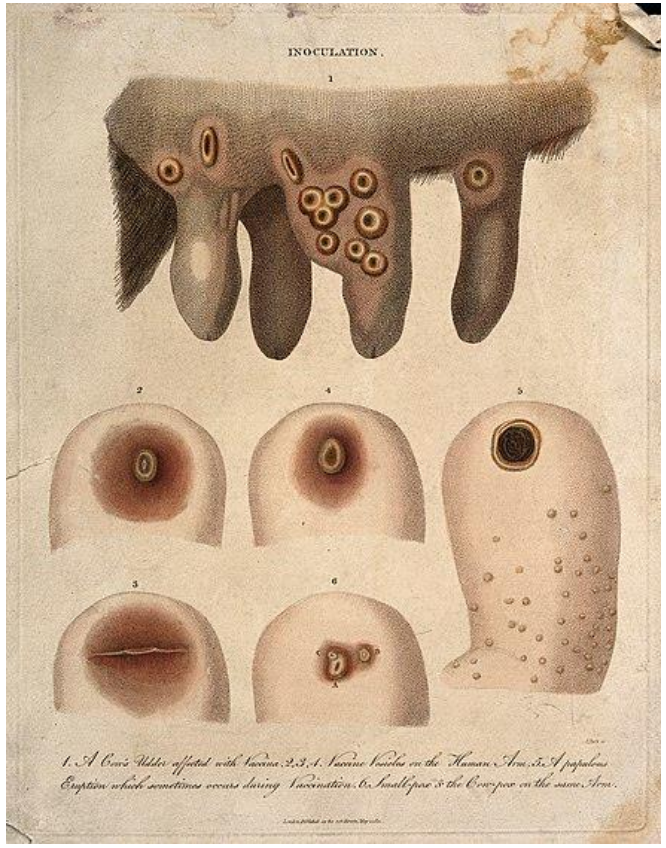
Beginnings of Vaccination

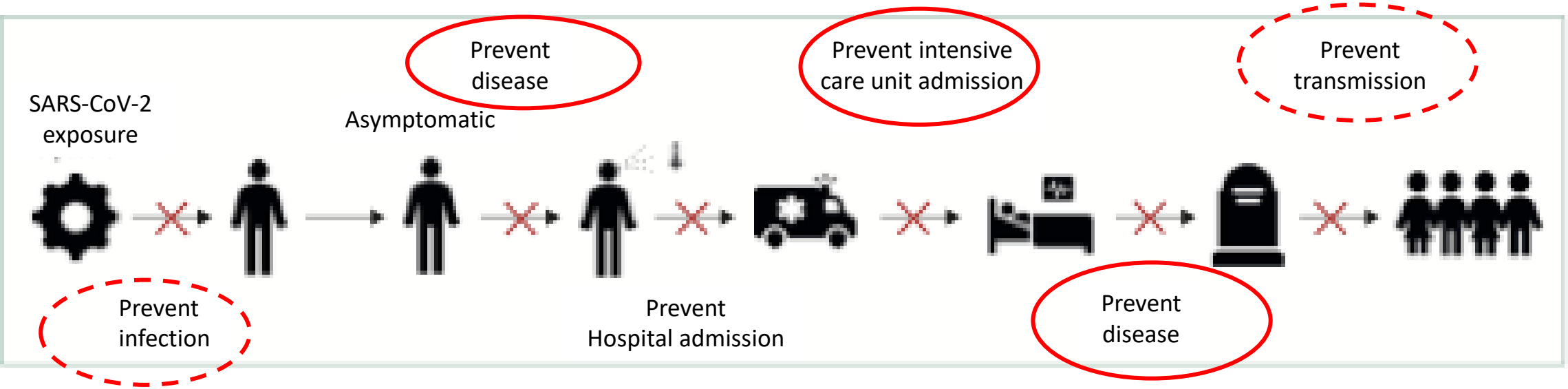


Edward Jenner, Vaccination, 1796 with cowpox material

Pandemic Situationer

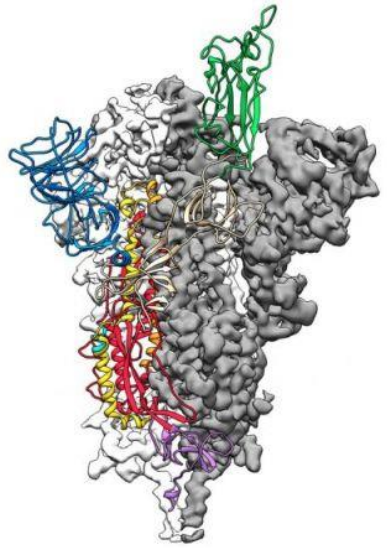
What we need to know about the Technology of Vaccines

Objectives of an Efficacious COVID-19 vaccine



- The most important efficacy endpoint = The ability of a vaccine to **protect against severe disease and mortality ,** as hospital and critical-care admissions place the greatest burden on health-care systems. = the vaccine is efficacious in **older adults** (eg, approximately >60 years)
- The other important efficacy endpoint = ability to **reduce the transmissibility of SARS-CoV-2**

