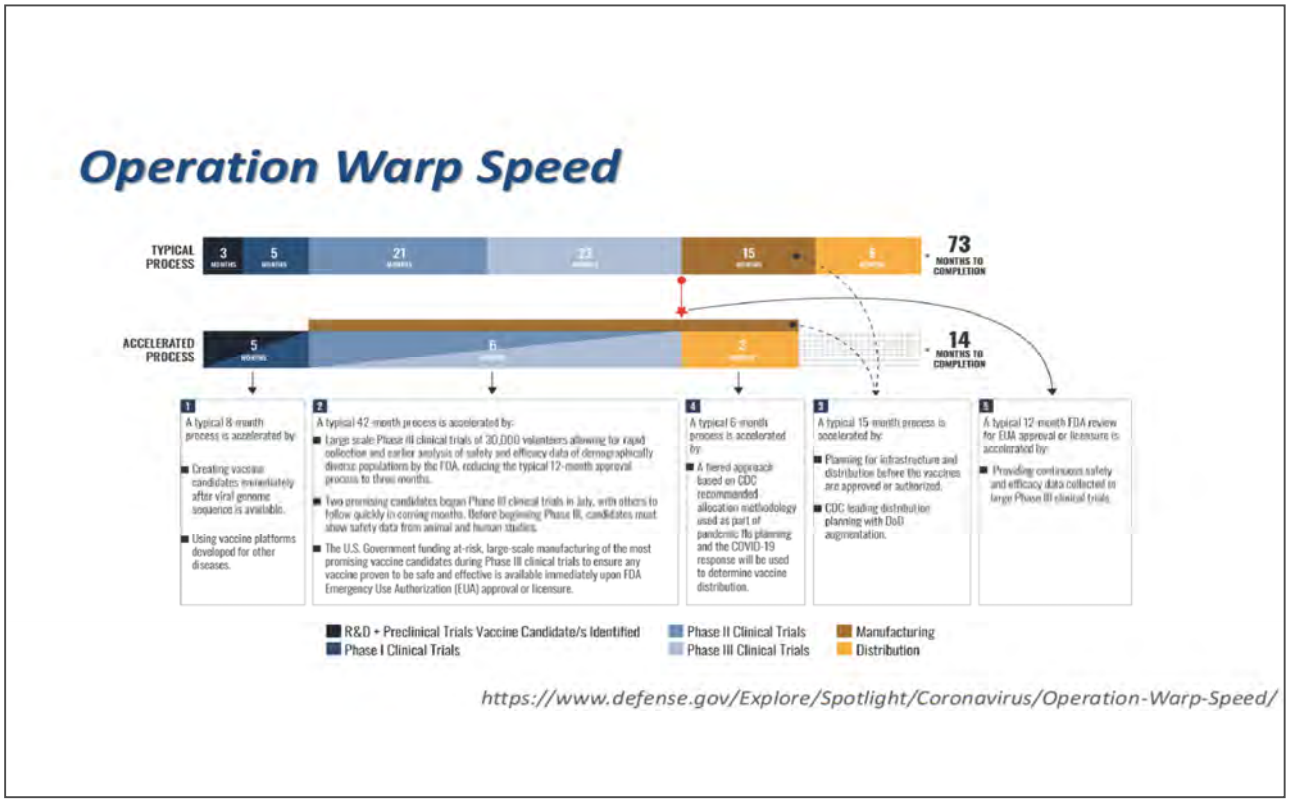
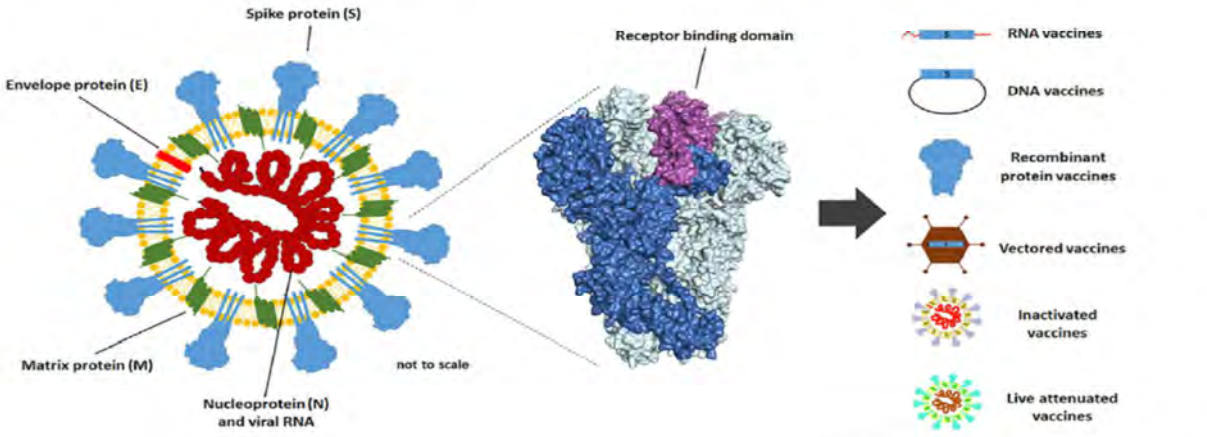
SARS-CoV-2 vaccine: efficacy and safety

최 평 균
서울의대 감염내과

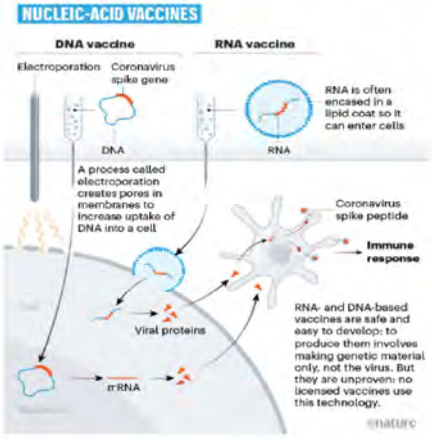


Potential COVID-19 vaccine Platform



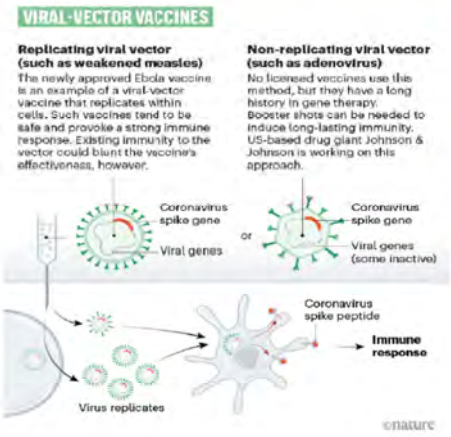
*Amanat et al. **Immunity** 2020;52:583-9*

