COVID-19 Vaccine Update

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mRNA Vaccines: How do they work?

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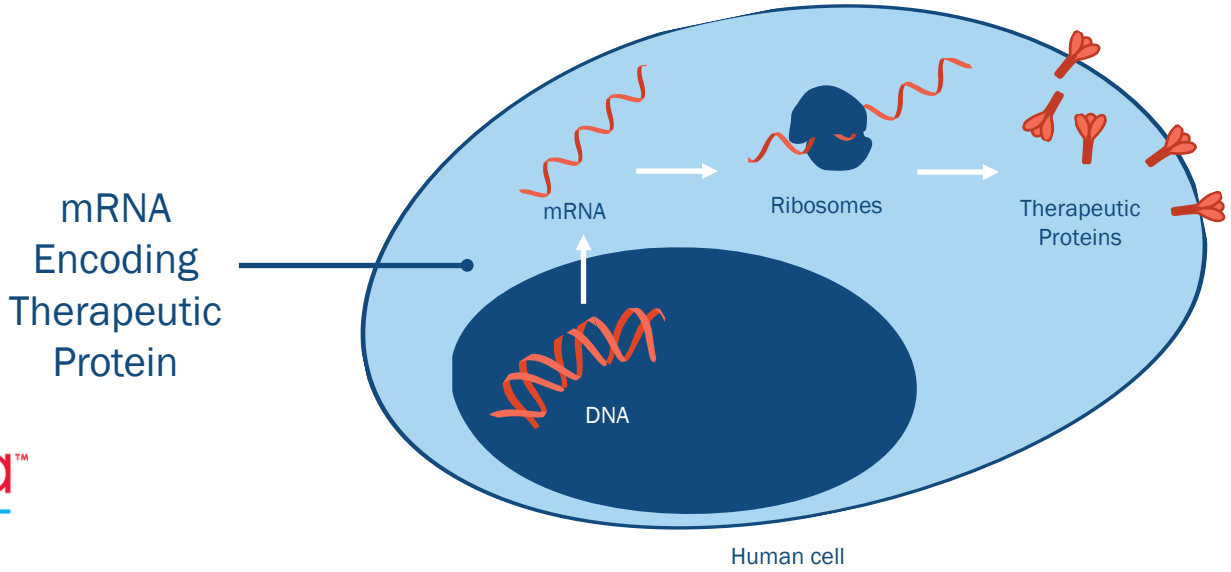
RNA is biological software, cellular instructions to make any protein

Pfizer

moderna



It does not enter the cell nucleus or incorporate into DNA

Why mRNA? Why Now?

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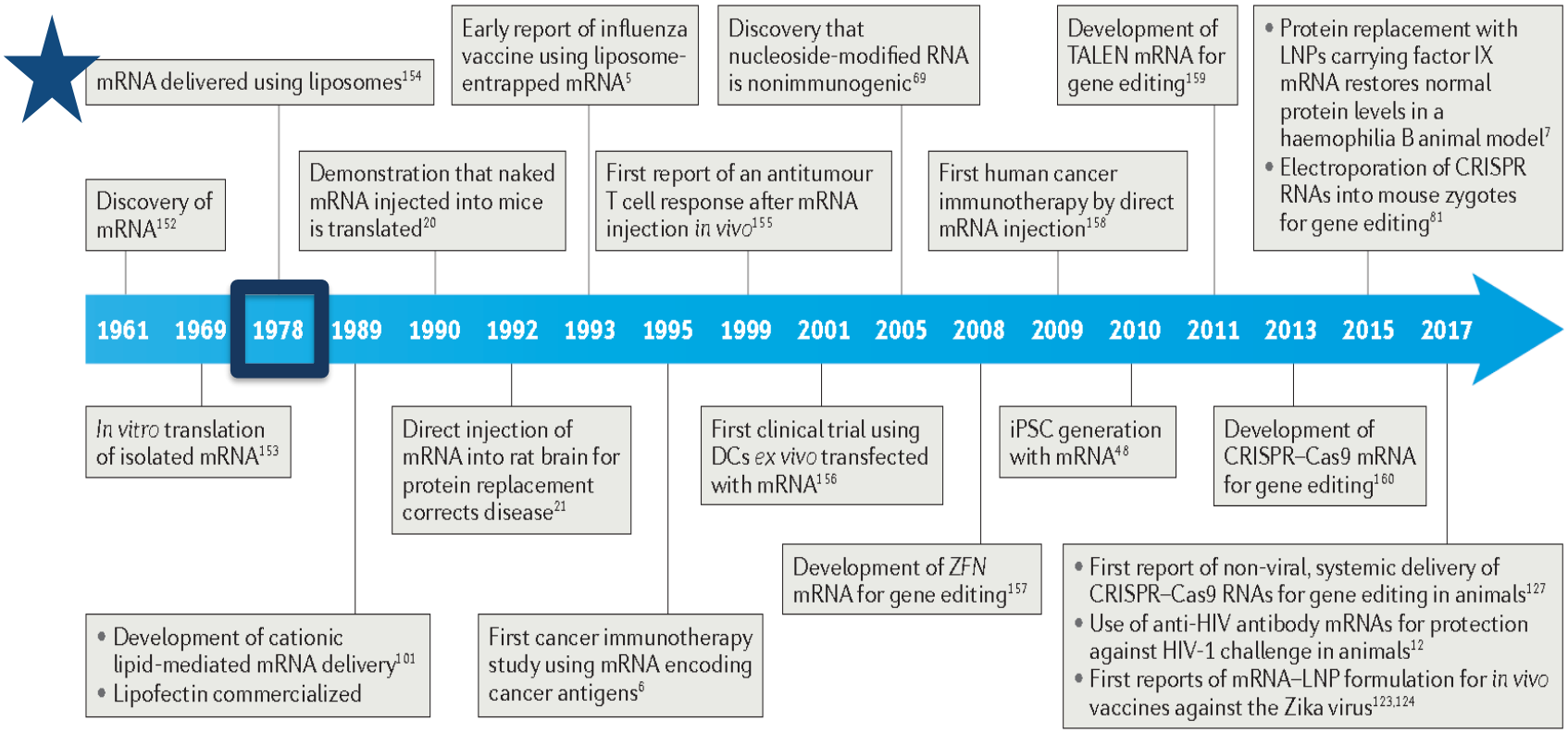
Research on mRNA therapy dates back more than 40 years



