Covid-19 Vaccines — Immunity, Variants, Boosters

Dr. Alexandra Christ

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

FRANKLIN H. EPSTEIN LECTURE

Franklin H. Epstein, M.D., served the New England Journal of Medicine for more than 20 years. A keen clinician, accomplished researcher, and outstanding teacher, Dr. Epstein was Chair and Professor of Medicine at Beth Israel Deaconess Medical Center, Boston, where the Franklin H. Epstein, M.D., Memorial Lectureship in Mechanisms of Disease has been established in his memory.

Covid-19 Vaccines — Immunity, Variants, Boosters

Dan H. Barouch, M.D., Ph.D.

Impact factor: 91.245

Good to know

- Barouch's laboratory collaborated with Johnson and Johnson to develop a non-replicating adenovirus COVID-19 vaccine candidate that entered clinical trials in July 2020 and is one of the five major vaccine efforts supported by the US government.

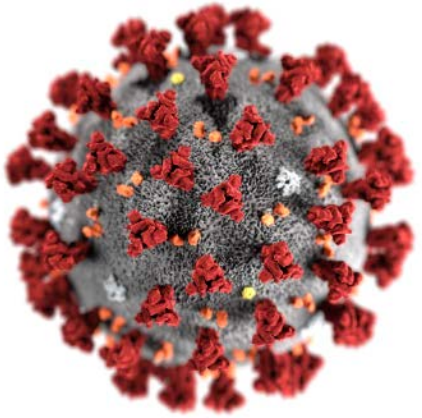
Background: SARS-CoV-2, Covid-19

- First identified in December 2019 in Wuhan
- WHO declared a Public health emergency of international concern on January 30th 2020, and a pandemic on March 11th 2020
- As of November 7th the outbreak has caused more than **632 million** cases and **15 million** confirmed deaths worldwide, making it one of the deadliest in history
  - In comparison:

    Plague 1346 – 1353 ≈ 25 million

    Spanish flu 1918 – 1920 ≈ 20 – 50 million

    SARS-CoV-1 2002 – 2003 ≈ 774



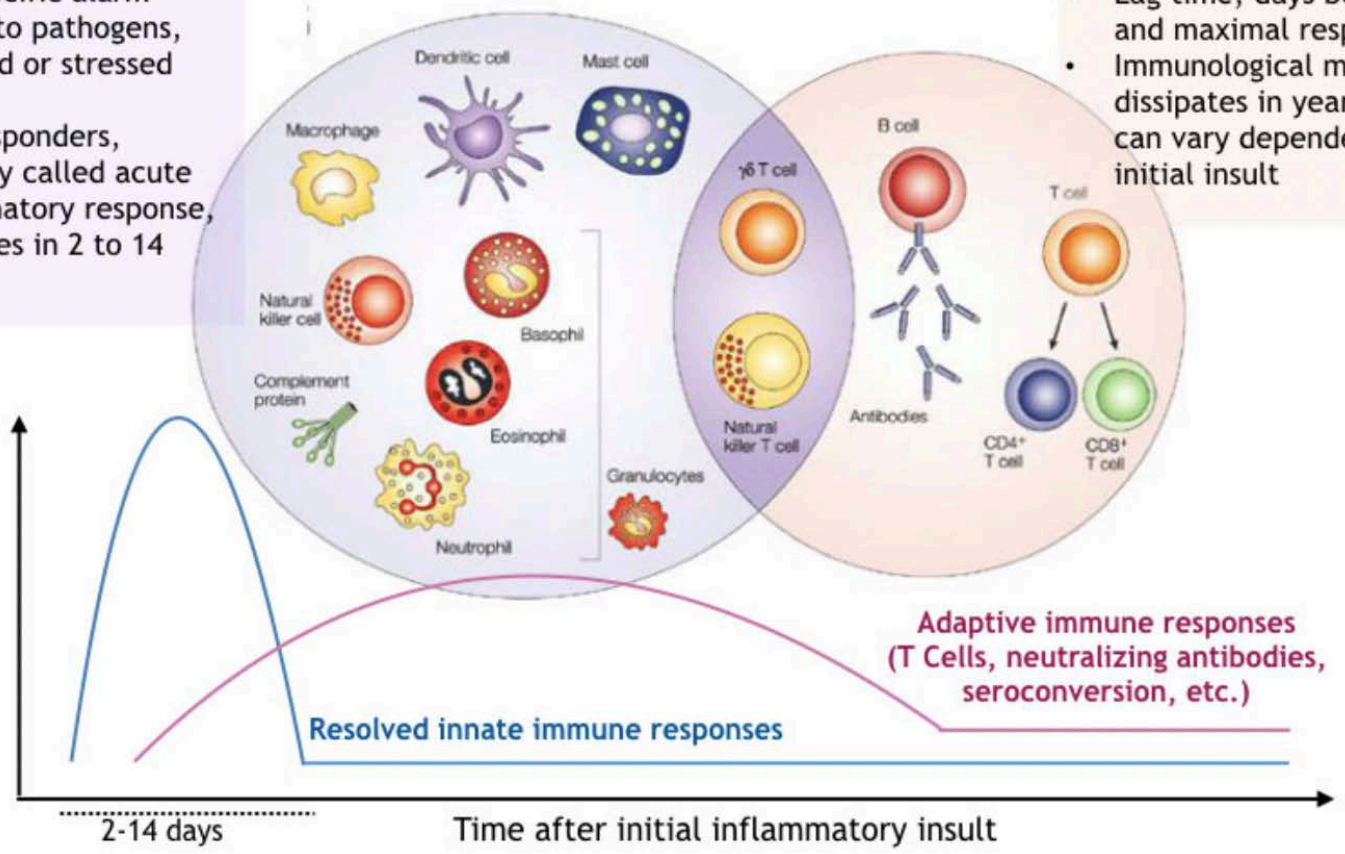
Antiviral Immunity (1)