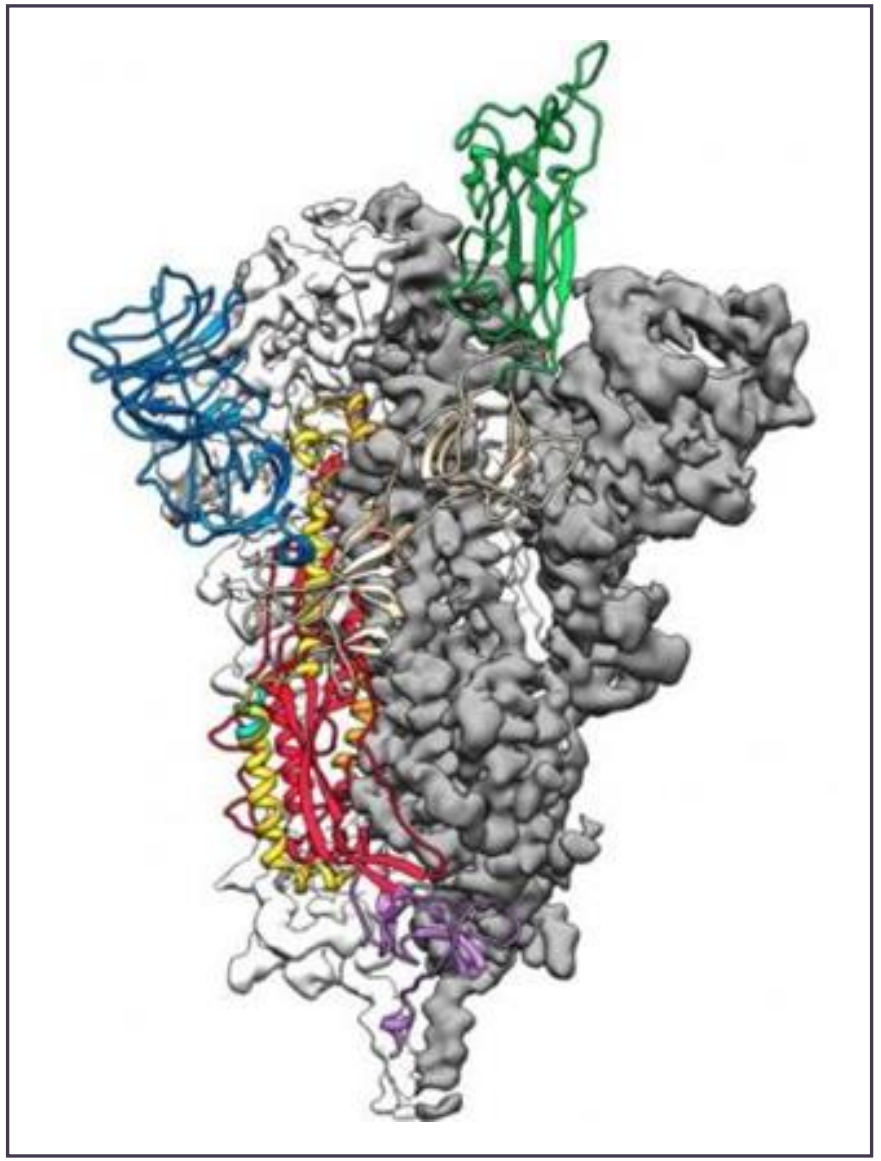
SH Hodgson et al. ***Lancet Infect Dis*** **2020** https://doi.org/10.1016/ S1473-3099(20)30773-8