개발이 완료되었거나 진행중인 코로나19 백신



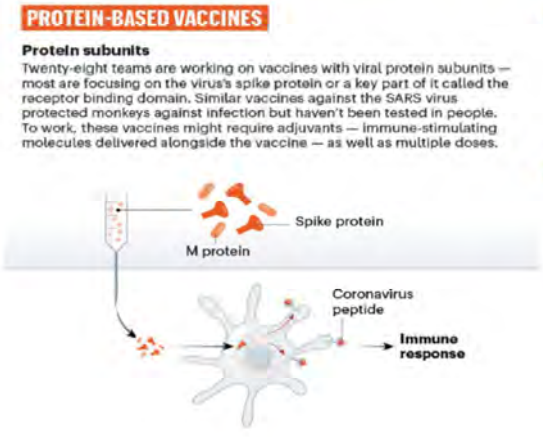
- ***Moderna/NIAID [mRNA-1273]***
  RNA vaccine, LNP-encapsulated mRNA
  EUA from UK, Canada, USA, EU
- ***BioNTech/Pfizer [BNT162b2]***
  RNA vaccine, 3LNP-mRNAs
  EUA from USA, Canada, EU, UK
- ***Inovio Pharmaceuticals/ International Vaccine Institute***
  DNA plasmid vaccine with electroporation

개발이 완료되었거나 진행중인 코로나19 백신

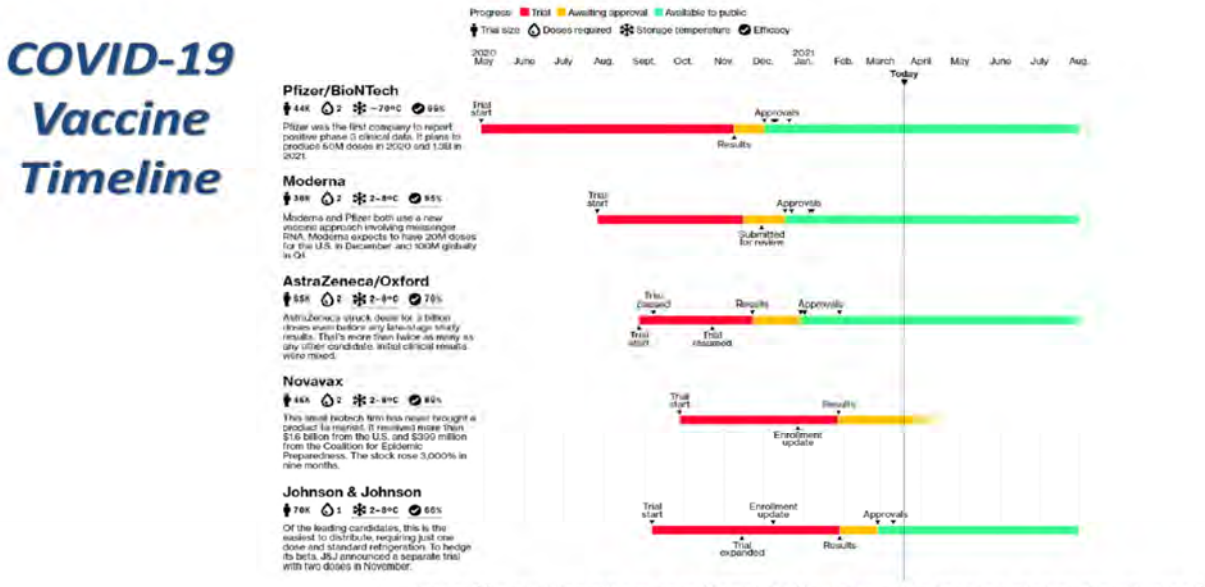


- ***University of Oxford/AstraZeneca***
  non-replicating viral vector, ChAdOx1-S
  EUA from UK, India
- ***Janssen Pharmaceutical***
  non-replicating viral vector, Ad26.COV2.S
- ***Cansino Biological Inc./Beijing Institute of Biotechnology***
  non-replicating viral vector, Adenovirus type 5 vector

개발이 완료되었거나 진행중인 코로나19 백신



- ***Novavax***
  SARS-CoV-2 rS/Matrix M1-Adjuvant
- ***SK Bioscience*** **[NBP2001]**
  recombinant protein subunit vaccine



https://www.bloomberg.com/graphics/covid-vaccine-tracker-global-distribution/

BIONTECH/PFIZER VACCINE

BioNTech/Pfizer BTN162b2, phase 2/3

- 6개국 (미국 130, 아르헨티나 1, 브라질 2, 남아공 4, 독일 6, 터키 9)
- 16세 이상 성인, 43,548명
- 두 번의 접종, 21일 간격
- 연구 대상의 나이 (중앙값) = 52세 (범위 16-89세), 55세 이상이 42.3%

Polack et al. **N Eng J Med** 2020 Dec 11;383:2603-15

백신의 효능 (efficacy)