Innate

- Non-Specific alarm system to pathogens, damaged or stressed cells
- First responders, clinically called acute inflammatory response, dissipates in 2 to 14 days

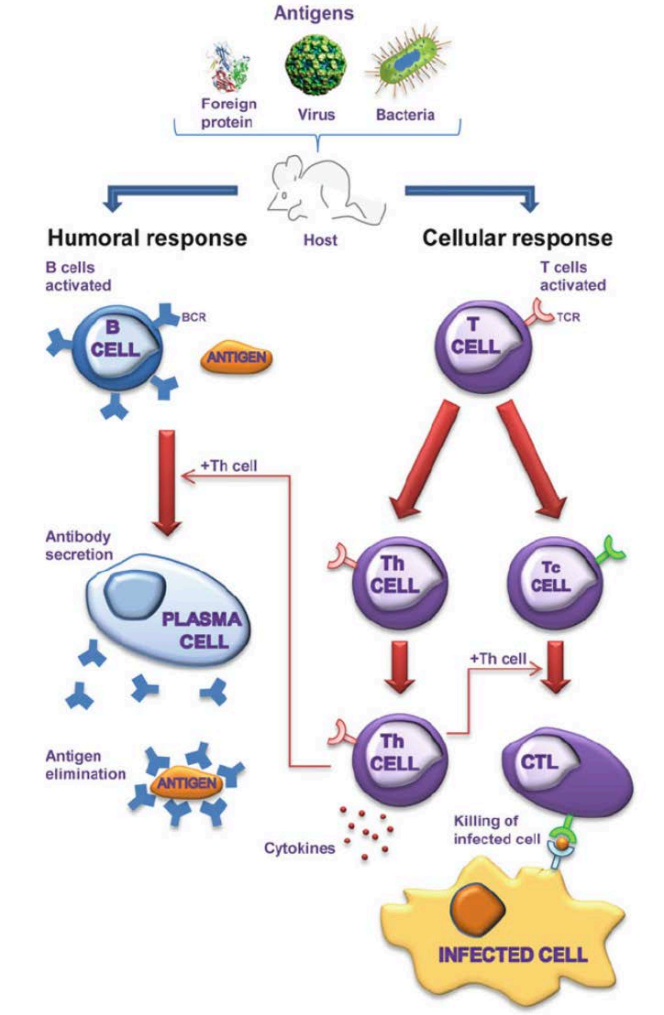
Adaptive

- Lag time, days between exposure and maximal response
- Immunological memory, response dissipates in years not days, and can vary dependent upon the initial insult



Dranoff G. Cytokines in cancer pathogenesis and cancer therapy. Nat Rev Cancer. 2004 Jan;4(1):11-22. doi: 10.1038/nrc1252. PMID: 14708024.

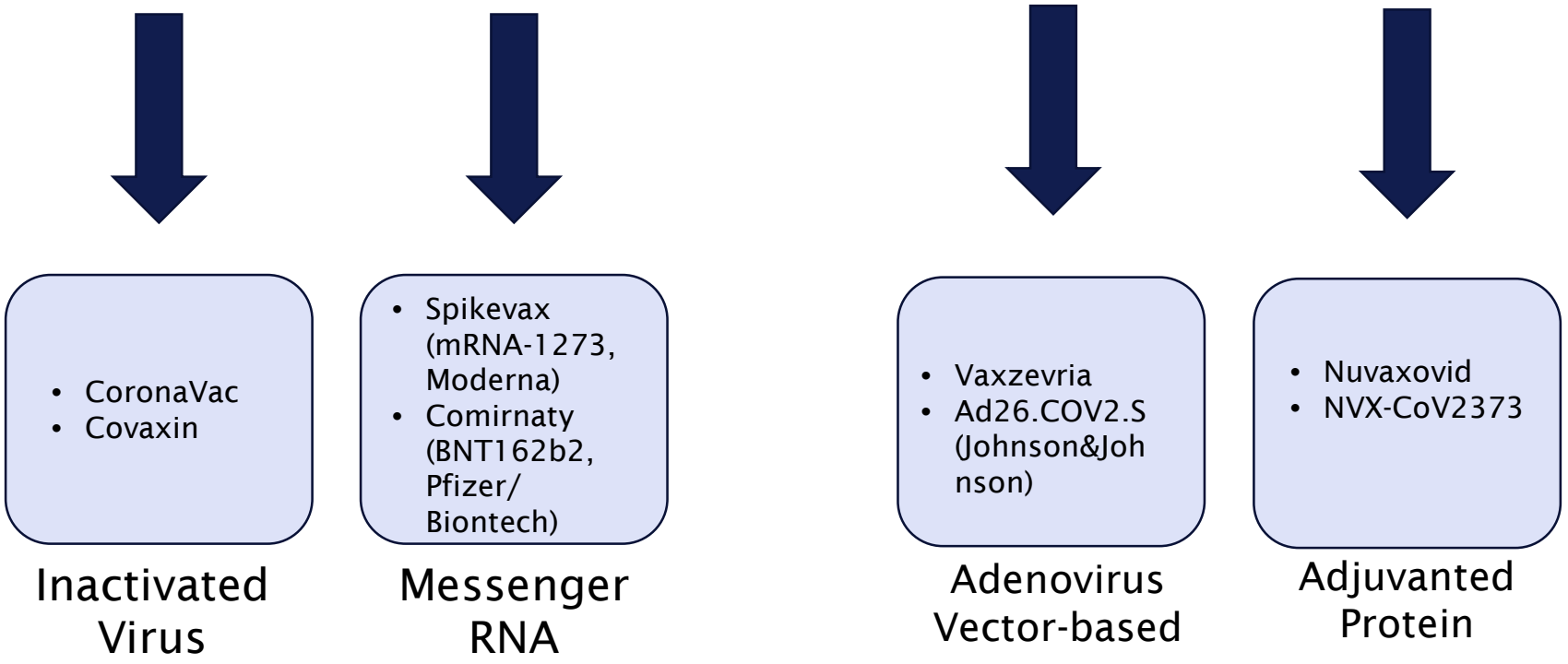
Antiviral Immunity (Adaptive Immune Response)



Bárcena J, Blanco E. Design of novel vaccines based on virus-like particles or chimeric virions. Subcell Biochem. 2013;68:631-65. doi: 10.1007/978-94-007-6552-8_21. PMID: 23737067.