Meet the novel Coronavirus, SARS CoV-2

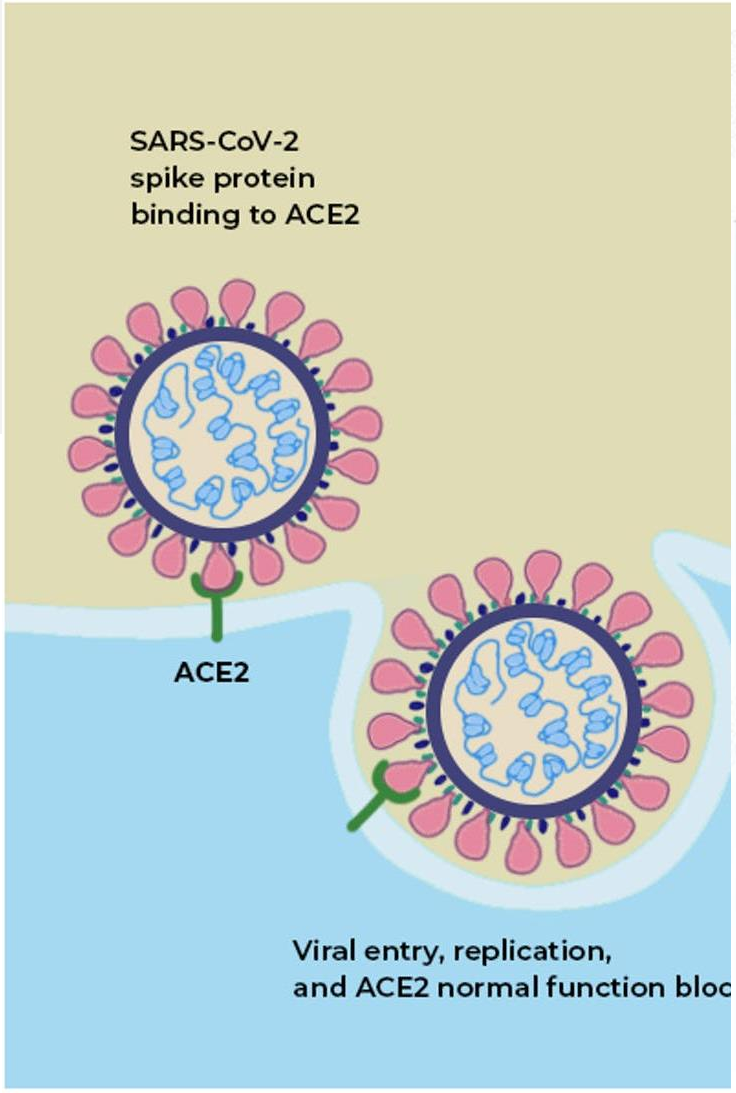
The Spike Protein

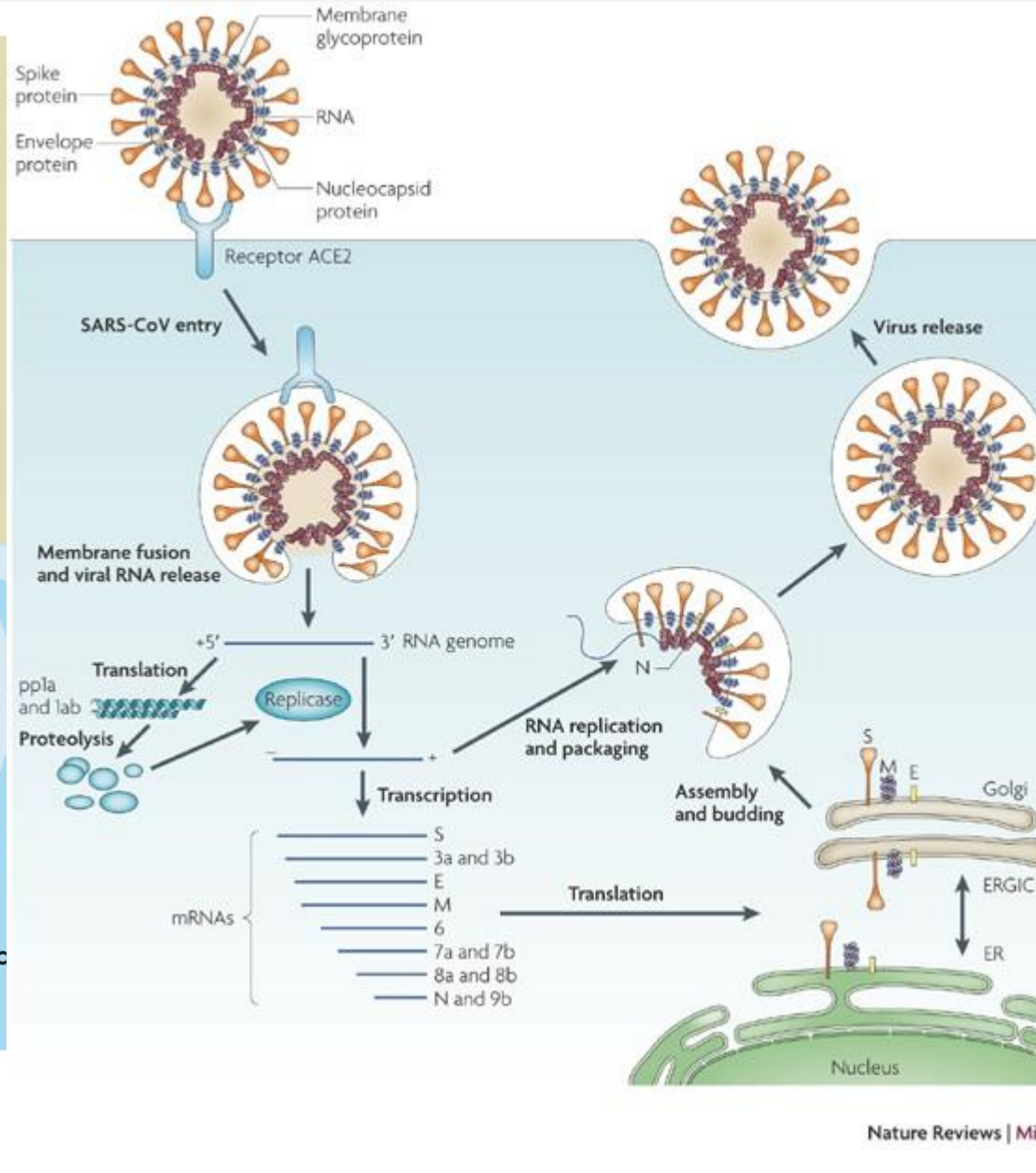
- the major surface protein that it uses to bind to a receptor — another protein that acts like a doorway into a human cell.
- Viral membrane fuses with the human cell membrane, allowing the genome of the virus to enter human cells and begin infection.
- Prevent Attachment and fusion, prevent infection…



Invasion of respiratory epithelial cell by SARS CoV 2

- The variant with spike G614 has replaced D614 as the dominant pandemic form,
- Now documented locally
- UK Variant B.1.1.7, So.African B1351, and now, the PH B.1.1.28





Vaccines Are Complex Biologic Products[1]

Composed of large and heterogeneous molecular compounds derived from biological materials.[1]

Quality testing that may take months.[2,3]

Longer production lead time than a traditional medicinal product.[2,4,5]

Requires stringent quality testing and regulation at all stages of the manufacturing and production process to generate a final product that is highly consistent in purity, potency, and safety.[2,3]

Rigorous quality compliance is required for batch release approval after each step of the manufacturing process.[2]

Primary Goals of Phase I/II Vaccine Trials

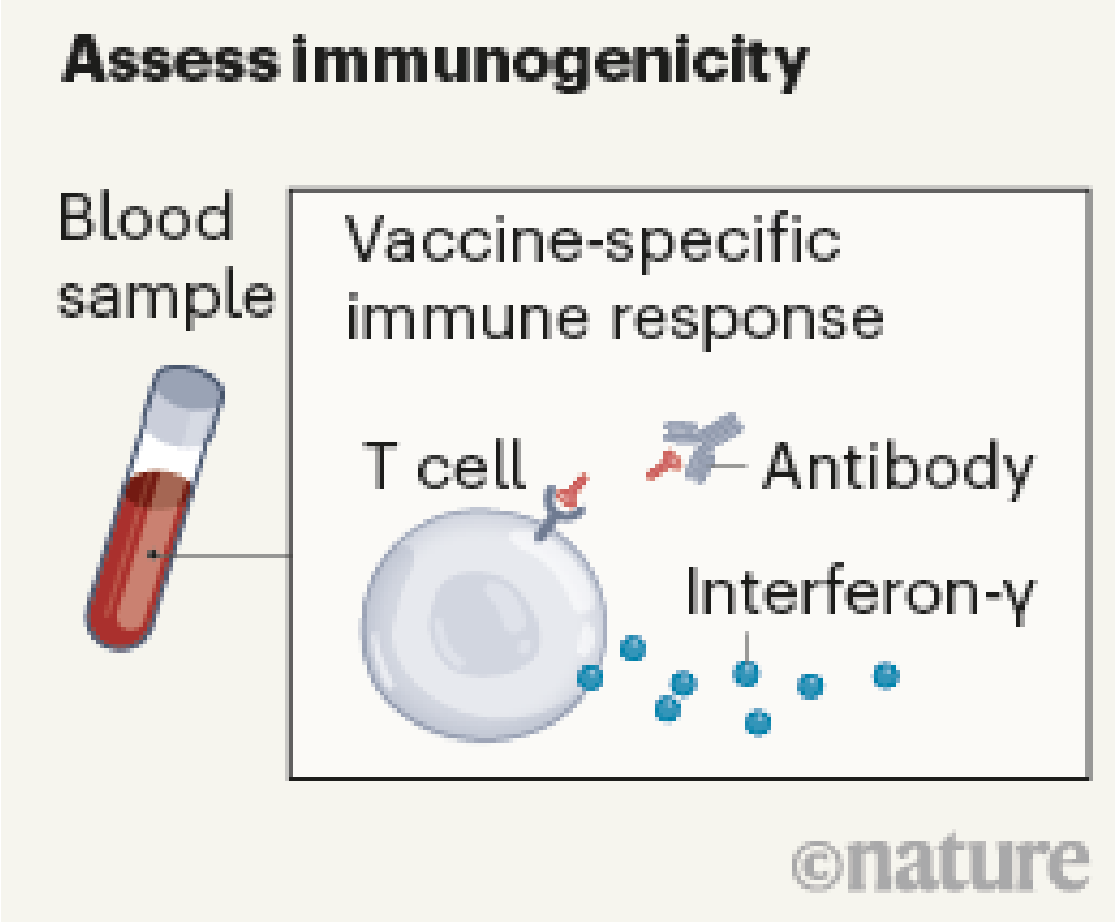
- Evaluate short-term safety, check dosage and assess aspects of the body's reaction to the vaccine… **REACTOGENICITY**
- Includes localized pain, redness or swelling at the site of vaccine injection, systemic symptoms elsewhere in the body, such as fever, muscle pain and headache.

https://www.nature.com/articles/d41586-020-02926-w

Secondary Goals Ph1/II

Immunogenicity — the ability of a vaccine to stimulate a detectable immune response to the vaccine target…the Adaptive branch of the immune system.

