Genetik Temelli Aşılar (mRNA ve DNA)

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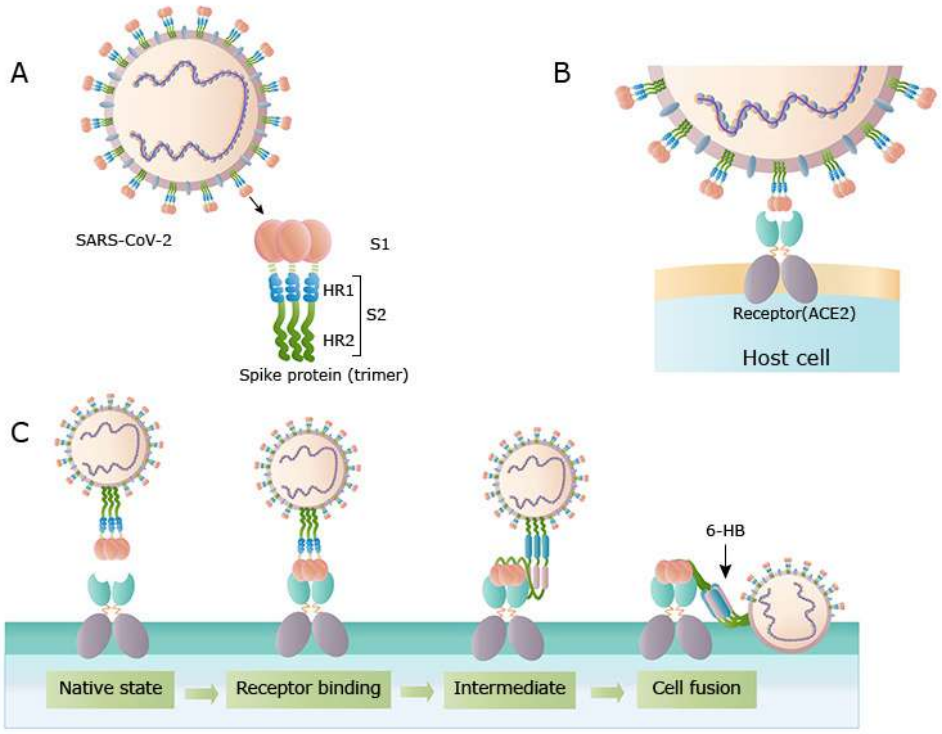
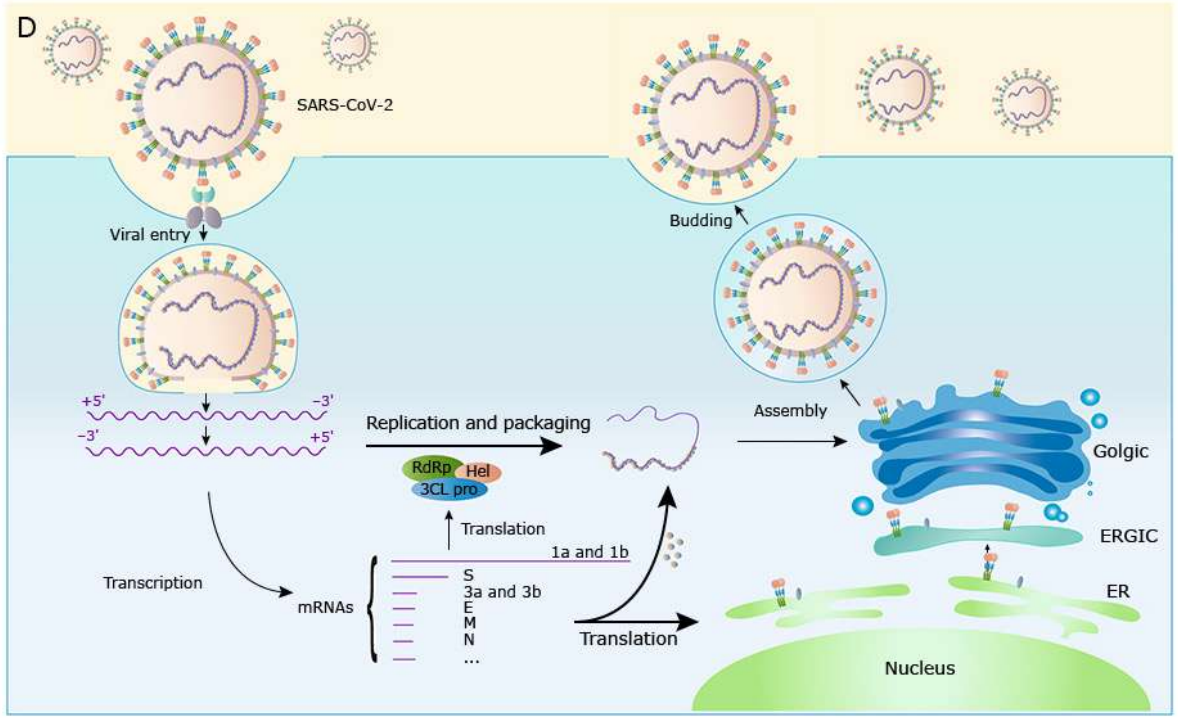
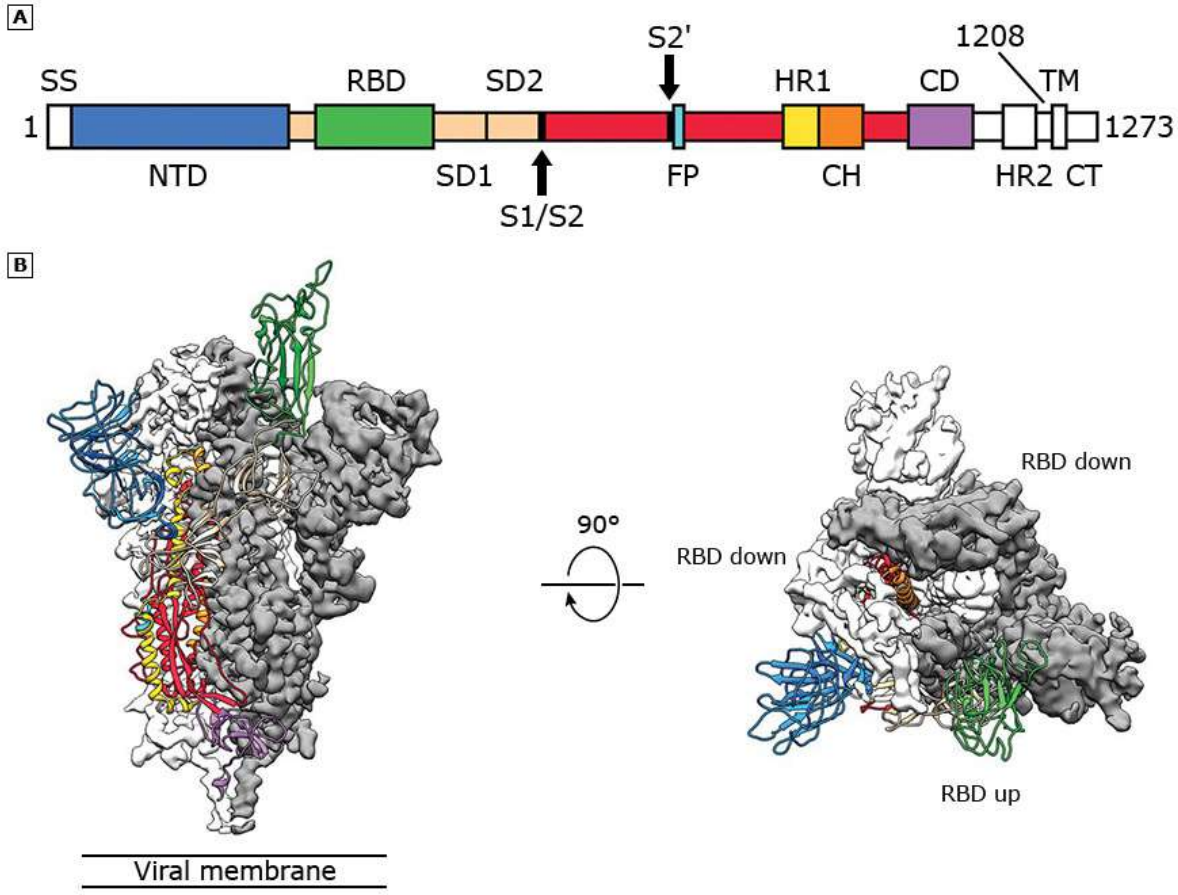
COVID-19


A
SARS-CoV-2
S1
HR1
S2
HR2
Spike protein (trimer)
B
Receptor(ACE2)
Host cell
C
6-HB
Native state
Receptor binding
Intermediate
Cell fusion


D
SARS-CoV-2
Viral entry
Budding
+5'
−3'
−3'
+5'
Replication and packaging
RdRp
Hel
3CL pro
Translation
1a and 1b
Transcription
mRNAs
S
3a and 3b
E
M
N
...
Translation
Assembly
Golgic
ERGIC
ER
Nucleus

Antijenik Hedef: S protein



Aşı platformları

Platform		Candidate vaccines (no. and %)	
PS	Protein subunit	47	33%
VVnr	Viral Vector (non-replicating)	20	14%
DNA	DNA	16	11%
IV	Inactivated Virus	21	15%
RNA	RNA	24	17%
VVr	Viral Vector (replicating)	4	3%
VLP	Virus Like Particle	6	4%
VVr + APC	VVr + Antigen Presenting Cell	2	1%
LAV	Live Attenuated Virus	2	1%
VVnr + APC	VVnr + Antigen Presenting Cell	1	1%
BacAg-SpV	Bacterial antigen-spore expression vector	1	1%
		144	

Español

January 31, 2022: **FDA approves second COVID-19 vaccine**. Read the press release.

On this page:

COVID-19 Vaccines Authorized for Emergency Use or FDA-Approved

Comirnaty and Pfizer-BioNTech COVID-19 Vaccine → 23 Ağustos 2021

Spikevax and Moderna COVID-19 Vaccine → 31 Ocak 2022

Janssen COVID-19 Vaccine

Fact sheets for health care providers and patients included
Report vaccine side effects toll-free at 1-800-822-7967 or online

Genetik Temelli Aşılar

mRNA	Hedef geni kodlayan mRNA Konakta mRNA hedef proteine translasyon ve immün yanıt	BNT162b2 (pfizer-Biontech) mRNA-1273 (moderna)	mRNA hücre stoplazmasında kalır, nükleusa integre olmaz, konak Dna'sı ile etkileşi yok Düşük ısı derecesi gerekebilir
DNA	Plazmid DNA. Hedef proteinin alıcıda eksprese edilmesi için memeli ekspresyon promotörlerini ve hedef geni içeren plazmit DNA'dan oluşur.	ZyCoV-D (Zydus Cadila)	Genellikle düşük immünojenisiteye sahiptirler. Özel uygulama cihazlarına ihtiyaç var (örneğin, elektroporatörler).

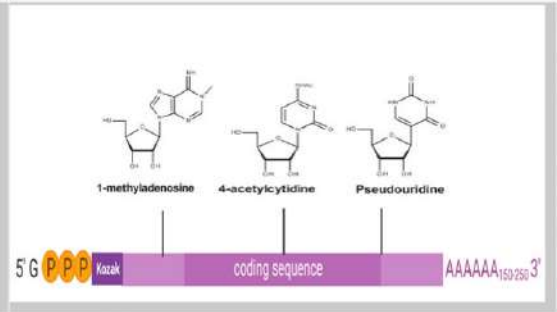
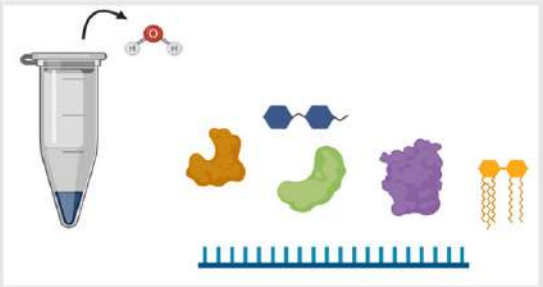
mRNA Temelli Aşılar - Tarihçesi

- Endojen ve in-vitro tanskripte mRNA; memeli hücrelere aktarılarak protein sentezi
  - Sınırlamalar
    - Protein translasyonun İnflamasyon aracılı sınırlanması
    - mRNA'nın kısa ömürlü oluşu (fiziko-kimyasal kararsızlık)
    - Nükleazlara karşı hassasiyet
    - Zayıf transfeksiyon

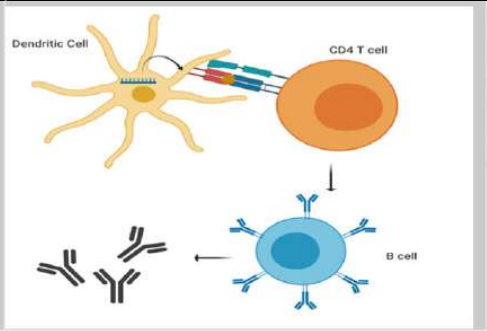
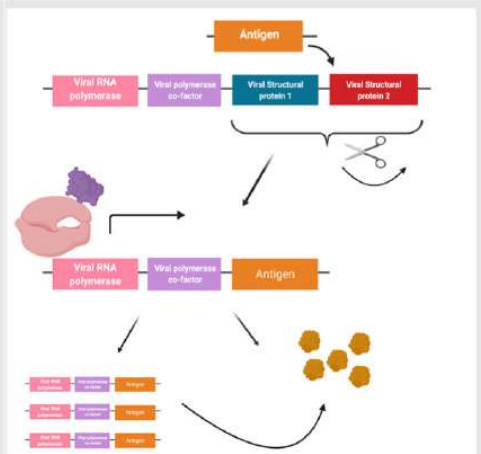
1-Dimitriadis, G.J. Translation of rabbit globin mRNA introduced by liposomes into mouse lymphocytes. Nature 1978
2-Malone, R.W. Cationic liposome-mediated RNA transfection. Proc. Natl. Acad. Sci. USA 1989
3-Wolff, J.A..Direct gene transfer into mouse muscle in vivo. Science 1990

RNA aşı geliştirme programları

RNA Vaccines

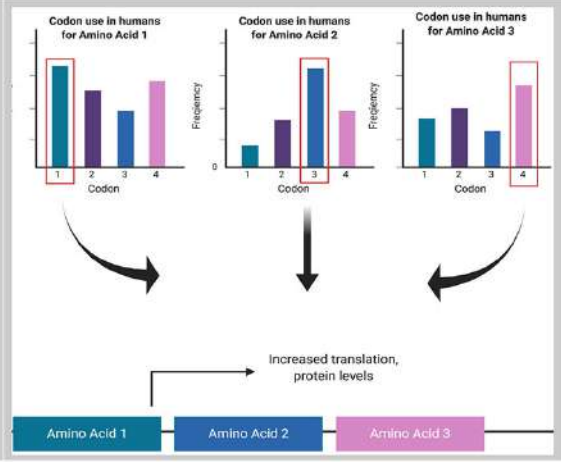
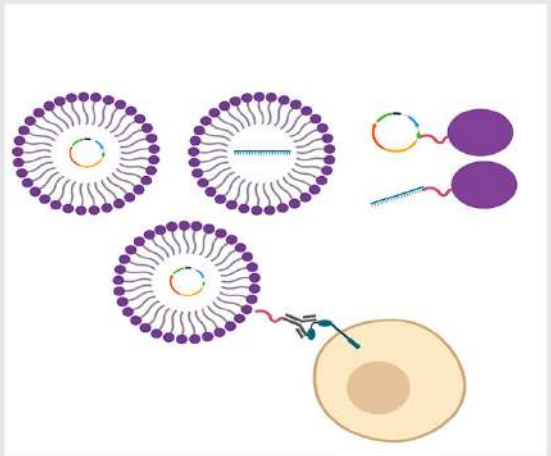
Method Name	Method Diagram	Description of Method	Results
RNA Engineering		Adding 5' cap and Kozak sequences and 3' poly-A sequence to mimic structure of endogenous mRNA to avoid detection by innate immune sensors, and adding modified nucleosides to increase RNA stability	Widely used in vaccine design
Thermostable RNA		Freeze-drying RNA and incubation with various biomolecules increase RNA stability even at high temperature	Widely used in vaccine design

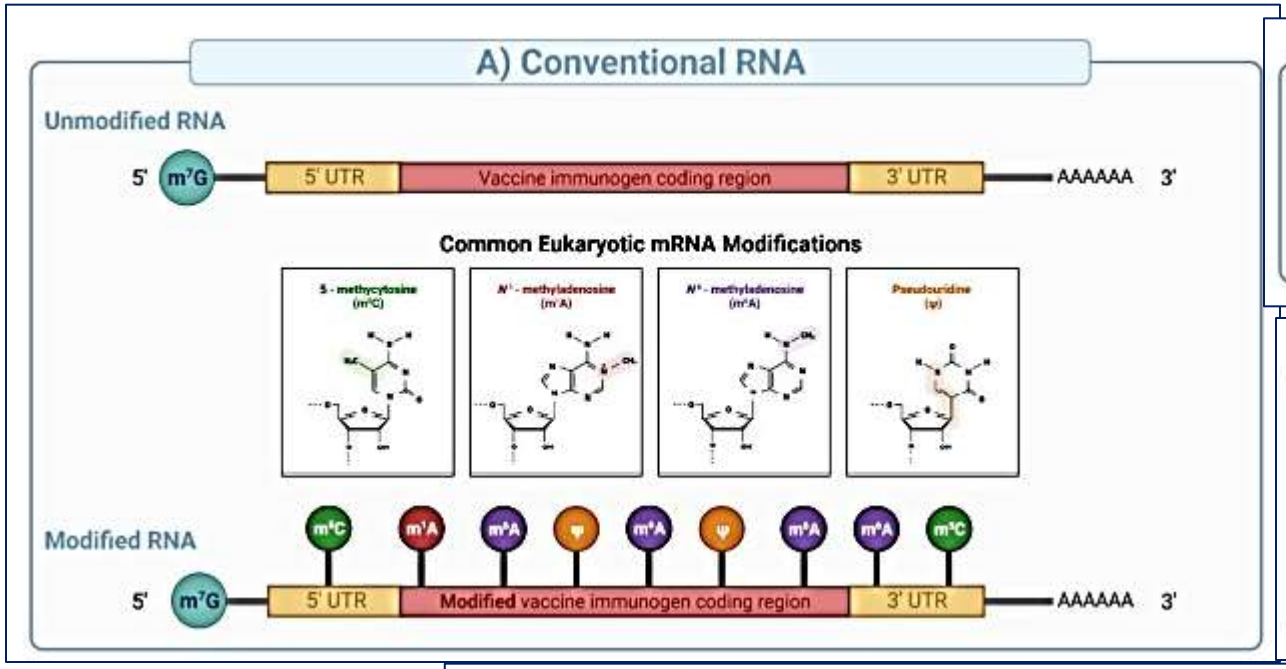
RNA Vaccines

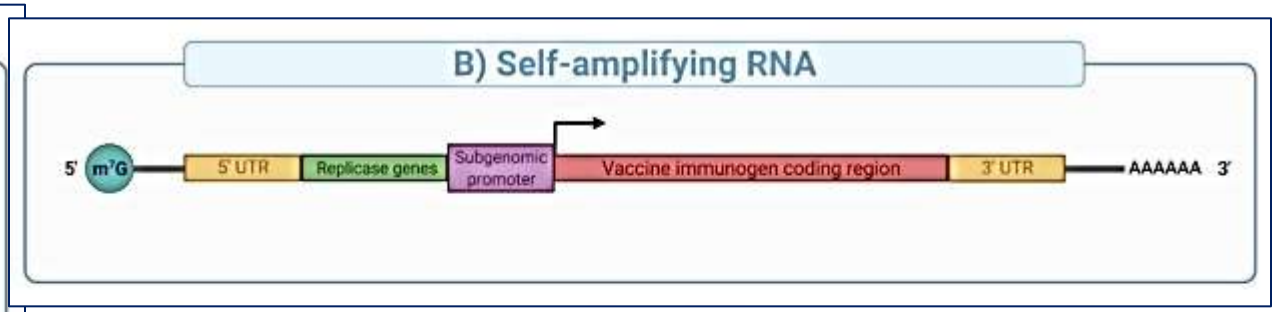
Method Name	Method Diagram	Description of Method	Results
Dendritic Cell Vaccines		RNA is transfected into dendritic cells in-vitro, which can then activate CD4 T cells and stimulates antibody production in vivo.	Most explored for use as cancer vaccines- several in clinical trials.
Self Replicating RNA		The structural proteins in the genome of an RNA virus are replaced with the coding sequence for the antigen- the viral polymerase can keep producing RNA which amplifies and maintains the amount of the antigenic protein.	Pre-clinical testing has shown effectiveness in inducing protection.

