COVID19 Aşıları: Daha Kaç Kere?

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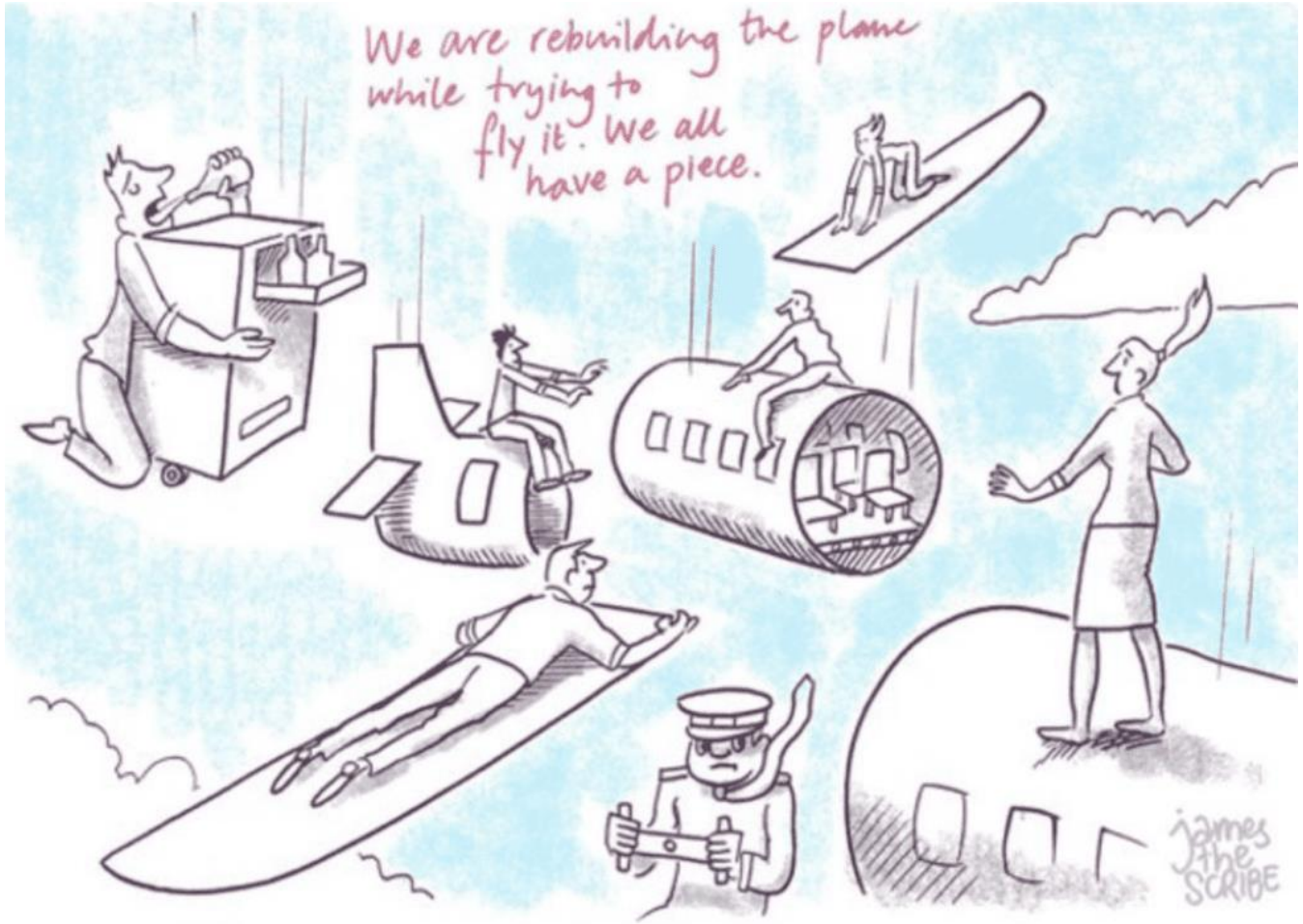
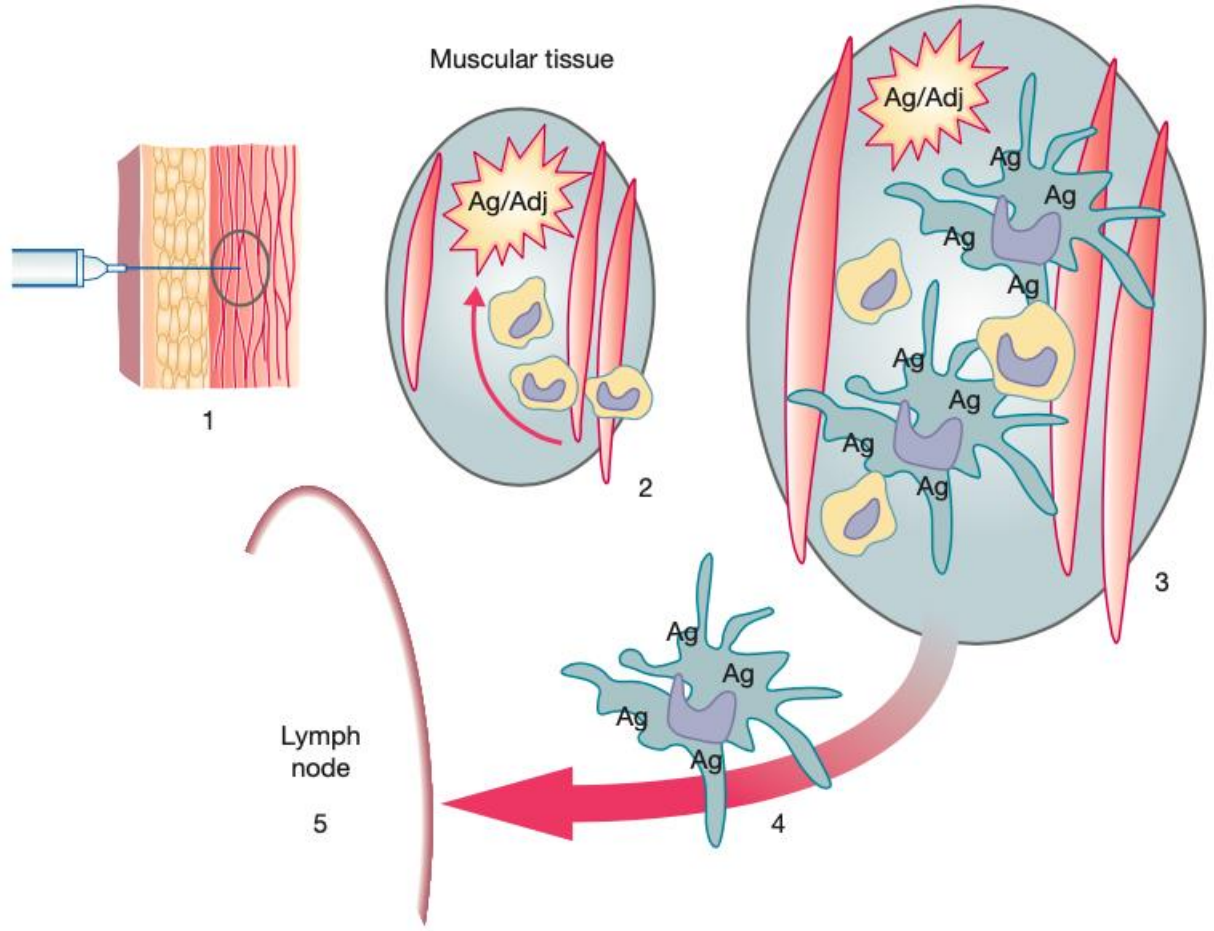
Building the airplane as we fly