Current Covid-19 Vaccines (The vaccines)

- 8 vaccine products have been approved by the WHO
  - 4 distinct vaccine platforms
  - All Vaccine products are based on the original Covid strain



Current Covid-19 Vaccines (Global Vaccination Rate)

- >70% of eligible persons in the US and most other developed countries
- <15% of eligible persons in Africa

→ limited use of mRNA vaccines due to cost, freezing requirements, distribution logistics and business priorities

→ a more equitable vaccine rollout would have saved 600.000 lives (WHO, 2021)

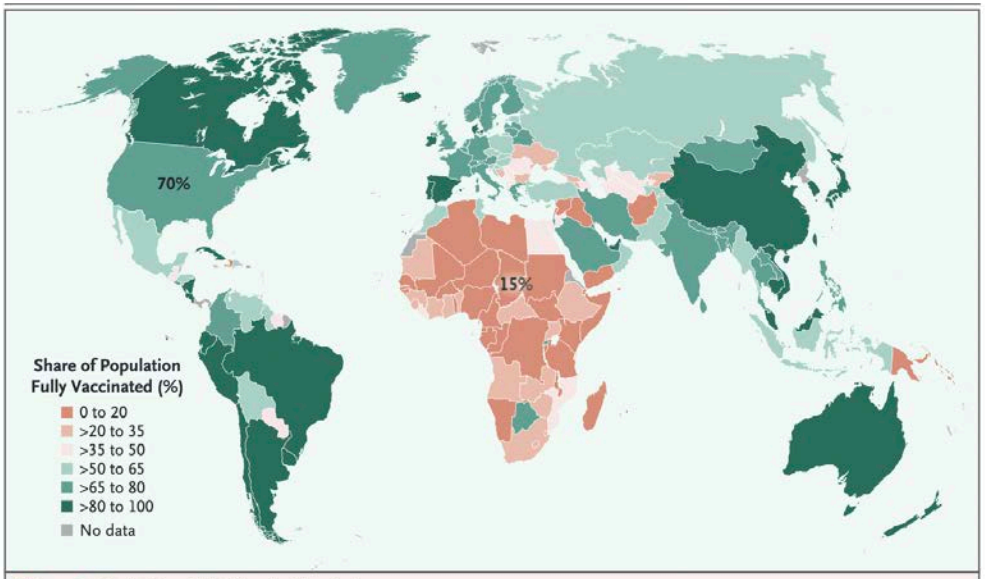


Figure 2. Global Covid-19 Vaccination Rates.
Shown is the percentage of fully vaccinated persons by country as of July 8, 2022. Data are from the *New York Times* (www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html).

Current Covid-19 Vaccines (Initial Efficacy)

Table 1. Protective Efficacy of Coronavirus Disease 2019 (Covid-19) Vaccines against the Ancestral Viral Strain in the United States and against the Omicron Variant in South Africa.

Vaccine (Dose)	Efficacy against Symptomatic Disease	[redacted]
	United States, Ancestral Strain*	[redacted]
	percent	[redacted]
Pfizer BNT162b2 (two shots)	95	[redacted]
Moderna mRNA-1273 (two shots)	94	[redacted]
Janssen Ad26.COV2.S (two shots)	94	[redacted]
Janssen Ad26.COV2.S (one shot)	72	[redacted]

* Data on protective efficacy of vaccines against symptomatic Covid-19 in the United States are from randomized, placebo-controlled phase 3 clinical trials.[14-17] Interim efficacy data before the emergence of the omicron variant are shown for each vaccine. The global efficacy of Ad26.COV2.S was lower, at 66% for the one-shot vaccine and 75% for the two-shot vaccine, as a result of the beta, lambda, and mu variants in Africa and South America.

† Shown are data on clinical effectiveness of BNT162b2 and Ad26.COV2.S against hospitalization and admission to the intensive care unit (ICU) during the omicron surge in South Africa (November 15, 2021, to January 14, 2022).[18] Data are for effectiveness 1 to 2 months after the second immunization. ND denotes no data.

Current Covid-19 Vaccines (VITT)

- FDA and CDC have recently restricted the use of Ad26.COV2.S (J&J) in the US because of the rare but serious occurrence of **vaccine-induced immune thrombotic thrombocytopenia (VITT)**
  - 54 reported cases, 9 deaths
  - 3 – 4 cases : 1 million vaccinated persons

- VITT has also been reported with ChAdOx1 (AstraZeneca)
  - 13 – 39 cases : 1 million vaccinated persons

- Adenovirus vector-based vaccines remain first-line vaccines in much of the developing world

- VITT has also been reported in 3 patients who received mRNA-1273 (Moderna)
  - 1 death

Current Covid-19 Vaccines (Myocarditis and pericarditis)

- Myocarditis and pericarditis have been reported as complications with BNT162b2 (Pfizer) and mRNA-1273 (Moderna)
  - 52 – 137 cases : 1 million vaccinated adolescent boys and young men after the 2nd dose
  - At least 10 reported deaths

- Myocarditis has been reported as a complication within 7 days after the 2nd mRNA dose in a different study
  - 566 cases : 1 million vaccinated person-years

- Most cases are mild
- Cardiac magnetic resonance imaging changes have been reported to persist in a substantial fraction of young men for 3– 8 months after recovery

→ Both thrombosis and myocarditis occur far more frequently after Covid-19 infection than after Covid-19 vaccination!