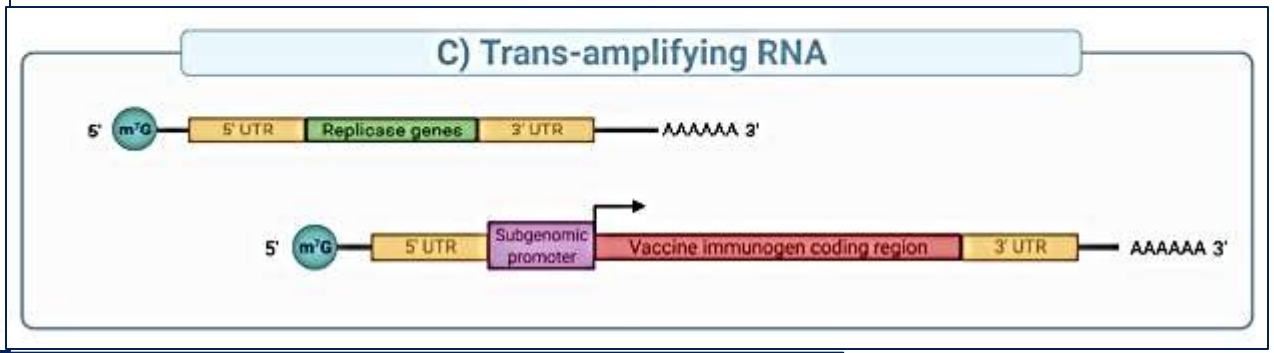
RNA aşı geliştirme programları

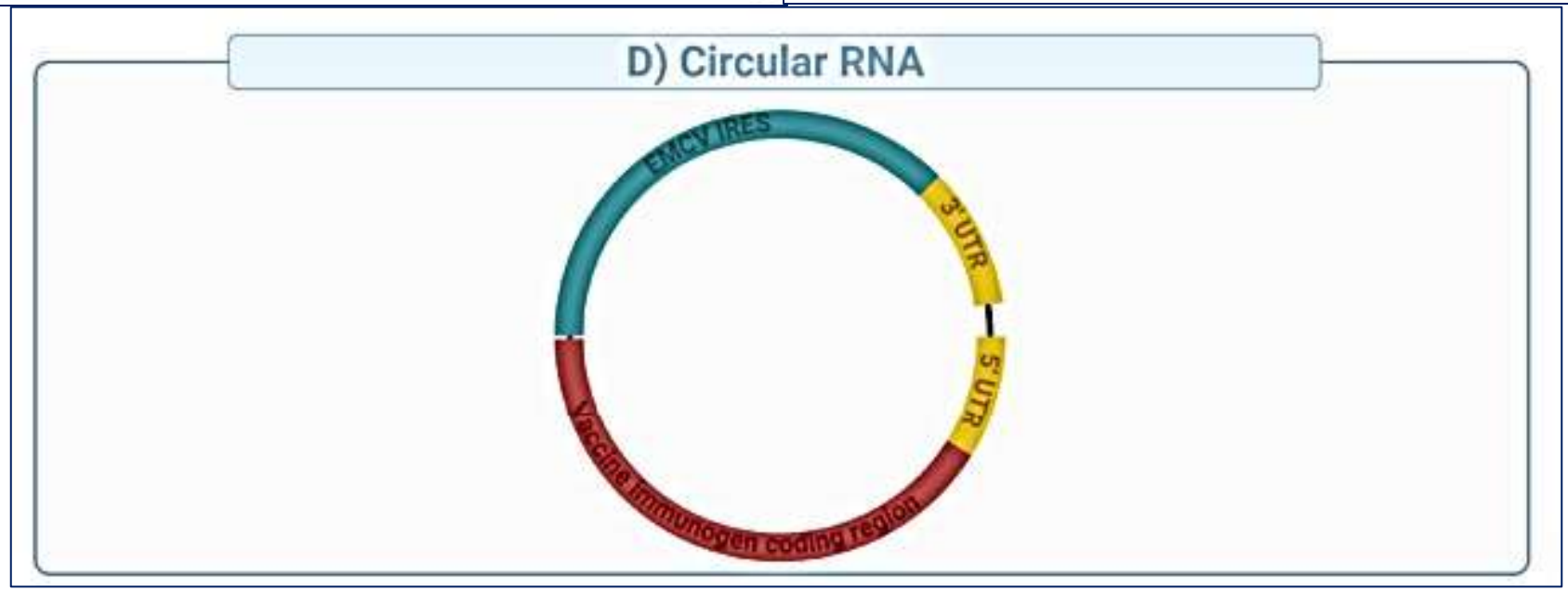
DNA and RNA Vaccines

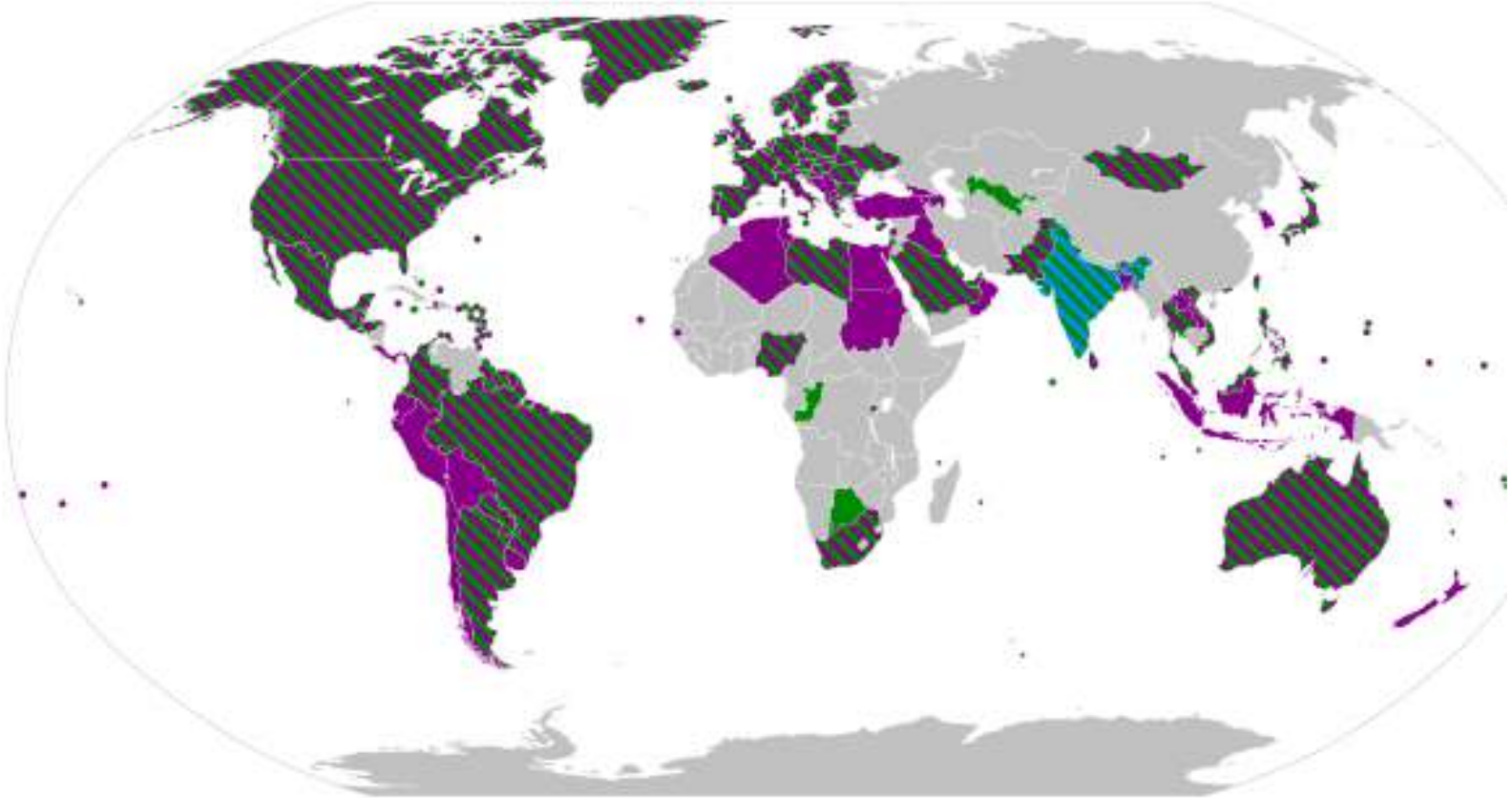
Method Name	Method Diagram	Description of Method	Results
Codon Optimization		The codons with the most usage in the species of the vaccine target are used in the sequence of the antigen.	Widely used in vaccine design
Nanoparticle Vaccines		Nucleic acids are attached to or encapsulated by a carrier, which can also be attached to an antibody for specific cell targeting.	Wide variety of techniques undergoing preclinical and clinical testing


A) Conventional RNA
Unmodified RNA
5'
m7G
5' UTR
Vaccine immunogen coding region
3' UTR
AAAAAA
3'
Common Eukaryotic mRNA Modifications
5 - methycytosine (m5C)
N1 - methyladenosine (m1A)
N6 - methyladenosine (m6A)
Pseudouridine (ψ)
Modified RNA
m5C
m1A
m6A
ψ
m6A
ψ
m6A
m6A
m5C
5'
m7G
5' UTR
Modified vaccine immunogen coding region
3' UTR
AAAAAA
3'


B) Self-amplifying RNA
5'
m7G
5' UTR
Replicase genes
Subgenomic promoter
Vaccine immunogen coding region
3' UTR
AAAAAA
3'


C) Trans-amplifying RNA
5'
m7G
5' UTR
Replicase genes
3' UTR
AAAAAA 3'
5'
m7G
5' UTR
Subgenomic promoter
Vaccine immunogen coding region
3' UTR
AAAAAA 3'


D) Circular RNA
5'UTR
Vaccine immunogen coding region
3'UTR
5'UTR



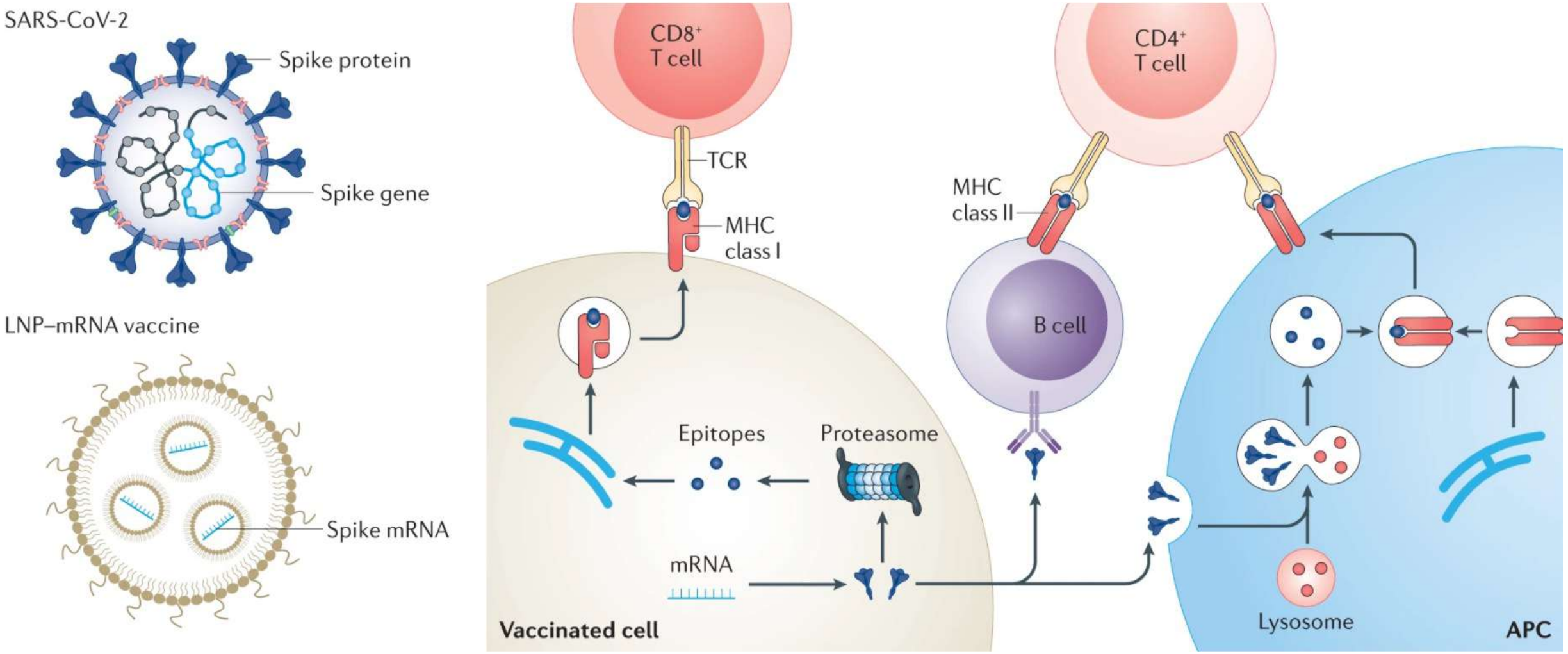
RNA vaccines and DNA vaccines

Pfizer–BioNTech

Moderna

ZyCoV-D → DNA plazmid tabanlı

mRNA Aşıları



mRNA Aşıları

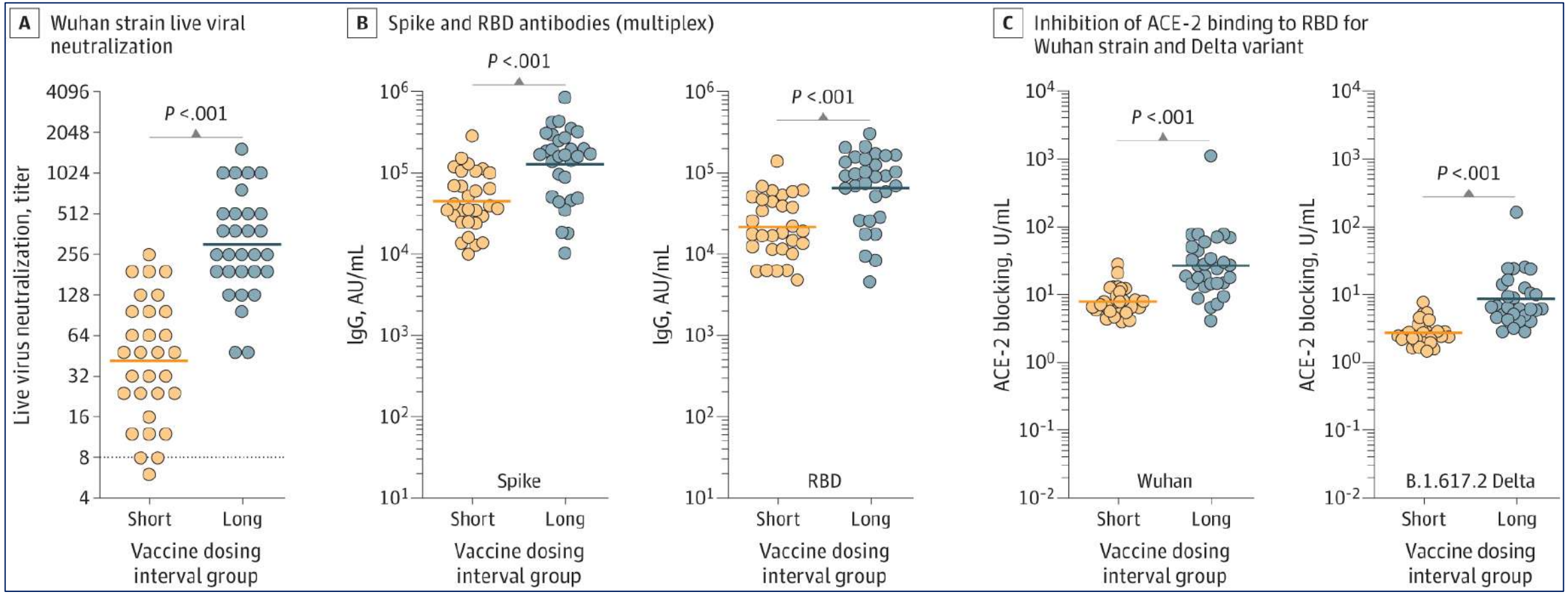
	Pfizer-BioNTech ≥ 16 yaş FDA onayı	Moderna ≥ 18 yaş FDA
Yaş	>5 yaş	>18 yaş
Primer seri	• 2 doz; 3 hft (21 gün) ara • 3 doz İmmünkompromize, 2. dozdan 28 gün sonra	• 2 doz; 4 hft (28 gün) ara • 3 doz İmmünkompromize, 2. dozdan 28 gün sonra
Tam aşılı	Son dozdan 2 hft sonra	Son dozdan 2 hft sonra
Booster doz	• >12 yaş son dozdan 5 ay sonra • 12-17 yaş Biontech • >18 yaş BioNTech veya Moderna	• >18 yaş son dozdan 5 ay sonra • BioNTech veya moderna

mRNA Aşıları

Aşı	Doz	Doz volümü	Doz sayısı	Doz aralık
Pfizer-BioNTech	30 µg; mor veya gri kapak formülasyonu	0,3 ml	• ≥12 yaş: 2 + 1 (booster) • İmmünkompromize 3 doz	• 3 hft (21 gün) + 5 ay • 0-21-47. gün
	10 µg; turuncu kapak formülasyonu	0,2ml	• 5-11 yaş 2 doz • İmmünkompromize 3 doz	• 3 hft (21 gün) • 0-21-47. gün
Moderna	100 µg	0,5 ml	• ≥18 yaş 2 + 1 (booster-0,25ml) • İmmünkompromize 3 doz	• 4 hft (28 gün) + 5 ay • 4 hft (28 gün)

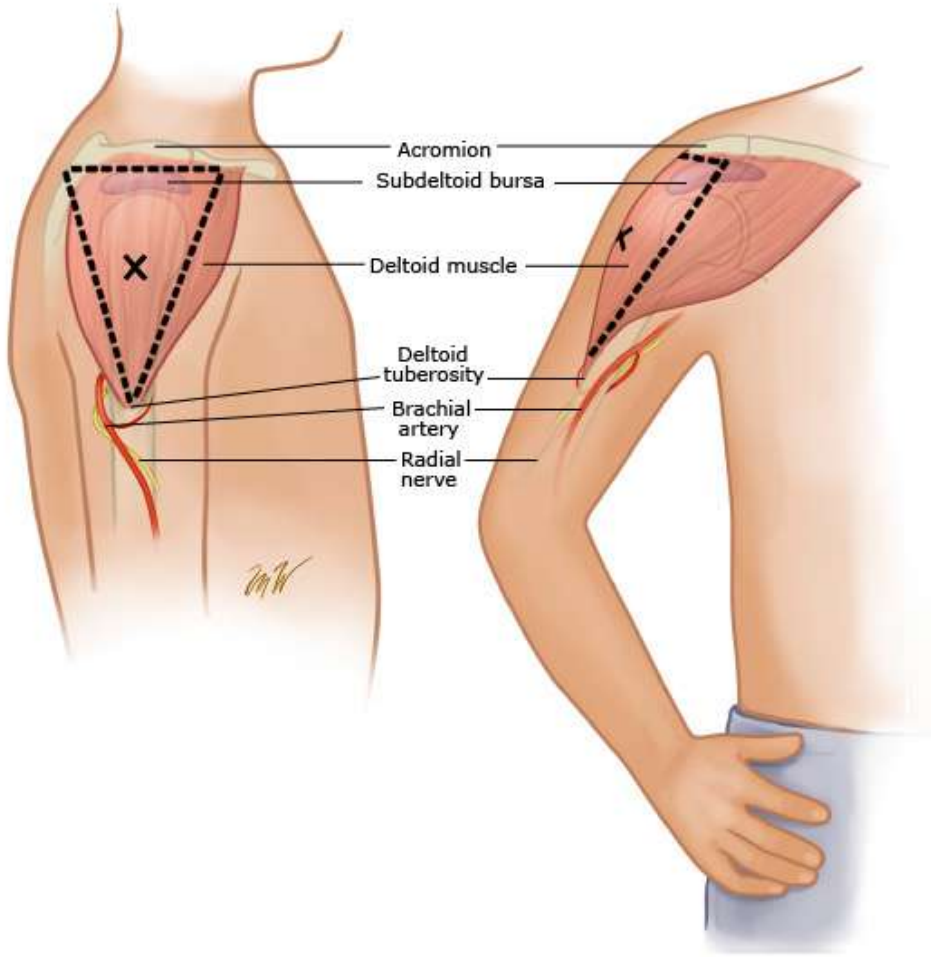
Doz aralıkları artırılmalı mı?

separating them by 6 to 14 weeks rather than 3 to 4 weeks



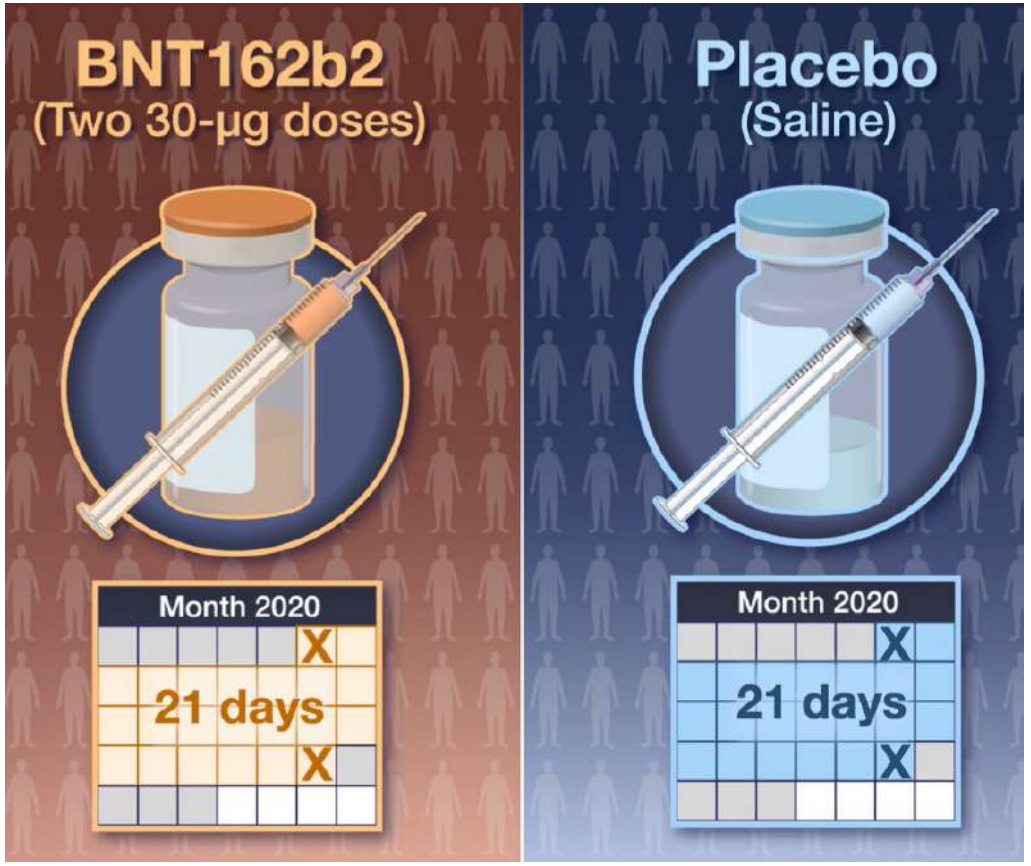
Grunau B. Immunogenicity of Extended mRNA SARS-CoV-2 Vaccine Dosing Intervals. JAMA. 2022;327(3):279.