Hajj and Whitehead Nature Reviews Materials 2017

Why mRNA? Why Now?

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Because long-standing obstacles are being overcome

Systemic Delivery

Requires carrier that protects mRNA integrity and preferentially delivers to target cell

Intracellular Delivery

Requires carrier to cross cytoplasmic membrane

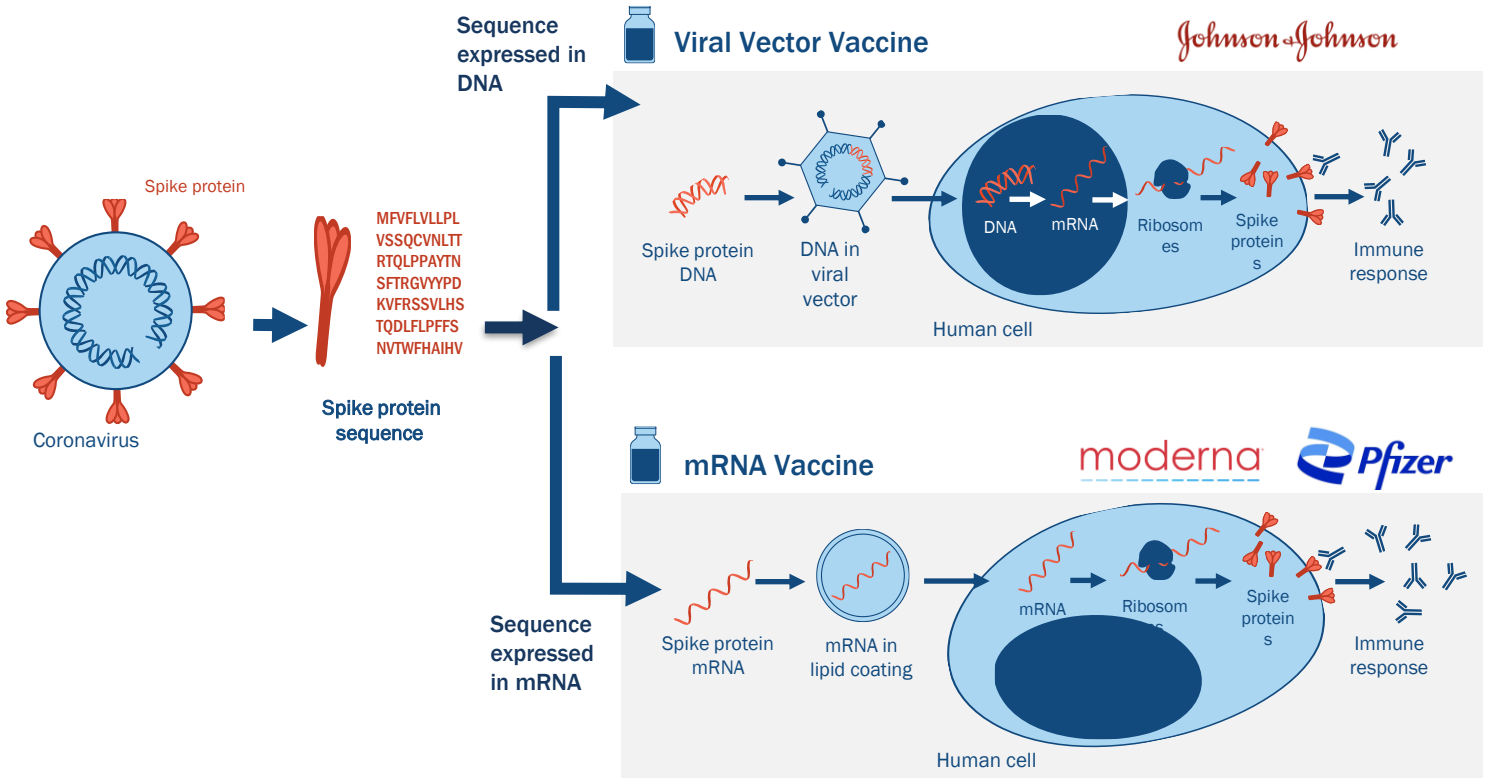
Protection from rapid degradation

Minor modifications protect the RNA long enough to give the cell its instructions

Thanks to advances in nanotechnology and virology

Vaccine Technology: mRNA vs Viral Vector

How is the viral vector technology different from the mRNA technology?