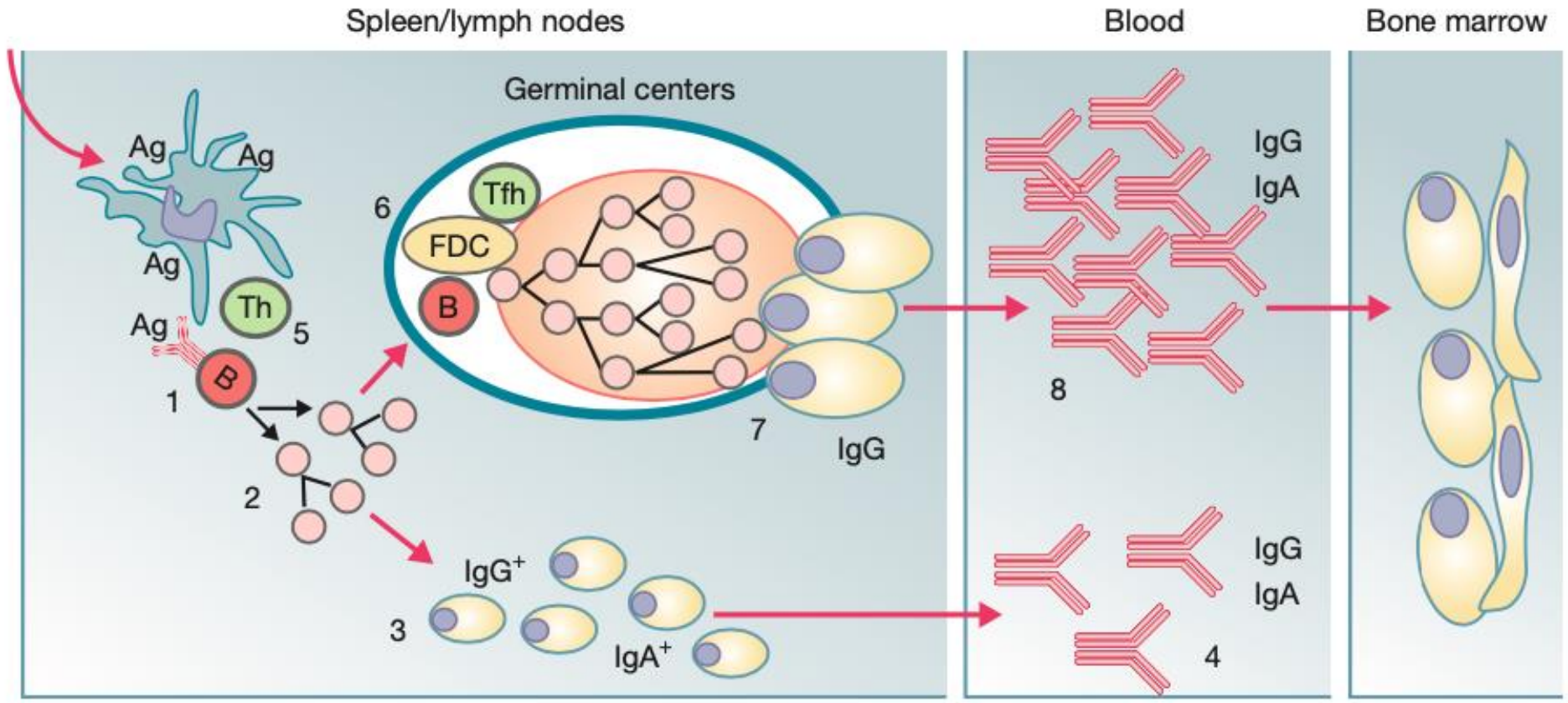


Aşı İmmünolojisi



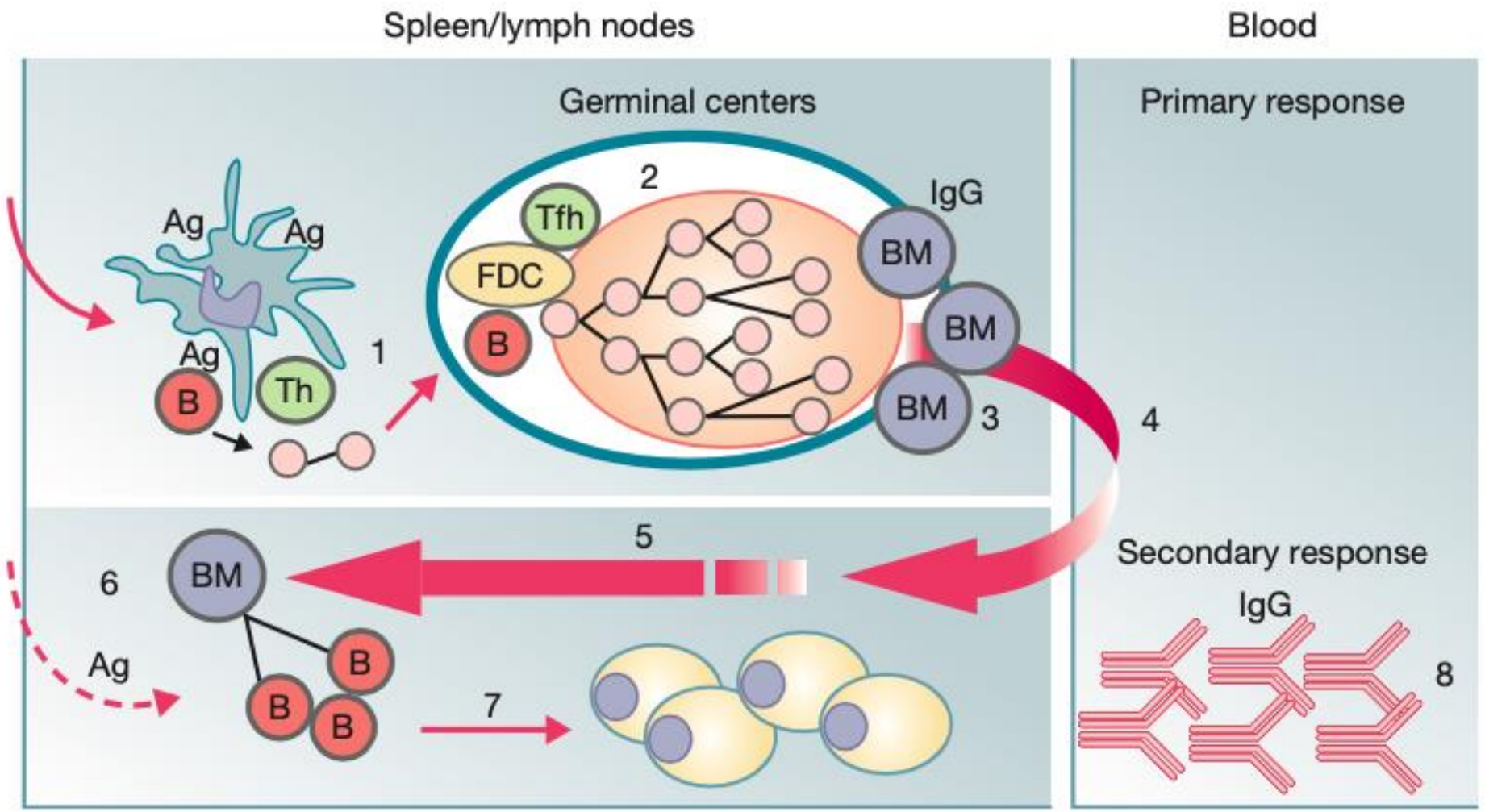
Siegrist CA *2017 Vaccine Immunology* Vaccines

Aşı İmmünolojisi II



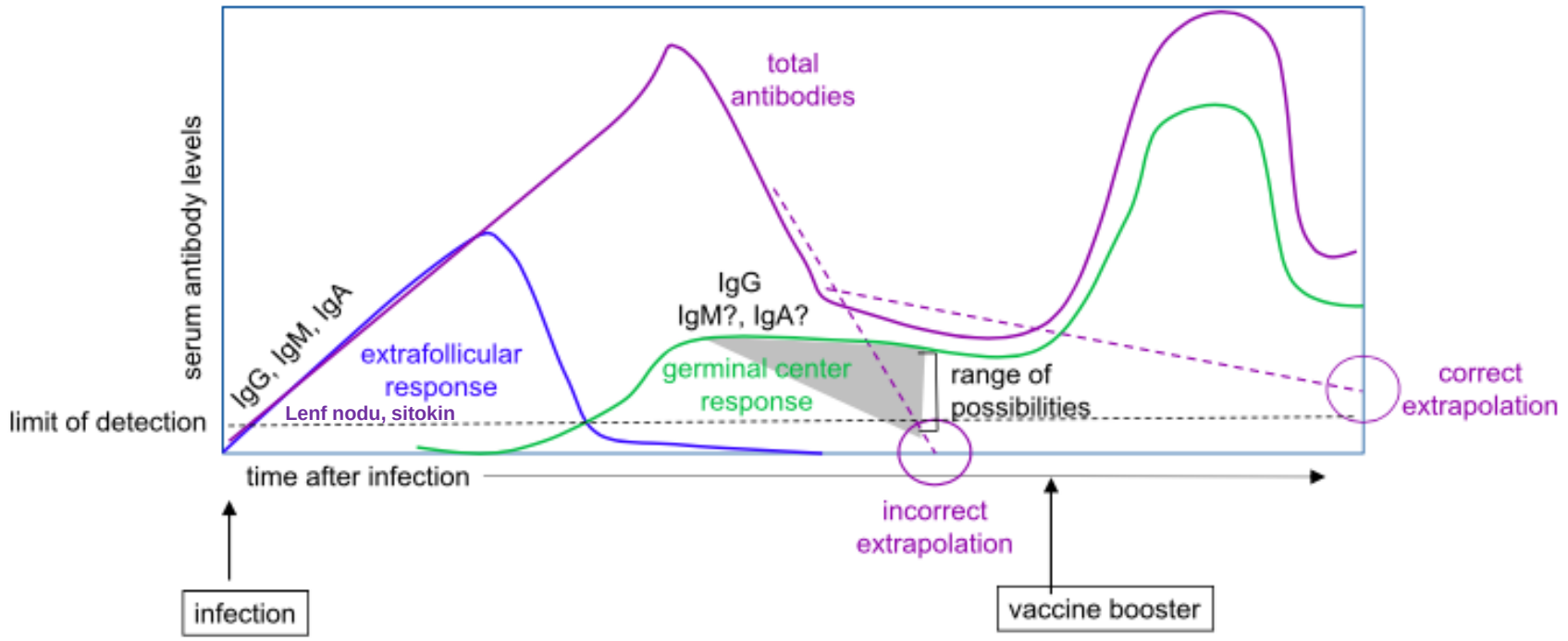
Siegrist CA *2017 Vaccine Immunology* Vaccines