Vaccine durability (mRNA vaccines)

+ Outstanding short-term neutralizing antibody responses
+ Great protective efficacy

- Initial serum neutralizing antibody wane by 3 – 6 months and decline further by 8 months, with a half life of approximately 60 days

Vaccine durability (Adenovirus Vector-based)

+ Neutralizing antibody responses and clinical effectiveness are fairly durable for at least 8 months

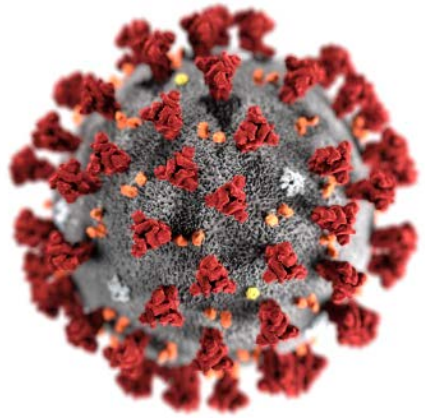
- Initial serum neutralizing antibody are lower compared to the mRNA vaccines

Vaccine durability (Conclusion)

- BNT162b2 (Pfizer) and mRNA-1273 (Moderna) induce high initial antibody titers, that wane after a few months
- Ad26.COV2.S (J&J) induces lower initial antibody responses with greater durability
- At 6 – 8 months, antibody responses are fairly similar with BNT162b2 (Pfizer), mRNA-1273 (Moderna) and Ad26.COV2.S (J&J)

Vaccine durability (Hybrid immunity)

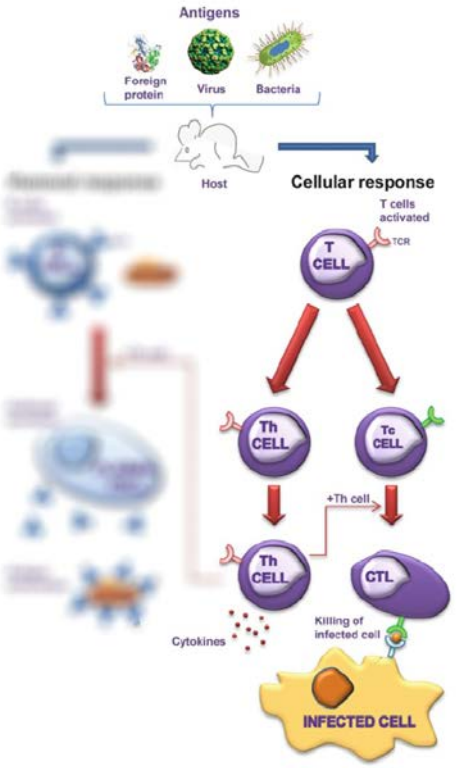
- Waning of immunity with mRNA vaccines is correlated with increased breakthrough infections with the SARS-CoV-2 delta variant (e.g. July 2021 in Provincetown, Massachusetts)
- Particularly robust immune responses developed
- Population immunity to SARS-CoV-2 will continue to increase through a combination of widespread vaccination and infection
- Data from this outbreak showed evidence of transmission between fully vaccinated people



Vaccine durability (Cellular immune response)

- Is induced by both mRNA vaccines and adenovirus vector-based vaccines
- Has shown greater durability than serum antibody titers
- CD 8+ T-cell responses are particularly high after Ad26.COV2.S (J&J) vaccination with durability for at least 6 – 8 months

→ Because CD 8+ T-cell responses control viral replication after infection, it is likely that SARS-CoV-2 vaccines will continue to **provide substantial protection against severe disease** even after serum neutralizing antibody titers wane



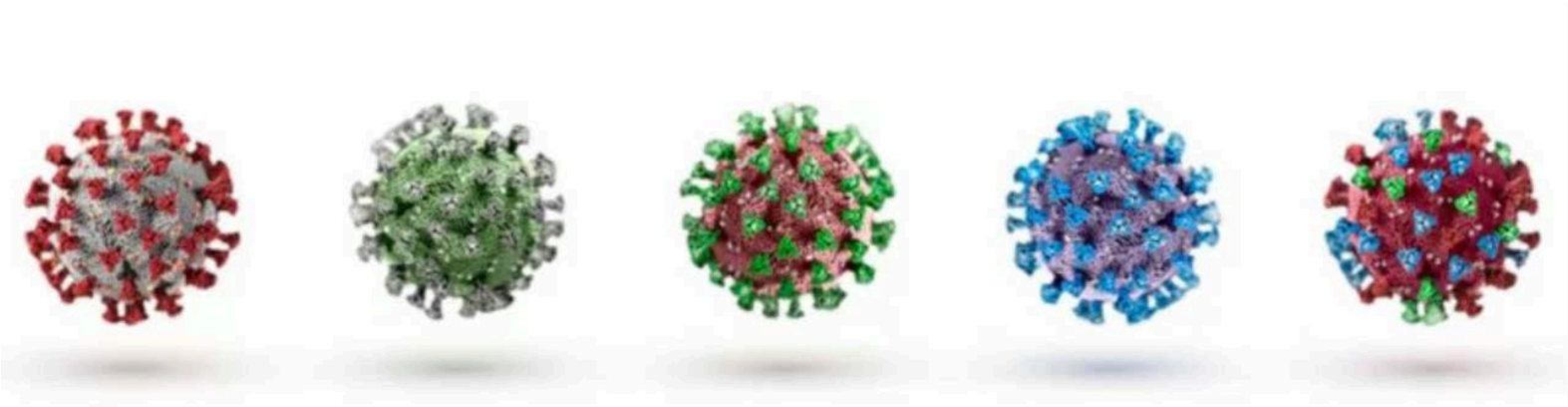
Vaccine durability (Immunosuppressed Patients)

- In immunocompromised persons, both antibody and T-cell responses to Covid-19 vaccines are reduced
- The degree of reduction depends on the extent and type of immunosuppression
- In these populations, additional vaccine doses and prophylactic treatment with monoclonal antibodies are recommended

