACOG. Vaccinating Pregnant and Lactating Patients Against COVID-19. Accessed May 17 2021

mRNA Vaccine Variant Data

	Alpha	Beta	Delta
Neutralization Reduction *In vitro*	0.8- to 2.6-fold[1-3]	4.9 to 10.3-fold	1.4 to 5.8-fold
References	1. Muik A, et al. Science 2021;371:1152-1153. 2. Wang P, et al. Nature 2021;593:130-135. 3. Wall EC, et al. Lancet 2021;397:2331-2333	1. Lancet Reg Health Eur. 2021;8:100171 2. Nature 2021;593:130-135.	1. Lancet Reg Health Eur. 2021;8:100171 2. Nature 2021;593:130-135.



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Tang et al. medRxiv [Preprint]. Doi: 10.1101/2021.08.11.21261885; Stowe et al. PHE. Preprint; Abu-Raddad et al. N Engl J Med. 2021:385;2; Lopez Bernal et al. medRxiv [Preprint]. Doi: 10.1101/2021.05.22.21257658; Sheikh et al. Lancet. 2021:397; Haas et al. Lancet. 2021;397:1819-29; Nasreen et al. medRxiv [Preprint]. Doi: 10.1101/2021.06.28.21259420; Israel MOH: https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_two-dose-vaccination-data.pdf, Puranik A, et al. medRxiv [Preprint] 2021.08.06.21261707,. Keener et al. N Engl J Med. 2021. doi: 10.1056NEJMc2112981, Nanduri S.et al. MMWR Morbidity and Mortality Weekly Report. 2021 2021;70.

mRNA Vaccines Additional Dose Data

- **8/12/21 EUA Approval**: Third dose of Pfizer-BioNTech COVID-19 vaccine administered at least 28 days following the second dose in people at least 12 years of age AND
  - Have undergone solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise

Difference between "Booster" and "Additional Dose"

- Booster is when primary vaccine series is likely to have waned over time
- Additional dose is when initial immune response following primary series is likely insufficient

Moderately and Severely Immunocompromised

- Treatment for solid tumor or heme malignancies
- Solid organ transplant or taking immunosuppressive therapy
- Receipt of CAR-T-cell or HSCT (within 2 years or taking medication)
- Moderate or severe primary immunodeficiency
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids, alkylating agents, antimetabolites, transplant-related immunosuppressives, chemotherapeutic agents, TNF blockers, and other biologics that are immunosuppressive

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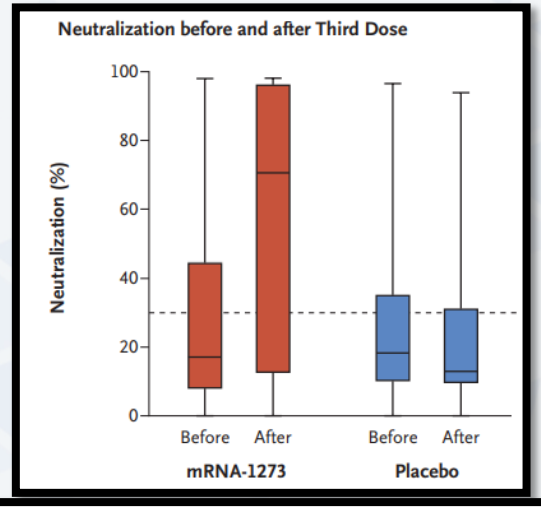
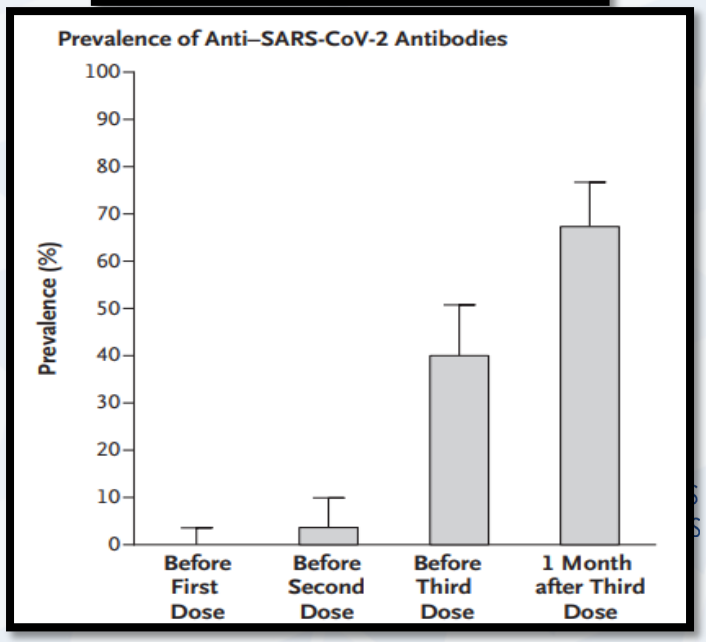
https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html

mRNA Vaccines

Additional Dose Data





- Antibody levels in immunocompromised patients shown to be well below immunocompetent vaccine patients
- Hall et al double-blind randomized controlled trial of 3rd dose (0, 1, 3 mo.) of mRNA-1273 vs placebo in transplant patients
  - Substantially higher immunogenicity compared to placebo (top)
  - Reactions following 3rd dose higher in vaccine group, no grade 3 or 4 events occurred
- Kamar et al studied 101 patients given 3rd dose 2 months after 2nd dose
  - 59 patients seronegative before 3rd dose, 26 (44%) seropositive 4 weeks after third dose (bottom)
  - Adverse events similar to post-second dose, no grade 3 or 4 events

Boyarsky et al. *JAMA.* 2021;325(21):2204-2206
Hall et al. N Engl J Med. 2021;10.1056/NEJMc2111462
Kamar et al. N Engl J Med. 2021; doi: 10.1056/NEJMc2108861

Useful Links

- CDC Website
  - https://www.cdc.gov/vaccines/covid-19/index.html
- CDC Vaccine Communication Toolkit
  - https://www.cdc.gov/vaccines/covid-19/health-systems-communication-toolkit.html
- CDC Guidance for Infection Prevention Considerations Post Vaccination
  - https://www.cdc.gov/coronavirus/2019-ncov/hcp/post-vaccine-considerations-healthcare-personnel.html
- COVID-19 ACIP Vaccine Recommendations
  - https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html
- COVID-19 Real-Time Learning Network (CDC and IDSA)
  - https://www.idsociety.org/covid-19-real-time-learning-network/
- ID Stewardship: COVID-19 Vaccine Resources for Pharmacists
  - https://www.idstewardship.com/covid-19-vaccine-resources-pharmacists/

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1. Get Vaccinated
2. Tell Others Why
3. Build the Confidence

SARS-CoV-2 mRNA Vaccines

A Review of Pertinent Drug Information for SARS-CoV-2

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September 13, 2021

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