İnjeksiyon bölgesi



BNT162b2 mRNA
Etkinlik ve Güvenlik Çalışması

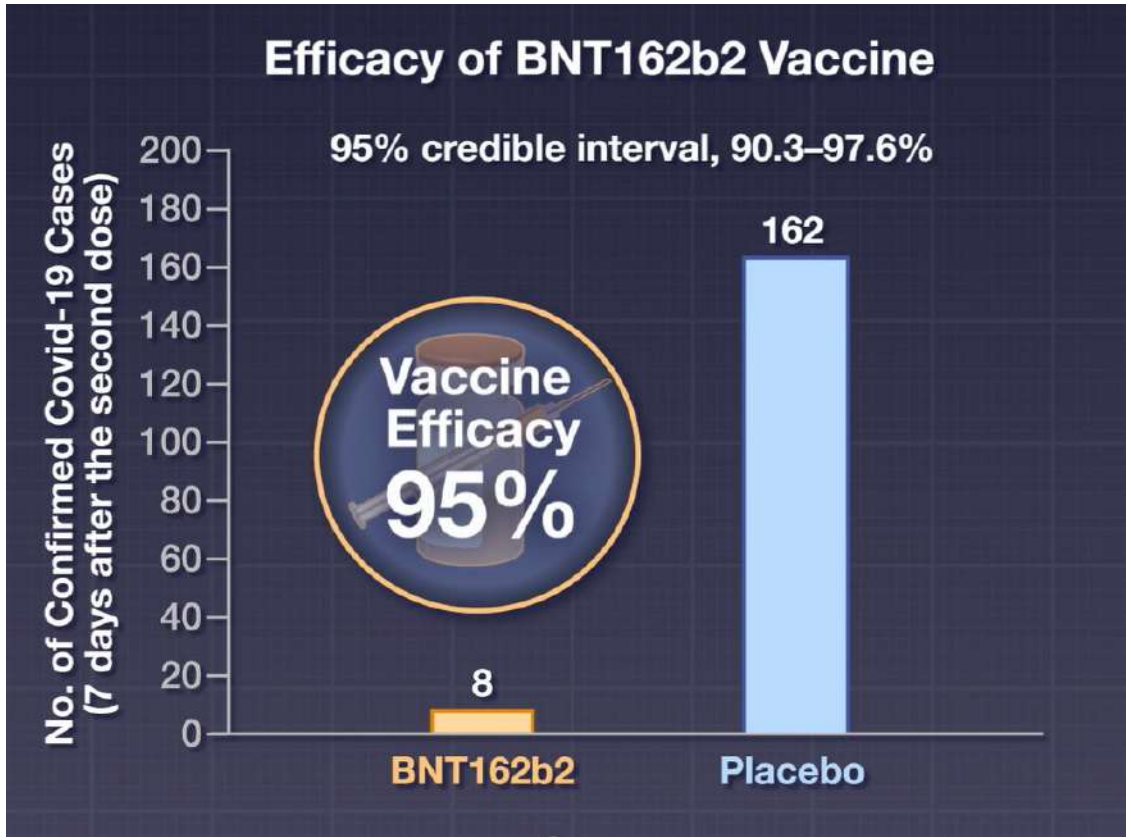
- 43.548 katılımcı randomize edildi ve bunlardan 43.448'ine enjeksiyon uygulandı.
- 21.720 katılımcıya BNT162b2, 21.728 katılımcıya ise plasebo verildi.
- Enjeksiyon sonrası ilk 30 dk. akut etki var mı?
- Başlangıç: Kasım 2020
  - Amerika 130, Arjantin 1, Brezilya 2, Güney Afrika 4 Almanya 6, Türkiye 9 (**152 bölge** katıldı)



Robert W. Frenck, Jr. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. July 15, 2021 N Engl J Med 2021; 385:239-250

BNT162b2 mRNA
Etkinlik ve Güvenlik Çalışması

- 36 523 öncesinde COVID19 enfeksiyon kanıtı olmayan katılımcı



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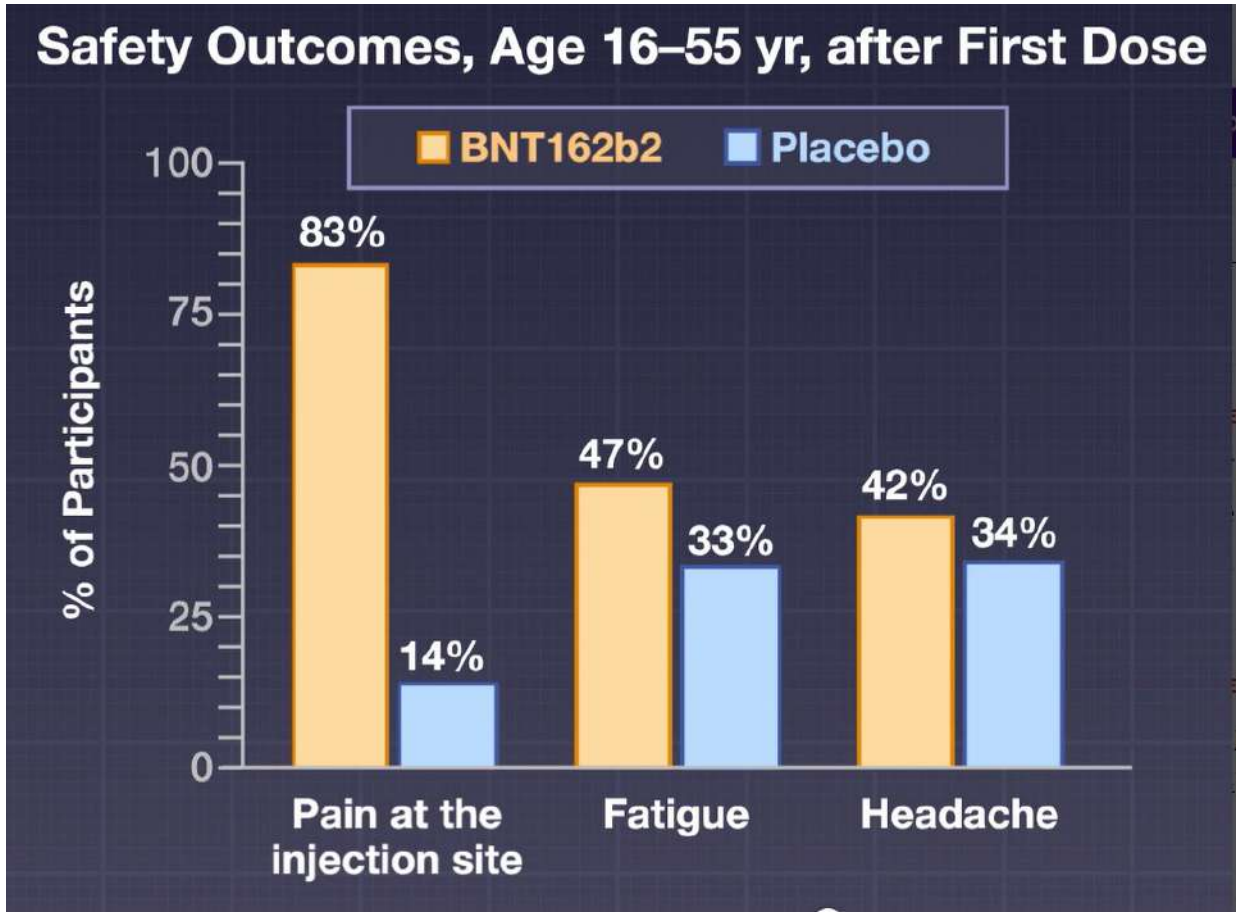

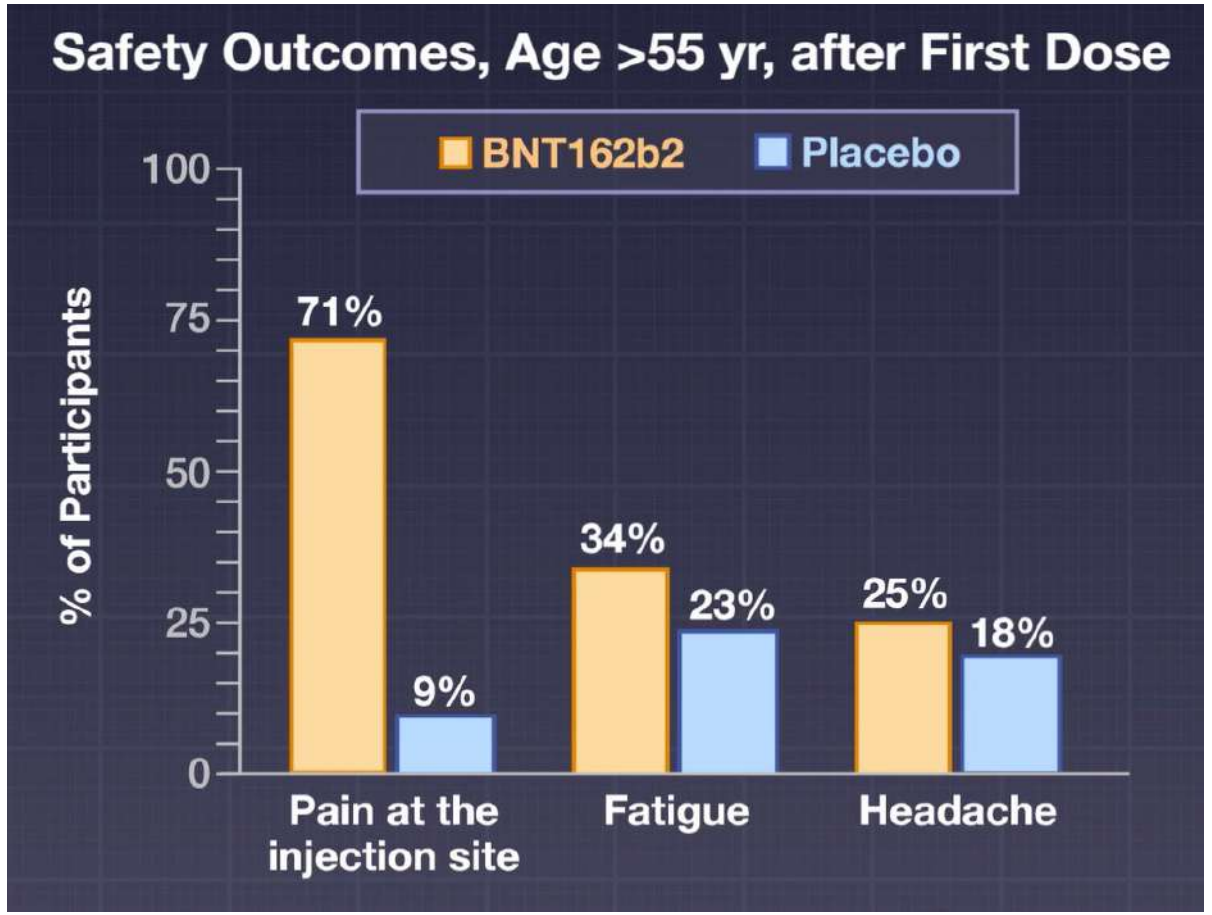

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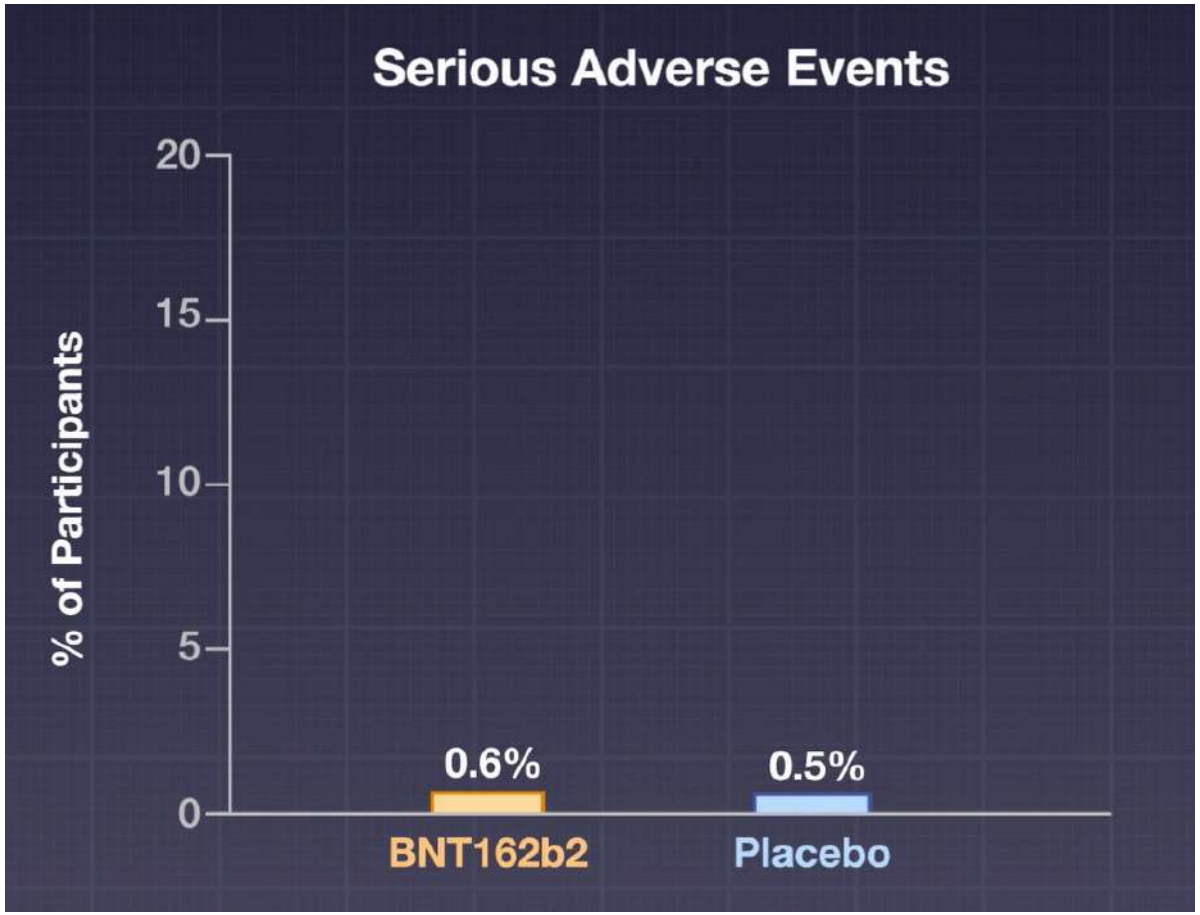
Etkinlik ve Güvenlik Çalışması



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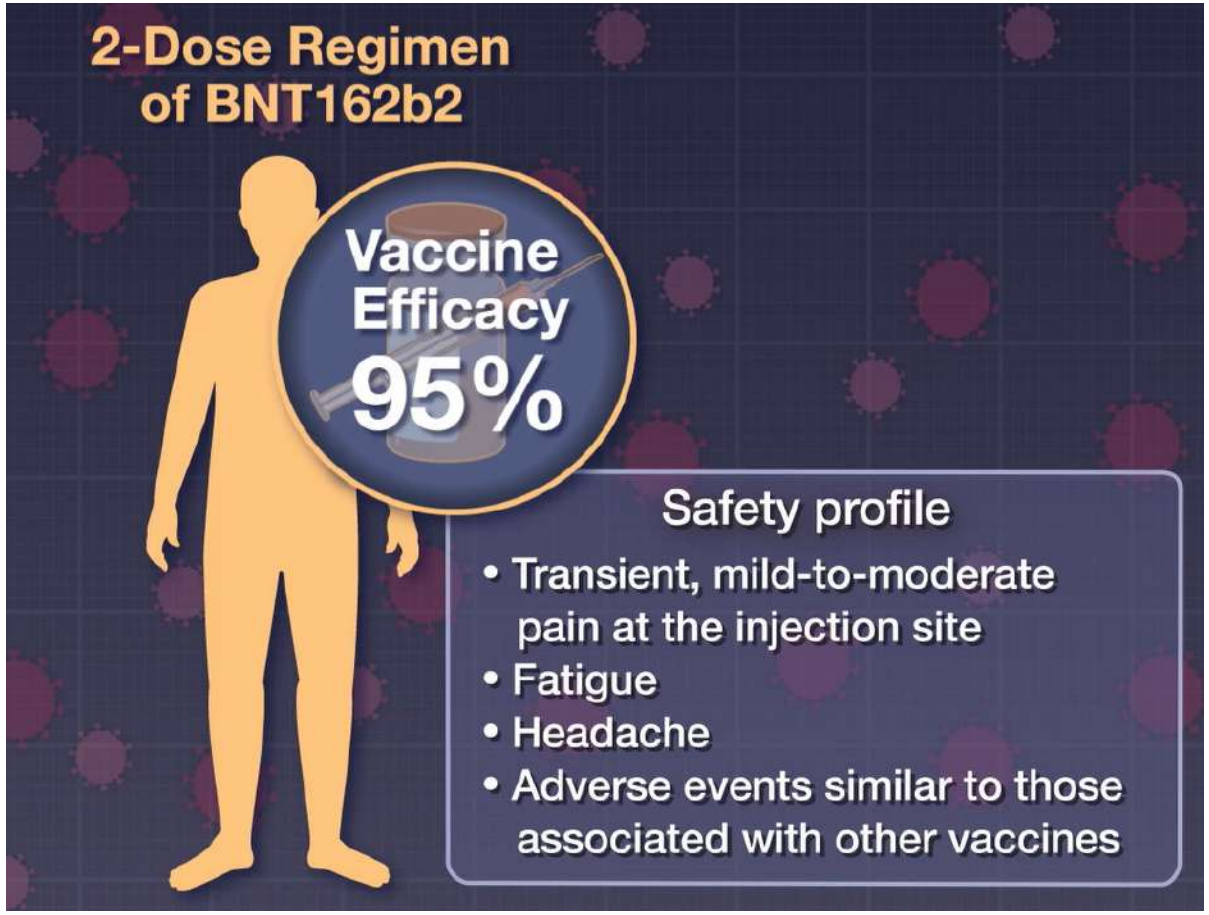
Etkinlik ve Güvenlik Çalışması



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mRNA-BNT162b2-Etkinlik Gerçek Yaşam Verisi

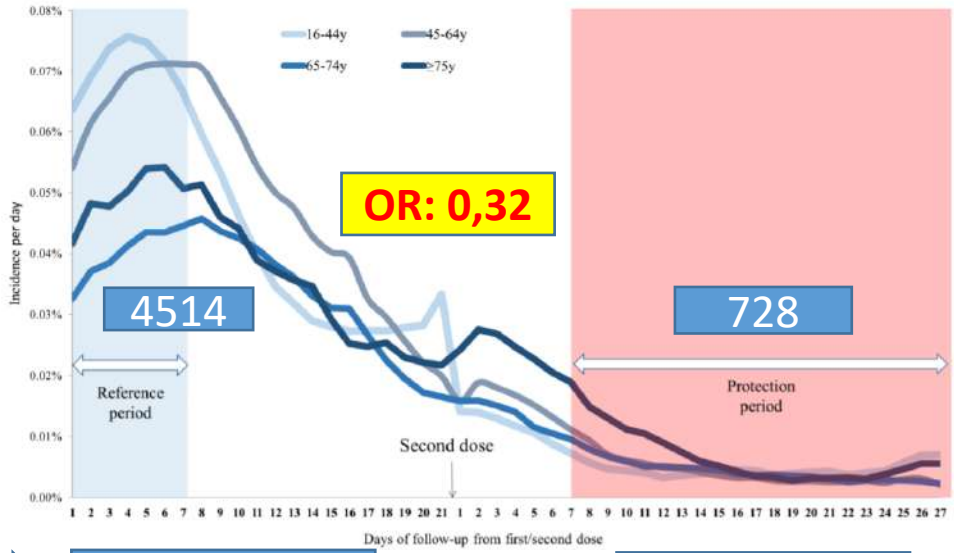
Clin Infect Dis. 2021 May 17;ciab438. doi: 10.1093/cid/ciab438. Online ahead of print.

The effectiveness of the TWO-DOSE BNT162b2 vaccine: analysis of real-world data

Gabriel Chodick [1 2], Lilac Tene [1], Ran S Rotem [1 3], Tal Patalon [1], Sivan Gazit [1], Amir Ben-Tov [1 2], Clara Weil [1], Inbal Goldshtein [1 2], Gilad Twig [2 4 5 6], Dani Cohen [2], Khitam Muhsen [2]

- ≥16 yaş
- 19 Aralık 2020-20 Şubat 2021
- 1. doz aşıdan sonra 1 178 597 (aşı öncesi (+) olanlar hariç)
- 2 doz aşıdan sonra 872 454

	Days 1-7 after 1st dose (reference period)		Days 7-27 after 2nd dose (protection period)	
	N	%	N	%
	1,178,597	(100)	872,454	(100)
Males	569,392	(48.4)	420,010	(48.1)
Females	608,277	(51.6)	452,444	(51.9)
Age y , mean ±SD	47.7	±18.1	52.3	±17.1



semptomatik → 3163 (%70,1) 281 (%38,6)

mRNA-BNT162b2-Etkinlik
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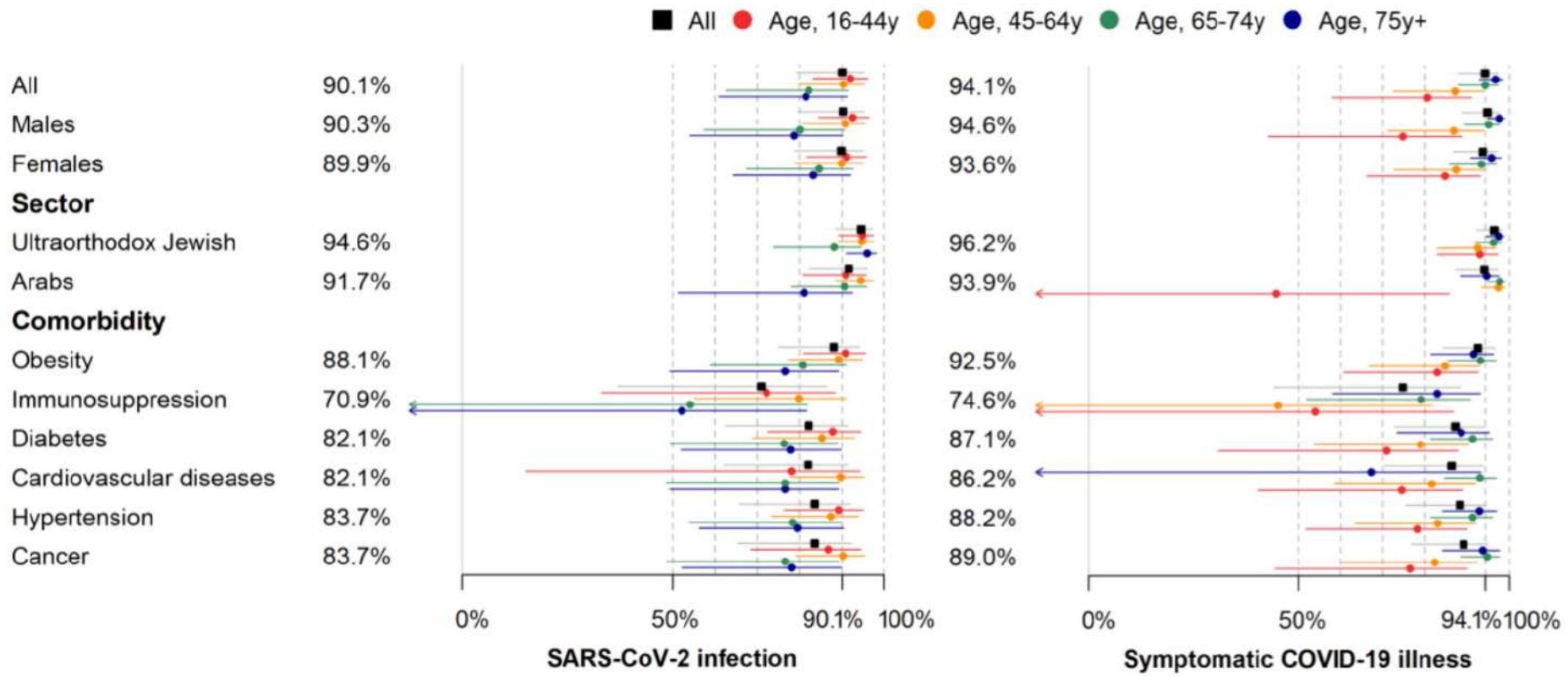
- Aşının enfeksiyonu önleme etkinliği 90% (95%CI:79%- 95%) ve 94% (95%CI:88%-97%)