Aşı İmmünolojisi III



Siegrist CA *2017 Vaccine Immunology* Vaccines

Viral Enfeksiyonlara Karşı Antikor Yanıtı

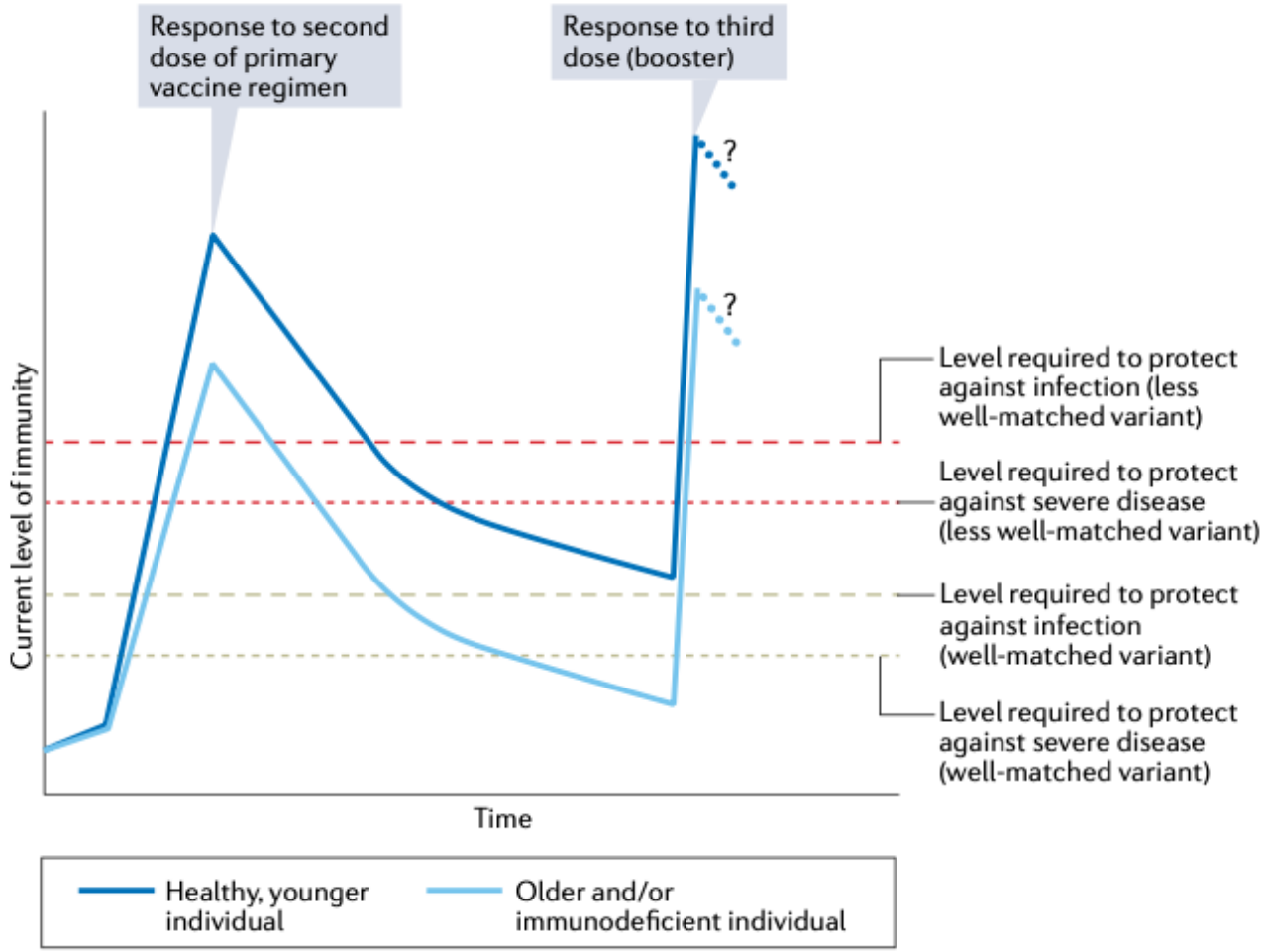


SARS CoV2, güçlü extrafoliküler yanıt uyarır

Hipermutasyon Affinite artışı

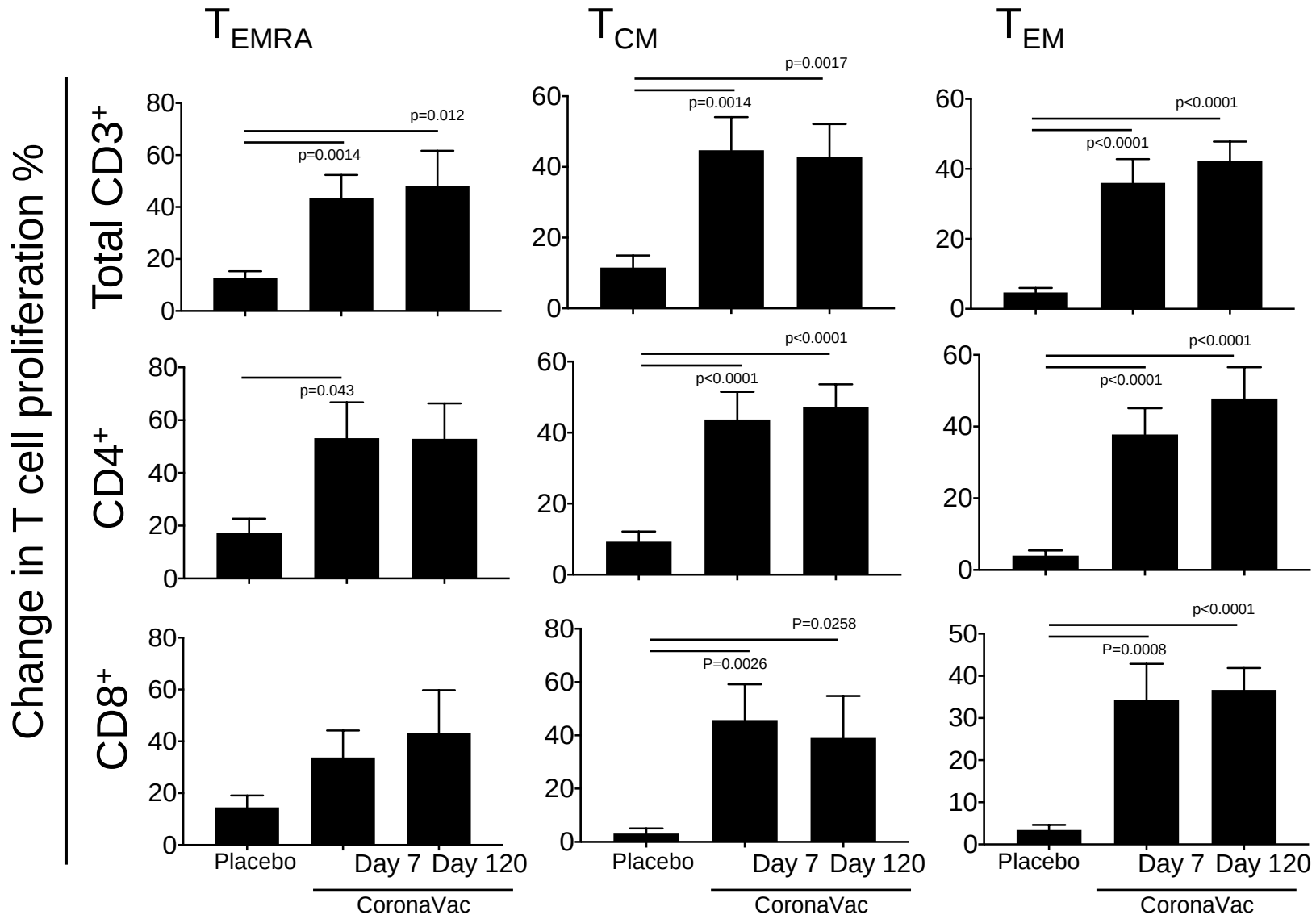
Baumgarth N etal 2020 *Antibody Responses to SARS-CoV-2: Let's Stick to Known Knowns* J Immunol