Viral vector delivers DNA, not RNA and uses non-replicating virus instead of lipid particles

EUA Authorized Vaccines

	EUA	Protection from Symptomatic Illness	Protection from Severe Illness	Protection from Hospitalization or Death
moderna	✓ (US, UK, EU)	94%	100%	100%
Pfizer	✓ (US, UK, EU)	95% (US) 100% (S Africa)	90%	100%
Johnson & Johnson	✓ (US, EU)	72% (US) 68% (LatAm) 64% (S. Africa)	82% - 88%	100%

Exact numbers quoted for vaccines vary depending on efficacy, AND:

- clinical trial or "real world evidence"
- outcome criteria
- length of follow up
- which country
- what time period

EUA Authorized Vaccines

	EUA	Protection from Asymptomatic Infection	Provides Sterilizing Immunity
moderna	✓ US, UK, EU	**66%** After 1st dose	**Yes (monkeys)**
Pfizer	✓ US, UK, EU	**90%** After second dose	**Yes (monkeys)**
Johnson & Johnson	✓ US, EU	**74%** Single dose	**Yes (monkeys)**

Accumulating evidence suggests vaccines will protect against asymptomatic infection – and transmission – with efficacy similar to their protection from symptomatic infection.

Vaccination in the Real World

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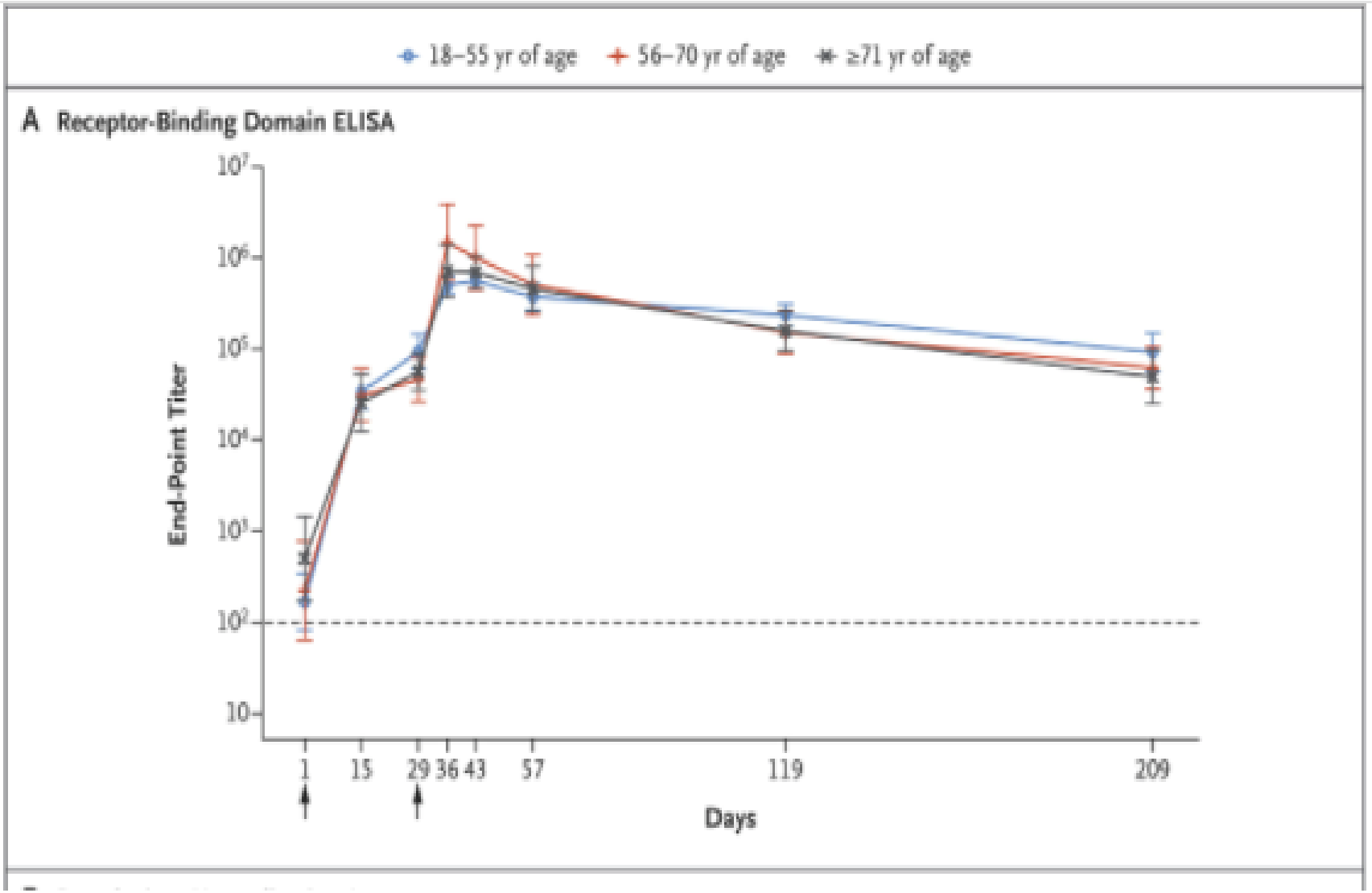
- Real World Data on vaccinated groups
  - Israel – 96% protection from infection
  - Scotland – hospitalization reduced by 85% (Pfizer) and 94% (Astra Zeneca)
  - Scotland – 30% reduction in household contact infections after one dose
  - England – vaccine efficacy 73% (Astra Zeneca) to 89% (Pfizer)
  - Houston Methodist – reduced employees' positive test rate 95%
  - CDC study – vaccination reduces incidence rate of all infections by 97%
  - Cambridge Health – 75% reduction in asymptomatic infection