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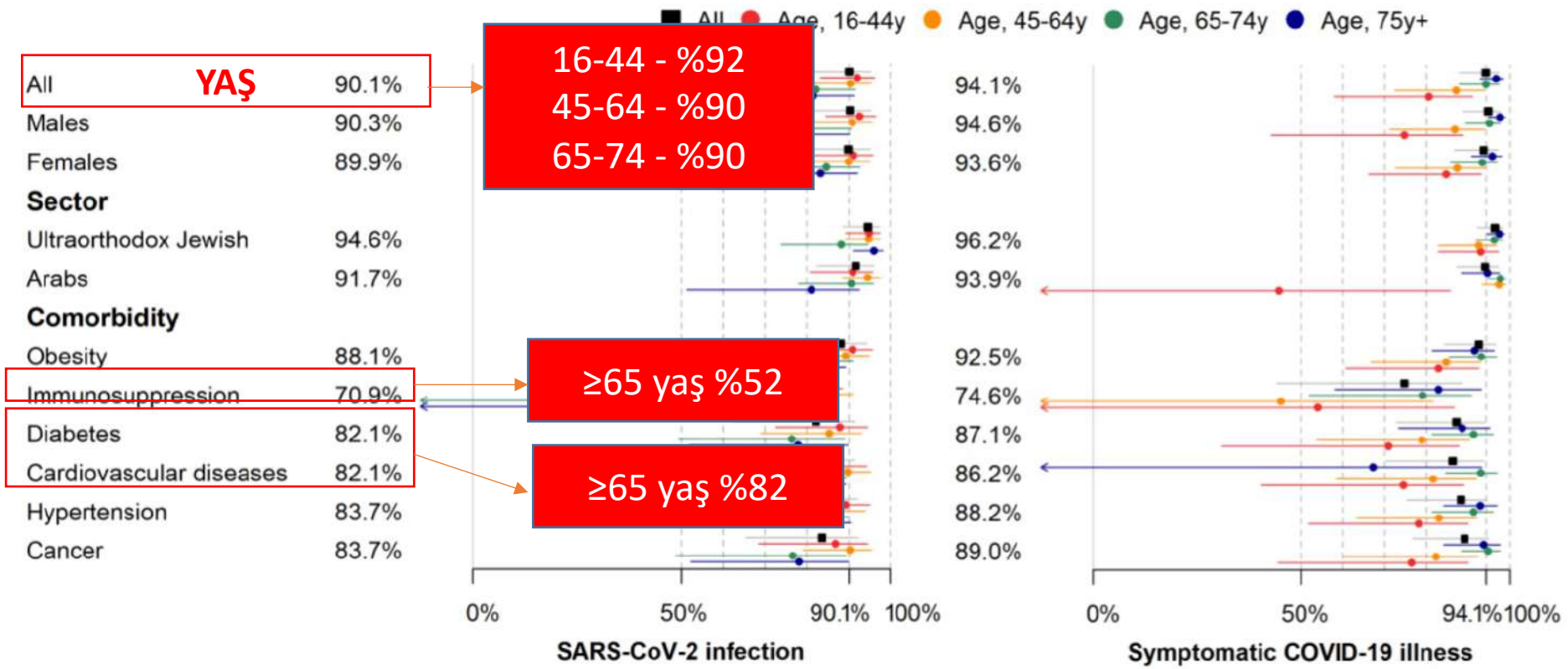
Etkinlik ileri yaşta, immünsüpresyon ve kronik hastalık varlığında azalmakta



mRNA-Etkinlik (B.1.1.7 (Alfa) varyantı)
Gerçek Yaşam Verisi

Lancet. 2021 15-21 May; 397(10287): 1819–1829.
Published online 2021 May 5. doi: 10.1016/S0140-6736(21)00947-8
PMCID: PMC8099315
PMID: 33964222

Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data

Eric J Haas, MD,[a,b] Frederick J Angulo, PhD,[c] John M McLaughlin, PhD,[c] Emilia Anis, MD,[a,d] Shepherd R Singer,

- Gözlemsel Çalışma, İsrail
- 24 Ocak-3 Nisan 2021
  - ≥ 16 yaş; 4714 932/ 6 538 911 (%71,1) 2 doz Biontech aşılı
  - ≥ 65 yaş; 1015620 /1127965 %90 aşılı
- Takip: 2. doz aşıdan 7 hafta sonraya kadar
- Semptomatik, asemptomatik enfeksiyon
- Hastaneye yatış
- Ağır ve kritik olgular
- Mortalite

mRNA-Etkinlik
Gerçek Yaşam Verisi

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- 232 268 SARS-CoV-2 enfeksiyonu saptandı
  - 186 109 (87·1%) veri toplandı
  - ≥ 16 yaş ve üzeri 154 648 (66·6%)
    - 109876 (%71) aşısız, 6266 (4,1) 2 doz aşılı
  - 54677 semptomatik enfeksiyon
    - 39065 (%71,4) aşısız, 1692 (%3,1) 2 doz aşılı
  - 7694 hastaneye yatış
    - 5526 (%71,8) aşısız, 596 (%7,7) 2 doz aşılı
  - 4481 şiddetli veya kritik yatış
    - 3201 (%71,4) aşısız, 364 (%8,1) 2 doz aşılı
  - 1113 mortalite (≥ 16 yaş)
    - 715 (%64,2) aşısız, 138 (12,4) 2 doz aşılı
- B.1.1.7 (Alfa) varyantı %94,5 olarak saptandı (Bulaşıcılık %40-80 daha fazla)

	Unvaccinated		Fully vaccinated*		Vaccine effectiveness	
	Cases	Incidence rate per 100 000 person-days†	Cases	Incidence rate per 100 000 person-days‡	Unadjusted	Adjusted§
SARS-CoV-2 infection¶						
Age 16–44 years	84 611	95·1	1801	2·3	95·4% (94·0–96·5)	96·1% (95·7–96·5)
Age 45–64 years	19 579	86·1	2264	3·4	93·6% (91·4–95·3)	94·9% (94·2–95·5)
Age ≥65 years	5686	67·7	2201	3·8	93·4% (91·3–95·0)	94·8% (93·9–95·5)
All ages	109 876	91·5	6266	3·1	94·2% (93·2–95·1)	95·3% (94·9–95·7)
Asymptomatic SARS-CoV-2 infection						
Age 16–44 years	40 088	45·1	1174	1·5	92·8% (90·3–94·7)	93·6% (92·8–94·4)
Age 45–64 years	7414	32·6	1343	2·0	89·1% (84·7–92·3)	90·8% (89·6–91·9)
Age ≥65 years	1636	19·5	1115	1·9	85·9% (80·2–89·9)	88·5% (86·4–90·3)
All ages	49 138	40·9	3632	1·8	90·1% (88·0–91·8)	91·5% (90·7–92·2)
Symptomatic COVID-19						
Age 16–44 years	28 196	31·7	352	0·5	97·8% (97·0–98·3)	97·6% (97·3–97·8)
Age 45–64 years	7790	34·3	560	0·8	96·3% (95·0–97·3)	96·7% (96·3–97·0)
Age ≥65 years	3079	36·6	780	1·4	96·1% (94·8–97·1)	96·4% (95·9–97·0)
All ages	39 065	32·5	1692	0·8	96·6% (95·8–97·2)	97·0% (96·7–97·2)

	Unvaccinated		Fully vaccinated*		Vaccine effectiveness	
	Cases	Incidence rate per 100 000 person-days†	Cases	Incidence rate per 100 000 person-days‡	Unadjusted	Adjusted§
COVID-19-related hospitalisation						
Age 16–44 years	2043	2·3	33	<0·1	98·1% (97·1–98·8)	98·1% (97·3–98·7)
Age 45–64 years	1687	7·4	112	0·2	97·6% (96·9–98·2)	97·6% (97·1–98·1)
Age ≥65 years	1826	21·7	451	0·8	96·6% (95·3–97·6)	96·8% (96·2–97·3)
All ages	5526	4·6	596	0·3	96·7% (95·5–97·6)	97·2% (96·8–97·5)
Severe or critical COVID-19-related hospitalisation						
Age 16–44 years	644	0·7	7	0·01	98·8% (97·3–99·5)	98·9% (97·6–99·5)
Age 45–64 years	1132	5·0	62	0·1	98·1% (97·2–98·6)	98·1% (97·5–98·5)
Age ≥65 years	1425	17·0	295	0·5	97·2% (95·9–98·1)	97·3% (96·8–97·8)
All ages	3201	2·7	364	0·2	97·2% (95·9–98·1)	97·5% (97·1–97·8)
COVID-19-related death						
Age 16–44 years	36	0·04	0	0·0	100	100
Age 45–64 years	125	0·5	14	<0·1	96·2% (92·6–98·0)	95·8% (92·6–97·6)
Age ≥65 years	554	6·6	124	0·2	96·8% (94·6–98·1)	96·9% (96·0–97·6)
All ages	715	0·6	138	0·1	96·6% (93·9–98·1)	96·7% (96·0–97·3)

mRNA-Etkinlik- Gerçek Yaşam Verisi

Estimated effectiveness of two doses of BNT162b2 (≥7 days after the second dose) against laboratory-confirmed SARS-CoV-2 outcomes in the oldest age groups (Jan 24 to April 3, 2021)

	Vaccine effectiveness*		
	Age ≥65 years	**Age ≥75 years**	**Age ≥85 years**
SARS-CoV-2 infection†	94·8% (93·9–95·5)	95·1% (93·9–96·0)	94·1% (91·9–95·7)
Asymptomatic SARS-CoV-2 infection	88·5% (86·4–90·3)	87·5% (84·2–90·1)	83·2% (76·3–88·1)
Symptomatic COVID-19	96·4% (95·9–97·0)	96·7% (95·9–97·4)	96·6% (95·2–97·6)
COVID-19-related hospitalisation	96·8% (96·2–97·3)	97·0% (96·2–97·7)	96·9% (95·5–97·9)
Severe or critical COVID-19-related hospitalisation	97·3% (96·8–97·8)	97·6% (96·8–98·1)	97·4% (95·9–98·3)
COVID-19-related death	96·9% (96·0–97·6)	97·1% (96·0–97·9)	97·0% (94·9–98·3)

Breakthrough Enfeksiyon-BNT162b2

- Çok merkezli (**17 hastane-İsrail**) kohort, 10 Ocak-20 Nisan)
- 2 doz B-Aşısı alanlar
- PCR ile doğrulanmış 152 COVID-19 enfeksiyon tanısıyla hospitalize
- Yatış esnasında
  - 2. doz yatış öncesi ortalama 39,5 gün
  - **Ortalama Yaş 71,1**
  - %70 erkek
  - %38 Uzun süreli bakım evi
  - **%96 komorbidite** VAR
  - **%40 immünosüpresyon** (Kronik KS kullanımı, Kemoterapi, antimetabolit kullanımı, SOT, anti-CD20 kullanımı)

Tal Brosh-Nissimov, BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. Clin Microbiol Infect. 2021 Jul 7

Breakthrough Enfeksiyon-BNT162b2

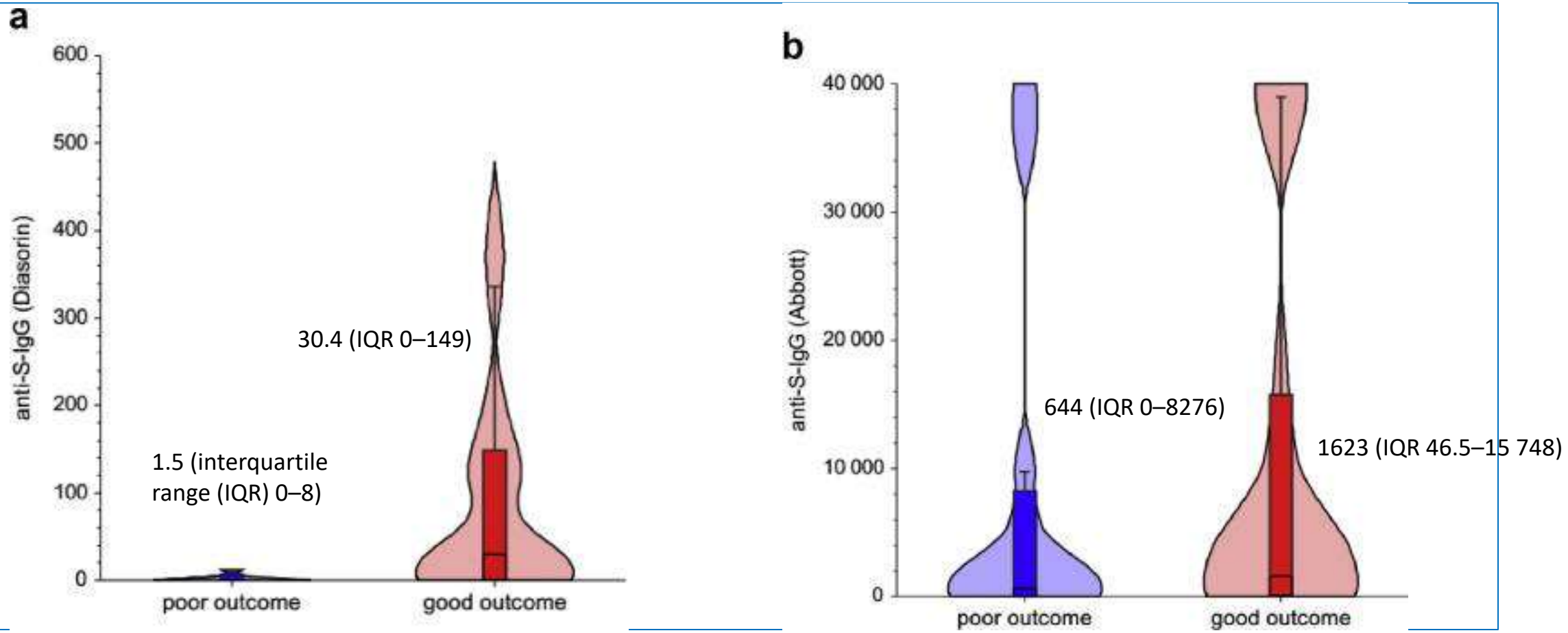
- %61 (93) **şiddetli** enfeksiyon
- Mortalite %22 (34/152)-Aşısız kritik hastalardaki mortalite oranına benzer
- 45 hastada sekanslama
  - %89 (40) B.1.1.7 (Alfa)
  - %7 (2) wild-type
  - %4 (2) B.1.351 (beta)

	Olumlu Sonuç	Kötü sonuç	
Anti-CD20 tedavi	%4	%13	P 0,12
Kanser	%22	%32	P 0,22
Konjestif Kalp Yetmez	%25	%34	P 0,25
Demans	%17	%26	P 0,19

Tal Brosh-Nissimov, BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. Clin Microbiol Infect. 2021 Jul 7

Breakthrough Enfeksiyon-BNT162b2

Anti-Spike IgG



Tal Brosh-Nissimov, BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. Clin Microbiol Infect. 2021 Jul 7

Breakthrough Enfeksiyon-BNT162b2

Comparison of the clinical characteristics of fully vaccinated and non-vaccinated hospitalized COVID-19 patients cohorts

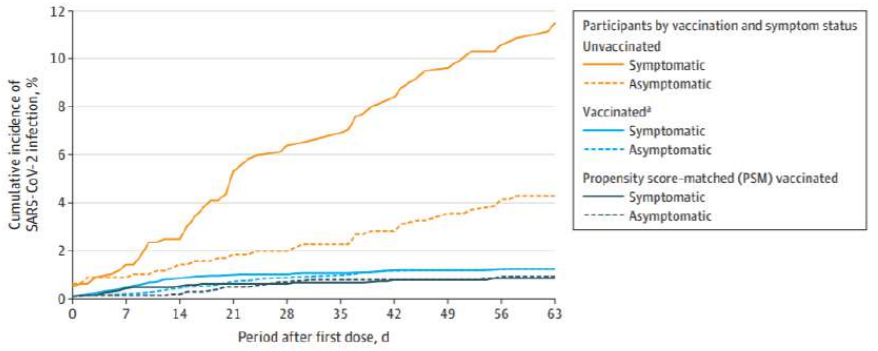
	Fully vaccinated cohort	Non-vaccinated COVID-19 patients cohorts		
		Karagiannidis et al. [17]	Myers et al. [18]	Petrilli et al. [19]
No. of patients	152	10 021	377	2741
No. of hospitals	17	920	21	4
Time period	January–April 2021	February–April 2020	March 2020	March–April 2020
Country	Israel	Germany	California, USA	New York, USA
Inclusion	All fully vaccinated patients with PCR-confirmed COVID-19 and admitted to hospital	All patients with PCR-confirmed COVID-19 and admitted to hospital	All patients with PCR-confirmed COVID-19 and admitted to hospital	All patients with PCR-confirmed COVID-19 and admitted to hospital
Age (years), mean ± SD or median (IQR)	71 ± 14.3	68 ± 17.3	61 (50–73)	63 (51–74)
Hypertension	71%	55.6%	43.5	62%
Diabetes mellitus	48%	27.9%	31.3	34.7%
Heart failure	32%	19.6%	5.8	12.8%
Chronic lung disease	24%	13.6%	7.4	16.5%
Chronic kidney disease	27%	22.8%	12.7	21.2%
BMI >30 kg/m^2	32%	5.9%	NR	39.5%
Cancer	24%	NR	4.8	10.8%

Tal Brosh-Nissimov, BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. Clin Microbiol Infect. 2021 Jul 7

Breakthrough Enfeksiyon, Sağlık Çalışanları-BNT162b2

- 20 Aralık 2020-25 Şubat 2021
- Retrospektif kohort-İsrail
- 6710 Sağlık Çalışanı,
- Ort 63 gün izlendi
- (Ort.Yaş 44,3, %65 kadın)
- %88,7 (4465) en az bir doz
- %82,2 (5953) 2 doz
- %11 (757) aşısız

Figure 3. Cumulative Incidence of SARS-CoV-2 Infection Among Vaccinated, Propensity Score–Matched Vaccinated, and Unvaccinated Participants Screened for SARS-CoV-2 Infection



No. at risk

Unvaccinated	757	743	731	713	698	693	678	664	654	645
Vaccinated with first dose[a]	5953	5790	5640	766	79	28	21	12	8	4
Vaccinated with second dose[a]	0	0	0	4775	5370	5238	5093	4816	4322	3082
PSM vaccinated with first dose	2141	2098	2047	310	32	9	7	4	3	1
PSM vaccinated with second dose	0	0	0	1686	1926	1846	1777	1636	1425	970

Yoel Angel, Association Between Vaccination With BNT162b2 and Incidenceof Symptomatic and Asymptomatic SARS-CoV-2 Infections Among Health Care Workers. JAMA. 2021;325(24):2457-2465

Breakthrough Enfeksiyon, Sağlık Çalışanları-BNT162b2

Semptomatik İnf:

8 Aşılı/38 aşısız

İnsidans: 4,7 / 149,8 / 100000 kişi/gün

IRR: 0,03 (95% CI, 0.01-0.06)

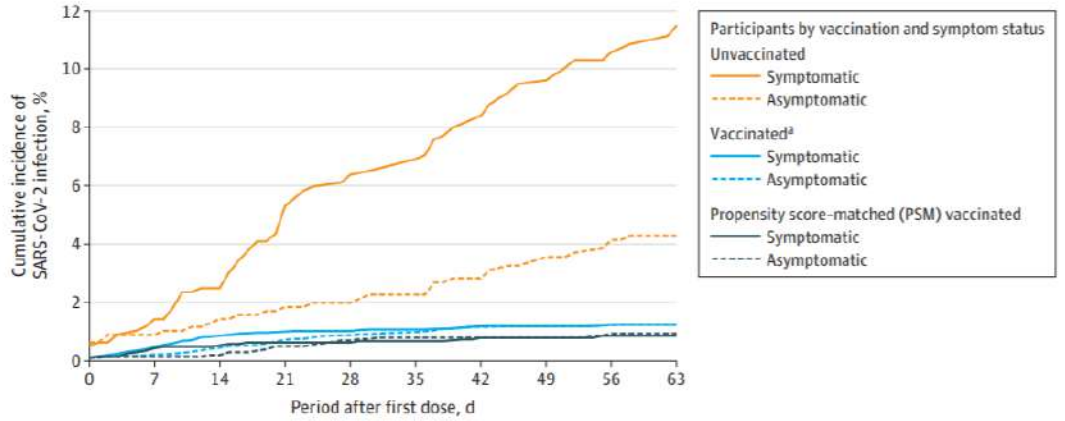
Asemptomatik

19 aşılı/17 aşısız

İnsidans: 11,3 /67 /100000

IRR: 0,14 (95% CI, 0.07-0.31)

Figure 3. Cumulative Incidence of SARS-CoV-2 Infection Among Vaccinated, Propensity Score–Matched Vaccinated, and Unvaccinated Participants Screened for SARS-CoV-2 Infection



No. at risk

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PSM vaccinated with second dose	0	0	0	1686	1926	1846	1777	1636	1425	970