SARS-CoV-2 Variants of Concern

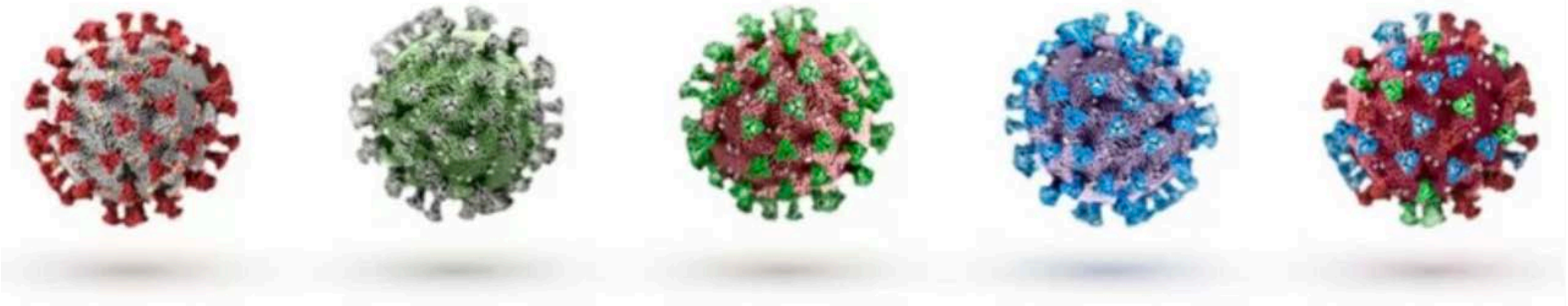
- In the spring of 2020 the predominant global form of the original virus rapidly transitioned to a variant that carried 4 mutations in the SARS-CoV-2 genome, including a single D614G point mutation in the spike protein that conferred a fitness advantage

- Typical features of new variants:
  - Increased transmissibility
  - Greater antibody escape

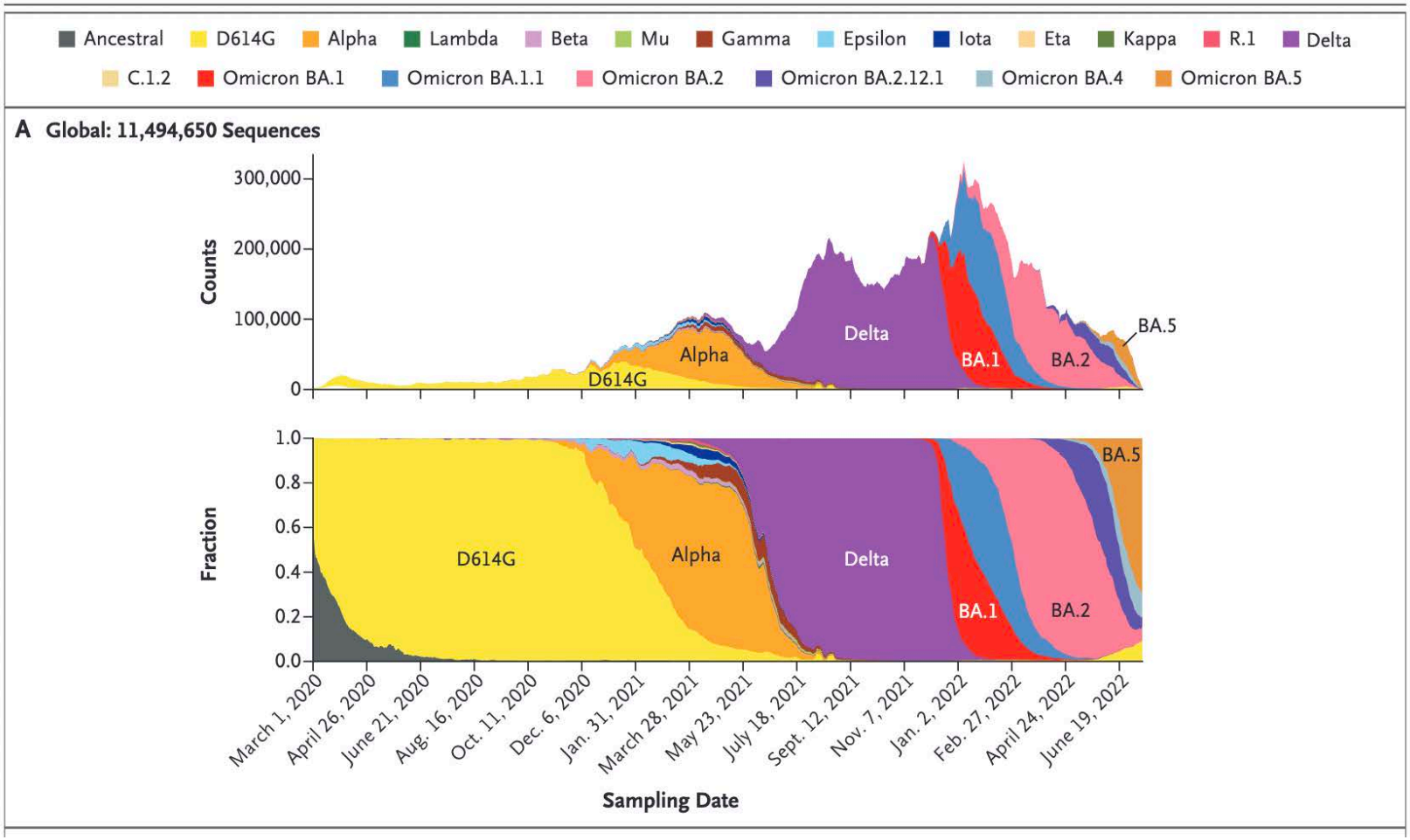


SARS-CoV-2 Variants of Concern (1)