Durability of Antibody Response (Moderna)



Vaccine Safety Overview

Phase 3 Clinical Trials

- How many people received the vaccine?
  - Pfizer – 46,307
  - Moderna – 15,208
  - J&J – 23,190
- Severe reactions in vaccine groups?
  - Nothing beyond what was seen in placebo group or general population
- There is 6 months of safety follow up on thousands of people

Real World Experience

- A few rare reactions seen with wide deployment of vaccines:
  - Small number of severe allergic reactions (mostly Moderna and Pfizer)
  - Extended duration of local reaction in injected arm (mostly Moderna)
  - Systemic rashes
  - Possible rare blood clot risk (J&J)
- 121 million people have been vaccinated in the US!

Johnson & Johnson Clot Risk?

- FDA & CDC have ”paused” use of J&J vaccine to investigate reports of cerebral venous clots
- 6 cases in 6.8 million vaccinations (maybe now 8 cases)
- Is it due to the vaccine? Reasons why it might not be
  - Baseline incidence of CVST is 1 / 100,000 people / year, much more than seen with vaccine so far
  - Devasgayam Stroke July 2016; Coutinho Stroke September 2012
- Is it due to the vaccine? Reasons why it might be
  - Only seen in young women
  - Similar clinical picture seen in Europe with Astra Zeneca vaccine that also uses adenoviral vector technology
  - Schultz NEJM April 2021; Greinacher April 2021

Safety Databases Monitored by FDA and CDC

- CDC V-Safe
- CDC National Healthcare safety network (NHSN)
- FDA – insuror / payor databases
- CDC / FDA – Vaccine Adverse Event Reporting System (VAERS)
- CDC – Vaccine Safety Datalink (VSD)
- CDC. - Clinical Immunization Safety assessment (CISA) Project
- FDA - Biologics Effectiveness and Safety System (BEST)
- FDA – Sentinel Initiative
- DOD – DOD VAERS
- DOD – Vaccine Adverse Event Clinical System
- VA – VA Adverse Drug Event Reporting System (VA ADERS)
- VA - VA Electronic Health Record and Active Surveillance System

Other Life Risks

- Major bleeding from low dose aspirin – 1 /500 / year
- Death from COVID – 1/600 / year
- Fatal stroke – 1 /2,000 / year
- Motor vehicle fatality – 1 / 10,000 / year
- Cerebral venous sinus thrombosis (baseline) – 1 / 100,000 / year
- Blood clot with Astra Zeneca vaccine – 1 / 100,000 / vaccination
- Severe nonfatal reaction to Pfizer vaccine – 1 /300,000 / vaccination
- Blood clot with J&J vaccine - 1 / 1,000,000 / vaccination
- Death from lightning strike – 1 / 15,000,000 / year

What is the Risk of COVID?

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Risks of COVID-19 in the USA

- Risk of COVID infection = 10% (9.2%)
- Risk of long term side effects and disability = 30%
- Risk of hospitalization if infected = 10% (9% - 40%)
- Risk of death if hospitalized = 10% (7% - 70%)
- Actual risk of death from COVID in the USA = 1/600 (0.17%)

What Could Go Wrong?