		질병		총계
		+	-	
백신	+	10	990	1,000
	-	100	900	1,000
총계		110	1,890	2,000

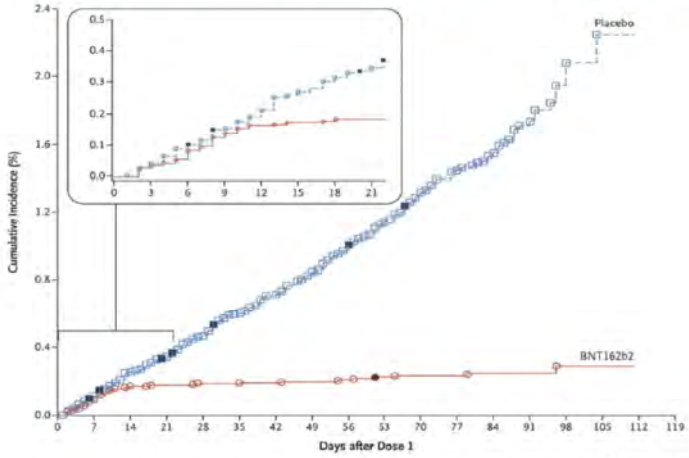
- 백신의 효능
  = [1- (백신을 맞은 사람 발생률)/(백신을 맞지 않은 사람 발생률)] x 100
  = [1- (10/1,000) / (100/1,000)] x 100 = 90%

BioNTech/Pfizer BTN162b2, phase 2/3

- 6개국 (미국 130, 아르헨티나 1, 브라질 2, 남아공 4, 독일 6, 터키 9)
- 16세 이상 성인, 43,548명
- 두 번의 접종, 21일 간격
- 연구 대상의 나이 (중앙값) = 52세 (범위 16-89세), 55세 이상이 42.3%
- 백신의 효능: 두 번째 접종 7일 후 증상 동반한 COVID-19 확진 여부
  - 두 번째 접종 7일 이후 **95.0%** (95% CI: 90.3 ~ 97.6)
  - 첫 번째 ~ 두 번째 접종 사이 52.4% (95% CI: 29.5 ~ 68.4)

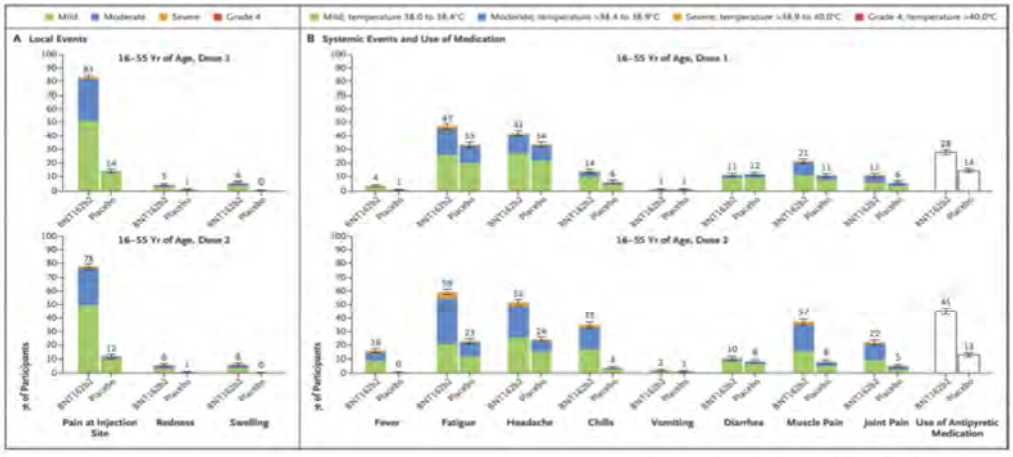
*Polack et al. **N Eng J Med** 2020 Dec 11;383:2603-15*

BioNTech/Pfizer BTN162b2, phase 2/3



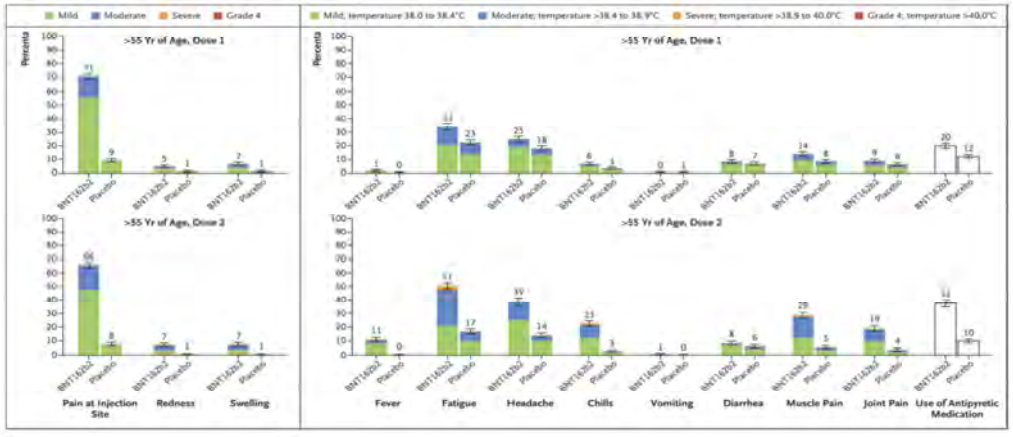
*Polack et al. **N Eng J Med** 2020 Dec 11;383:2603-15*

BioNTech/Pfizer BTN162b2, phase 2/3



Polack et al. **N Eng J Med** 2020 Dec 11;383:2603-15

BioNTech/Pfizer BTN162b2, phase 2/3



Polack et al. **N Eng J Med** 2020 Dec 11;383:2603-15

BioNTech/Pfizer BTN162b2, phase 2/3

- 백신과 연관된 심각한 부작용
  - 어깨 손상
  - 우측 경부 림프절 종대
  - 우측 발저림
  - 심실 부정맥
- 사망사례
  - 백신군: 2명 (동맥경화, 심정지) – 백신과 무관하다고 판정
  - 위약군: 4명 (원인미상 2명, 뇌출혈, 심근경색) – 위약과 무관하다고 판정

Polack et al. **N Eng J Med** 2020 Dec 11;383:2603-15

BioNTech/Pfizer BTN162b2, effectiveness in Israel

Table 2. Estimated Vaccine Effectiveness against Covid-19 Outcomes during Three Time Periods.*