Features of interest are vaccine-specific antibody responses and immune cells called CD4 (or helper) T cells and CD8 (cytotoxic) T cells. These T cells can directly target cells infected with the virus, or collaborate with antibody-producing B cells.



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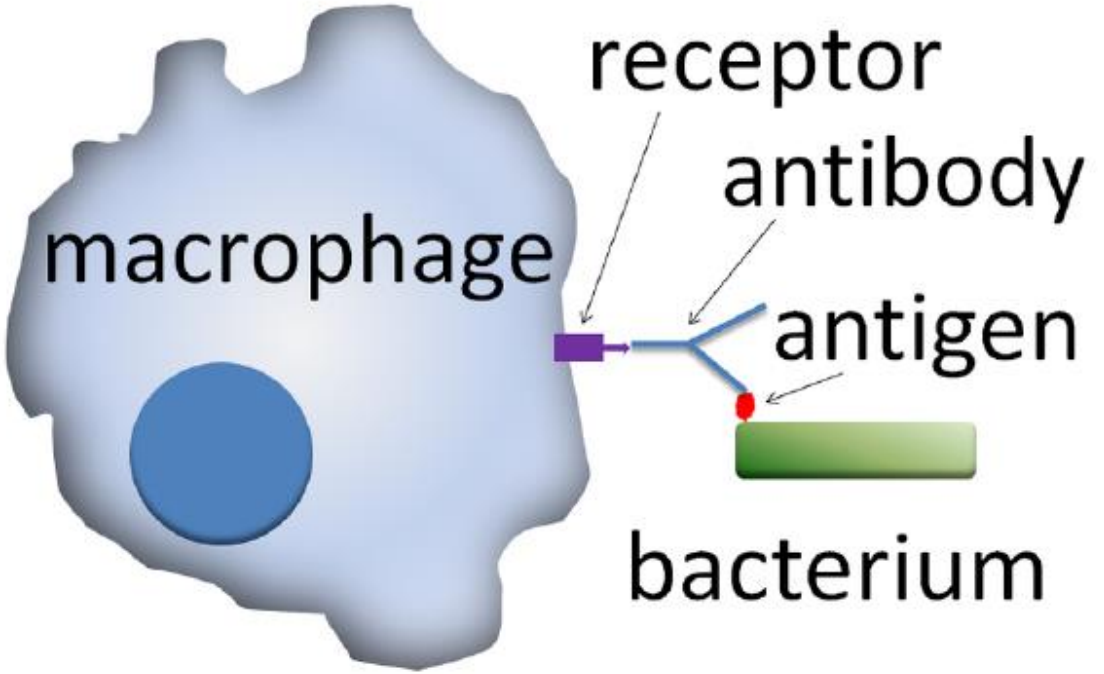


Figure 1: Opsonization

https://pediaa.com/difference-between-humoral-and-cell-mediated-immunity/

Humoral Response

- Aim is to destroy the extracellular foreign invader…
- Antibodies specifically target the antigen. End up NEUTRALIZING. Prevent entry into cells. Trap also any toxins.
- Recruit macrophages for opsonization…
- Complement System recruits more macrophages