Update on Viral Variants

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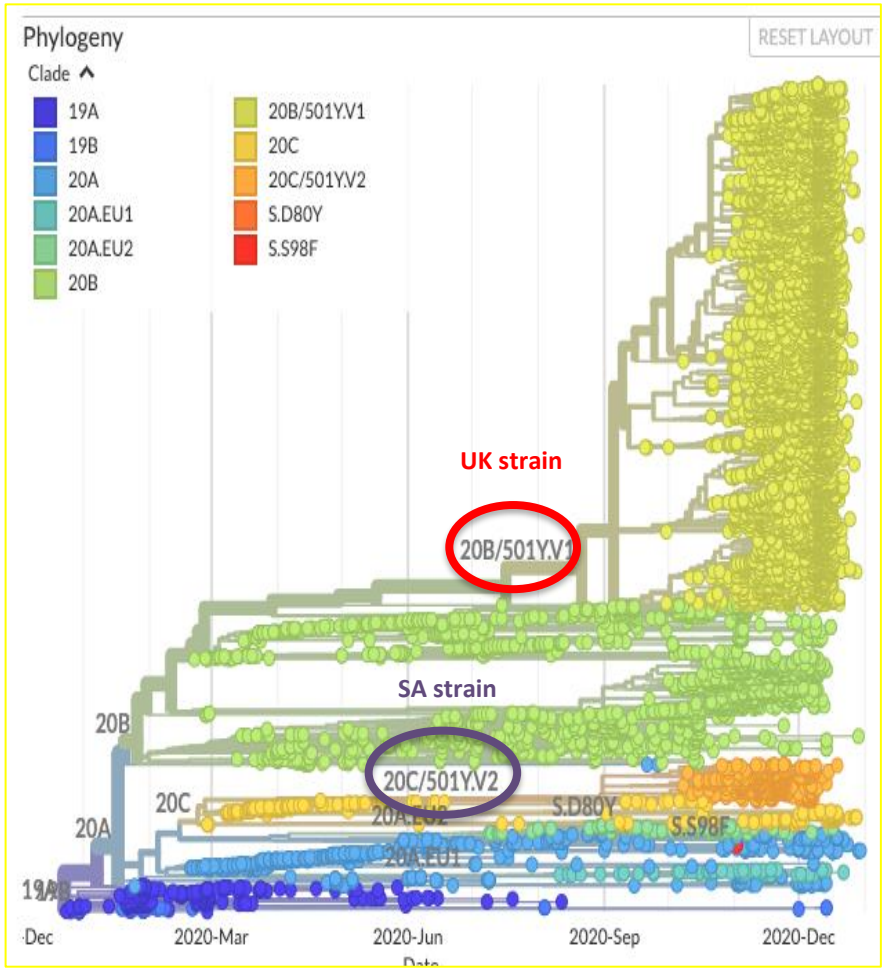
What Could Go Wrong?

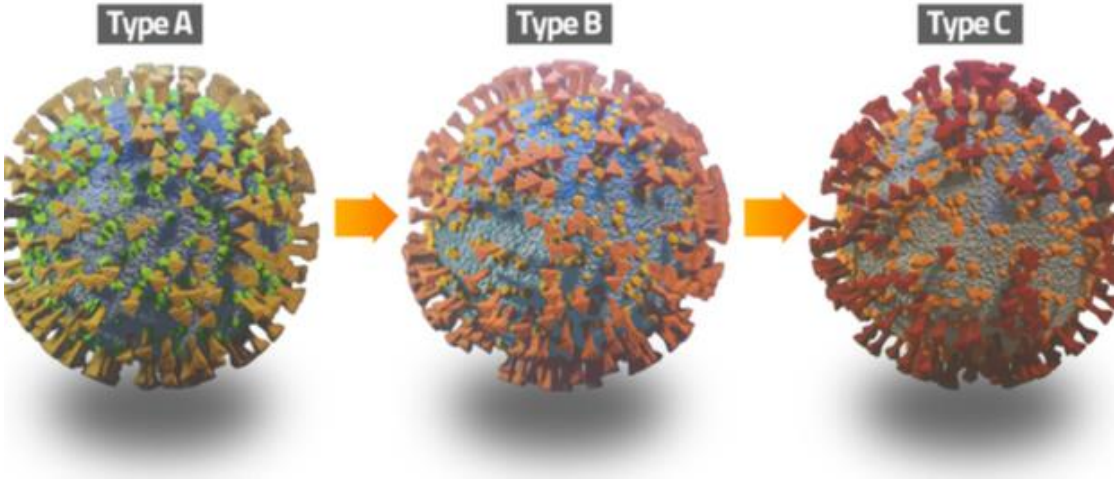
- All viruses mutate - and evolve with selective pressure
- SARS-CoV-2 mutates relatively slowly, but huge number of infections gives it many chances
- Concern is if mutants have dangerous new properties
  - Increased transmission
  - Increased severity
  - Resistance to treatments (esp Abs)