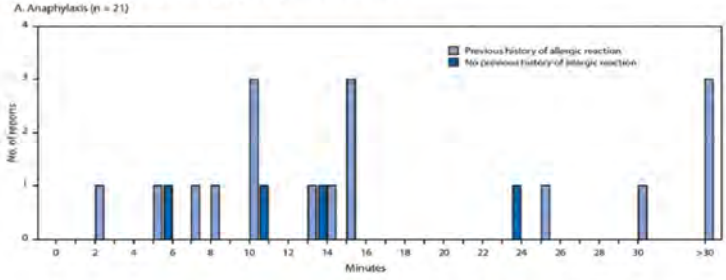
Period	Documented Infection		Symptomatic Illness		Hospitalization		Severe Disease		Death	
	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference	1–RR	Risk Difference
	% (95% CI)	no./1000 persons (95% CI)	% (95% CI)	no./1000 persons (95% CI)	% (95% CI)	no./1000 persons (95% CI)	% (95% CI)	no./1000 persons (95% CI)	% (95% CI)	no./1000 persons (95% CI)
14 to 20 days after first dose	46 (40–51)	2.06 (1.70–2.40)	57 (50–63)	1.54 (1.28–1.80)	74 (56–86)	0.21 (0.13–0.29)	62 (39–80)	0.14 (0.07–0.21)	72 (19–100)	0.03 (0.01–0.07)
21 to 27 days after first dose	60 (53–66)	2.31 (1.96–2.69)	66 (57–73)	1.34 (1.09–1.62)	78 (61–91)	0.22 (0.13–0.31)	80 (59–94)	0.18 (0.10–0.27)	84 (44–100)	0.06 (0.02–0.11)
7 days after second dose to end of follow-up	92 (88–95)	8.58 (6.22–11.18)	94 (87–98)	4.61 (3.29–6.53)	87 (55–100)	0.22 (0.08–0.39)	92 (75–100)	0.32 (0.13–0.52)	NA	NA

* Confidence intervals were estimated using the percentile bootstrap method with 500 repetitions. Estimates were calculated only for cells with more than 10 instances of an outcome across the two groups. NA denotes not available, and RR risk ratio.

Dagan et al. **N Eng J Med** 2021 Feb 24;Epub ahead

BioNTech/Pfizer BTN162b2, 백신 접종 후

- 아나필릭시스
  (1,000,000명 당 11.1명 정도 발생하는 것으로 보고)
  - 백신 성분인 polyethylene glycol, polysorbate



MMWR Morb Mortal Wkly Rep 2021 Jan 15;70:46-51

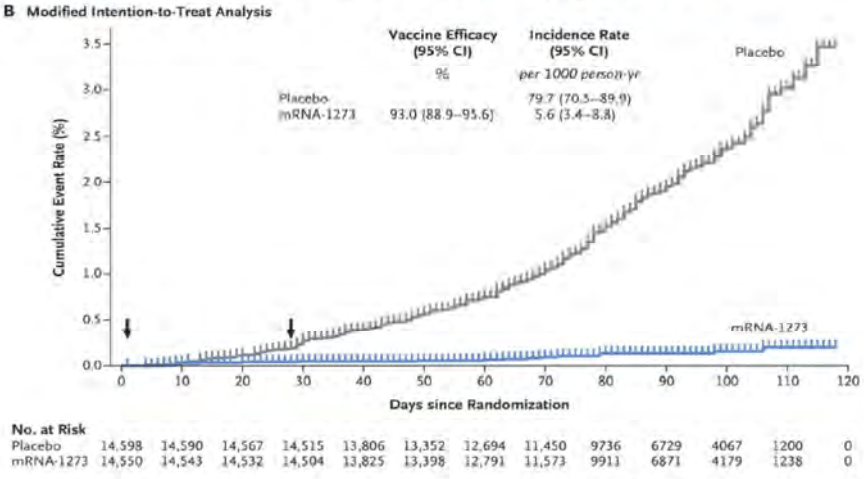
MODERNA VACCINE

Moderna/NIAID mRNA-1273, phase 3

- 미국 (99개 site)
- 18세 이상 성인, 30,420명
- 두 번의 접종, 28일 간격
- 연구 대상의 나이 (평균값) = 51.4세 (범위 18-95세), 65세 이상이 24.8%
- 백신의 효능: 두 번째 접종 14일 후 증상 동반한 COVID-19 확진 여부
  - 두 번째 접종 14일 이후 **94.1%** (95% CI: 89.3 ~ 96.8)

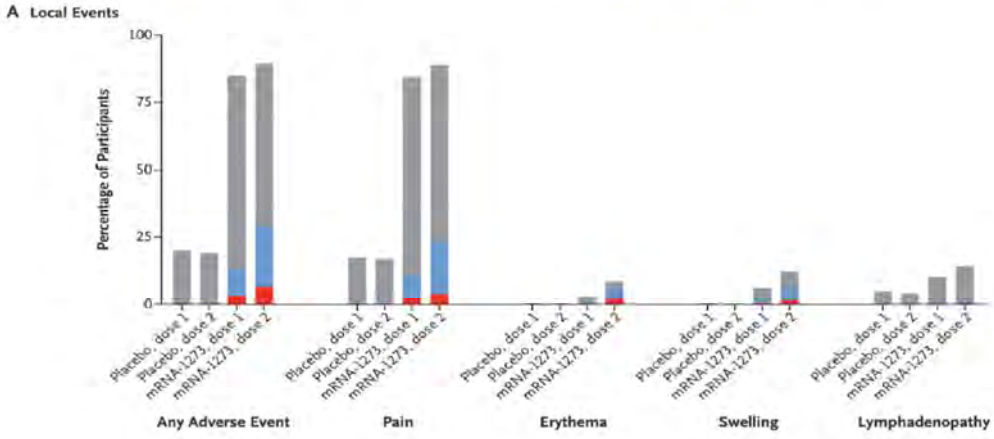
*Baden et al. **N Eng J Med** 2020 Dec 30;384:403-16*