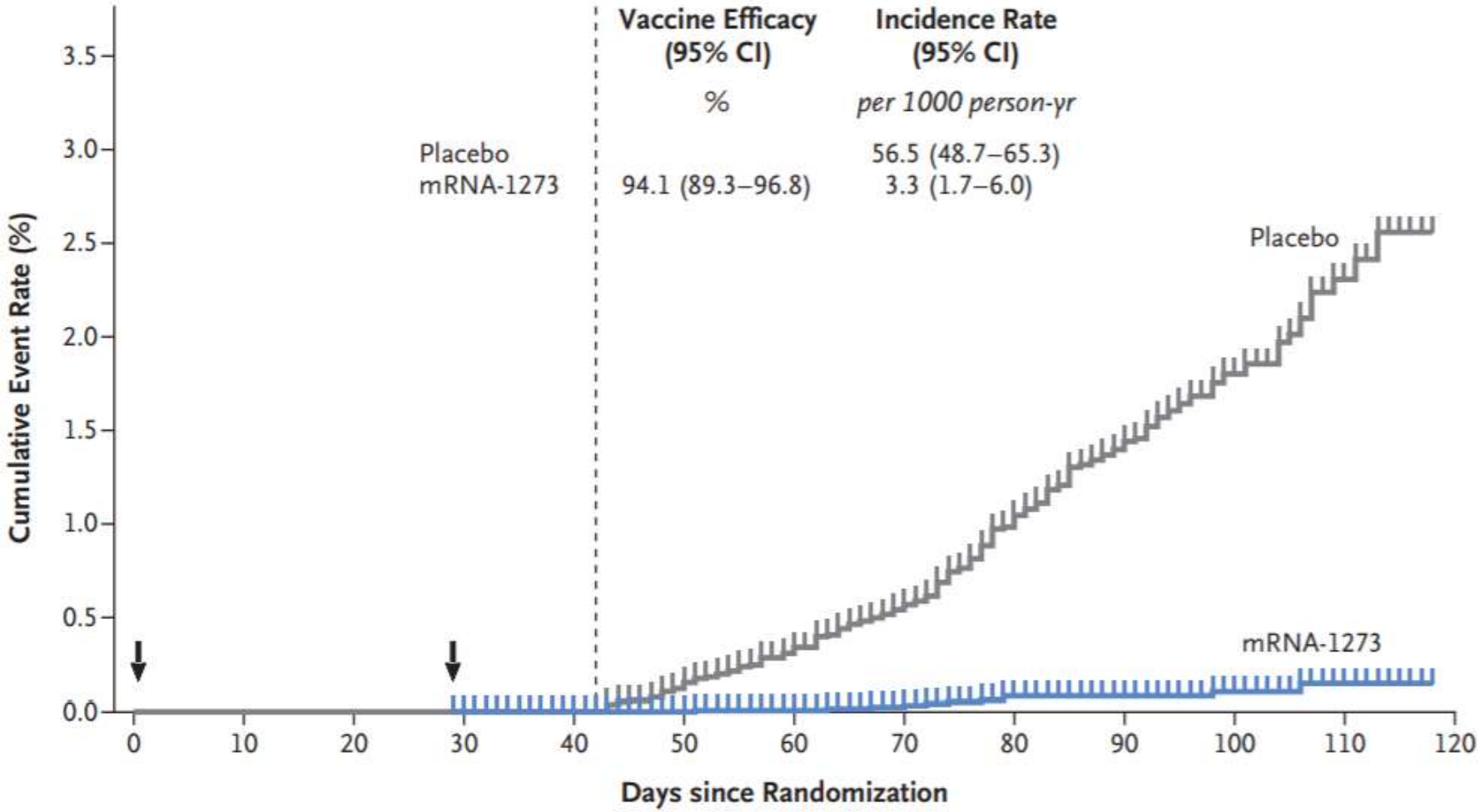
mRNA-1273
etkinlik ve güvenlik (Faz3) Çalışması

- Faz-3 randomize, araştırmacı kör, Plesebo kontrollü
- USA, 99 merkez
- 30 420 gönüllü (≥18 yaş) ; 1:1 (15 210 iki gruba randomize)
- mRNA-1273 (100 mikrogram/0,5 ml)/plesebo 28 gün arayla 2 doz IM
- Saklama: 2° - 8°C aşı hazırlık ve uygulama, oda sıcaklığında 8h kadar
- 2. dozdan 14 gün sonra COVID-19 önleme
- Öncesinde SARS-Cov-2 enfeksiyonu olmayan

mRNA-1273
etkinlik ve güvenlik (Faz3) Çalışması

- Plasebo: 185 enfeksiyon (56,5 /1000 kişi-yıl)
- Aşı gurubu: 11 enfeksiyon (3,3/1000 kişi/yıl)
- **VE (Aşı etkinliği): %94,1 (%95CI; 89,3-96,8) p<0,001**
- Ağır enfeksiyon 30, 1 mortalite
  - Plasebo gurubu
- Reaktojenite: Orta, geçici; aşı grubunda daha fazla
- Ciddi yan etki: Nadir, iki grupta benzer sıklıkta

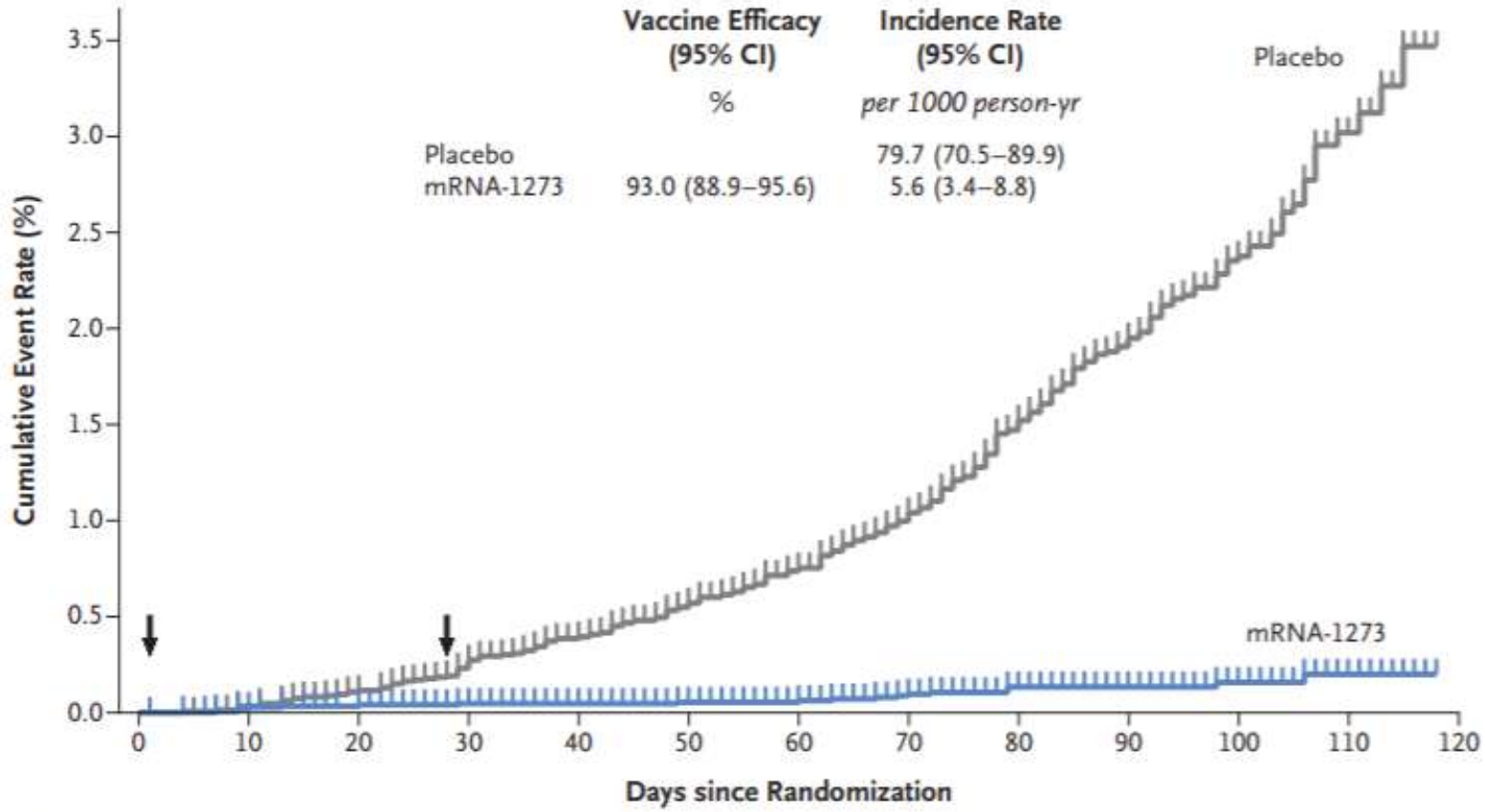
A **Per-Protocol Analysis**



No. at Risk

Placebo	14,073	14,073	14,073	14,072	13,416	12,992	12,361	11,147	9474	6563	3971	1172	0
mRNA-1273	14,134	14,134	14,134	14,133	13,483	13,073	12,508	11,315	9684	6721	4094	1209	0

B **Modified Intention-to-Treat Analysis**



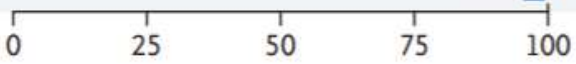
No. at Risk

Placebo	14,598	14,590	14,567	14,515	13,806	13,352	12,694	11,450	9736	6729	4067	1200	0
mRNA-1273	14,550	14,543	14,532	14,504	13,825	13,398	12,791	11,573	9911	6871	4179	1238	0

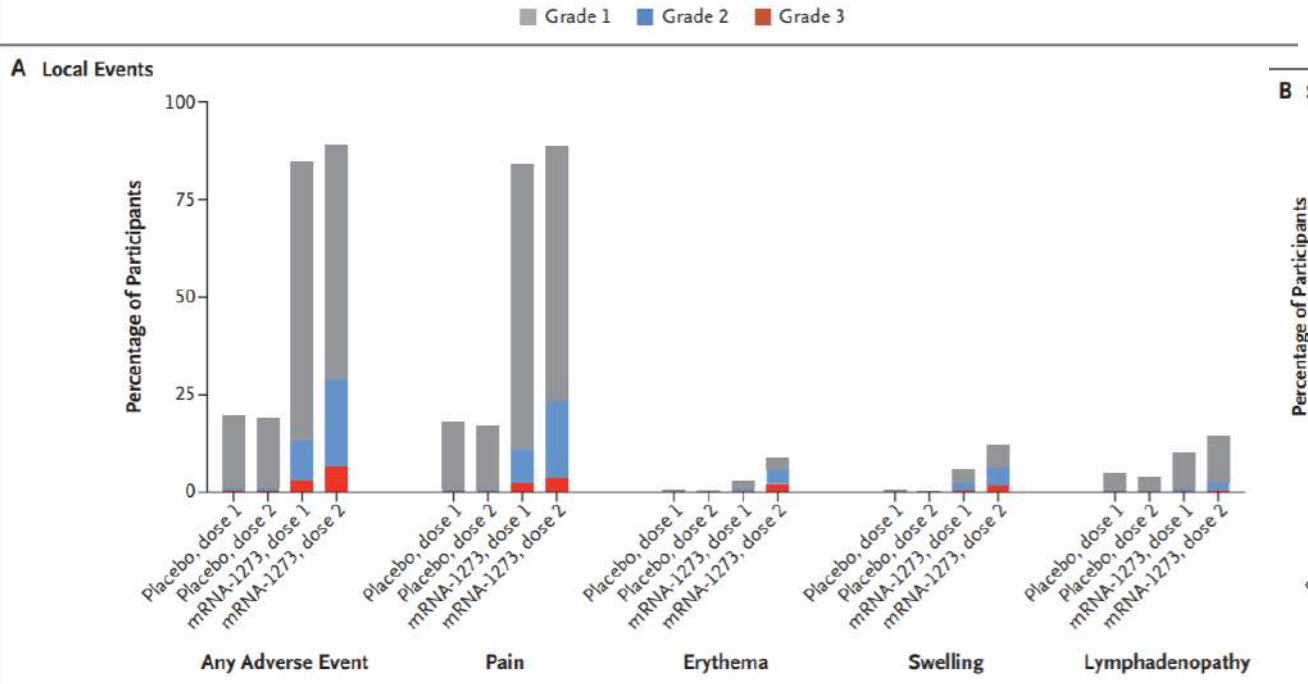
Covid-19 Onset	Placebo (N=14,598)	mRNA-1273 (N=14,550)
Randomization to 14 days after dose 1	11	5
14 Days after dose 1 to dose 2	35	2
Dose 2 to 14 days after dose 2	19	0
Starting 14 days after dose 2	204	12
Total (any time after randomization)	269	19

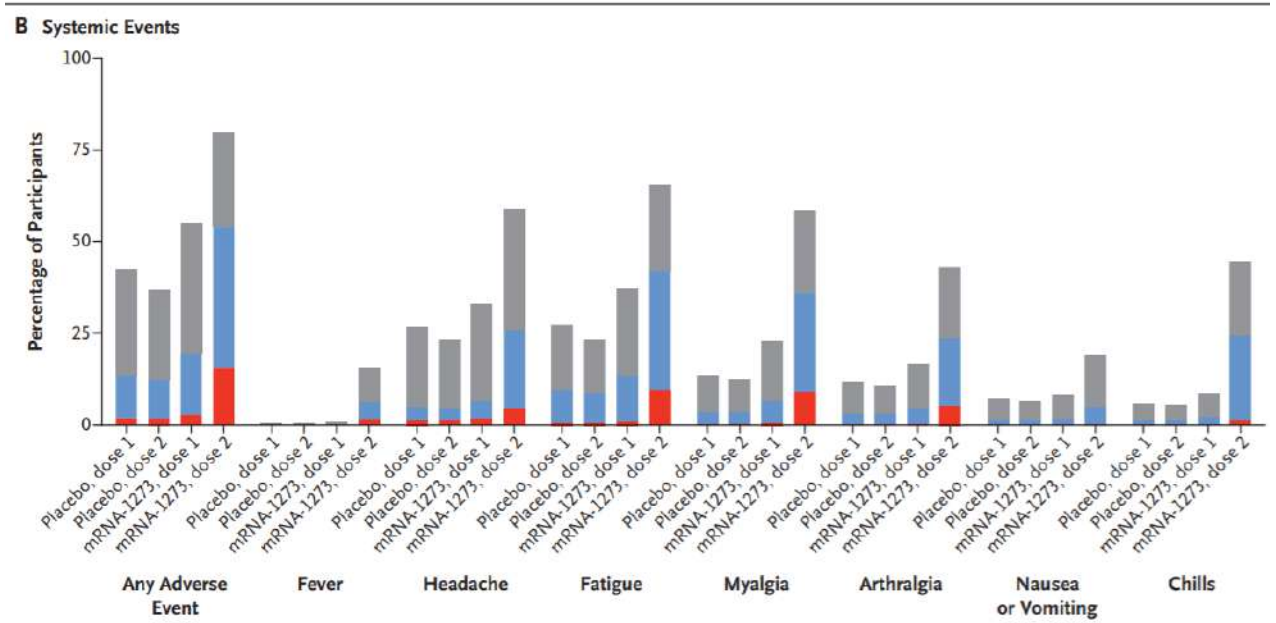
mRNA-1273
Etkinlik ve güvenlik (Faz3) Çalışması: Alt grup analizi

Subgroup	Placebo (N=14,073)	mRNA-1273 (N=14,134)	Vaccine Efficacy (95% CI)
	no. of events/total no.		
All patients	185/14,073	11/14,134	94.1 (89.3–96.8)
Age			
≥18 to <65 yr	156/10,521	7/10,551	95.6 (90.6–97.9)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Age, risk for severe Covid-19			
18 to <65 yr, not at risk	121/8403	5/8396	95.9 (90.0–98.3)
18 to <65 yr, at risk	35/2118	2/2155	94.4 (76.9–98.7)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Sex			
Male	87/7462	4/7366	95.4 (87.4–98.3)
Female	98/6611	7/6768	93.1 (85.2–96.8)
At risk for severe Covid-19			
Yes	43/3167	4/3206	90.9 (74.7–96.7)
No	142/10,906	7/10,928	95.1 (89.6–97.7)
Race and ethnic group			
White	144/8916	10/9023	93.2 (87.1–96.4)
Communities of color	41/5132	1/5088	97.5 (82.2–99.7)



mRNA-1273
Etkinlik ve güvenlik (Faz3) Çalışması: Yan etki





Pfizer-BioNTech - Moderna: Gerçek Yaşam Verisi

- **Prospektif Kohort** 14 Aralık 2020 – Mart 2021/USA
- Sağlık Çalışanları
  - Kadın (62.1%), Yaş 18–49 (71.9%), Beyaz (86.3%), ve non-Hispanik (82.9%) Komorbid hastalığı olmayan (68.9%).
- Her hafta semptomdan bağımsız PCR testi
- 3 950 kişi
  - 2470 (%62,8) mRNA aşılı
    - **62.7% Pfizer-BioNTech ve 29.6% Moderna**

Thompson MG, et al. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021. MMWR Morb Mortal Wkly Rep 2021;70:495–500.

Pfizer-BioNTech - Moderna: Gerçek Yaşam Verisi

- Çift doz aşılı (2. Dozdan ≥14 gün) 0,04/1000 kişi gün
- Parsiyel aşılı (1. Dozdan ≥14 gün – 2. doz) 0,19/1000
- Aşısız 1,38/1000

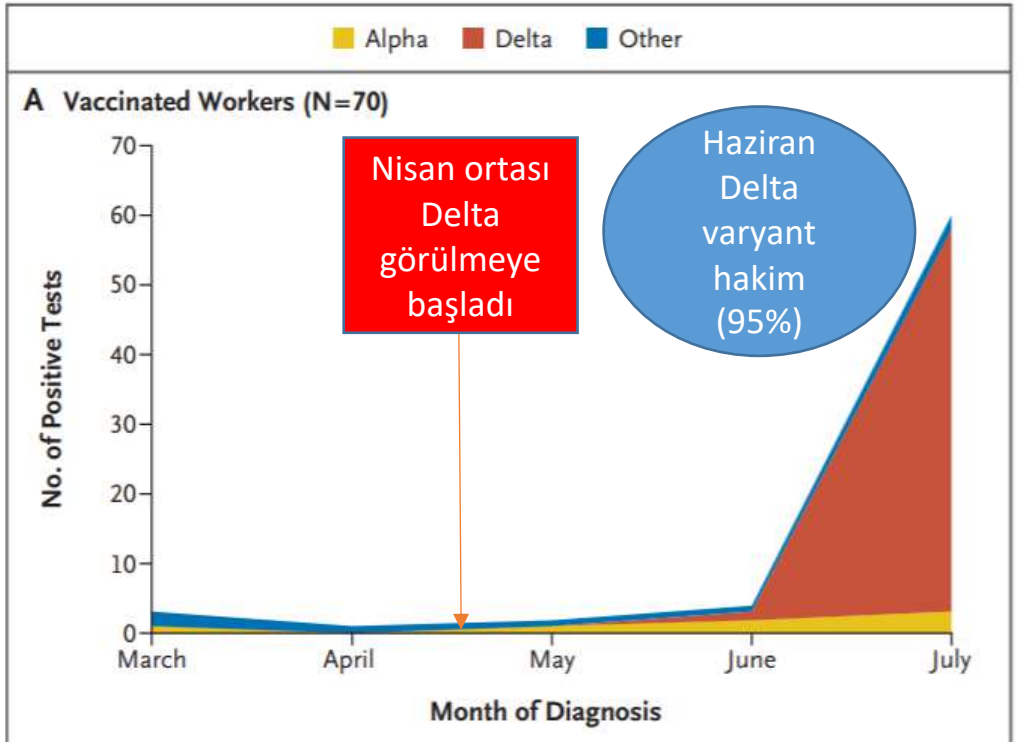
VE: 100% × (1−hazard ratio)

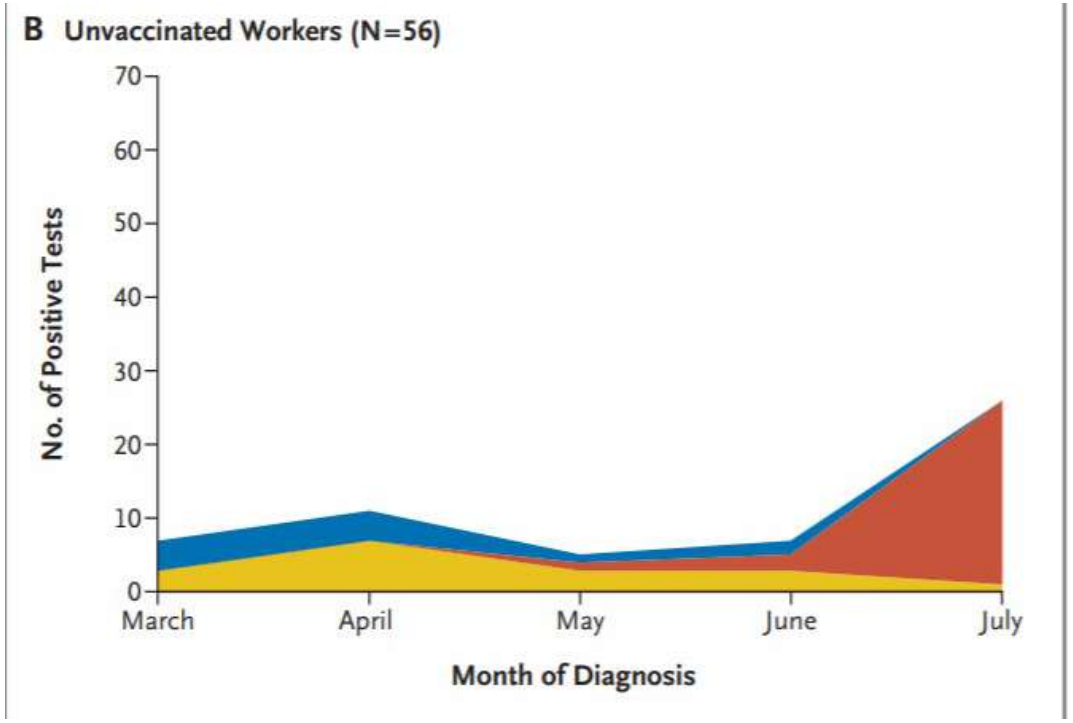
COVID-19 immunization status	Person-days	SARS-CoV-2 infections		Unadjusted vaccine effectiveness*	Adjusted vaccine effectiveness*,†
		No.	Incidence rate per 1,000 person-days	% (95% CI)	% (95% CI)
Unvaccinated	116,657	161	1.38	N/A	N/A
Partially immunized	41,856	8	0.19	82 (62–91)	80 (59–90)
≥14 days after receiving first dose only§	15,868	5	0.32		
≥14 days after first dose through receipt of second dose	25,988	3	0.12		
Fully immunized					
≥14 days after second dose	78,902	3	0.04	91 (73–97)	90 (68–97)

Thompson MG, et al. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021. MMWR Morb Mortal Wkly Rep 2021;70:495–500.v

Delta (B.1.617.2) Varyant: Aşı Etkinliği?

Nancy J. Binkin. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. N Engl J Med. D. September 2021





SARS-CoV-2 Variants among Symptomatic Health Workers. Shown is the distribution of the B.1.1.7 (alpha), delta, and other SARS-CoV-2 variants according to vaccination status and month of diagnosis among **health workers at University of California San Diego Health**, March through July 2021. The number of workers indicates those who were symptomatic and had available variant data, and the number of positive tests indicates those that included data on variants

Semptomatik

Delta (B.1.617.2) Varyant: Aşı Etkinliği?