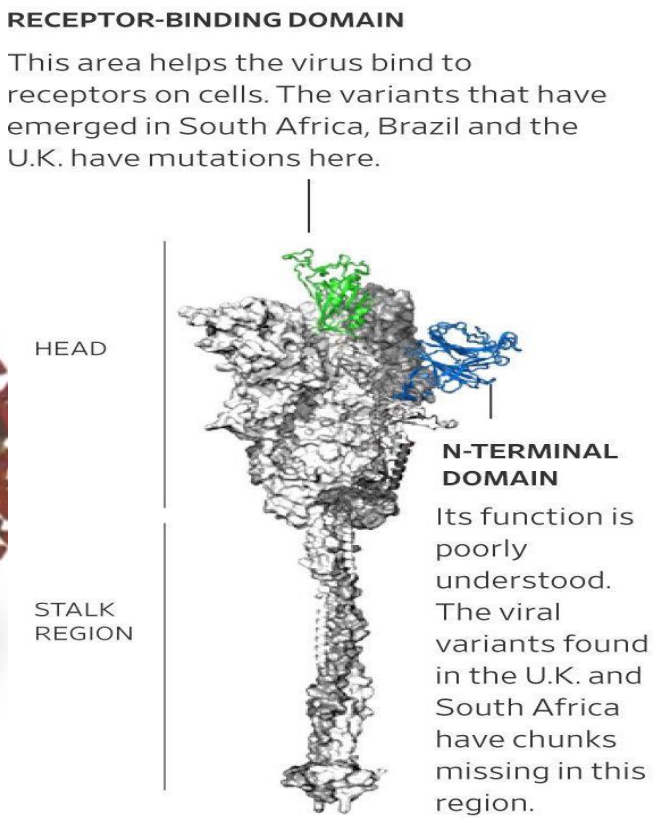
SARS-CoV-2 Evolution During 2020



What Could Go Wrong?

Antibodies May Not “Recognize” Spike Protein with Too Much Change

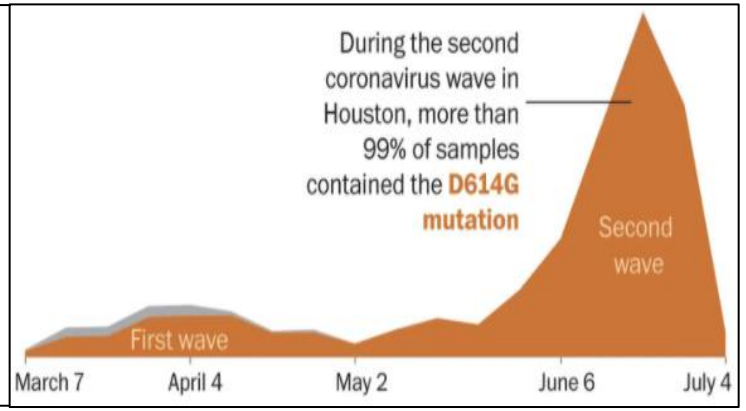


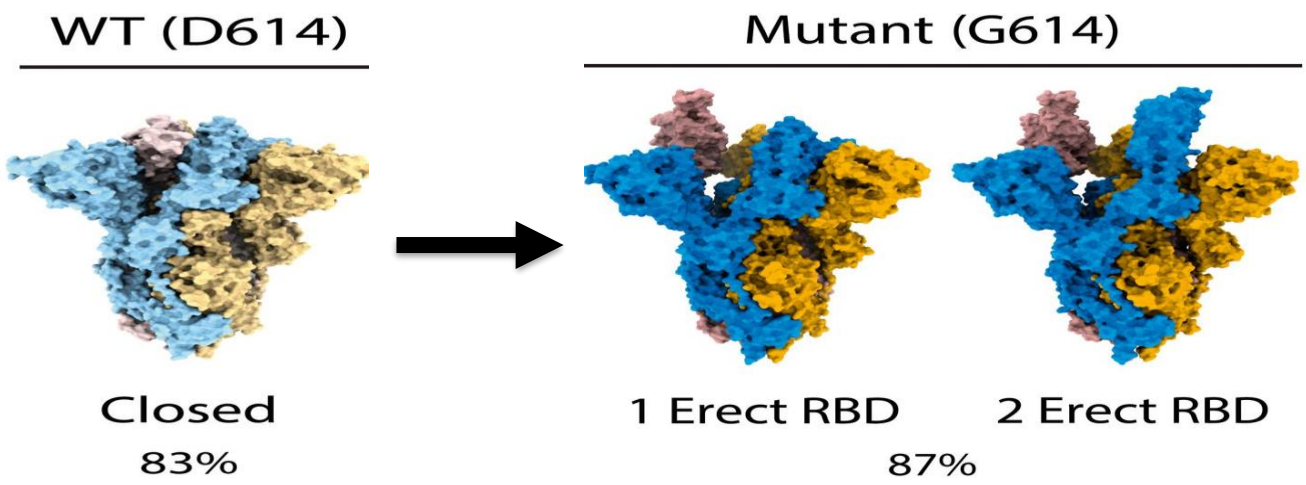


What Could Go Wrong?