COVID19 Aşıları Sonrası Nötralizan Humoral Yanıt



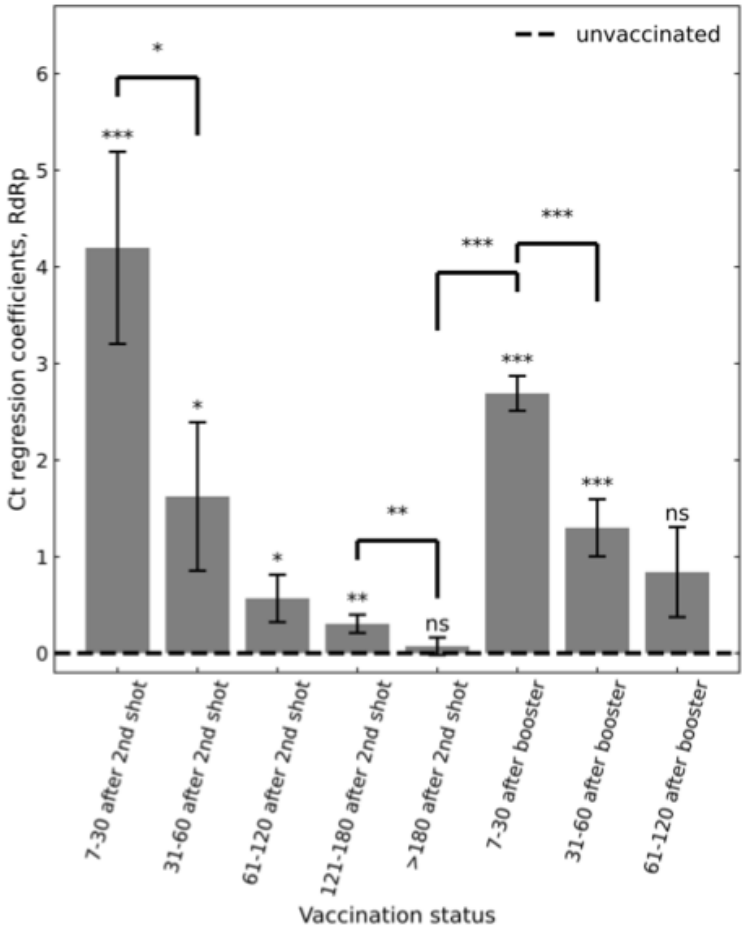
Lipstich M etal 2021 *SARS-CoV-2 breakthrough infections in vaccinated individuals: measurement, causes and impact* Nat Rev İmmunol
Altmann D etal 2022 *COVID-19 Vaccination: The Road Ahead* Science

Coronavac Türkiye: T hücre Verisi



Tavukçuoğlu E etal Manuscript in prep

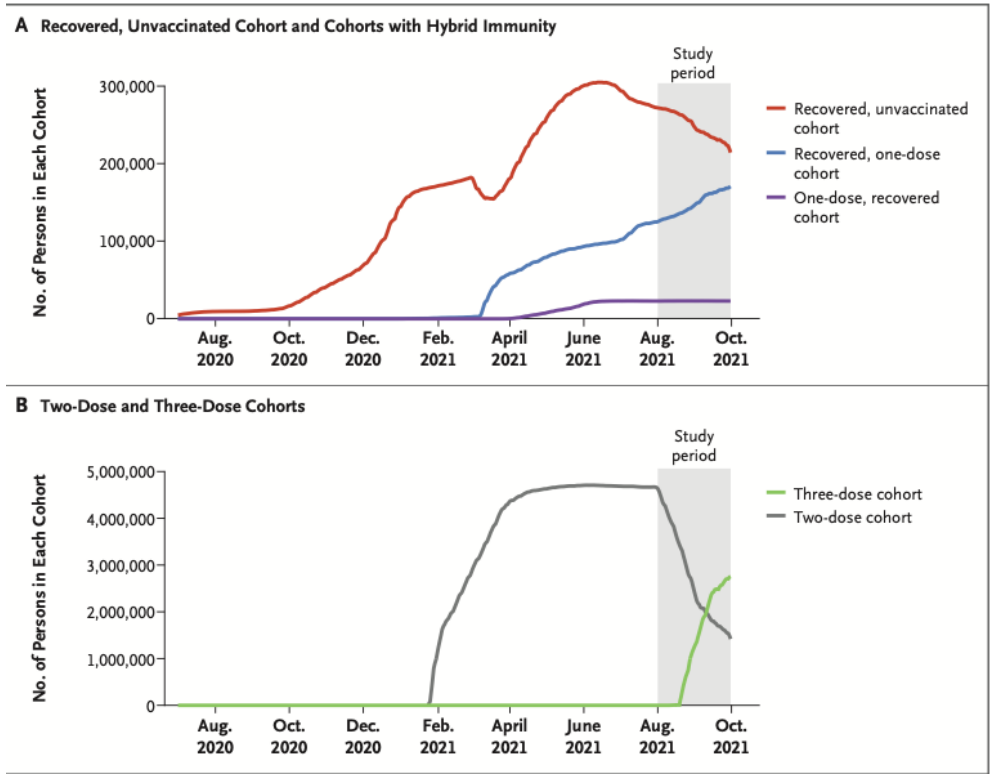
COVID19 Aşıları Sonrası Breakthrough Enfeksiyonlar: Cyclethreshold



Levine-Tiefenbrun M etal 2022 *Waning of SARS-CoV-2 booster viral-load reduction effectiveness* Nat Comm

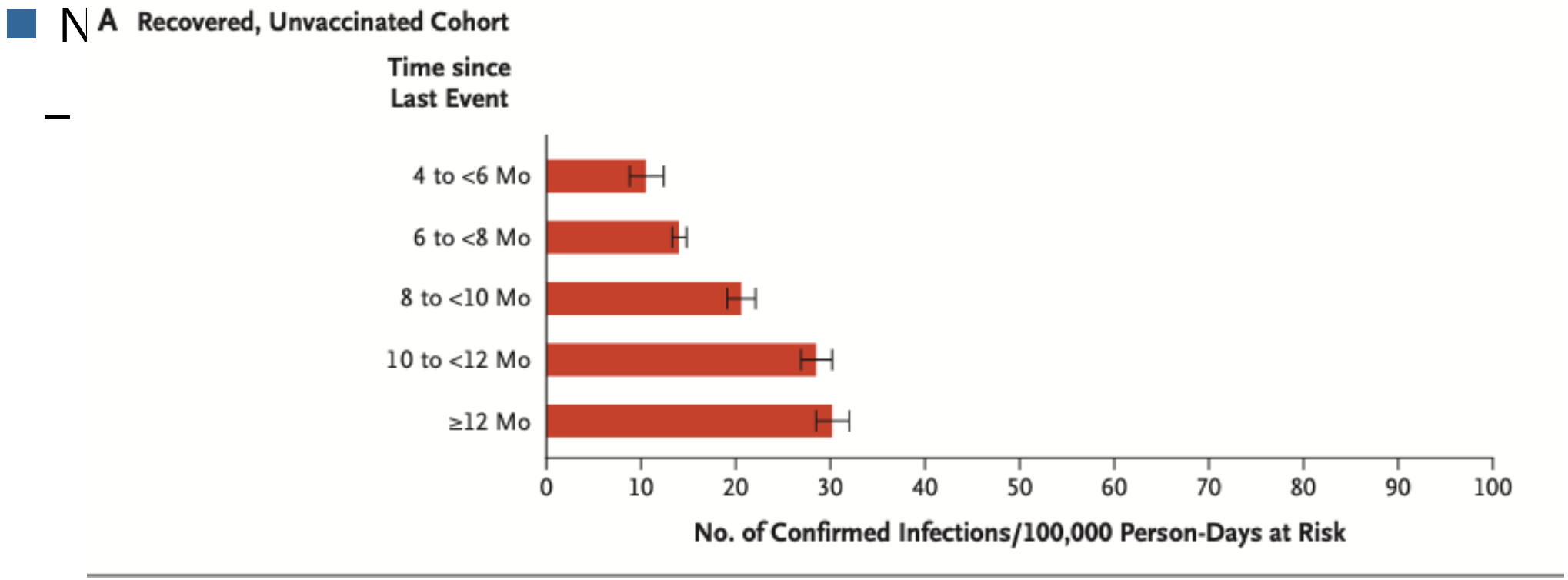
Reenfeksiyon İhtimali

- İsrail Sağlık Bakanlığı Veri Tabanı
- Delta salgını sırası
  - Ağustos – Eylül 2021