- 1 Mart- 31Temmuz 2021 University of California San Diego Health
- 227 Sağlık Çalışanı PCR (+)
- 130/227 (%57,3) tam aşılı, 7 parsiyel aşılı (mRNA)
- 109/130 (aşılı) semptomatik (%83)
- 80/90 aşısız semptomatik (%88,9)

Nancy J. Binkin. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. N Engl J Med. D. Sep 2021

Delta (B.1.617.2) Varyant: Aşı Etkinliği?

Table 1. Symptomatic SARS-CoV-2 Infection and mRNA Vaccine Effectiveness among UCSDH Health Workers, March through July 2021.*

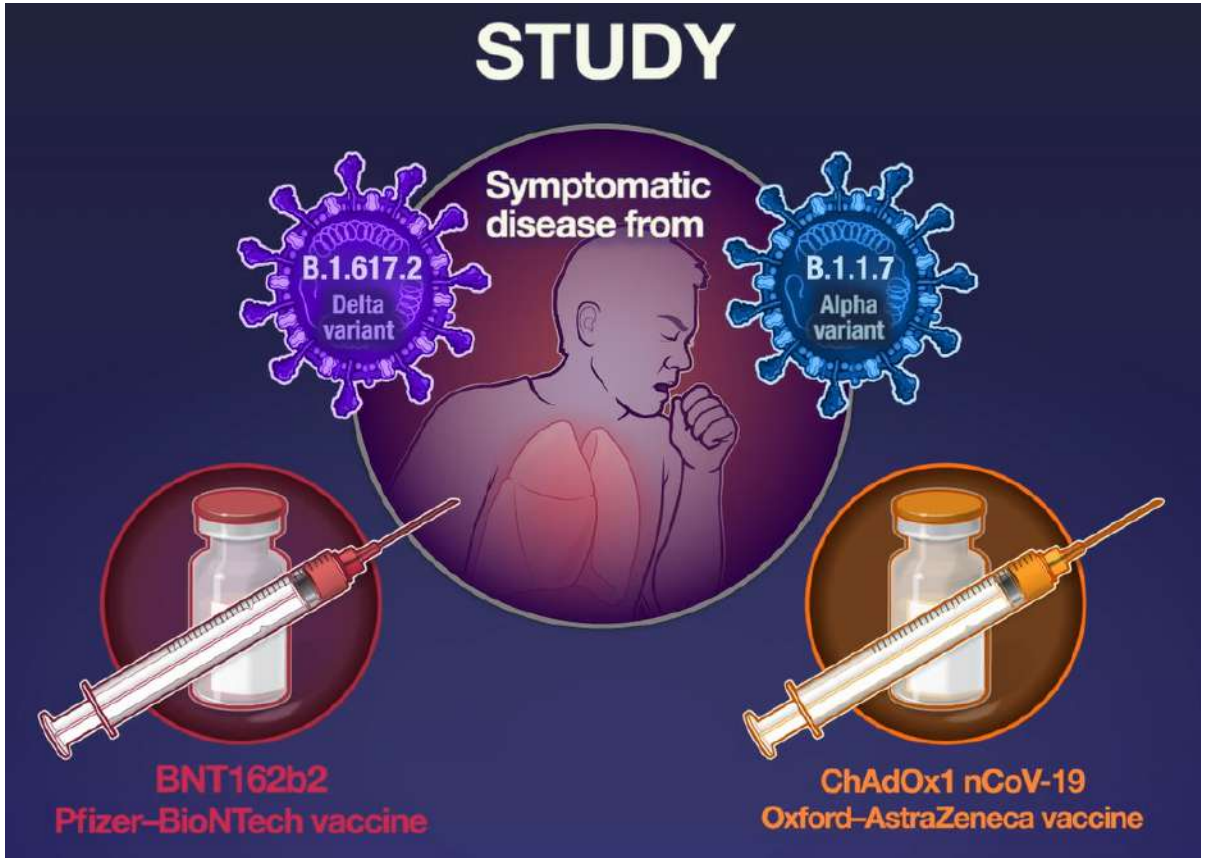
	March	April	May	June	July
UCSDH workforce — no. of persons	18,964	18,992	19,000	19,035	19,016
Vaccination status — no. of persons					
Fully vaccinated†	14,470	15,510	16,157	16,426	16,492
mRNA-1273 (Moderna)	6,608	7,005	7,340	7,451	7,464
BNT162b2 (Pfizer–BioNTech)	7,862	8,505	8,817	8,975	9,028
Unvaccinated	3,230	2,509	2,187	2,059	1,895
Percentage of workers fully vaccinated	76.3	81.7	85.0	86.3	86.7
Symptomatic Covid-19					
Fully vaccinated workers	3	4	3	5	94
Unvaccinated workers	11	17	10	10	31
Percentage of cases in fully vaccinated workers	21.4	19.0	23.1	33.3	75.2
Attack rate per 1000 (95% CI)					
Fully vaccinated workers	0.21 (0.21–0.47)	0.26 (0.26–0.50)	0.19 (0.21–0.40)	0.30 (0.31–0.53)	5.7 (5.4–6.2)
Unvaccinated workers	3.4 (2.1–5.9)	6.8 (4.5–10.6)	4.6 (2.6–8.2)	4.9 (2.9–8.7)	16.4 (11.8–22.9)
Vaccine effectiveness — % (95% CI)	93.9 (78.2–97.9)	96.2 (88.7–98.3)	95.9 (85.3–98.9)	94.3 (83.7–98.0)	65.5 (48.9–76.9)

* UCSDH denotes University of California San Diego Health.
† Data are the total number of workers who had received two doses of an mRNA vaccine as of the last day of the month.

Nancy J. Binkin. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. N Engl J Med. D. Sep 2021

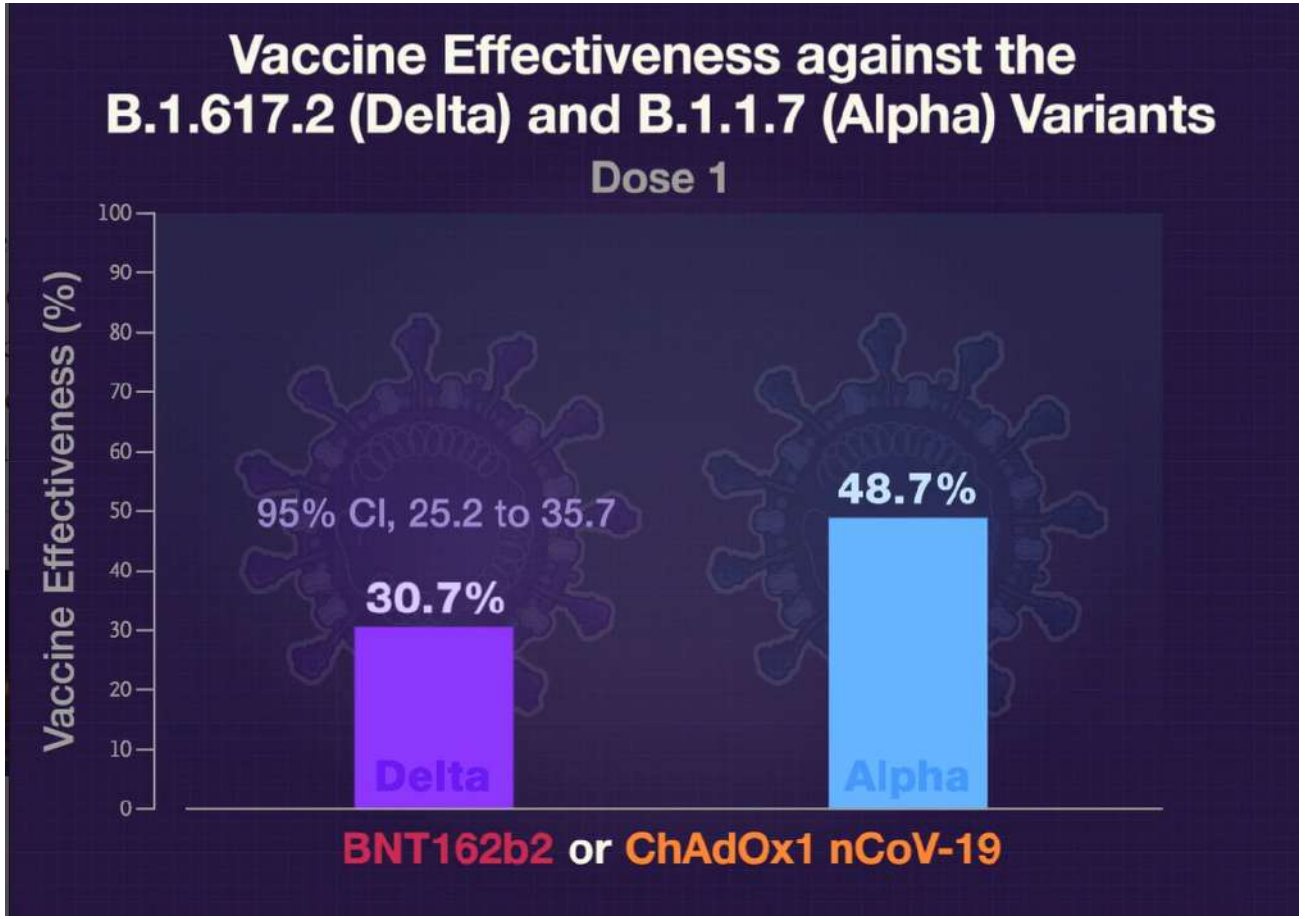
Delta Varyant Etkinlik:
BNT162b2 ve ChAdOx1 nCoV-19 v

- Vaka-kontrol
- İngiltere
- Kasım 2020-Mayıs 2021
- Semptomatik Enfeksiyon
  - 4272 Delta
  - 14 837 alfa
- Test negatif kontrol grubu
  - 96 371



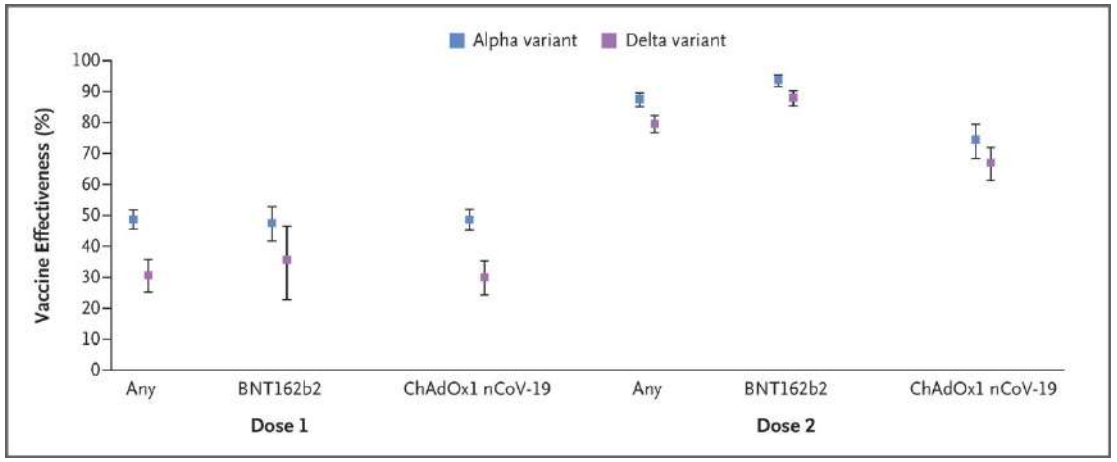
Jamie Lopez Bernal. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. August 12, 2021N Engl J Med 2021; 385:585-594.

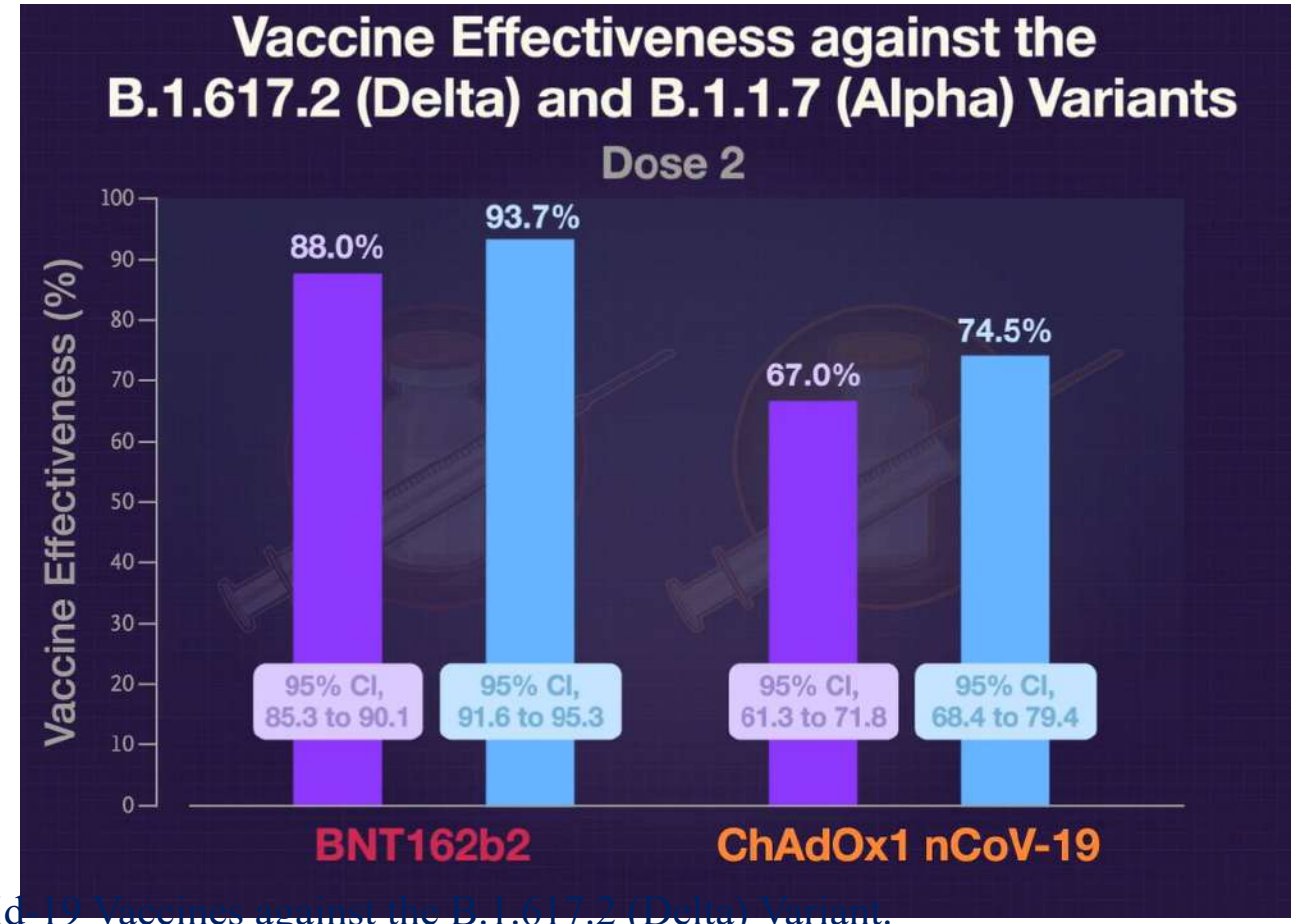
Delta Varyant Etkinlik:
BNT162b2 ve ChAdOx1 nCoV-19 v



Jamie Lopez Bernal. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. August 12, 2021N Engl J Med 2021; 385:585-594.

Delta Varyant Etkinlik:
BNT162b2 ve ChAdOx1 nCoV-19 v





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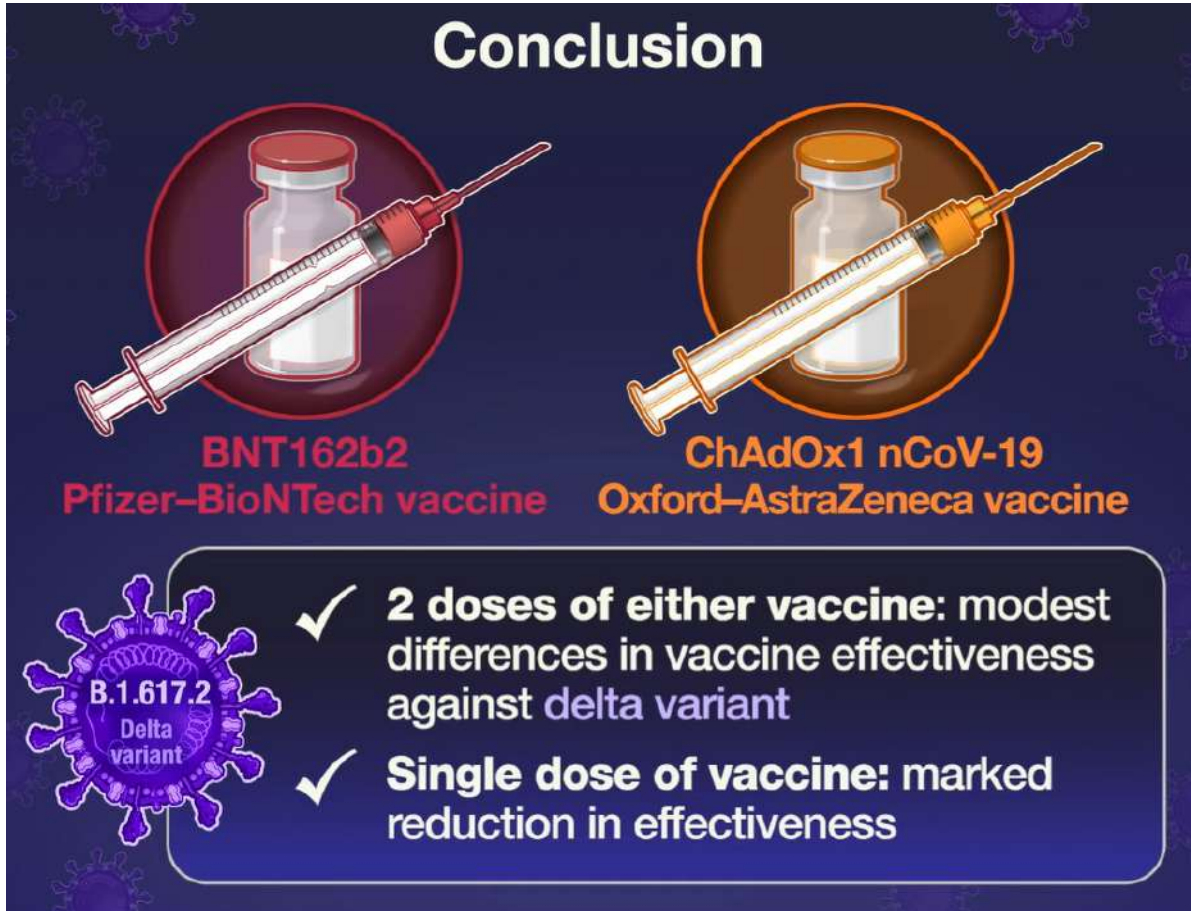
BNT162b2 ve ChAdOx1 nCoV-19 v



Jamie Lopez Bernal. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. August 12, 2021N Engl J Med 2021; 385:585-594.

Pfizer-BioNTech (BNT162b2 Covid-19 Vaccine) B.1.1.7 (Alfa) ve B.1.351 (Beta) Varyantlarına Etkinlik

- Katar 21.12.2020 -31.03.2021, 385,853 kişi 1 doz, 265,410 kişi 2 doz

Type of Infection or Disease	PCR-Positive Persons		PCR-Negative Persons		Effectiveness (95% CI)*
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
	number of persons				percent
PCR-confirmed infection with the B.1.1.7 variant†					
After one dose	892	18,075	1241	17,726	29.5 (22.9–35.5)
≥14 days after second dose	50	16,354	465	15,939	89.5 (85.9–92.3)
PCR-confirmed infection with the B.1.351 variant‡					
After one dose	1329	20,177	1580	19,926	16.9 (10.4–23.0)
≥14 days after second dose	179	19,396	698	18,877	75.0 (70.5–78.9)
Disease§					
Severe, critical, or fatal disease caused by the B.1.1.7 variant					
After one dose	30	468	61	437	54.1 (26.1–71.9)
≥14 days after second dose	0	401	20	381	100.0 (81.7–100.0)
Severe, critical, or fatal disease caused by the B.1.351 variant					
After one dose	45	348	35	358	0.0 (0.0–19.0)
≥14 days after second dose	0	300	14	286	100.0 (73.7–100.0)
Severe, critical, or fatal disease caused by any SARS-CoV-2					
After one dose	139	1,966	220	1,885	39.4 (24.0–51.8)
≥14 days after second dose	3	1,692	109	1,586	97.4 (92.2–99.5)

Laith J. Abu-Raddad. N Engl J Med. 2021 May 5 : NEJMc2104974.