Viral mutations

- D614G
  - Set of 4 mutations
  - Rapidly became dominant
  - May be more sensitive to antibodies

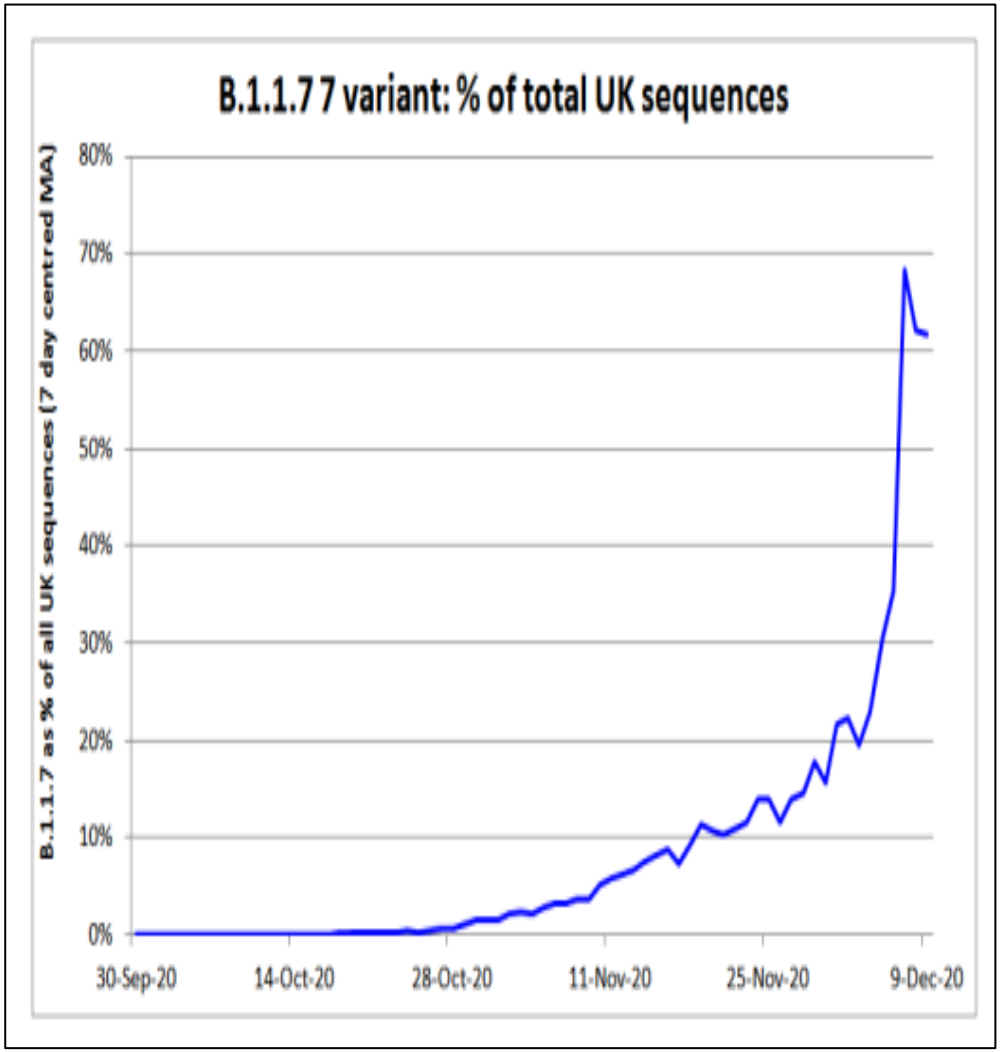




What Could Go Wrong?

Viral mutations

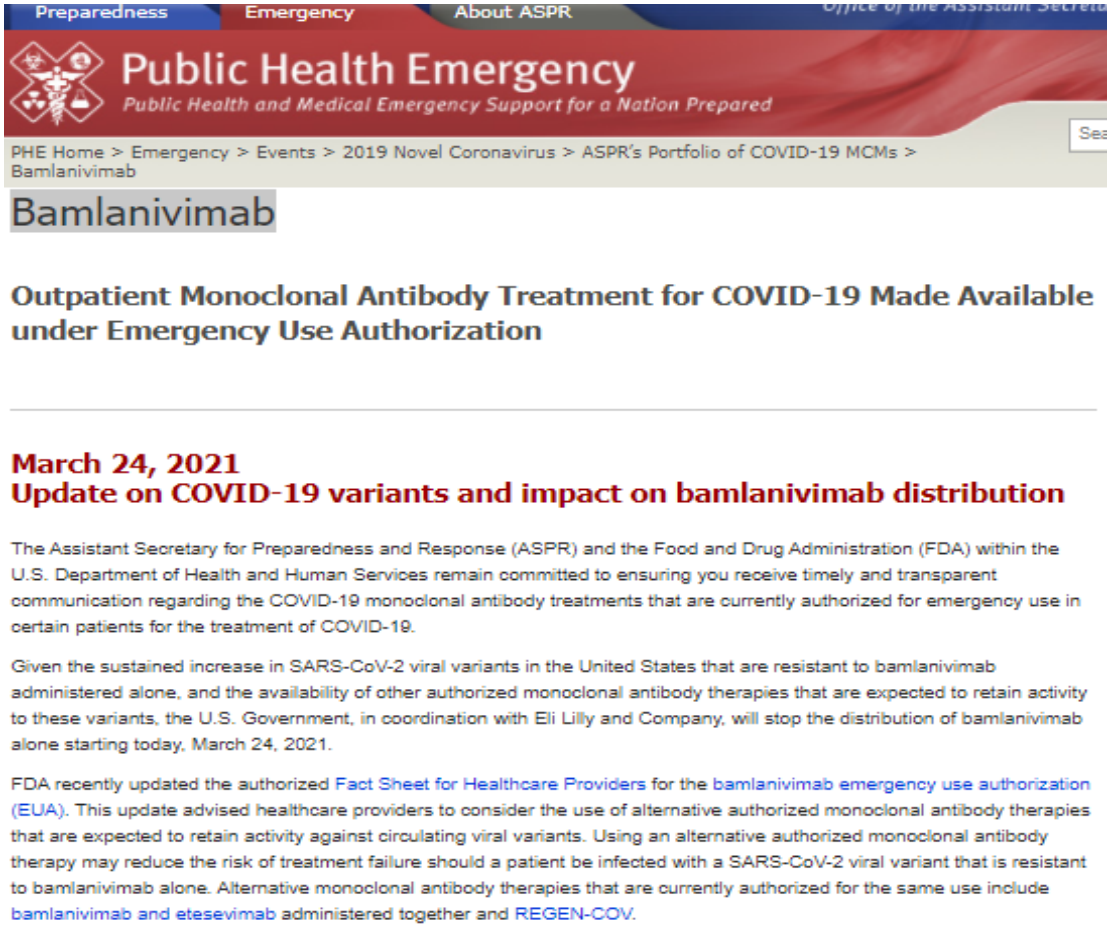
- N501Y
  - B.1.1.7 (501.Y.V1) – U.K.
  - 501.Y.V2 – S. Africa
  - P.1 – Brazil
  - All have other mutations
  - All appear more transmissible