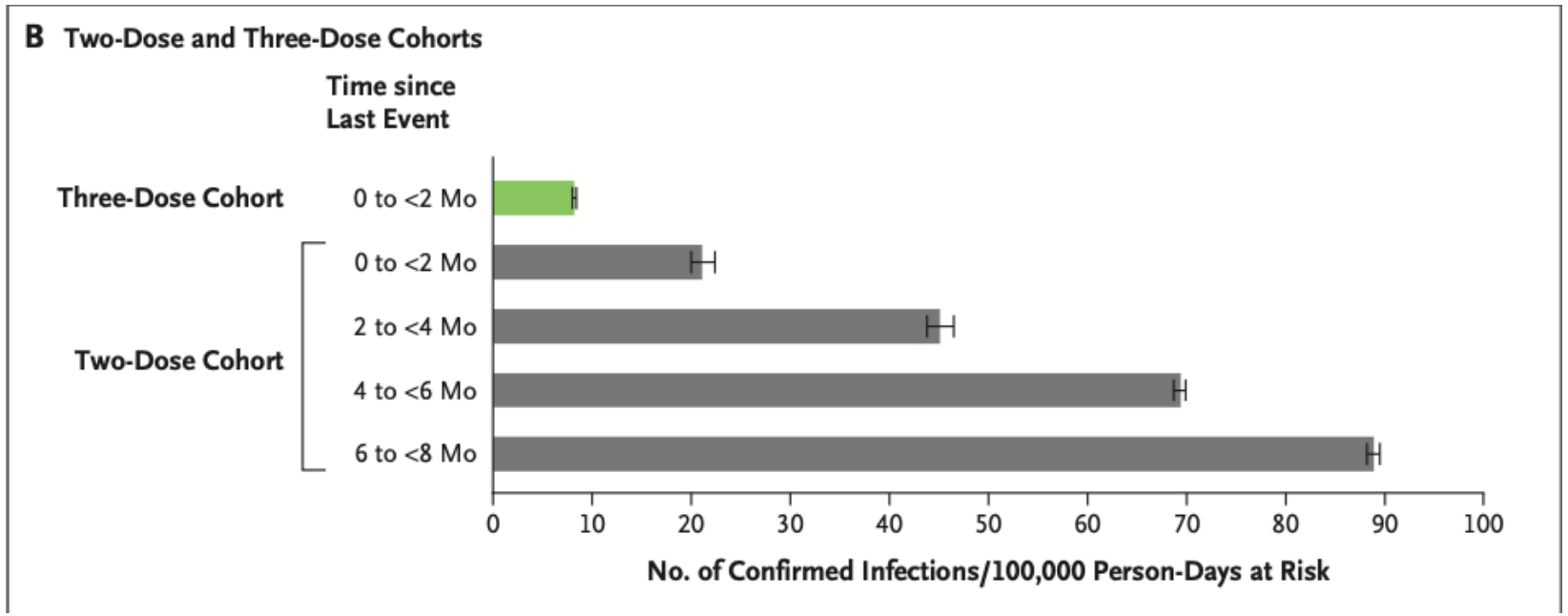
Goldberg Y etala 2022 *Protection and Waning of Natural and Hybrid Immunity to SARS-CoV-2* NEJM

Reenfeksiyon İhtimali



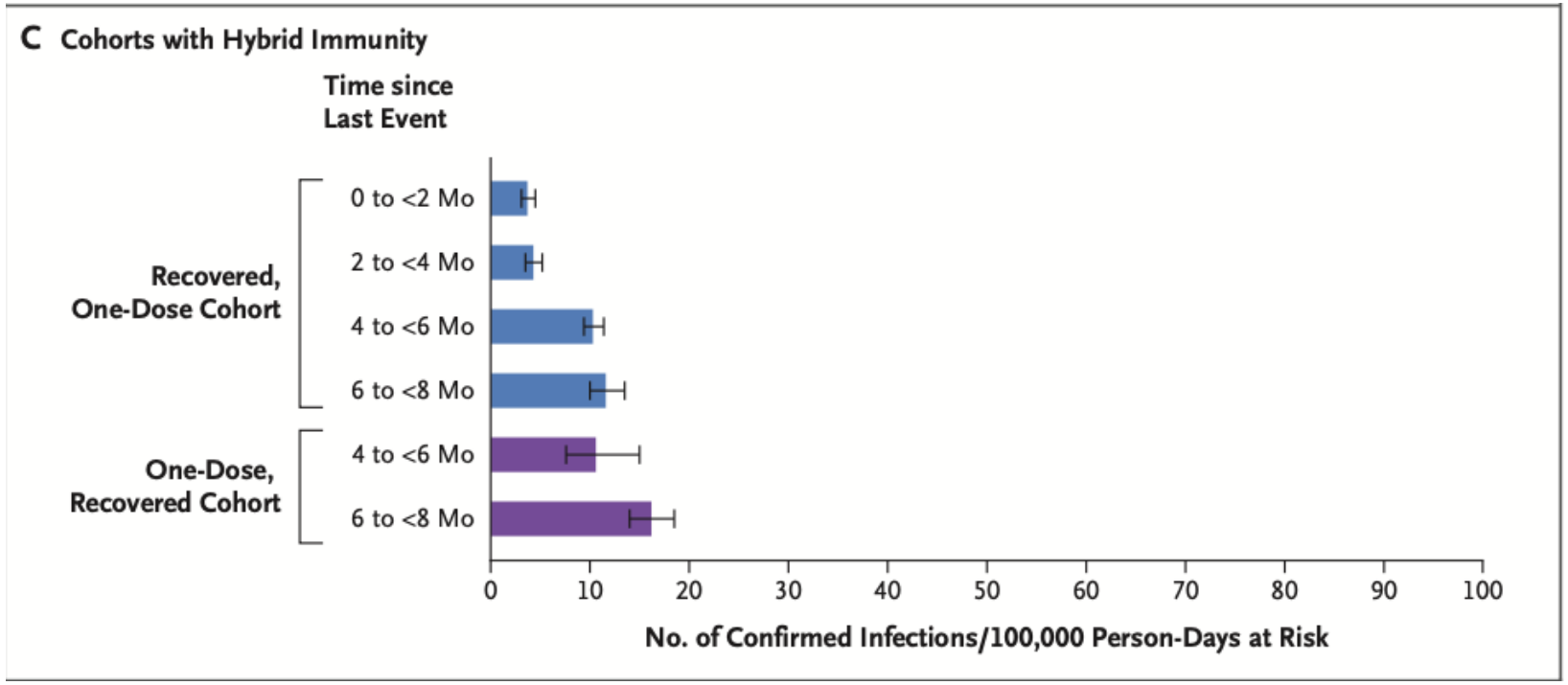
Goldberg Y etala 2022 *Protection and Waning of Natural and Hybrid Immunity to SARS-CoV-2* NEJM

Reenfeksiyon İhtimali: Aşı Sonrası



Goldberg Y etala 2022 *Protection and Waning of Natural and Hybrid Immunity to SARS-CoV-2* NEJM

Reenfeksiyon İhtimali: Hibrit İmmünite



Goldberg Y etala 2022 *Protection and Waning of Natural and Hybrid Immunity to SARS-CoV-2* NEJM

COVID19 Aşısı Ne zaman Maliyet Etkin?

Main Scenario	Health Outcomes		Direct Costs		Indirect Costs	
	Deaths	QALYs Lost	Health Care	Vaccination	Sickness Leave	Premature Death
Baseline without vaccination or imposed measures	211,415	1,538,105	407,011,036	-	6,417,051,139	433,671,346
Equal effectiveness on disease and transmission (90% effectiveness)	3994	31,604	9,302,328	1,168,014,610	183,562,183	8,806,634
Limited effectiveness on transmission (90% disease and 45% transmission effectiveness)	88,865	645,570	171,275,569	1,168,014,610	2,676,371,116	182,019,930