Cell Mediated Immunity

https://pediaa.com/difference-between-humoral-and-cell-mediated-immunity/

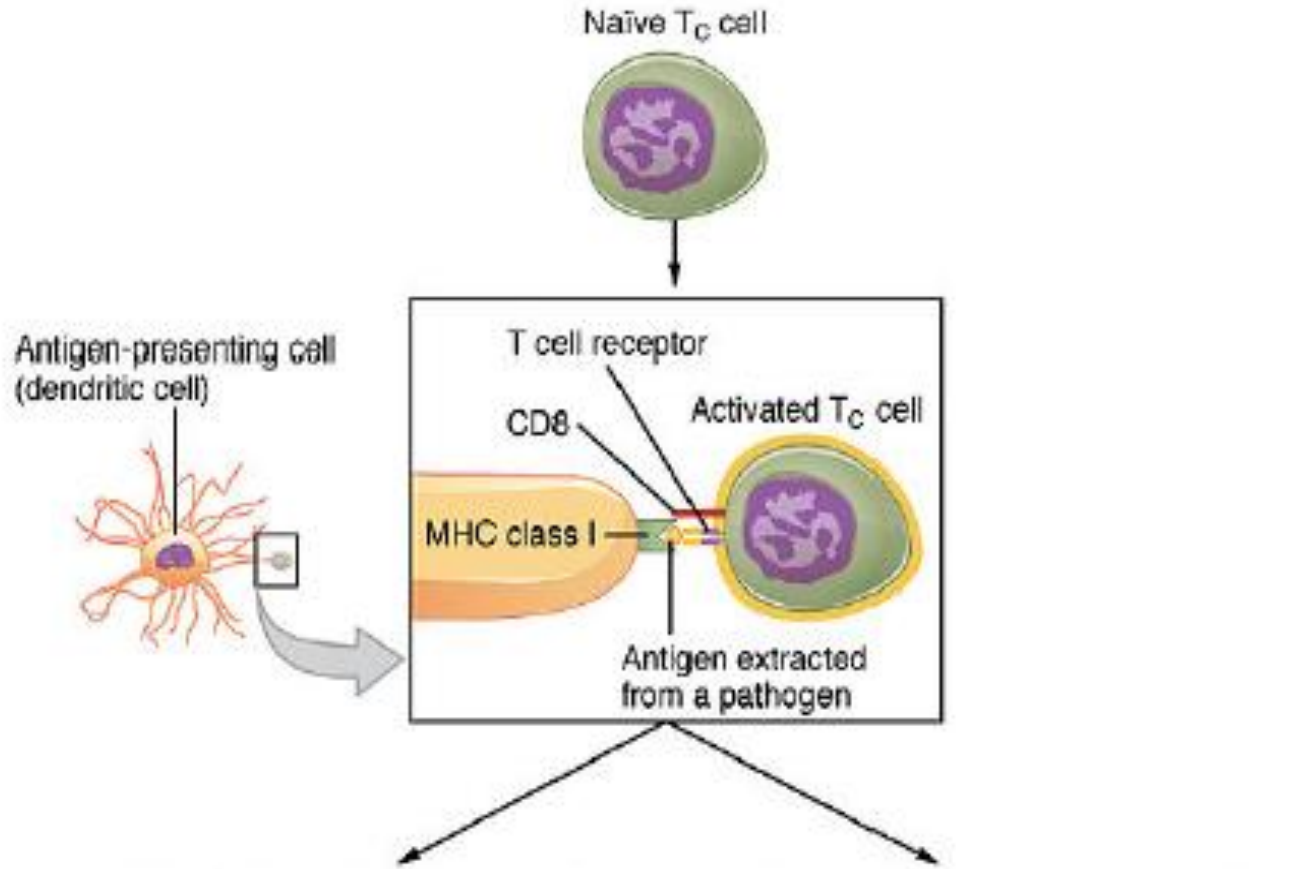


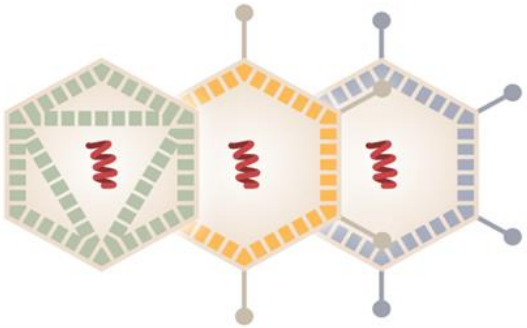
Figure 2: Cell Mediated Immunity

Whole-Virus Vaccines

Vaccines that use a weakened or inactivated version of the coronavirus to provoke an immune response.

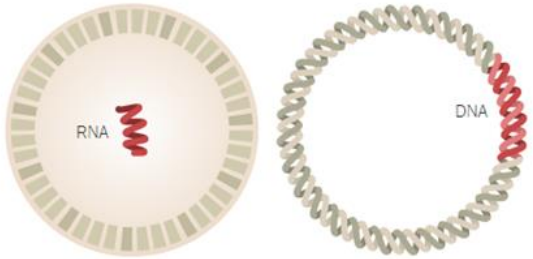
Viral Vector Vaccines

Vaccines that use a virus to deliver coronavirus genes into cells and provoke an immune response.



Genetic Vaccines

Vaccines that use one or more of the coronavirus's own genes to provoke an immune response.



Protein-Based Vaccines

Vaccines that use a coronavirus protein or a protein fragment to provoke an immune response.

Different Vaccine Platforms

Aim to elicit responses that produce long lasting 'neutralizing' antibodies

Viral Vectors

Replicating

- live attenuated, replicating vaccines, highly effective protection against viral infection and disease
- Potential lifetime immunity
- Concerns arise over the possibility of disease induction in vaccinated immunocompromised individuals

Non-Replicating

- generally of more limited duration.
- Key factor is safety.

Current Opinion in Biotechnology 2007, 18:546–556

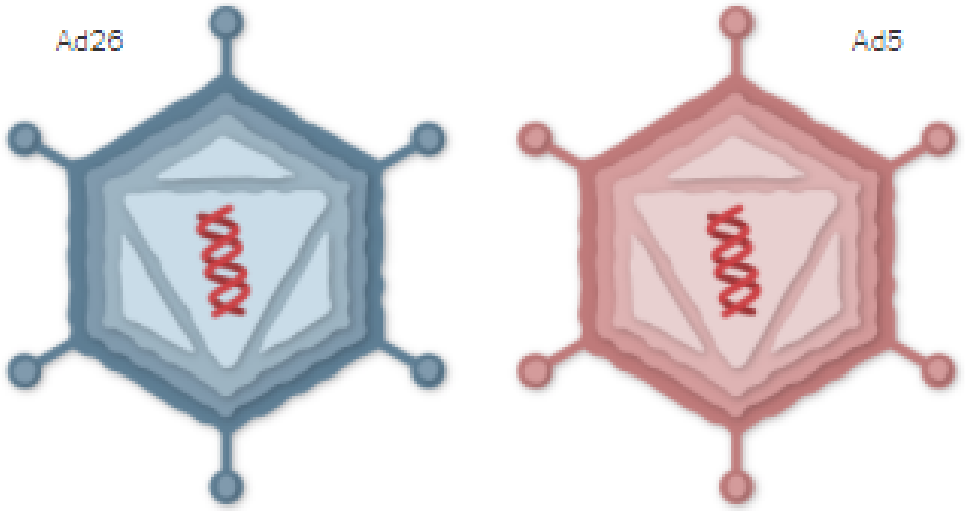
Adenovirus… a highly attractive vector

- As Ad target epithelial cells, they are prime candidates for elicitation of mucosal as well as systemic immunity.
  - Infection of both dividing and non-dividing cells,
- High levels of transgene expression,
- Ability to grow to high titers in vitro, physical and genetic stability.
- Lack of integration in the host genome
- Importantly, Ad infect dendritic cells, upregulate co-stimulatory molecules, and elicit cytokine and chemokine responses
- Effectively presenting antigens to the immune system and eliciting potent immune responses