Viral Variants and mAb Therapy

March 24, 2021:

US government and Eli Lilly stop distributing single monoclonal antibody preparation



Preparedness | Emergency | About ASPR

Public Health Emergency

Public Health and Medical Emergency Support for a Nation Prepared

PHE Home > Emergency > Events > 2019 Novel Coronavirus > ASPR's Portfolio of COVID-19 MCMs > Bamlanivimab

Bamlanivimab

Outpatient Monoclonal Antibody Treatment for COVID-19 Made Available under Emergency Use Authorization

March 24, 2021
Update on COVID-19 variants and impact on bamlanivimab distribution

The Assistant Secretary for Preparedness and Response (ASPR) and the Food and Drug Administration (FDA) within the U.S. Department of Health and Human Services remain committed to ensuring you receive timely and transparent communication regarding the COVID-19 monoclonal antibody treatments that are currently authorized for emergency use in certain patients for the treatment of COVID-19.

Given the sustained increase in SARS-CoV-2 viral variants in the United States that are resistant to bamlanivimab administered alone, and the availability of other authorized monoclonal antibody therapies that are expected to retain activity to these variants, the U.S. Government, in coordination with Eli Lilly and Company, will stop the distribution of bamlanivimab alone starting today, March 24, 2021.

FDA recently updated the authorized Fact Sheet for Healthcare Providers for the bamlanivimab emergency use authorization (EUA). This update advised healthcare providers to consider the use of alternative authorized monoclonal antibody therapies that are expected to retain activity against circulating viral variants. Using an alternative authorized monoclonal antibody therapy may reduce the risk of treatment failure should a patient be infected with a SARS-CoV-2 viral variant that is resistant to bamlanivimab alone. Alternative monoclonal antibody therapies that are currently authorized for the same use include bamlanivimab and etesevimab administered together and REGEN-COV.

Viral Variants and Vaccines

Vaccine Efficacy	UK - B.1.1.7	S Africa - B.1.351
Pfizer	85% (SIREN study)	1.25 - 6x reduction*
Moderna	89%	4x -10x reduction*
J&J	72% (USA data)	57%
Astra Zeneca	76%	10%

***Data from the lab in model systems. May not reflect real life.**

For example, Pfizer vaccine was 100% effective in preventing COVID-19 infection in S Africa trial

Variants in Houston

- Houston Methodist Department of Pathology and Genomic Medicine is sequencing genomes of virtually all SARS-CoV-2 infections detected in our population
- Based on 10,300 viral genomes to date
- Variant of interest
  - B.1.526 (*n* = 19), B.1.525 (*n* = 21), P.2 (*n* = 84)
- Variant of concern
  - **B.1.1.7 (*n* = 1243)**, B.1.351 (*n* = 4), P.1 (*n* =14)
  - B.1.427 (*n* = 78), **B.1.429 (*n* = 326)**
- **Most recent samples show the B.1.1.7 variant is ~70% of samples**
  - Fortunately, all three approved vaccines are efficacious against this variant
  - If variant acquires E484K mutation, that could change

Summary: Viral Variants

- Viral variants are an expected development
- Medical significance varies
- Variants are a minority of cases in Houston Methodist population
  - B.1.1.7 will be the dominant strain in Houston this spring
- Reduction in antibody (post-infection or post-vaccination) effectiveness?
  - Variants have evaded single monoclonal antibody preparation – two mAb's needed now
  - Lab data suggest reduced – but preserved - efficacy of immune (convalescent or vaccinated) serum against model viruses
  - Data do not show significant reduction in clinical efficacy of FDA-cleared vaccines against current variants
  - Likely that boosters will be needed in future

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