Delta varyant Etkinlik

Fowlkes A, Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December 2020–August 2021. MMWR Morb Mortal Wkly Rep 2021;70:1167-1169

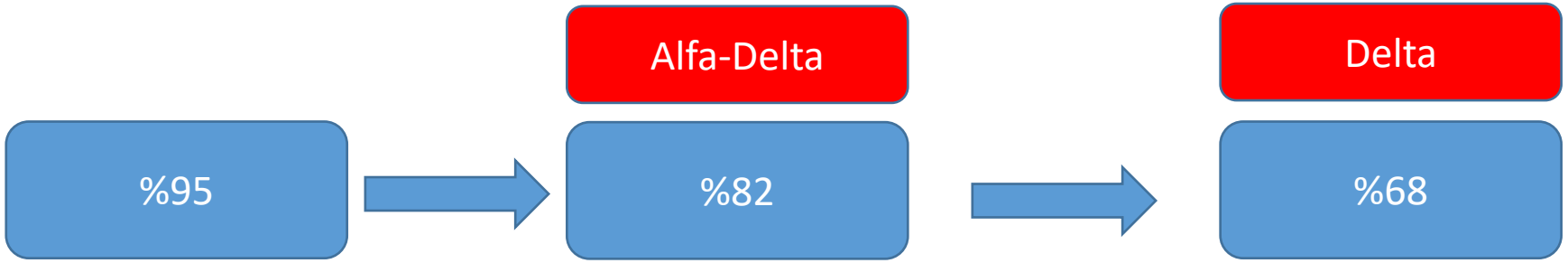
İnfeksiyon

91% (81–96%) to 66% (26–84%)

Period and vaccination status	No. of contributing participants*	Total no. of person-days	Median days (IQR)	No. of SARS-CoV-2 infections	Adjusted VE,† % (95% CI)
Full cohort to date					
Unvaccinated	4,136	181,357	20 (8–45)	194	N/A
Fully vaccinated§	2,976	454,832	177 (115–195)	34	80 (69–88)
14–119 days after full vaccination	2,923	284,617	106 (106–106)	13	85 (68–93)
120–149 days after full vaccination	2,369	66,006	30 (30–30)	3	81 (34–95)
≥150 days after full vaccination	2,129	104,174	52 (37–64)	18	73 (49–86)
Pre-Delta variant predominance					
Unvaccinated	4,137	156,626	19 (8–43)	175	N/A
Fully vaccinated	2,875	329,865	124 (95–149)	10	91 (81–96)
Delta variant predominance					
Unvaccinated	488	24,871	43 (37–69)	19	N/A
Fully vaccinated	2,352	119,218	49 (35–56)	24	66 (26–84)

mRNA Aşı Etkinliği - Varyant

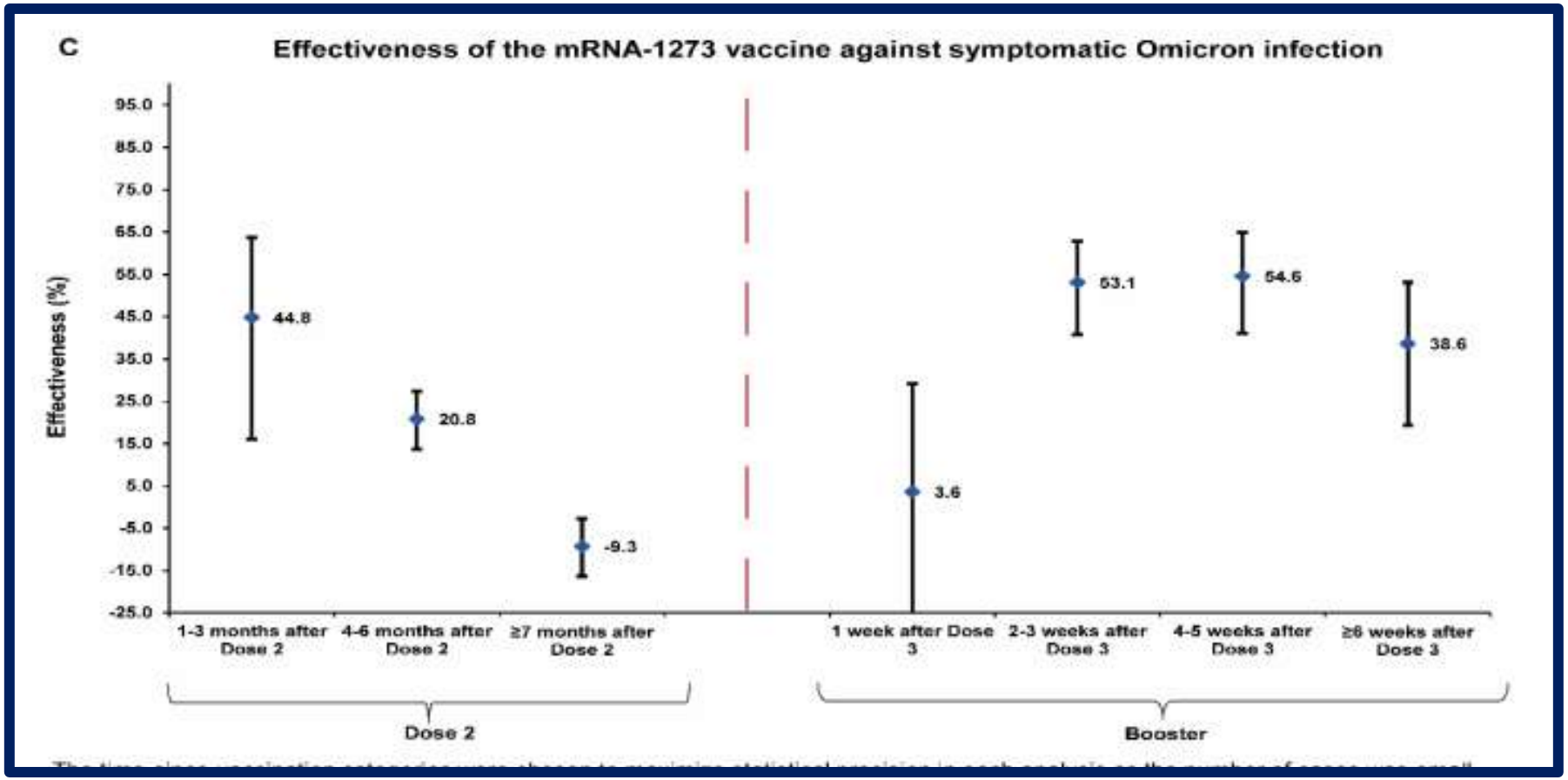
N4.	Reference (date)	Country	Design	Population	Dominant Variants	History of COVID	Vaccine Product	Outcome Measure	1st Dose VE % (95%CI)	Days post 1st dose‡	2nd Dose VE % (95% CI)	Days post 2nd dose	Max Duration of follow up after fully vaccinated
189	Filon et al* (February 15, 2022)	Italy	Retrospective cohort	4251 HCWs	Non-VOC and Alpha††	Excluded	BNT162b2	Documented infection(March)	—	—	95(92-98)	14+	~16 weeks
								Documented infection(April)			95(92-98)		
								Documented infection(May)			80(70-84)		
188	Gazit et al* (February 15, 2022)	Israel	Retrospective cohort	107,413 members	Alpha and Delta^	Included	BNT162b2	Documented infection	—	—	82(80-85)	14+	~40 weeks
								Symptomatic infection			76(71-80)		
181	Butt et al* (February 9, 2022)	USA	Test-negative case control	4,229 cases and controls on haemodialysis	Delta^	Excluded	BNT162b2	Documented infection	60.6 (25.5-79.2)	14+	68.9 (61.9-74.7)	14+	~31 weeks
							mRNA-1273		37.2 (27.1-69.0)		66.7 (58.9-73.0)		



Duration of protection of BNT162b2 and mRNA-1273 COVID-19 vaccines against symptomatic SARS-CoV-2 Omicron infection in Qatar

Hiam Chemaitelly, PhD[1,2,3], Houssein H. Ayoub, PhD[4], Sawsan AlMukdad, MSc[1,2], Patrick

133,417
Test-Negatif Vaka Kontrol



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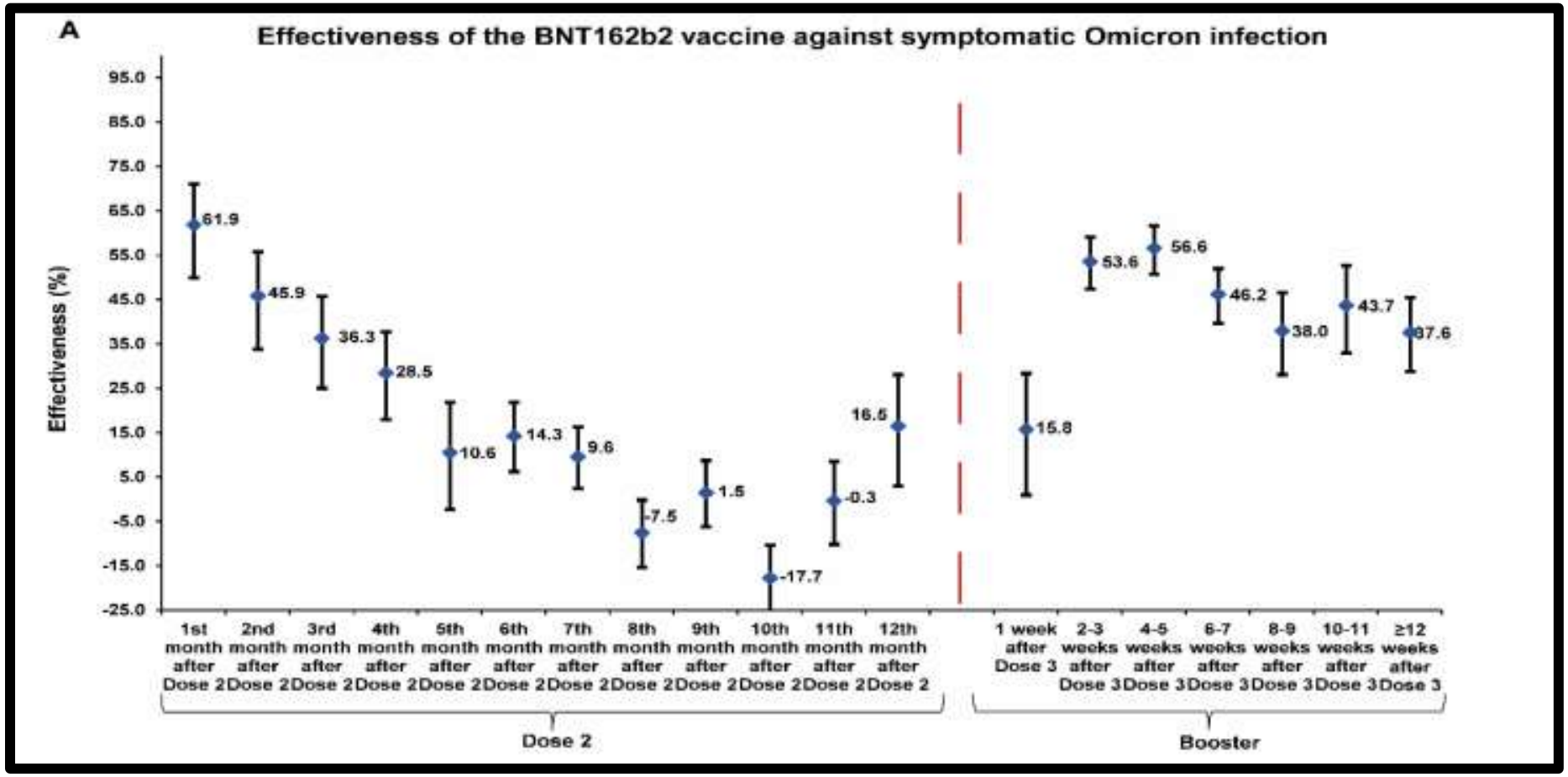

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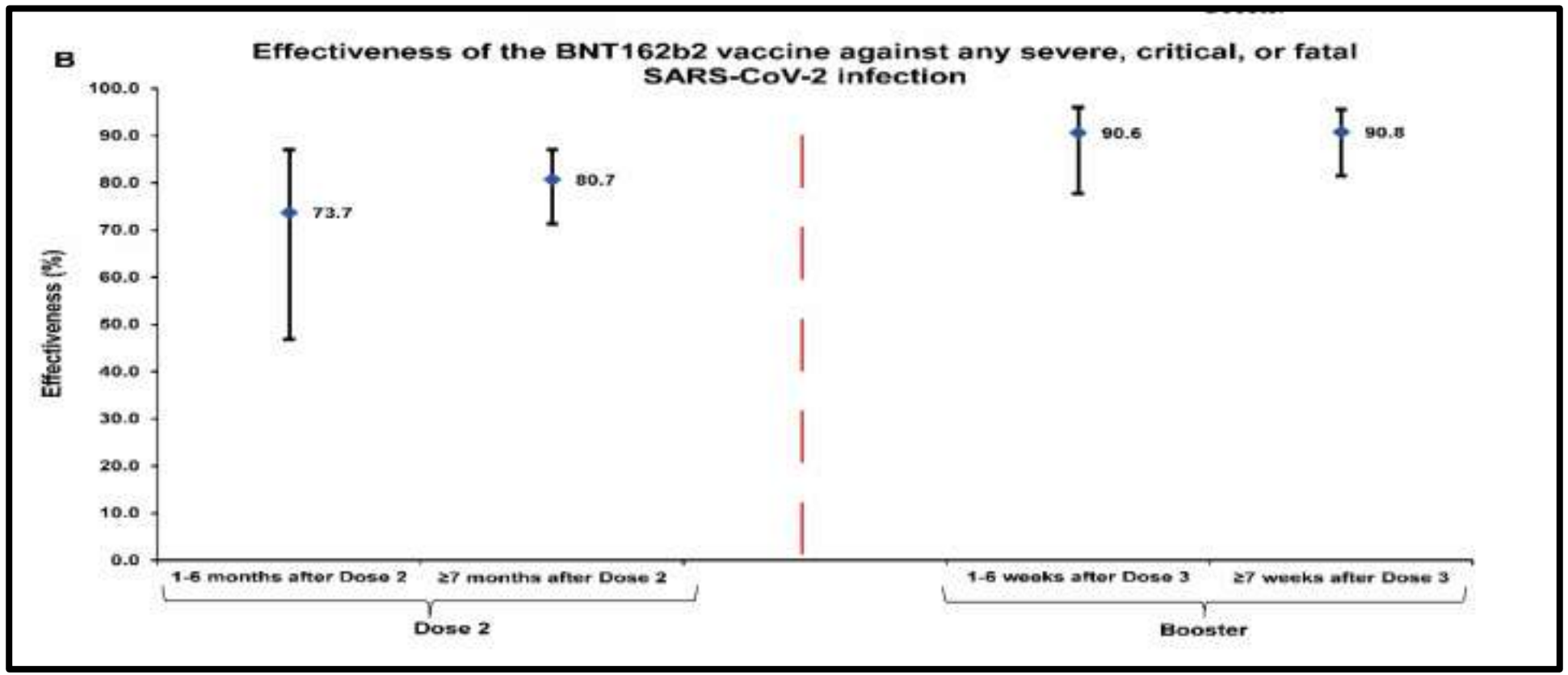
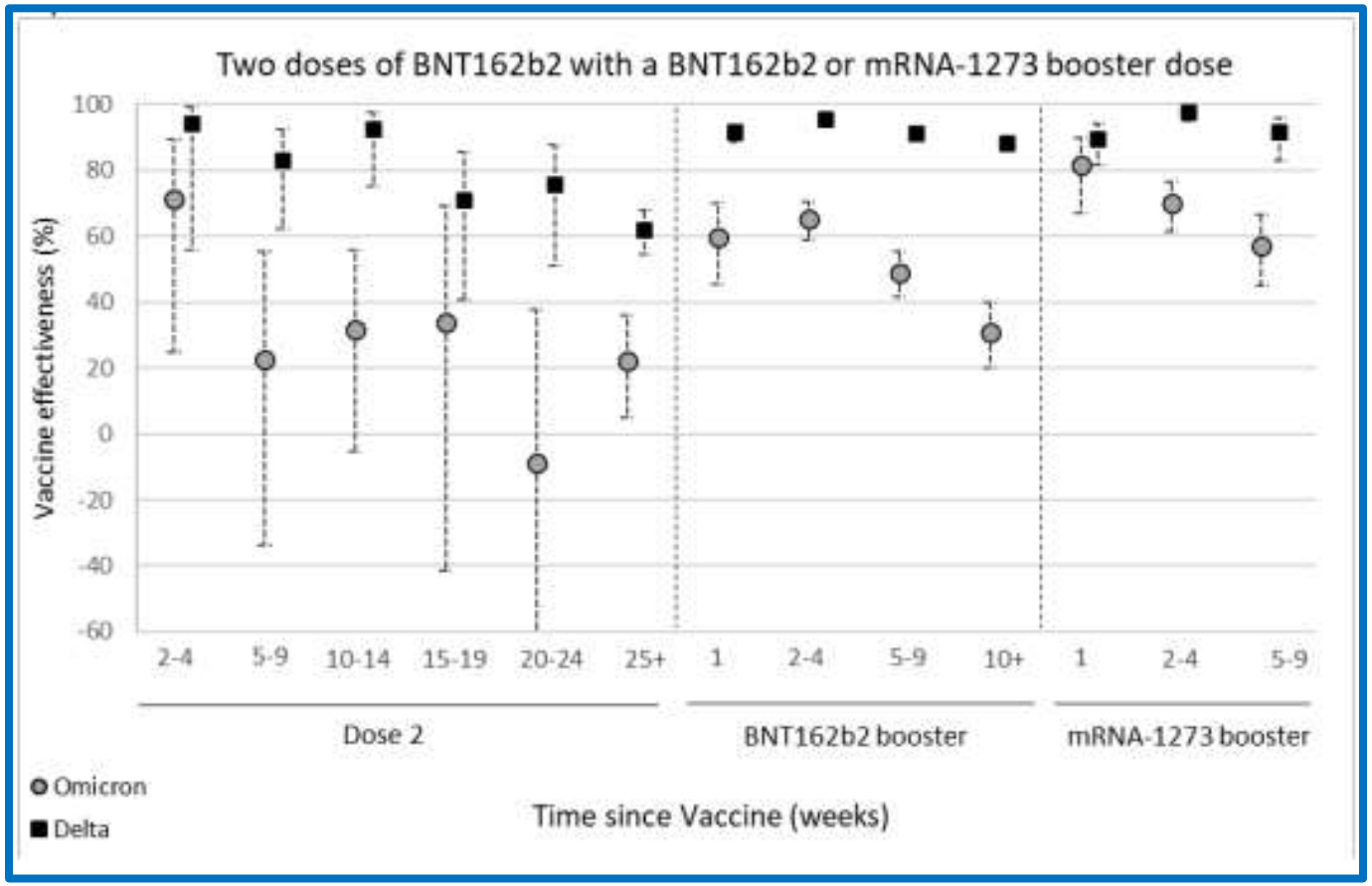


mRNA Aşı Etkililiği (semptomatik hastalık) >65 yaş - İngiltere



https://www.gov.uk/guidance/monitoring-reports-of-the-effectiveness-of-covid-19-vaccination

mRNA Aşı Etkinliği (3 doz sonrası) >65 yaş - İngiltere

Table 1. Vaccine effectiveness against hospitalisation for Omicron (all vaccine brands combined). OR = odds ratio, HR = hazard ratio, VE = vaccine effectiveness, (CI=Confidence interval).

Interval after dose	OR against symptomatic disease (95% CI)	HR against hospitalisation (95% CI)	VE against hospitalisation (95% CI)
2 to 9 weeks	0.51 (0.43-0.6)	0.11 (0.06-0.21)	94% (89-97)
10+ weeks	0.72 (0.61-0.85)	0.15 (0.08-0.27)	89% (80-95)

https://www.gov.uk/guidance/monitoring-reports-of-the-effectiveness-of-covid-19-vaccination

Omicron

- Semptomatik infeksiyona karşı etkililiğinde azalma
- Hastaneye yatışı engelleme etkilliği diğer varyantlara göre azalma
  - Booster alanlarda etkililik daha yüksek
- 2 doz BNT162b (Güney Amerika)
  - Genel (herhangi infeksiyon sonucu) etkililik %33
  - Hastaneye katışı önleme **etkililiği %70**
  - Delta hakim dönemde %93
    - *N Engl J Med. 2022;386(5):494*
- *Omicron / Delta 12 000 infekte birey (3 doz aşılı; USA)*
  - *İnfeksiyon riskinde azalma (OR 0.33 / 0.065)*
    - *MMWR Morb Mortal Wkly Rep. 2022;71(4):139.*

mRNA Aşı Etkinliği – Hastaneye Yatış (Delta)

Ferdinands JM. MMWR Morb Mortal Wkly Rep 2022;71:255–263. DOI: http://dx.doi.org/10.15585/mmwr.mm7107e2

Characteristic	Total	SARS-CoV-2 positive test result no. (%)	VE fully adjusted % (95% CI)*	Waning trend p value††
Delta-predominant period				
Unvaccinated (Ref)	**36,214**	14,445 (40)	—	—
Any mRNA vaccine, 2 doses	**38,707**	3,315 (9)	85 (84–85)	<0.001
<2 mos	**1,574**	49 (3)	94 (92–96)	
2–3 mos	**2,790**	154 (6)	91 (89–92)	
4 mos	**3,129**	192 (6)	90 (89–92)	
≥5 mos	**31,214**	2,920 (9)	82 (82–83)	
Any mRNA vaccine, 3 doses	**8,124**	195 (2)	95 (95–96)	<0.001
<2 mos	**6,071**	118 (2)	96 (95–97)	
2–3 mos	**2,030**	74 (4)	93 (91–95)	
≥4 mos	**23**	3 (13)	76 (14–93)	

93,408 hastaneye yatış
Ağustos 2021 – Ocak 2022
ABD

mRNA Aşı Etkinliği – Hastaneye Yatış (omicron)

Ferdinands JM. MMWR Morb Mortal Wkly Rep 2022;71:255–263. DOI: http://dx.doi.org/10.15585/mmwr.mm7107e2

Characteristic	Total	SARS-CoV-2 positive test result no. (%)	VE fully adjusted % (95% CI)*	Waning trend p value††
Omicron-predominant period				
Unvaccinated (Ref)	**3,911**	1,890 (48)	—	—
Any mRNA vaccine, 2 doses	**3,619**	979 (27)	55 (50–60)	0.01
<2 mos	**88**	22 (25)	71 (51–83)	
2–3 mos	**294**	69 (23)	65 (53–74)	
4 mos	**150**	42 (28)	58 (38–71)	
≥5 mos	**3,087**	846 (27)	54 (48–59)	
Any mRNA vaccine, 3 doses	**2,833**	276 (10)	88 (86–90)	<0.001
<2 mos	**1,261**	103 (8)	91 (88–93)	
2–3 mos	**1,383**	137 (10)	88 (85–90)	
≥4 mos	**189**	36 (19)	78 (67–85)	

93,408 hastaneye yatış
Ağustos 2021 – Ocak 2022
ABD

mRNA aşı etkinliği Omicron (B.1.1.529)

Ferdinands JM. MMWR Morb Mortal Wkly Rep 2022;71:255–263. DOI: http://dx.doi.org/10.15585/mmwr.mm7107e2

3. DOZ AŞI	Hastane Başvurusu	Hastaneye Yatış
2 ay	%87	%91
4 ay	%66	%78

Booster Doz Gerekli mi?

- 10 000 primer aşılı randomizasyon (USA)
  - BNT162b2 Booster Semptomatik infeksiyona etkinliği %95
  - 2 şiddetli infeksiyon (plasebo)
    - *Perez JL, Efficacy and safety of BNT162b2 booster - C4591031 2 month interim analysis.*
- 4 milyon (>16 yaş) iki doz aşılılarda (İsrail)
  - **Booster doz alanlarda 10 kat düşük infeksiyon hızı**
    - *N Engl J Med. 2021;385(26):2421*
- 3. dozu son 4 ay / 2 ay içerisinde alanlar
  - Omicron varyantına karşı hastaneye yatışı önlemede etkililiği % 78 / 91
    - *MMWR Morb Mortal Wkly Rep. 2022;*

3 doz aşı sonrası Breakthrough infeksiyon

MMWR Morb Mortal Wkly Rep. 2022;71(1):19.