Current Opinion in Biotechnology 2007, 18:546–556

DNA Inside Adenoviruses

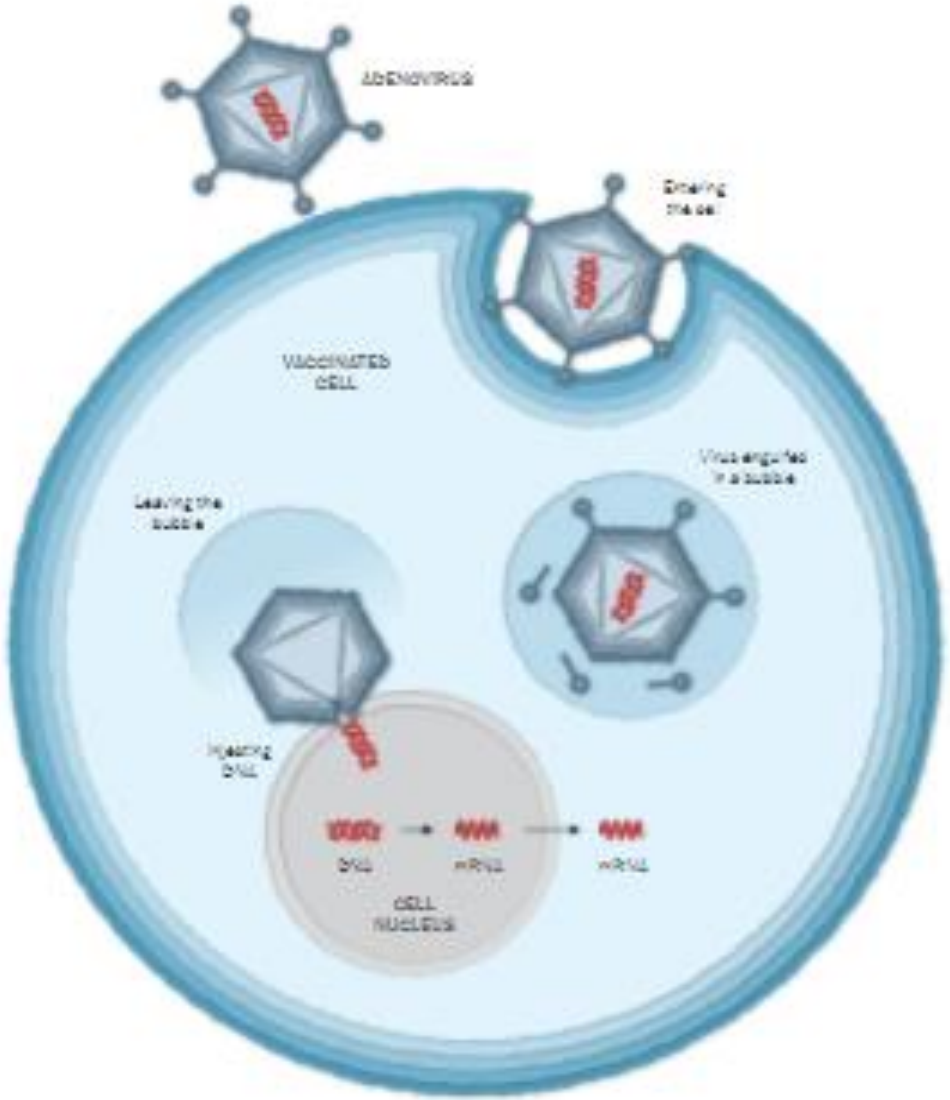
The researchers developed their vaccine from adenoviruses, a kind of virus that causes colds. They added the gene for the coronavirus spike protein gene to two types of adenovirus, one called Ad26 and one called Ad5, and engineered them so they could invade cells but not replicate.



Sputnik V comes out of decades of research on adenovirus-based vaccines. The first one was approved for general use last year — a vaccine for Ebola, made by Johnson & Johnson. Some other coronavirus vaccines are also based on adenoviruses, such as one from Johnson & Johnson using Ad26, and one by the University of Oxford and AstraZeneca using a chimpanzee adenovirus.

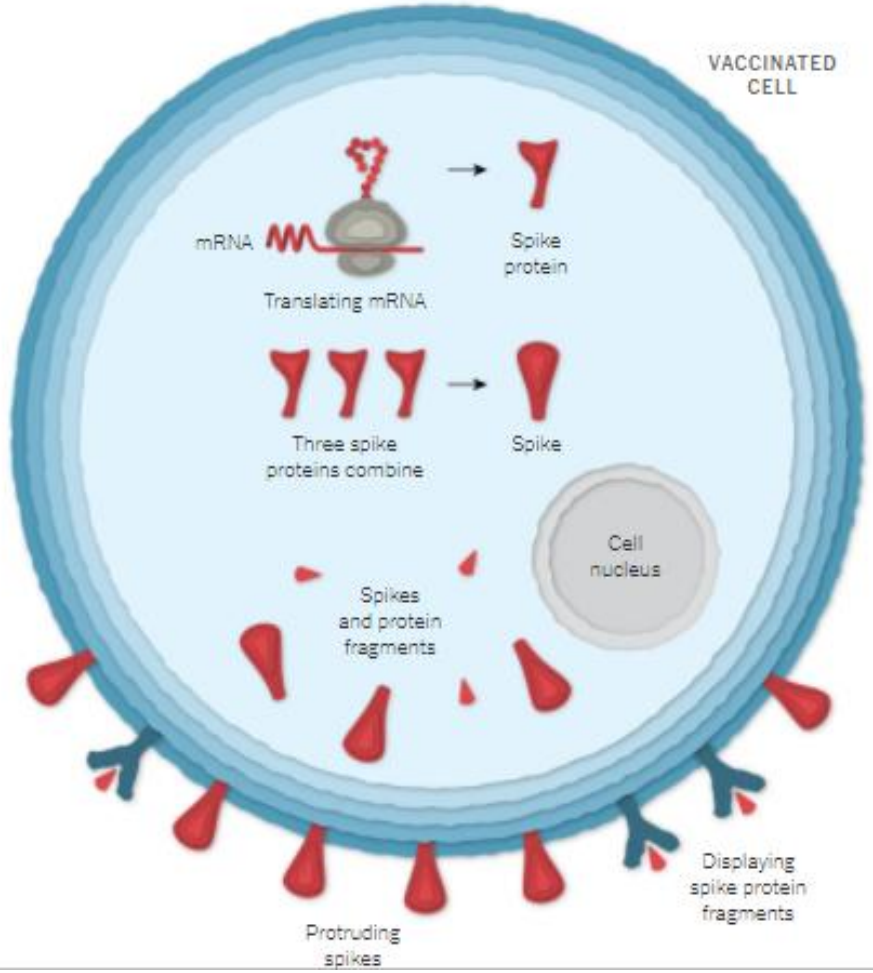
Entering a Cell

After Sputnik V is injected into a person's arm, the adenoviruses bump into cells and latch onto proteins on their surface. The cell engulfs the virus in a bubble and pulls it inside. Once inside, the adenovirus escapes from the bubble and travels to the nucleus, the chamber where the cell's DNA is stored.