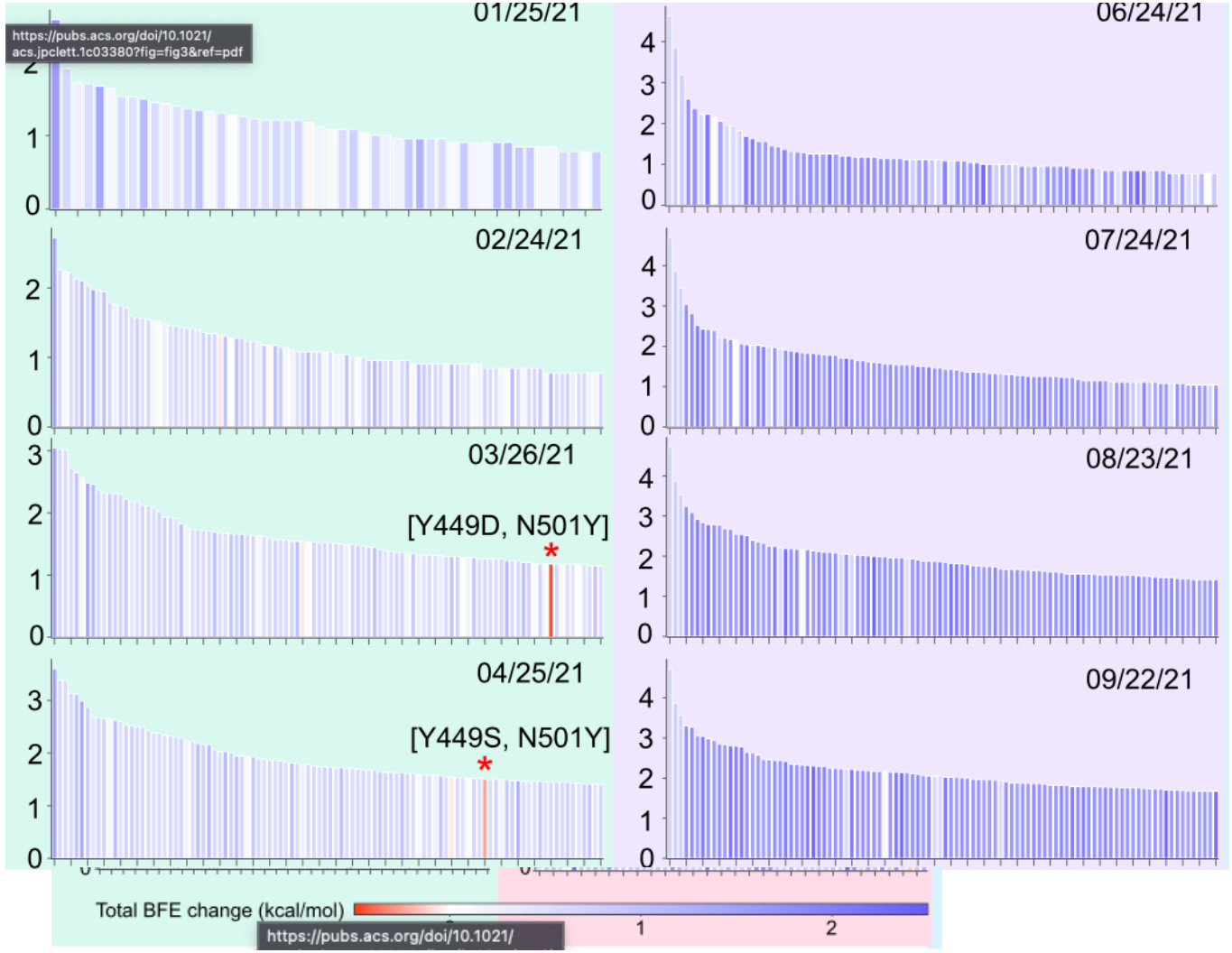
Hagens A etal 2021 *COVID-19 Vaccination Scenarios: A Cost-Effectiveness Analysis for Turkey* Vaccines

COVID19 Aşısı Ne zaman Maliyet Etkin?

Scenario	Incremental Health Outcomes		Incremental Direct Costs	Incremental Indirect Cost Savings	Total Incremental Cost Savings	ICERs	
	Lives Saved	QALYs Gained				Health Perspective	Societal Perspective
Equal effectiveness on transmission and disease (90%)	207,421	1,506,501	770,305,902	6,658,353,668	5,888,047,767	511	Cost saving
Limited effectiveness on transmission (90% on disease and 45% on transmission)	122,550	892,536	932,279,143	3,992,331,439	3,060,052,296	1045	Cost saving

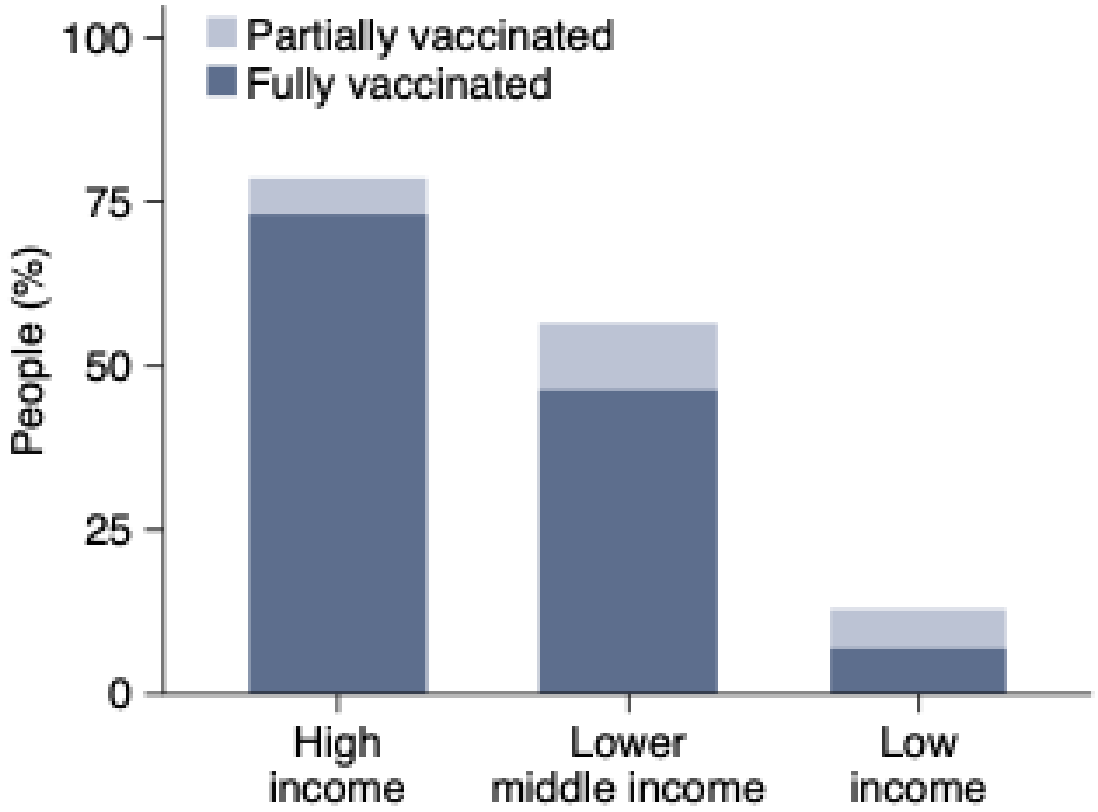
Hagens A etal 2021 *COVID-19 Vaccination Scenarios: A Cost-Effectiveness Analysis for Turkey* Vaccines

Aşı Sonrası Sorunlar: SARSCoV2 ve Mutasyonları



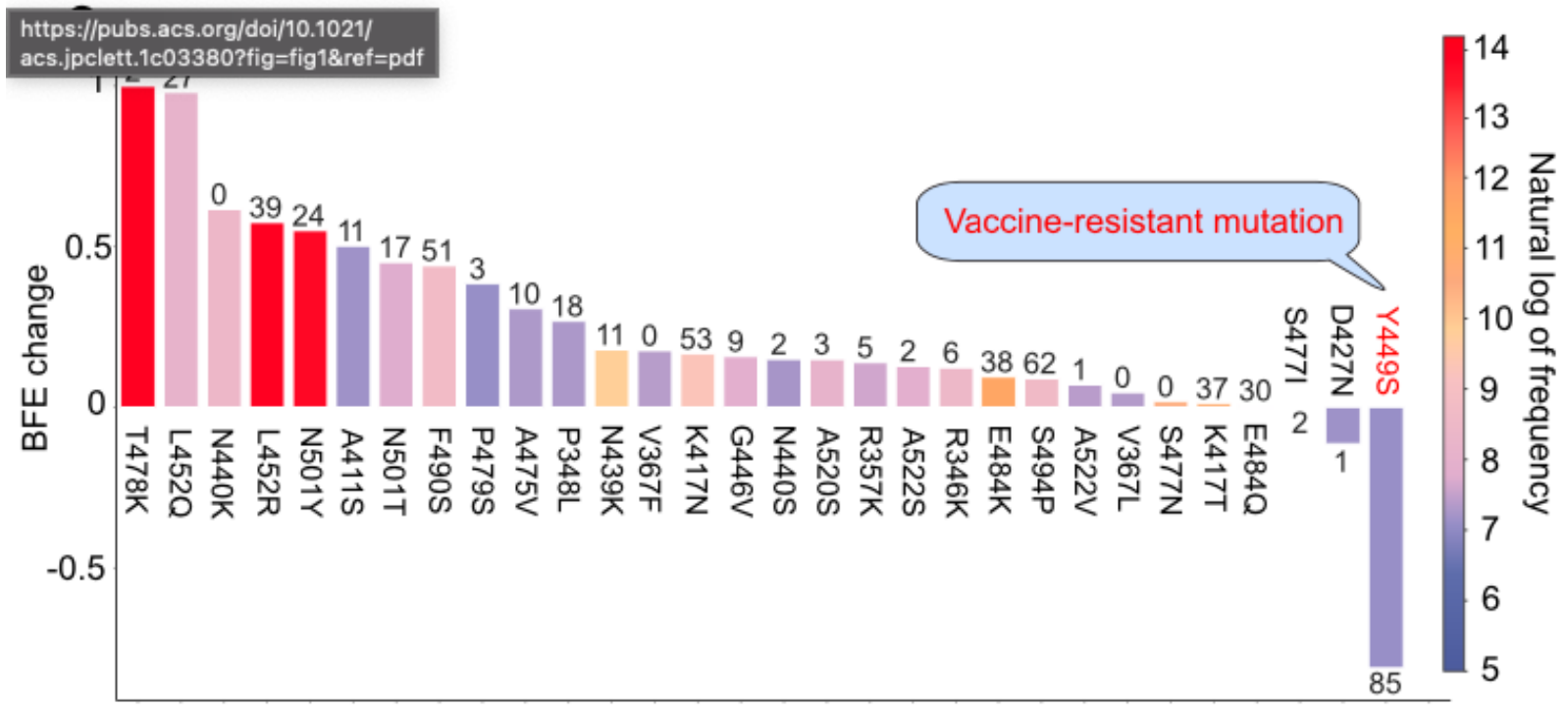
Wang R etal 2021 *Mechanisms of SARS-CoV-2 Evolution Revealing Vaccine-Resistant Mutations in Europe and America* J Phys Chem Lett