Moderna/NIAID mRNA-1273, phase 3



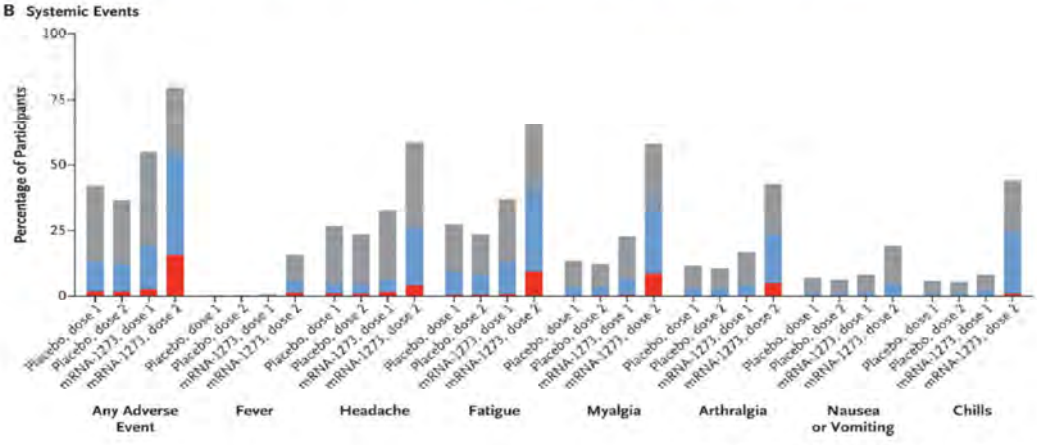
*Baden et al. **N Eng J Med** 2020 Dec 30;384:403-16*

Moderna/NIAID mRNA-1273, phase 3



Baden et al. **N Eng J Med** 2020 Dec 30;384:403-16

Moderna/NIAID mRNA-1273, phase 3



Baden et al. **N Eng J Med** 2020 Dec 30;384:403-16

Moderna/NIAID mRNA-1273, phase 3

- 심각한 부작용: 양 군 사이 유의한 차이 없음
  - 과민반응 (백신군 1.5% vs. 위약군 1.1%)
  - 발진, 두드러기, 맥관부종
  - 안면신경 마비 (백신군 3명 vs. 위약군 1명)
- 사망사례
  - 백신군: 2명 (자살 1명, 심정지 1명) – 백신과 무관하다고 판정
  - 위약군: 3명 (장천공 1명, 백혈병 1명, 심정지 1명)

*Baden et al. **N Eng J Med** 2020 Dec 30;384:403-16*

ASTRAZENECA/OXFORD VACCINE

Astrazeneca/Oxford ChAdOx1, phase 3

- 3개국 (영국, 브라질, 남아공)에서 시행 중인 4개의 RCT 결과 정리
- 18세 이상 성인, 23,848명 (efficacy 분석은 11,636명 자료)
- 두 번 접종, 최대 12주 간격 (target 4주 간격)
- LD = 2.2 X 10^{10} viral particles, SD = 5 X 10^{10} viral particles
- 연구대상자의 연령 분포: 대부분 18 ~ 55세 (86.7 ~ 89.9%)
- 백신의 효능: 두 번째 접종 14일 후 증상 동반한 COVID-19 확진 여부

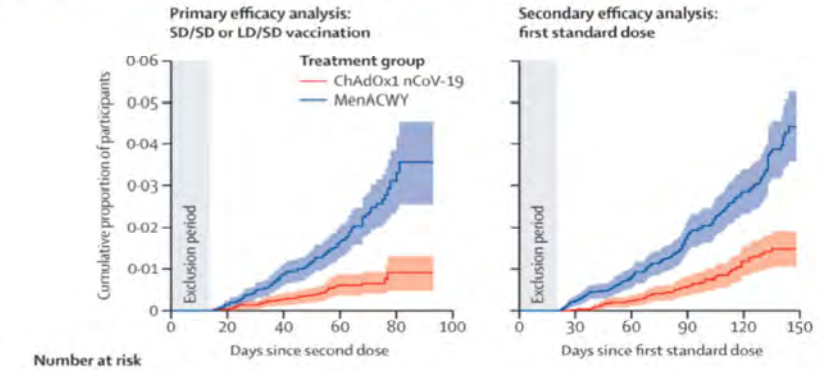
*Voysey et al. **Lancet** 2020 Dec 12;397:99-111*

Astrazeneca/Oxford ChAdOx1, efficacy 1st analysis

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0·5%)	44·1 (248 299)	101/5829 (1·7%)	149·2 (247 228)	70·4% (54·8 to 80·6)†
COV002 (UK)	86	18/3744 (0·5%)	38·6 (170 369)	68/3804 (1·8%)	145·7 (170 448)	73·5% (55·5 to 84·2)
LD/SD recipients	33	3/1367 (0·2%)	14·9 (73 313)	30/1374 (2·2%)	150·2 (72 949)	90·0% (67·4 to 97·0)‡§
SD/SD recipients	53	15/2377 (0·6%)	56·4 (97 056)	38/2430 (1·6%)	142·4 (97 499)	60·3% (28·0 to 78·2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0·6%)	56·2 (77 930)	33/2025 (1·6%)	157·0 (76 780)	64·2% (30·7 to 81·5)‡
All SD/SD recipients	98	27/4440 (0·6%)	56·4 (174 986)	71/4455 (1·6%)	148·8 (174 279)	62·1% (41·0 to 75·7)
Other non-primary symptomatic COVID-19 disease¶	18	7/5807 (0·1%)	10·3 (248 299)	11/5829 (0·2%)	16·3 (247 228)	36·4% (−63·8 to 75·3)‡
Any symptomatic COVID-19 disease	149	37/5807 (0·6%)	54·4 (248 299)	112/5829 (1·9%)	165·5 (247 228)	67·1% (52·3 to 77·3)

*Voysey et al. **Lancet** 2020 Dec 12;397:99-111*

Astrazeneca/Oxford ChAdOx1, phase 3



Number at risk (number censored)												
ChAdOx1 nCoV-19	5807	5639	4779	3181	499	0	6307	5732	4857	3681	2490	0
	(0)	(189)	(1162)	(2620)	(5300)	(5777)	(0)	(645)	(1443)	(2636)	(3811)	(6256)
MenACWY	5829	5657	4765	3146	435	0	6297	5718	4836	3652	2452	0
	(0)	(182)	(1164)	(2636)	(5322)	(5728)	(0)	(639)	(1424)	(2599)	(3760)	(6156)