- > 1 milyon aşılı /USA
- **Şiddetli hastalık :** 1,5 / 10,000
- **Mortalite :** 0,3 / 10,000
- **Risk Faktör:** ileri yaş ve çoklu komorbidite
- Aşılılarda - Aşısızlara göre
  - **Semptomlar** daha hafif ve az, süre kısa, komplikasyon az

İmmün süpresyon / tedavi ve aşı

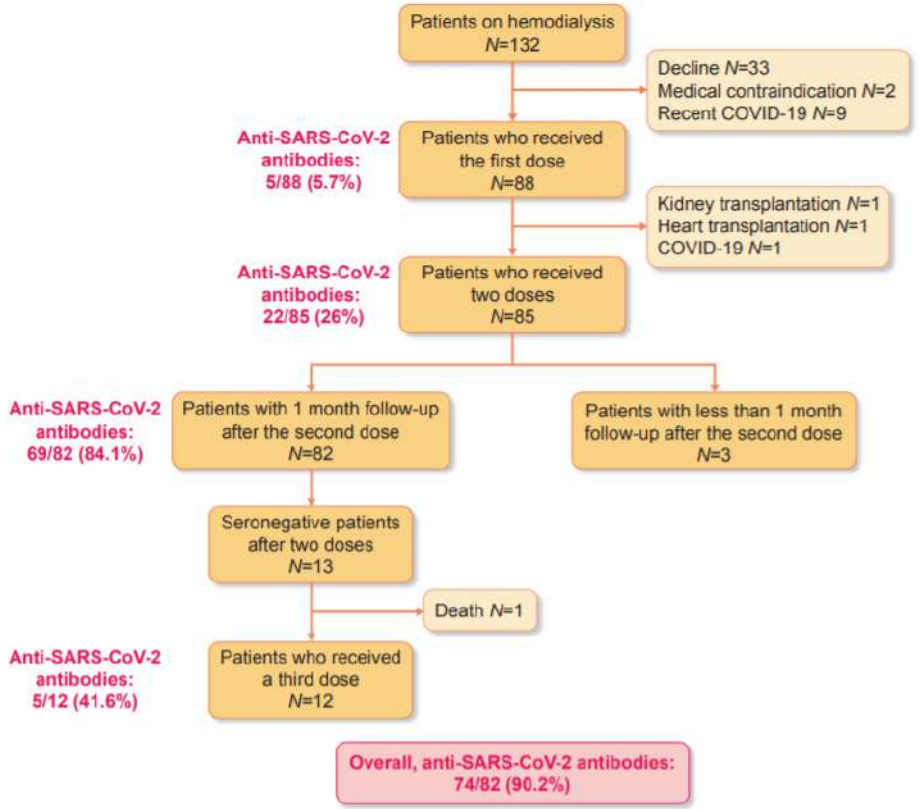
- Solid-hematolojik malignite
- SOT ve imm. süp. Tedavi
- CAR-T-cell tedavisi, HSST (transplantasyondan 2 yıl sonrasına kadar veya immün süpresif tedavi süresince)
- Primer immün yetmezlik
- CD4<200
- Diğer immün süpresif tedaviler
  - Yüksek doz KS (≥20 mg prednizon…)
  - Alkilleyici ajanlar, antimetabolitler, tranplantla ilişkili ilaçlar, Biyolojik ajanlar (Rituximab, TNF blokörleri...)

mRNA Aşı – Renal Yetmezlik

Table 1. Patients' characteristics at vaccination and comparison between patients who converted and those who did not one month after the second dose

Variables	All population *N*=112	Patients who seroconverted *N=88*	Patients who didn't seroconvert *N=11*	*P*-value
Age (years)	64±14	64±14	70±12	0.12
Gender M/F	77/35	56/30	9/2	0.33
Hemodialysis/Peritoneal dialysis	88/24	69/17	8/3	0.69
Time on dialysis (months)	39±40	37±36	31±49	0.61
History of kidney transplantation (Y/N)*	19/93	13/73	4/7	0.1
Non-Kidney-transplantation (Y/N)**	5/107	1/85	4/7	0.0004
Diabetes mellitus	33%	37%	36%	0.99
Immunosuppressive therapy (Y/N)	20/92	10/76	7/4	0.0003
Calcineurin inhibitors (Y/N)	5/107	1/85	4/7	0.004
mTOR inhibitors (Y/N)	3/109	1/85	2/9	0.03
Mycophenolic acid (Y/N)	4/108	1/85	2/9	0.03
Steroid (Y/N)***	19/93	10/76	6/5	0.002
Hemoglobin level at baseline (g/dL)	11.6±1.8	11.6±1.8	11.6±1.8	0.96
Leucocyte count at baseline (/mm^3)	6735±2121	6707±2060	6947±2630	0.72
Neutrophils at baseline (/mm^3)	4761±1826	4462±1792	4755±2173	0.99
Lymphocyte count at baseline (/mm^3)	1021±660	993±490	1249±664	0.30
CD4-positive cell count (/mm^3)	386±228	394±227	308±237	0.34
CD8-positive cell count (/mm^3)	243±164	237±153	308±263	0.31
CD19-positive count (/mm^3)	104±85	103±160	80±84	0.45

Abbreviations: M, male; F, female; Y, yes; N, no; mTOR, mammalian target of rapamycin.



Longlune N, at al. High immunogenicity of a messenger RNA based vaccine against SARS-CoV-2 in chronic dialysis patients. Nephrol Dial Transplant. 2021 May 31:

mRNA Aşı – Renal Yetmezlik / 3 doz aşı Serokonversiyon oranını artırmakta

Table 1. Patients' characteristics at vaccination and comparison between patients who converted and those who did not one month after the second dose

Variables	All population	Patients who seroconverted	Patients who didn't seroconvert	*P*-value
Hemoglobin level at baseline (g/dL)	11.6±1.8	11.6±1.8	11.6±1.8	0.96
Leucocyte count at baseline (/mm³)	6735±2121	6707±2060	6947±2630	0.72
Neutrophils at baseline (/mm³)	4761±1826	4462±1792	4755±2173	0.99
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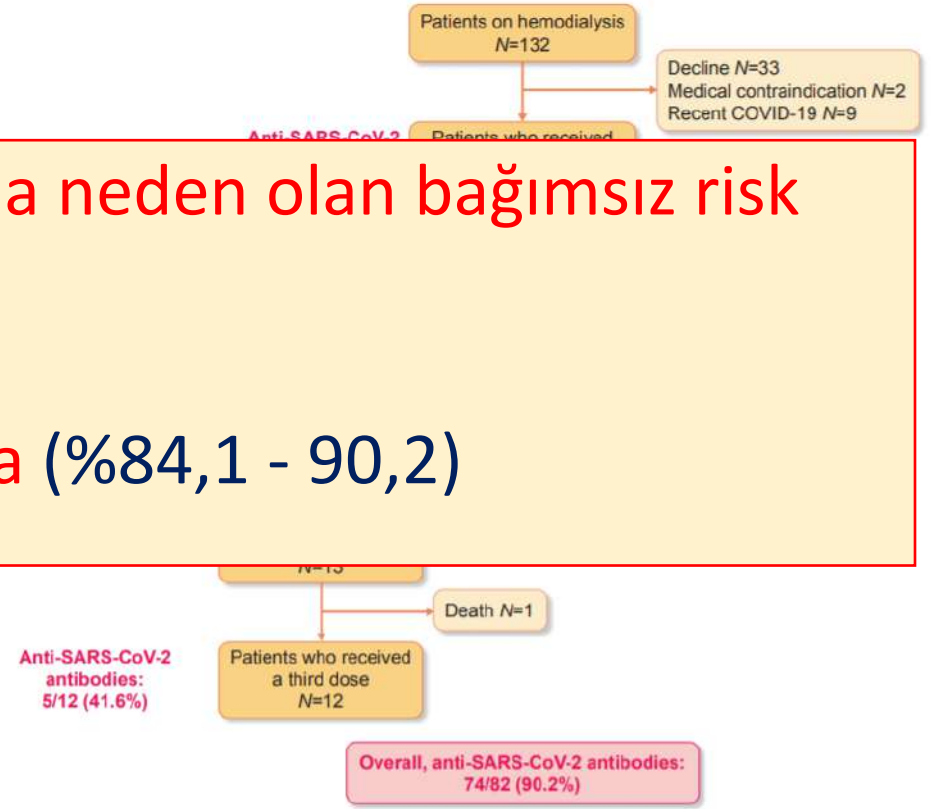


İmmünosüpresif tedavi aşı yanıtsızlığına neden olan bağımsız risk faktörü

3. Doz aşı yanıtını artırmakta (%84,1 - 90,2)

Longlune N, at al. High immunogenicity of a messenger RNA based vaccine against SARS-CoV-2 in chronic dialysis patients. Nephrol Dial Transplant. 2021 May 31:

İmmün süpresif tedavi ve aşı

- Primer şema: 3 doz
- Son doz 5 ay sonra booster verilebilir (1)
- Rituximab vb. immün süpresif tedavi alanlar (2)
  - Sonraki immün süpresif ilaç dozundan 4 hafta önce aşıya başlanması
  - Primer aşı şeması tamamlandıktan 2-4 hafta sonra immün süpresif ted. Başlanması
  - Hastalık aktivitesi imkan tanıması durumunda

1-Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html (Accessed on November 03, 2021).

2-American College of Rheumatology. COVID-19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases.

İmmün süpresif tedavi ve aşı

- Hematopoetik Kök Hücre Transplant ve CAR-T tedavisi
- Transplant ve CAR-T öncesi aşılanlar
  - Tedaviden en 3 ay sonra tekrar primer aşı şeması

Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html (Accessed on November 03, 2021).

İmmün süpresif tedavi ve aşı

- Semptomatik COVID19 etkilliği (>1 milyon kişi)
  - Genel popülasyonda %94
  - İmmünkopromise %75
    - *Chodick G. Clin Infect Dis. 2021; İsrail*
- Aşılı; COVID-19 nedenli Hastaneye Yatış (152 hasta; İsrail)
  - Mortalite %25
  - %40 immünkompromise hasta
    - *Brosh-Nissimov T. Clin Microbiol Infect. 2021;27(11):1652.*
- 658 SOT 2 doz mRNA aşı
  - %46 anti-spike veya anti-RBD Ab saptanamadı
    - *Boyarsky BJ. JAMA. 2021;325(21):2204.*

Ciddi yan etki

- PEG alerjisi varlığında kontrendike
- Şiddetli alerjik reaksiyon
  - 11 / 1milyon doz
  - %71'i ilk 15 dk ortaya çıktı
  - %81'inde öyküsünde alerji veya alerjik reaksiyon var
- İngiltere (Medicines and Healthcare products Regulatory Agency (MHRA)
  - Ciddi alerji öyküsü olanlar mRNA aşı yaptırmamalı

Ciddi yan etki

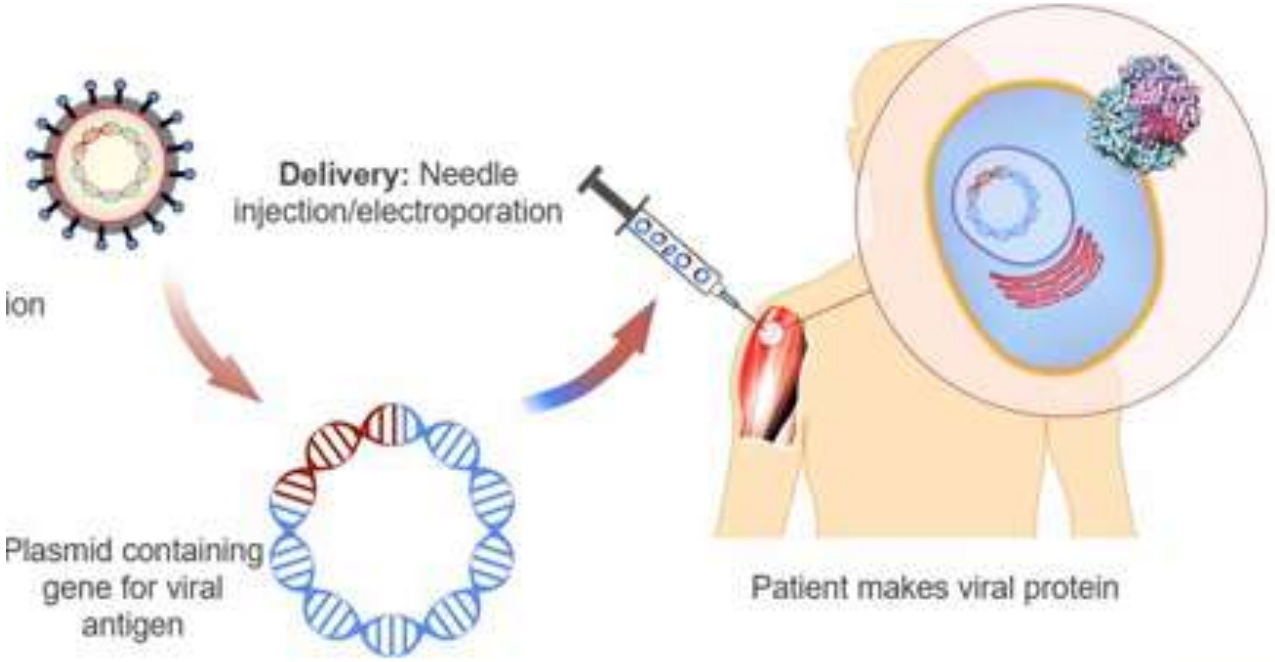
- The European Medicines Agency (EMA)
- Deri döküntüsü ve kaşıntı nadir 1 /100
- Ürtiker 1/1000
- Anjioödem 1 /1000
- Anafilaksi: 4.5/ 1 million doz
- Miyokardit-perikardit
  - İsrail 55 vaka / 1 milyon doz, %95 hafif şiddette
  - USA: 13 / 1milyon doz
  - 11/8,7 milyon doz 5-11 yaş
    - MMWR Morb Mortal Wkly Rep. 2021

Miyokardit

- 192 milyon mRNA aşılı; Aralık 2020 -Ağustos 2021,
- 1626 ışı ile ilişkili miyokardit
- Vakaların çoğu 2. dozdan sonra
- Ortalama yaş 21, %82 erkek
  - 12 - 16 yaş– 70,7 / 1 milyon doz BNT162b2
  - 16 - 17 yaş– 105,9 / 1 milyon doz BNT162b2
  - 18 - 24 yaş – 52.4 - 56.3 / 1 milyon doz BNT162b2 ve mRNA-1273, sırasıyla
    - *Oster ME. JAMA. 2022;327(4):331*.

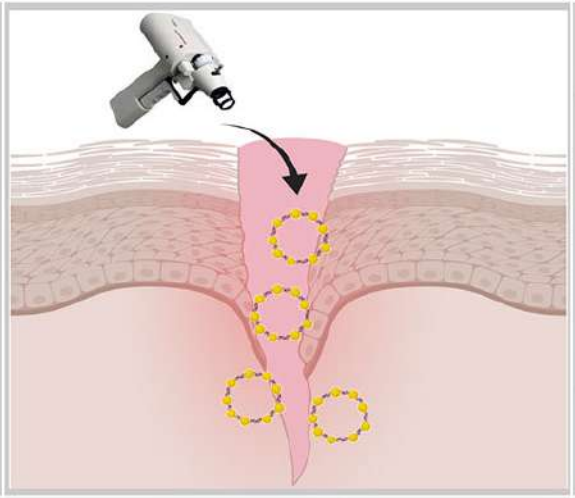
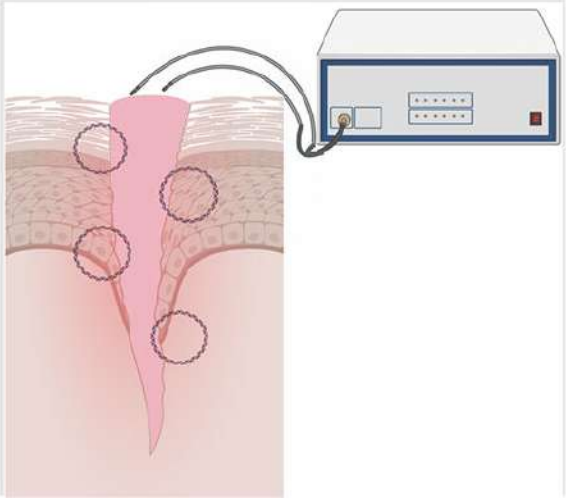
DNA Aşıları

- Sentetik DNA aşıları (1990s)
  - HIV, EBOLA, HPV, Zika
  - SARS-CoV-2
- Veteriner
  - Melonama – köpekler
  - WNV - Atlar
- Özellikleri
  - Büyük, polianyonik
  - Nükleazlara duyarlı
  - Hücre içine pasif girişi sınırlı

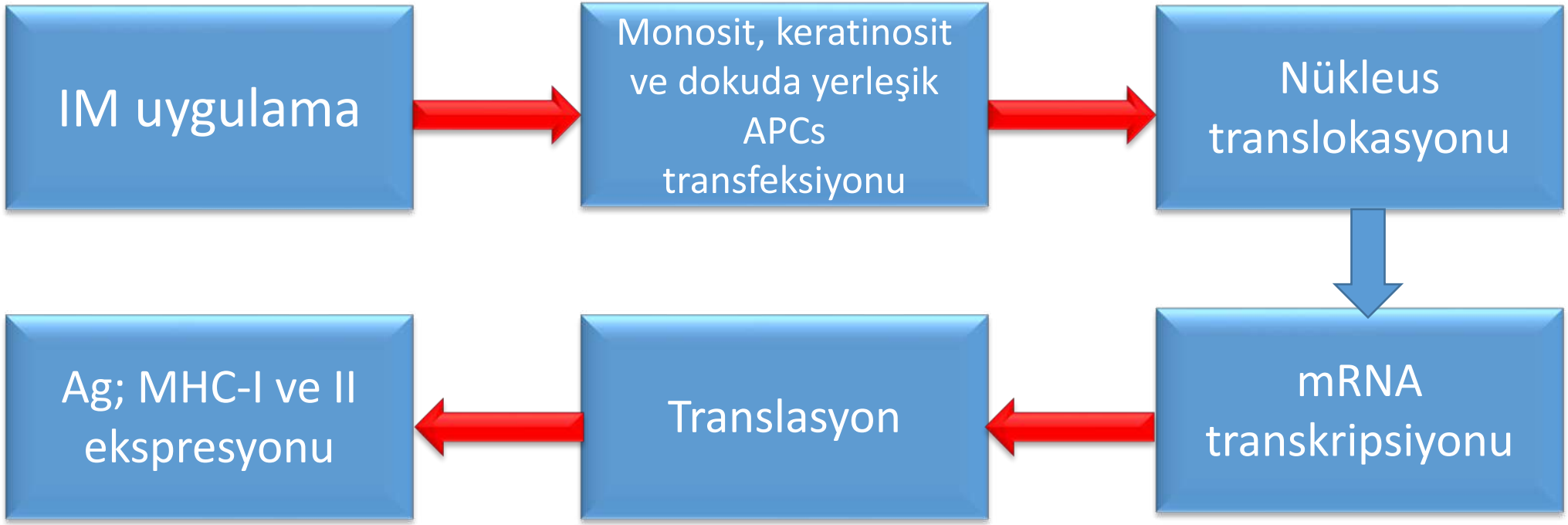


DNA aşıları

DNA vaccines

Method Name	Method Diagram	Description of Method	Results
Gene Gun		DNA plasmid is coated with gold particles and is taken up by cells via a blast of pressurized helium gas from a gene gun.	May increase humoral responses but is limited in allowable dosage
Electroporation		Plasmid is taken up by permeabilized skin followed by an electric current.	Maximizes DNA vaccine delivery efficiency. Currently in clinical trials

DNA aşıları


IM uygulama
Monosit, keratinosit ve dokuda yerleşik APCs transfeksiyonu
Nükleus translokasyonu
mRNA transkripsiyonu
Translasyon
Ag; MHC-I ve II ekspresyonu

DNA aşıları

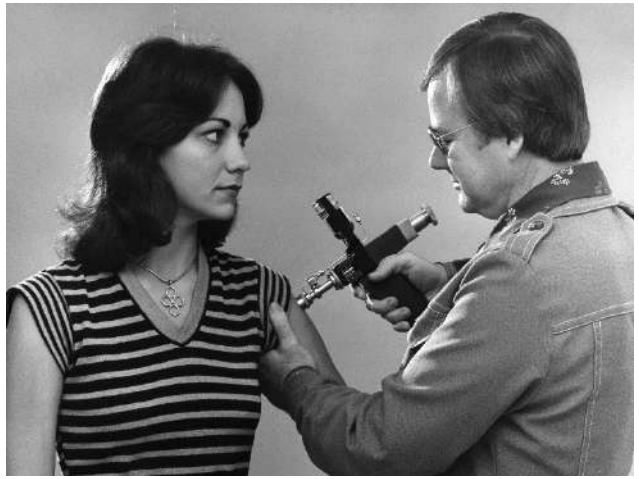
- **Avantajları**
  - Uzun süreli antijen ekspresyonu
  - Tfh yanıtı ve GC fenotoip uyarımı
  - Konvansiyonel yöntemlere göre hızı, ucuz, kolay
- **Dezavantaj**
  - Çekirdekte DNA’nın kalıcılığı - genomik DNA'ya (gDNA) entegrasyon olasılığı
    - FDA limitinin altında (<100 kopya plazmit/mg konakçı DNA)
  - Güçlü T ve B yanıtı için Prime + 2-3 doz booster gerekir

DNA aşıları


CORONAVIRUS
COVID-19
VACCINE
VACCINE
2019-nCoV
TH
ZyCov-D
World's first DNA vaccine

ZyCoV-D

- DNA plazmid tabanlı aşı
- Plazmid çoğaltılması - E. coli
- Cadila Healthcare / Hindistan
- Acil Kullanım izni
- İntradermal - jet enjektör
  - Transfeksiyon için
    - Hücre ve nüklear membranın aşılması gerekir
- Geleneksel enjektör ile düşük immonojenite



ZyCoV-D Farkı ?

- 3 doz, ID, The PharmaJet®
- 2-8 ^{o}C depolanabilir,
- Oda sıcaklığında (25 ^{o} C) 3 ay stabilite gösterir
  - Taşınma – depolanma avantajı
- Biyogüvenlik (BSL-1) gereksinimi minimal
- Kolay ve hızlı üretim
- Vektör tabanlı aşılardaki önceki immünite sorunu yok
- Olası mutant virüslere karşı aşının geliştirilmesi daha kolay

ZyCoV-D Faz-III

- Kasım 2020
- 12-99 yaş grubu 28 216 gönüllü
- Etkinlik
  - %66,6 semptomatik COVID-19
  - %100 orta-ağır hastalık
- 1 Haziran 2021 Hindistan Acil Kullanım Onayı

Mallapaty S. Nature. 2021;597(7875):161.

1. *"Zydus applies to the DCGI for EUA to launch ZyCoV-D, the world's first Plasmid DNA vaccine for COVID-19" (PDF). Cadila Healthcare (Press release). 1 July 2021. Retrieved 1 July 2021.*