Aşı Paylaşım Problemi



Mukaigawara M etal 2022 *An equitable roadmap for ending the COVID-19 pandemic* Nat Med

SARSCoV2 Evrimi



Wang R etal 2021 *Mechanisms of SARS-CoV-2 Evolution Revealing Vaccine-Resistant Mutations in Europe and America* J Phys Chem Lett

İletişim Hatamız

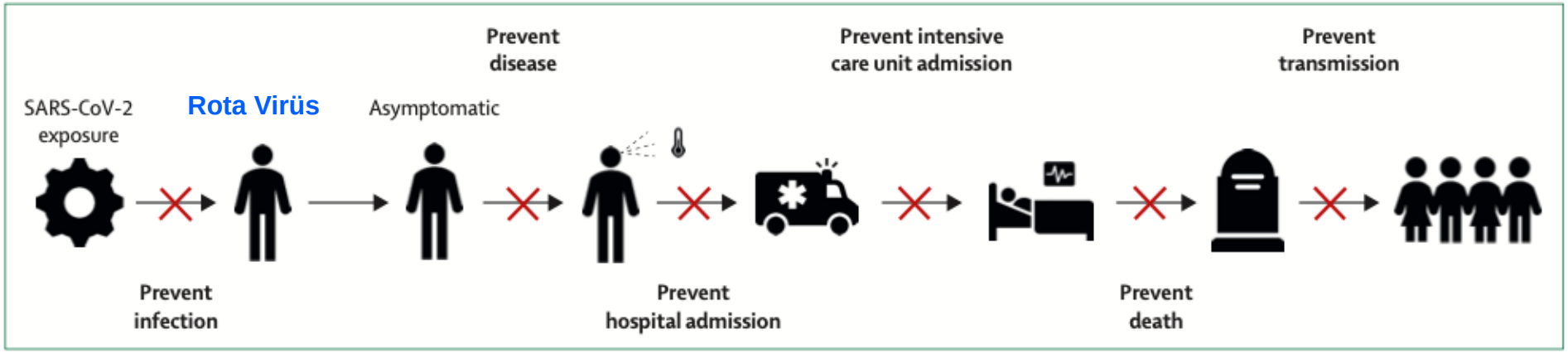
- COVID19 aşılaması 3 dozdur
- 3. doz rapel/booster doz değildir

Primer aşılama serisinin tamamlanmasıdır

Daha Kaç Kere?

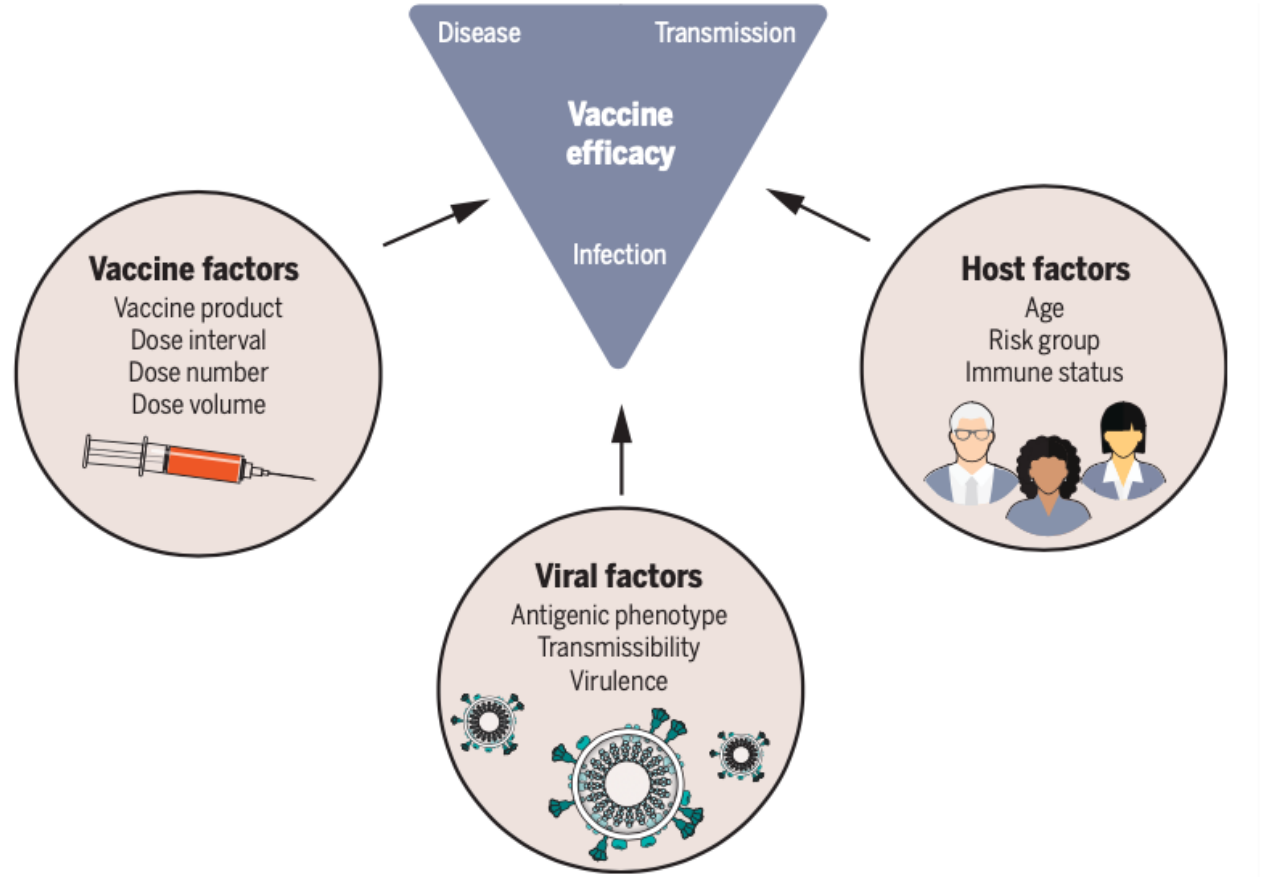
Risk Algınız Hangi Düzeyde?

Aşıdan Ne Bekliyoruz?



Hodgson S etal 2021 *What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2* Lancet Inf Dis

Aşı Etkinlik



Koelle K etal 2022 *The changing epidemiology of SARS-CoV-2* Science

Daha Kaç Kere? Güvenlik

- Aşı tereddütü önemli bir sorun
- Tüm Dünayda 11.8 Milyar doz;
  - 4.7 Milyar tam aşılı
- Genel olarak güvenli
  - 260 VITT / 31 Milyon
  - Myokardit 1-6 / 1 Milyon
- Nötralizan antikor yanıtları
  - Zamanla azalır

Altmann D etal 2022 *COVID-19 Vaccination: The Road Ahead* Science
https://ourworldindata.org/covid-vaccinations - *29 Mayıs 2022*

Daha Kaç Kere? Nötralizan Antikorlar

- Nötralizan antikor yanıtları
  - Zamanla azalır
- Özellikle duyarlı konakların korunması elzem
  - Yaşlılar
  - İmmün düşkünler
  - Sağlık Çalışanları

Altmann D etal 2022 *COVID-19 Vaccination: The Road Ahead* Science

Gelişmiş Ülkeler Yaygın İmmünizasyon ile Pandemiyi Bitiriyor mu?