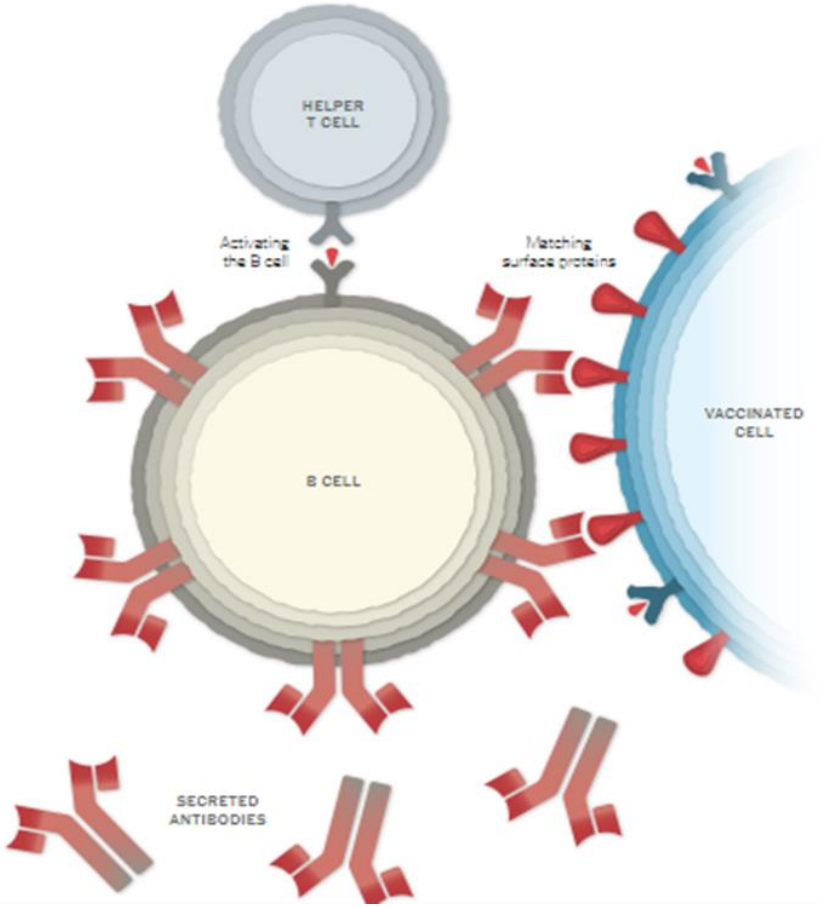
Building Spike Proteins

The mRNA leaves the nucleus, and the cell's molecules read its sequence and begin assembling spike proteins.



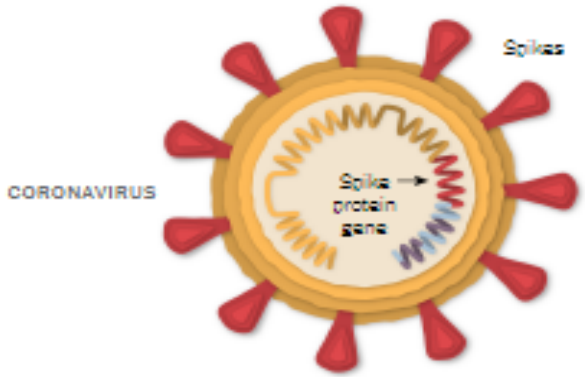
Making Antibodies

Other immune cells, called B cells, may bump into the coronavirus spikes on the surface of vaccinated cells, or free-floating spike protein fragments. A few of the B cells may be able to lock onto the spike proteins. If these B cells are then activated by helper T cells, they will start to proliferate and pour out antibodies that target the spike protein.



A Piece of the Coronavirus

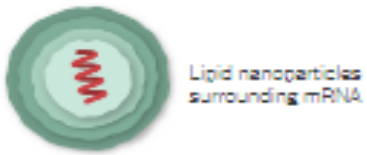
The SARS-CoV-2 virus is studded with proteins that it uses to enter human cells. These so-called spike proteins make a tempting target for potential vaccines and treatments.



Like the Pfizer-BioNTech vaccine, Moderna's vaccine is based on the virus's genetic instructions for building the spike protein.

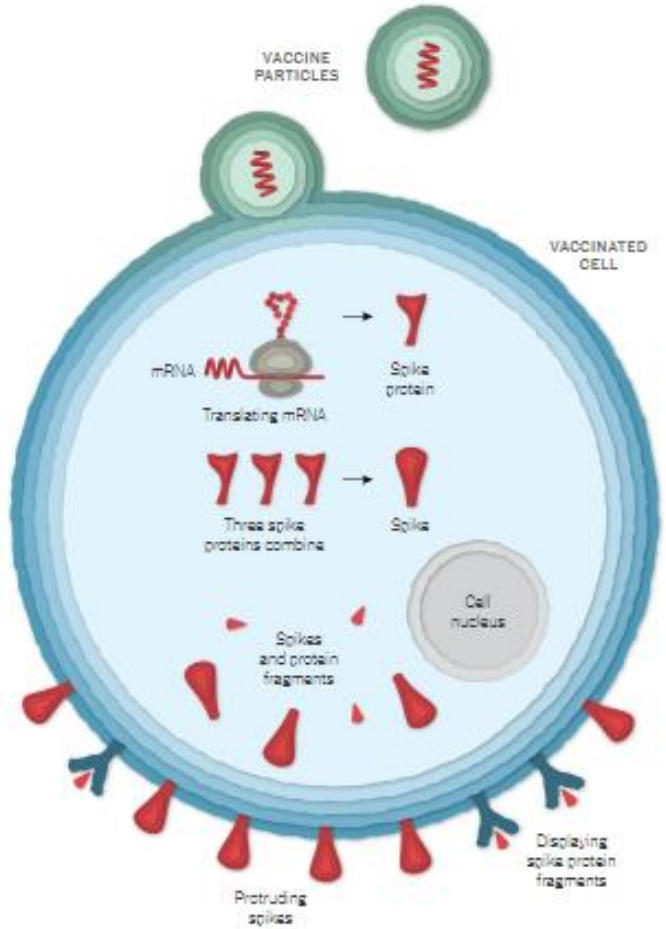
mRNA Inside an Oily Shell

The vaccine uses messenger RNA, genetic material that our cells read to make proteins. The molecule — called mRNA for short — is fragile and would be chopped to pieces by our natural enzymes if it were injected directly into the body. To protect the vaccine, Moderna wraps the mRNA in oily bubbles made of lipid nanoparticles.



Entering a Cell

After injection, the vaccine particles bump into cells and fuse to them, releasing mRNA. The cell's molecules read its sequence and build spike proteins. The mRNA from the vaccine is eventually destroyed by the cell, leaving no permanent trace.