*Voysey et al. **Lancet** 2020 Dec 12;397:99-111*

Astrazeneca/Oxford ChAdOx1, phase 3

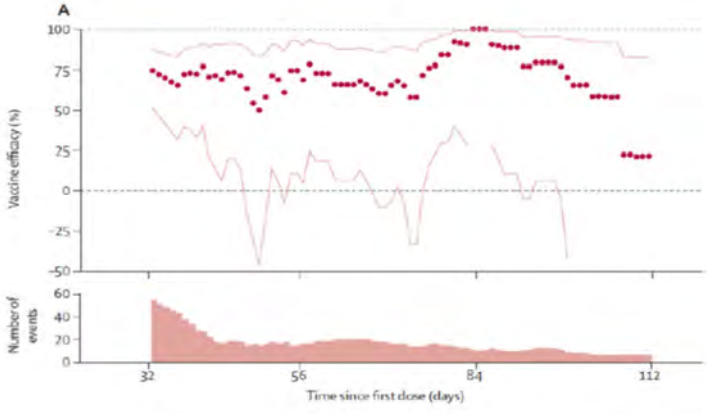
- 연구의 문제점들
  - 백신 Dose가 정확히 define되지 못하였음
    - 정량법의 차이 (spectrophotometer vs quantitative PCR)
    - LD = 2.2 X 10^{10} viral particles, SD = 5 X 10^{10} viral particles
    - SD = 3.5 ~ 6.5 X 10^{10} viral particles
  - 백신 schedule이 정확히 define되지 못하였음
    - 연구대상자에서 첫 번째 접종과 두 번째 접종 사이 시간 차이가 다양함
  - 55세 이상인 연구대상자가 적음

Astrazeneca/Oxford ChAdOx1, efficacy 2nd analysis

	Total cases	ChAdOx1 nCoV-19	Control	Vaccine efficacy (95% CI)*
Prespecified analyses				
Cases more than 14 days after second dose				
Primary symptomatic COVID-19	332	84/8597 (1·0%)	248/8581 (2·9%)	66·7% (57·4 to 74·0)
Two standard doses	271	74/7201 (1·0%)	197/7179 (2·7%)	63·1% (51·8 to 71·7)†
Low dose plus standard dose	61	10/1396 (0·7%)	51/1402 (3·6%)	80·7% (62·1 to 90·2)
Asymptomatic or unknown infection (COV002 UK only)	130	57/4071 (1·4%)	73/4136 (1·8%)	22·2% (−9·9 to 45·0)
Two standard doses	83	41/2692 (1·5%)	42/2751 (1·5%)	2·0% (−50·7 to 36·2)
Low dose plus standard dose	47	16/1379 (1·2%)	31/1385 (2·2%)	49·3% (7·4 to 72·2)
Any NAAT positive	507	161/8597 (1·9%)	346/8581 (4·0%)	54·1% (44·7 to 61·9)
Two standard doses	390	132/7201 (1·8%)	258/7179 (3·6%)	49·5% (37·7 to 59·0)
Low dose plus standard dose	117	29/1396 (2·1%)	88/1402 (6·3%)	67·6% (50·8 to 78·7)
Exploratory analyses by prime-boost interval				
Primary symptomatic COVID-19 cases more than 14 days after second dose				
Prime-boost interval (two standard doses)				
<6 weeks	111	35/3890 (0·9%)	76/3856 (2·0%)	55·1% (33·0 to 69·9)
6–8 weeks	64	20/1112 (1·8%)	44/1009 (4·4%)	59·9% (32·0 to 76·4)
9–11 weeks	43	11/906 (1·2%)	32/958 (3·3%)	63·7% (28·0 to 81·7)
≥12 weeks	53	8/1293 (0·6%)	45/1356 (3·3%)	81·3% (60·3 to 91·2)

Voysey et al. **Lancet** 2020 Feb 19;397:881-91

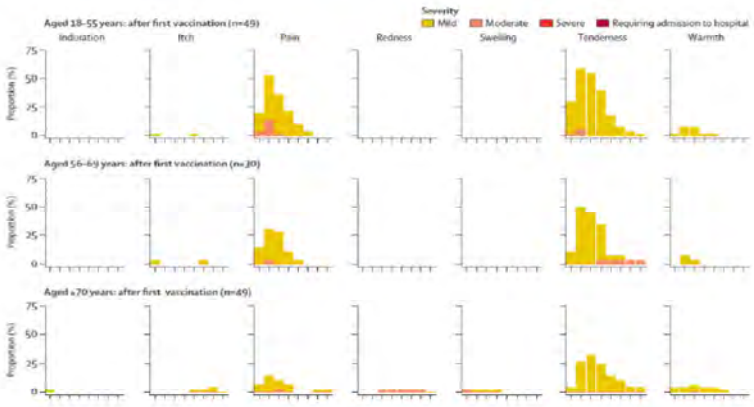
Astrazeneca/Oxford ChAdOx1
Efficacy from 22 days after a single dose



Voysey et al. **Lancet** 2021 Feb 19;397:881-91

Astrazeneca/Oxford ChAdOx1, phase 2/3

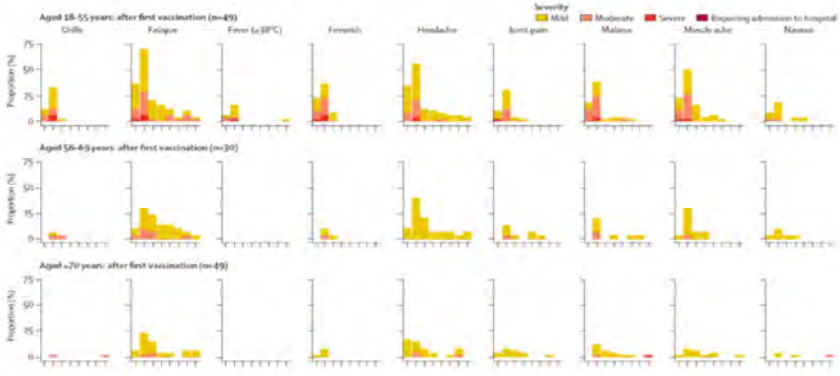
- Local adverse reaction profile in first 7 days after vaccination