- Etik tartışma
  - Duyarlı konak için hala risk var
- Mevcut omicron varlığında veriler analiz edilirse
  - İngiltere yıllık 15 milyon enfeksiyon, 50,000 fazla ölüm
  - ABD ~26 milyon enfeksiyon, 400,000 fazla ölüm

Altmann D etal 2022 *COVID-19 Vaccination: The Road Ahead* Science

Yarını Planlama Zamanı

Future protective immunity approach	Pros	Cons
Stop boosting and rely on existing memory	Cheap, simple; all rely on existing primed immunity	Immunity likely to wane; high probability of long-duration COVID-19 waves
Homologous first-generation spike vaccine boosters frequently (as needed)	Simple, safe, established, with supportive evidence of short-term protection against VOC	May be expensive (depending on which platforms); may be increasingly suboptimal against immune-selected variants; suboptimal immune boosting relative to heterologous boosters
Heterologous first-generation spike vaccine boosters frequently (as needed)	Simple, safe, established, with supportive evidence of short-term protection against VOC; strong supportive evidence for enhanced immunity, including the ability to rescue responses in those who may initially have received weaker vaccines	May be expensive (depending on which platforms); may be increasingly suboptimal against oncoming immune-selected variants
As above, but using spike boosters based on wider rollout of **second-generation** production platforms, e.g., DNA vaccines, self-amplifying RNA, recombinant protein with adjuvant	Likely to be effective, globally scalable, cheap, and therefore advantageous for global coverage	Little data thus far in large-scale heterologous boosting protocols
First-generation platforms modified for **specific** VOC spike inserts	Likely to be highly effective, against a given VOC; simple, safe, established	VOC waves tend to arise considerably faster than new vaccines can be modified and tested; unpredictability of protective phenotype due to prior imprinting; wave specific and lacks future-proofing
First-generation platforms modified for **polyvalent** VOC spike inserts	Likely to be highly effective, against multiple VOCs; potential for global relavence; simple, safe, established	Unpredictability of protective phenotype due to prior imprinting; lacks future-proofing

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Yarını Planlama Zamanı

Boost with a wider viral immunome: **Polyvalent adjuvanted proteins**	Accessible technologies: Enhanced potential to avoid immune evasion mutants	Lack of strong evidence to date for additional protection through non-spike immunogens; lack of data in heterologous protocols to date
Boost with a wider viral immunome: **Whole inactive virus**	Accessible with much prior data and production line infrastructure and safety; immunogen-agnostic potential to prime with much of the viral immunome; adaptability to modification for oncoming VOCs	In some cases, whole inactivated virus has been less immunogenic; would not give faithful expression of the full proteome as seen in infection
Boost with **live attenuated virus** carrying polyvalent spike for lifelong durability, e.g., YF17 platform	Good prior track record of YF17D platform	Relatively untried; greater safety concerns
Sequential immunization with spike from SARS-CoV clades for pan-coronavirus coverage	Potential for completely future-proofed pan-coronavirus protection	Would need further development; potential for unpredicted effects of immune imprinting
Immunization with **adjuvanted RBD nanoparticles** for pan-coronavirus coverage	Potential for completely future-proofed pan-coronavirus protection	Would need further development; potential for unpredicted effects of immune imprinting

Altmann D etal 2022 *COVID-19 Vaccination: The Road Ahead* Science

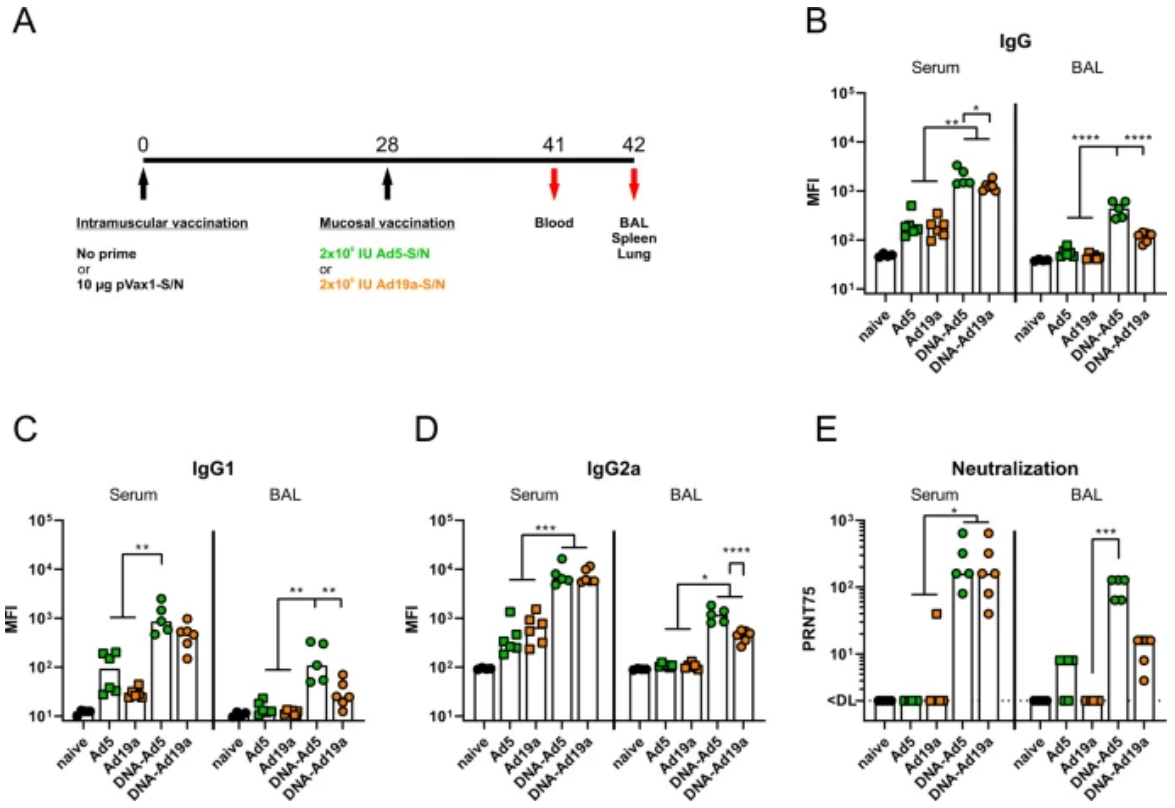
Çözüm I

- Pancoronavirüs aşısı
- Ferritin konjuge 24aa SARS-CoV-2 RBD nanopartükül
- Yarasa virüslerine dahi nötralizan yanıt

Burton DR etal 2020 *Rational vaccine design in the time of COVID-19* Cell Host & Microbe

Çözüm II

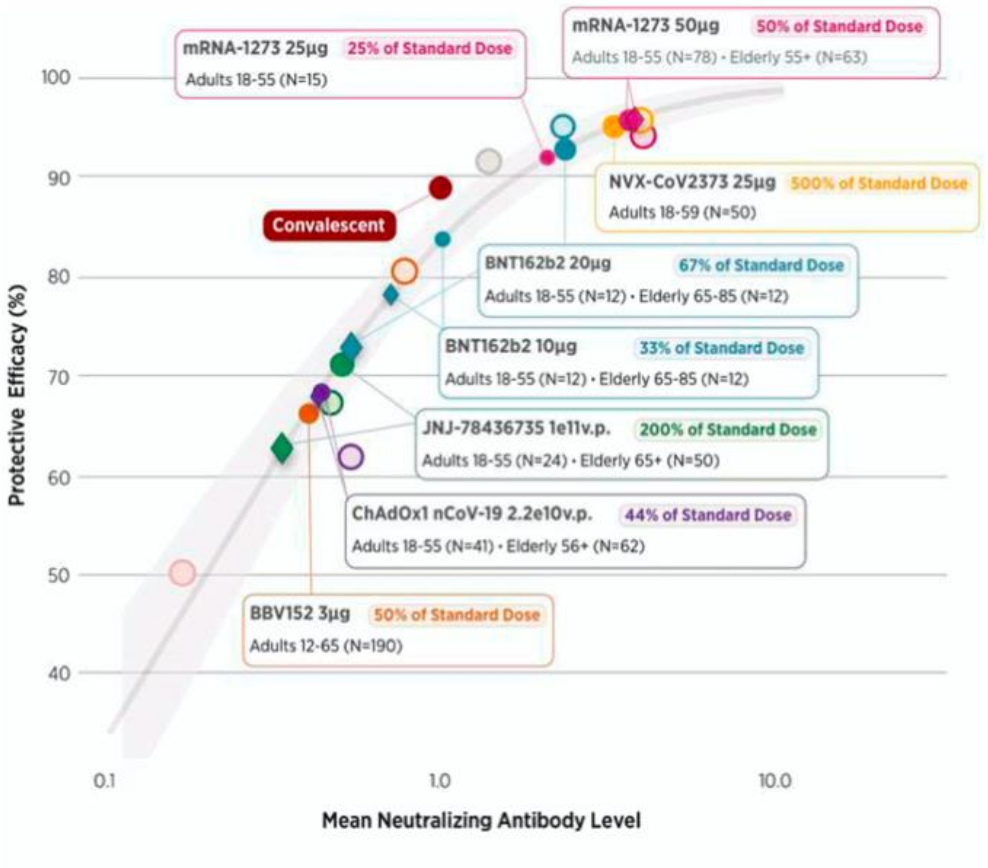
- Sistemik priming + Mukozal rapel



Lapuente D etal 2021 *Protective mucosal immunity against SARS-CoV-2 after heterologous systemic prime-mucosal boost immunization* Nat Comm

Çözüm III

- Düşük Doz Aşı
- %95 etkili aşı
  - Ölüm %22 - 47
- %70 etkili aşı
  - %20 - 35



Wiecek W etal 2022 *Testing fractional doses of COVID-19 vaccines* PNAS

Tüm Gayretlere Rağmen Umulmadık Anda

Samuel Johnson 26.03.2020