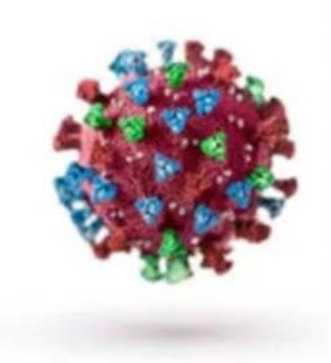
- Alpha (B.1.1.7) -> emerged in the United Kingdom
- Beta (B.1.351) -> emerged in South Africa
- Gamma (P.1) -> emerged in Brazil
- Delta (B.1.617.2) emerged in India in the summer of 2021 and globally replaced all previous variants
- Omicron (B.1.1.529) emerged in Africa and abruptly became the most prevalent virus globally



SARS-CoV-2 Variants of Concern (2)



SARS-CoV-2 Variants of Concern (Omicron)



- Omicron (B.1.1.529)
  - > 50 mutations in total
  - > 30 mutations in the spike protein

→ substantial escape from neutralizing antibody responses elicited by vaccination or prior infection with a non-omicron variant

SUBVARIANTS

BA.1	BA.1.1	BA.2
BA.2.12.1	BA.4	BA.5

SARS-CoV-2 Variants of Concern (Omicron BA.5)

- Omicron (BA.5)
  - Currently the predominant variant in the United States
  - Neutralizing antibody titers are decreased by the factor of ≈ 3 as compared with titers against BA.1 and BA.2

- Multiple studies have shown that neutralizing antibodies induced by all **primary vaccine regimens show little cross-reactivity with omicron**

- Boosting however leads to a substantial increase in omicron neutralizing antibodies
  - These antibody titers have been shown to wane by **4 months after a 3rd mRNA dose**
  - After the **4th mRNA dose** protection against infection wanes after just **4 weeks**, however protection against severe disease lasts longer

- **Hybrid immunity** provides greater and more durable protection

SARS-CoV-2 Variants of Concern (Omicron BA.5)

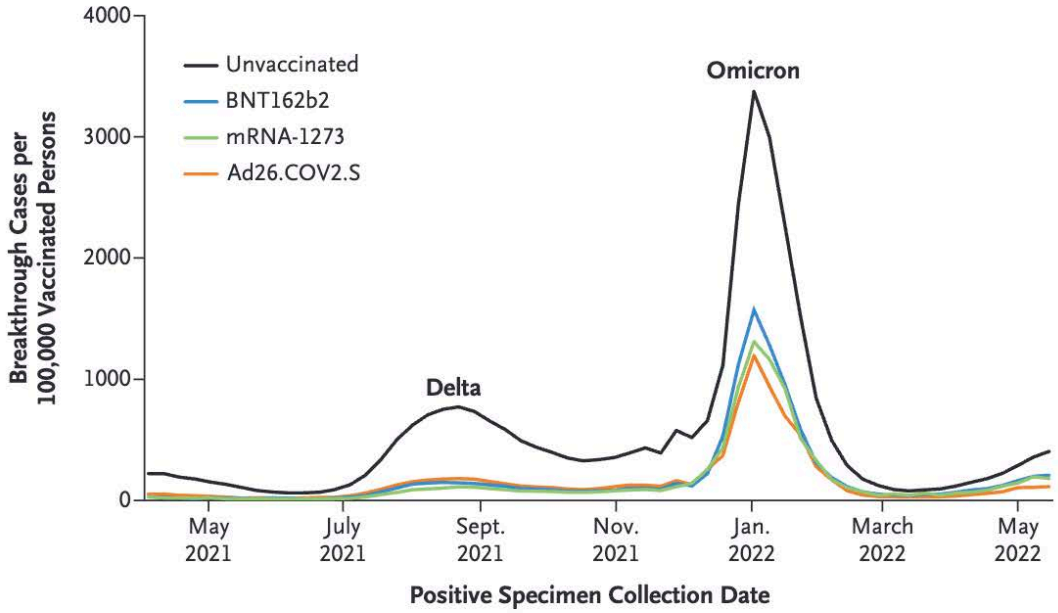
- T-cell responses induced by vaccines have very good (>80%) cross-reactivity to Omicron and prior variants

→ Cellular immunity to SARS-CoV-2 variants remains largely intact

The findings of the table on the right suggest the importance of other immune measures than neutralizing antibodies, such as CD8+ T-cell responses

Efficacy against Hospitalization	Efficacy against ICU Admission
South Africa, Omicron Variant†	
percent	
70	70
ND	ND
72	82
ND	ND

SARS-CoV-2 Variants of Concern (Delta and Omicron surge)



	Breakthrough Cases per 100,000 Vaccinated Persons	
	Peak	May 21, 2022
Unvaccinated	3381	395
BNT162b2	1566	198
mRNA-1273	1305	174
Ad26.COV2.S	1190	106

Figure 4. Protective Efficacy of Covid-19 Vaccines in the United States.

Covid-19 breakthrough rates (no. of cases per 100,000 vaccinated persons) are shown from April 4, 2021, to May 21, 2022, for persons who received the BNT162b2, mRNA-1273, or Ad26.COV2.S vaccines in the United States. Data are from the Centers for Disease Control and Prevention (https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status).