Ramasamy et al. **Lancet** 2020 Nov 23;396:1979-93

Astrazeneca/Oxford ChAdOx1, phase 2/3

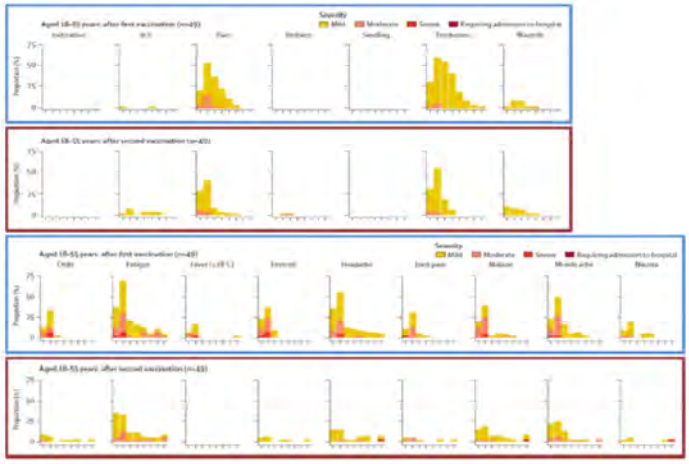
- Systemic adverse reaction profile in first 7 days after vaccination



Ramasamy et al. **Lancet** 2020 Nov 23;396:1979-93

Astrazeneca/Oxford ChAdOx1, phase 2/3

- Adverse reaction
  First vaccination
  vs
  Second vaccination



Ramasamy et al. **Lancet** 2020 Nov 23;396:1979-93

Astrazeneca/Oxford ChAdOx1, phase 3

- 심각한 부작용
  - 23,848명을 74,341 person-month 관찰
  - 백신투여군 79명 vs 대조군 89명

백신투여군	대조군
횡단 척수염 2례 (1례는 백신과 무관)	횡단척수염 1례
	용혈 빈혈 1례
사망 1례 (백신, COVID-19와 무관)	사망 3례 (백신, COVID-19와 무관)

*사인: 교통사고, 외상, 살인, 진균폐렴

Folegatti et al. **Lancet** 2020 Jul 20;396:467-78

코로나 백신에 거는 기대

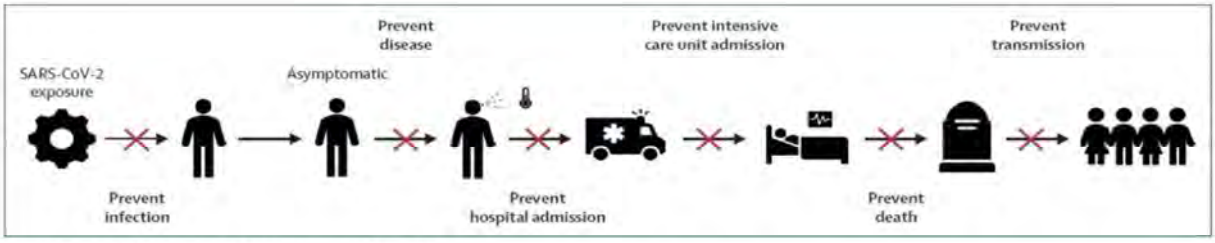
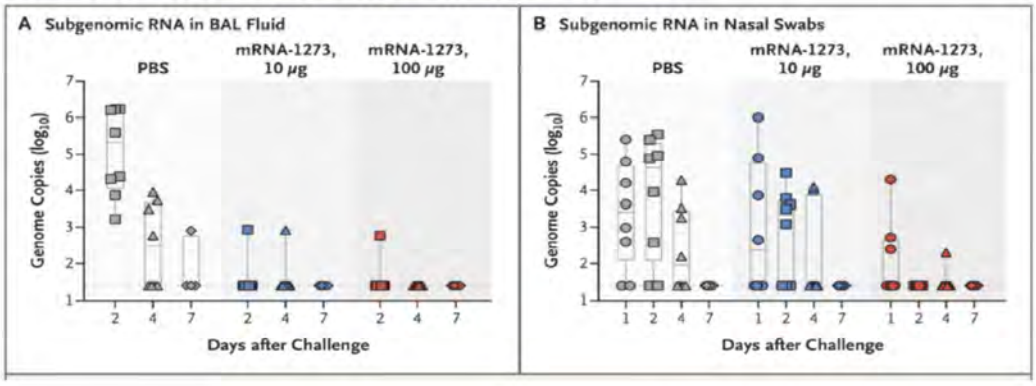


Figure 1: **Potential endpoints of an efficacious COVID-19 vaccine**
An efficacious COVID-19 vaccine could reduce the likelihood of infection of an individual, severity of disease in an individual, or degree of transmission within a population.

COVID-19 백신이 전파를 차단할 수 있을까?

- **Moderna mRNA-1273 in nonhuman primates**



Corbett et al. ***N Eng J Med*** 2020 July 28;383:1544-55

COVID-19 백신이 전파를 차단할 수 있을까?

- Astrazeneca/Oxford ChAdOx1, Phase 2/3 in UK
  - 백신 접종 후, 매주 nose and throat swab을 하여 asymptomatic infection 평가

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
Asymptomatic or symptoms unknown (COV002)	69	29/3288 (0·9%)	69·8 (151 673)	40/3350 (1·2%)	96·0 (152 138)	27·3% (−17·2 to 54·9)
LD/SD recipients	24	7/1120 (0·6%)	41·4 (61 782)	17/1127 (1·5%)	100·6 (61 730)	58·9% (1·0 to 82·9)‡
SD/SD recipients	45	22/2168 (1·0%)	89·4 (89 891)	23/2223 (1·0%)	92·9 (90 408)	3·8% (−72·4 to 46·3)
Any NAAT-positive swab	221	68/5807 (1·2%)	100·0 (248 299)	153/5829 (2·6%)	226·0 (247 228)	55·7% (41·1 to 66·7)