Immune Correlates of Protection (1)

- Early preclinical studies in NHP identified both neutralizing and other functional **antibodies as correlates of vaccine protection** against SARS-CoV-2

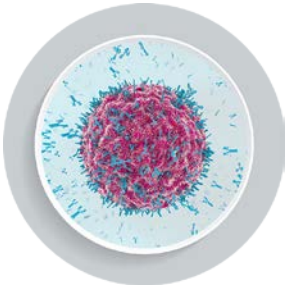
- Studies with purified IgG confirmed, that **antibodies alone were sufficient to block infection** in both NHP and hamsters, providing that the antibodies were administered at a sufficiently high dose

- In vivo CD8 depletion studies in NHP also showed, that **CD8+ T cells contribute to protection** when antibody titers were subprotective

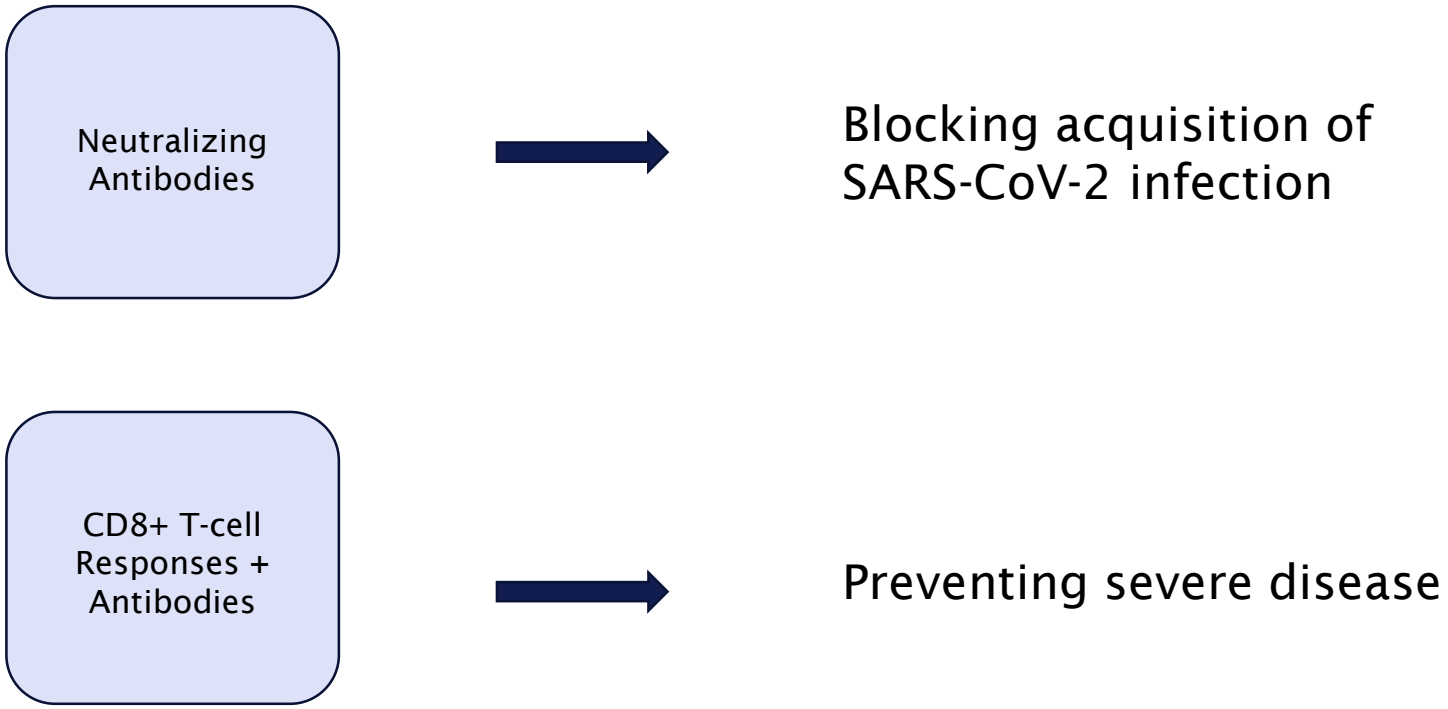
Immune Correlates of Protection (2)

- **Vaccine failure** in NHP was associated with **low levels of both omicron neutralizing antibodies and CD8+ cells**

- Analyses of immune correlates from the phase 3 clinical trials of mRNA-1273 (Moderna) and Ad26.COV2.S (J&J) confirmed that **antibody titers correlate with protection against Covid-19 infection**
    - Performed before the emergence of the omicron variant
    - T-cell responses were not included



Immune Correlates of Protection (3)



Immune Correlates of Protection (4)

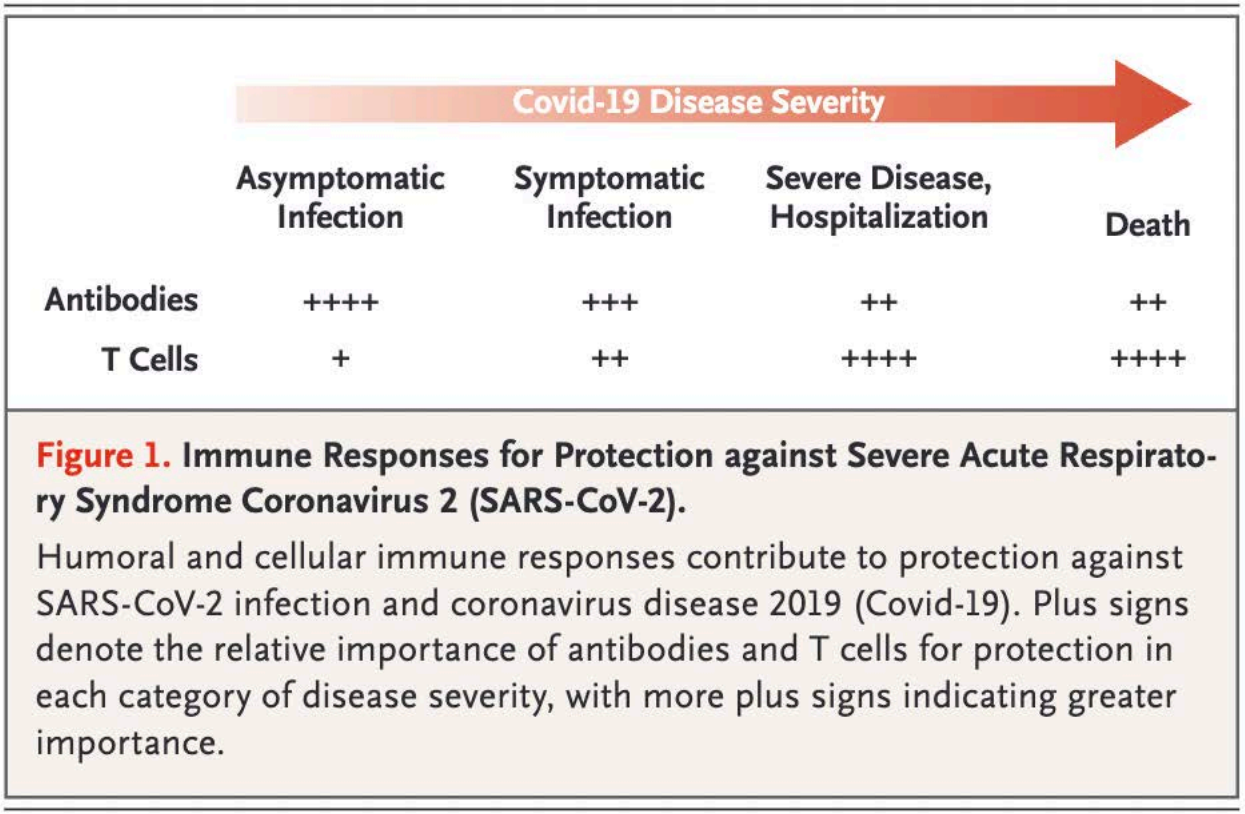


Figure 1. Immune Responses for Protection against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

Humoral and cellular immune responses contribute to protection against SARS-CoV-2 infection and coronavirus disease 2019 (Covid-19). Plus signs denote the relative importance of antibodies and T cells for protection in each category of disease severity, with more plus signs indicating greater importance.

Combination of humoral and cellular immunity is critical for viral control after breakthrough infection!

Immune Correlates of Protection (Omicron)

- Current vaccines provide only **modest protection** against infection and transmission with the omicron variant (even at peak immunity after boosting)
- It‘s likely that **neutralizing antibody titers may need to be substantially higher** for protection
- However CD8+ T-cell responses are **highly crossreactive**

→ Protection against severe disease is given

Proposed Framework for Covid-19 Vaccine Boosters (1)

- Substantial waning of serum neutralizing antibody titers
- Emergence of variants with increased transmissibility and antibody escape

Need for recalibration

Most important goals:

- Long-term protection against severe disease, hospitalization and death

Proposed Framework for Covid-19 Vaccine Boosters (2)

- What do we want from an Omicron-booster?
    - Combination of humoral and cellular immunity
    - Emphasis on long-term, rather than short-time immune response
- Where are we right now? (This paper was published in August 2022)
    - Study in NHP showed that an omicron-specific mRNA vaccine was not better than the original mRNA-1273 (Moderna) vaccine for protection against omicron
    - Early clinical studies have shown that boosting with a bivalent mRNA vaccine (ancestral strain + omicron BA.1 spike immunogens) induced peak omicron neutralizing antibody titers that were less than twice the peak titers induced by boosting with the original mRNA vaccines

Proposed Framework for Covid-19 Vaccine Boosters (3)

- Why is boosting every 4 – 6 months not a desirable long-term strategy?
    - Frequent boosting recommendations worsen „booster fatigue“ -> only 47% of people in the US have received any booster dose
    - Boosting is not risk-free
    - Confusing and overpromising as communicated by media
    - Priority should be to vaccine the number of unvaccinated people first
    - Global health inequities could be exacerbated

Conclusion

- Primary goals of Covid-19 vaccines should be to provide long-term protection against severe disease, hospitalization and death
- Studies of Covid-19 vaccines should evaluate not only the short-term neutralizing antibodies, but also durability of antibody responses, memory B-cell responses and cross-reactive T-cell responses
- Boosters not more frequently than once per year
- Improved durability of vaccines would be highly desirable

November 2022

- A study has shown superior neutralizing antibody responses with the bivalent Omicron-containing (BA.1) booster vaccine against Covid-19
  - Chalkias S, Harper C, Vrbicky K, Walsh SR, Essink B, Brosz A, McGhee N, Tomassini JE, Chen X, Chang Y, Sutherland A, Montefiori DC, Girard B, Edwards DK, Feng J, Zhou H, Baden LR, Miller JM, Das R. A Bivalent Omicron-Containing Booster Vaccine against Covid-19. N Engl J Med. 2022 Oct 6;387(14):1279-1291. doi: 10.1056/NEJMoa2208343. Epub 2022 Sep 16. PMID: 36112399; PMCID: PMC9511634.

- Another study has shown that both monovalent and bivalent mRNA boosters (BA.5) markedly increased antibody responses but did not substantially augment T cell responses. BA.5 NAb titers were comparable following monovalent and bivalent mRNA boosters, with a modest and nonsignificant trend favoring the bivalent booster by a factor of 1.3
  - Collier AY, Miller J, Hachmann NP, McMahan K, Liu J, Bondzie EA, Gallup L, Rowe M, Schonberg E, Thai S, Barrett J, Borducchi EN, Bouffard E, Jacob-Dolan C, Mazurek CR, Mutoni A, Powers O, Sciacca M, Surve N, VanWyk H, Wu C, Barouch DH. Immunogenicity of the BA.5 Bivalent mRNA Vaccine Boosters. bioRxiv [Preprint]. 2022 Oct 25:2022.10.24.513619. doi: 10.1101/2022.10.24.513619. PMID: 36324798; PMCID: PMC9628195.

Discussion

- Overall structure of the review
- Table 1: Different geographic locations, different outcomes, different strains
- Figure 4: What about mix & match doses? Does the author mean the breakthrough cases on a total of 100,000 vaccinated persons or on 100,000 persons immunized with this very vaccine? Why does the author include unvaccinated persons in a graph that has "breakthrough cases per 100,000 vaccinated persons" on the y-axis? Different graphs on the CDC homepage!
- Proposed framework: Almost no references, author mentions specific numbers and statistics without quoting (page 1017)