*Voysey et al. **Lancet** 2021 Feb 19;397:881-91*

현재 문제가 되고 있는 변이

B.1.1.7 (UK variant)

- 2020년 9월, 영국 남부에서 처음 발견
- 17개 변이 → S protein에 8개 변이
  : 69-70 del, Y144 del, N501Y, A570D, P681H, T716I, S982A, D1118H
- 전파가 용이해졌음
- 중증도 차이가 없음

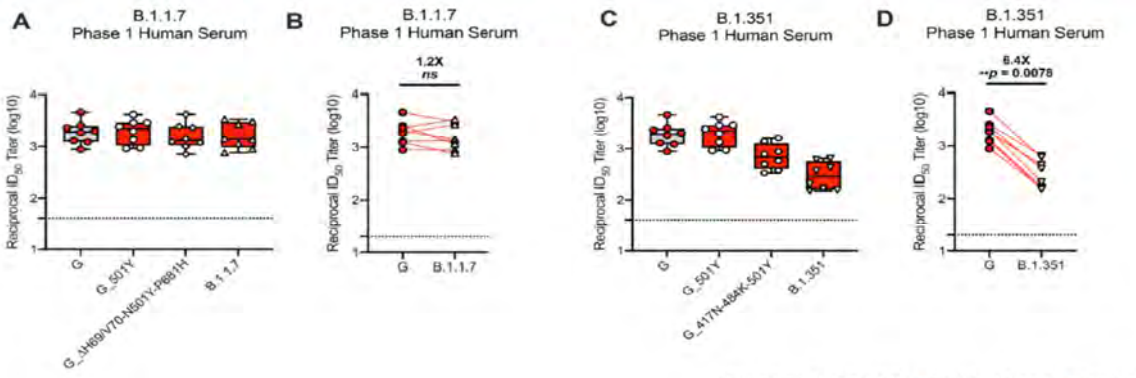
B.1.351 (South Africa variant)

- 2020년 11월, 남아공에서 처음 발견
- S protein 변이: K417T, E484K, N501Y
- 전파가 용이해졌음
- 중증도를 늘린다는 증거는 아직까지 없음

https://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/

변이 바이러스에 대한 백신 효과 예상

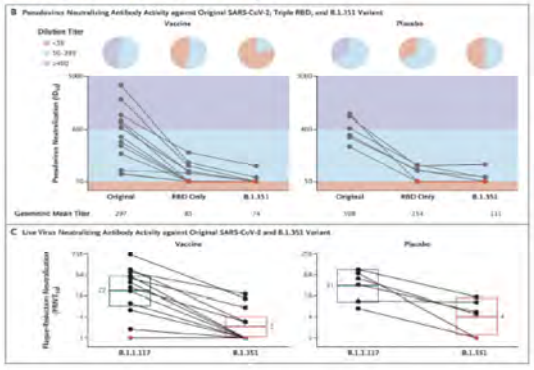
B.1.1.7 (UK variant) | **B.1.351 (South Africa variant)**



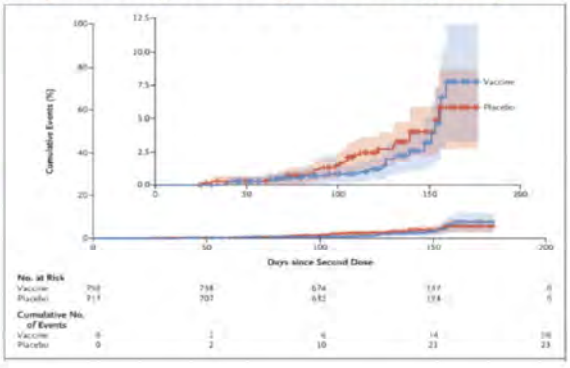
Wu et al. ***N Eng J Med*** *2021 Mar 17;Epub ahead*

변이 바이러스에 대한 백신 효과 임상시험 결과

Neutralization Assay



Kaplan-Meyer Plot of vaccine efficacy



Madhi et al. ***N Eng J Med*** *2021 Mar 16;Epub ahead*

변이 바이러스에 대한 백신 효과 임상시험 결과

Table 2. Vaccine Efficacy against Mild-to-Moderate Symptomatic Covid-19 Confirmed by Nucleic Acid Amplification Test.*

End Point	Baseline Serologic Status†	Total No. of Cases	Placebo	Incidence Risk	Vaccine	Incidence Risk	Vaccine Efficacy‡
			no./total no. (%)	*per 1000 person-yr (person-days)*	*no./total no. (%)*	*per 1000 person-yr (person-days)*	*% (95% CI)*
Mild-to-moderate illness with onset >14 days after second injection	Seronegative	42	23/717 (3.2)	93.6 (89,714)	19/750 (2.5)	73.1 (94,881)	21.9 (−49.9 to 59.8)
Mild-to-moderate illness associated with B.1.351 variant with onset >14 days after second injection	Seronegative	39	20/714 (2.8)	81.6 (89,448)	19/750 (2.5)	73.1 (94,881)	10.4 (−76.8 to 54.8)
Mild-to-moderate illness with onset >14 days after second injection, regardless of baseline serostatus	Any	46	24/865 (2.8)	81.9 (106,398)	22/884 (2.5)	73.2 (109,659)	10.6 (−66.4 to 52.2)
Mild-to-moderate illness with onset >14 days after one dose until October 31, 2020, a proxy for non-B.1.351 variant infection	Overall	15	12/938 (1.3)	31.1 (140,774)	3/944 (0.3)	7.6 (143,140)	75.4 (8.9 to 95.5)

Madhi et al. ***N Eng J Med*** *2021 Mar 16;Epub ahead*

요약

- SARS-CoV-2에 대한 백신도 유래없이 빠른 속도로 진행되어, 현재 mRNA 백신, adenovirus vector 백신의 투여가 시작되어 진행되고 있음.
- 지금까지 발표된 백신 효능은 70% ~ 95%, 심각한 부작용은 드물지만 발생 가능하므로 모니터링이 필요함
- 백신 접종 하여도 마스크 착용, 사회적 거리 두기 유지 필요