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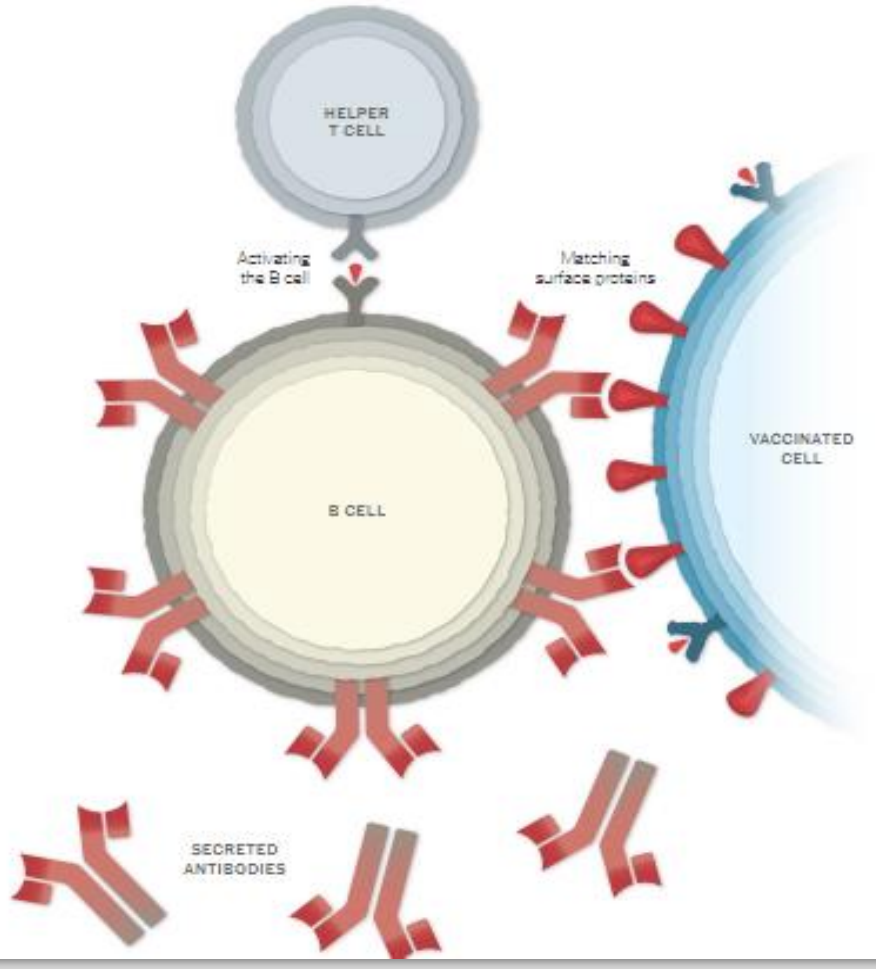
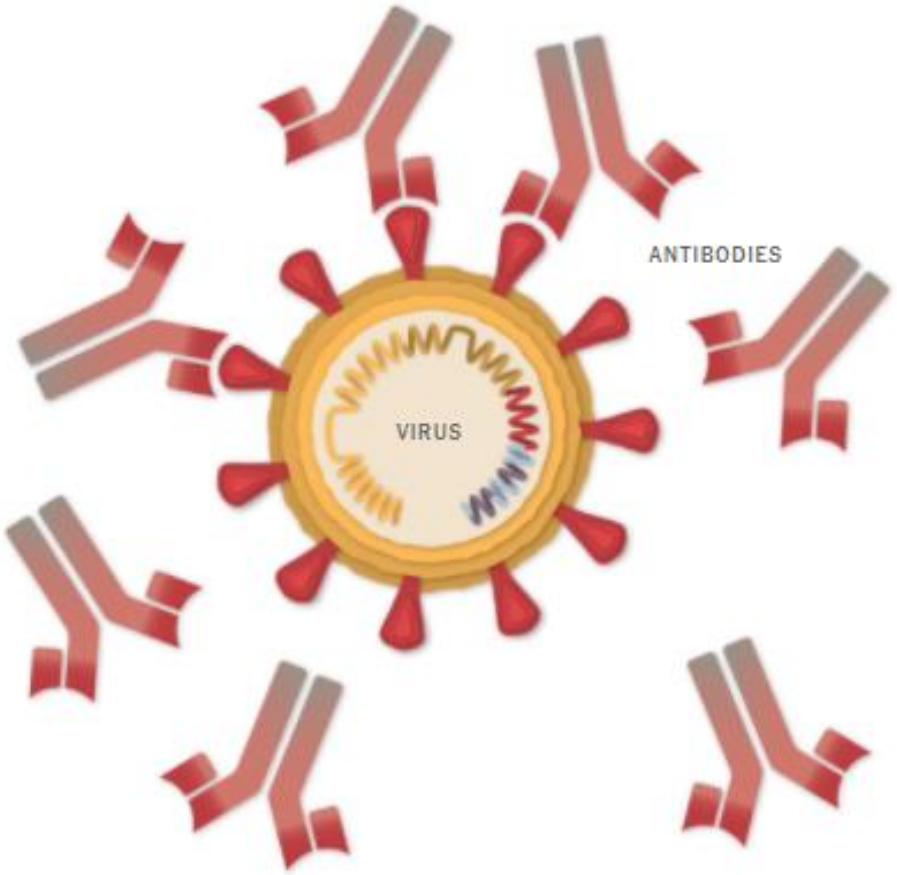
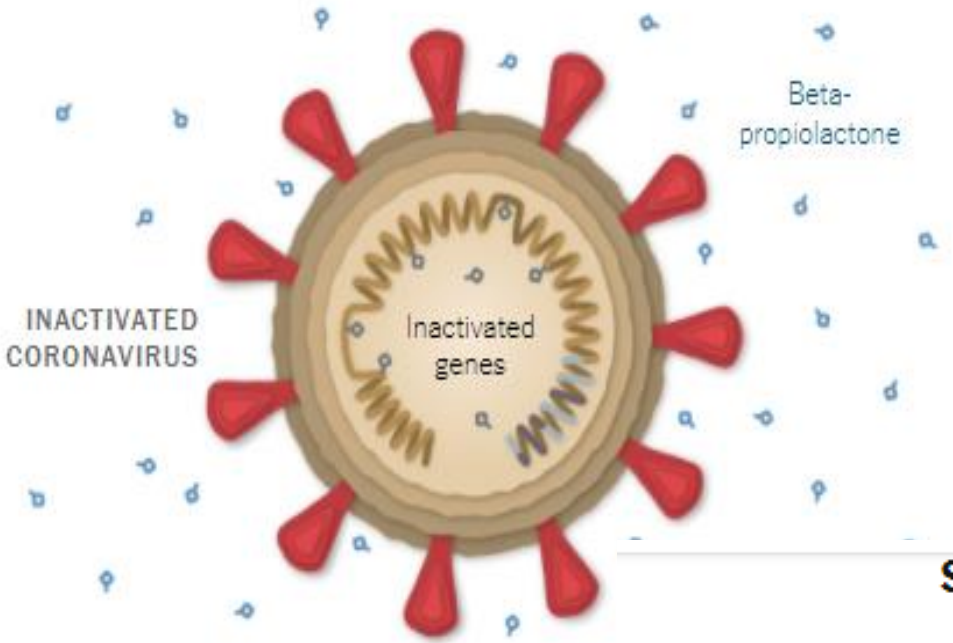


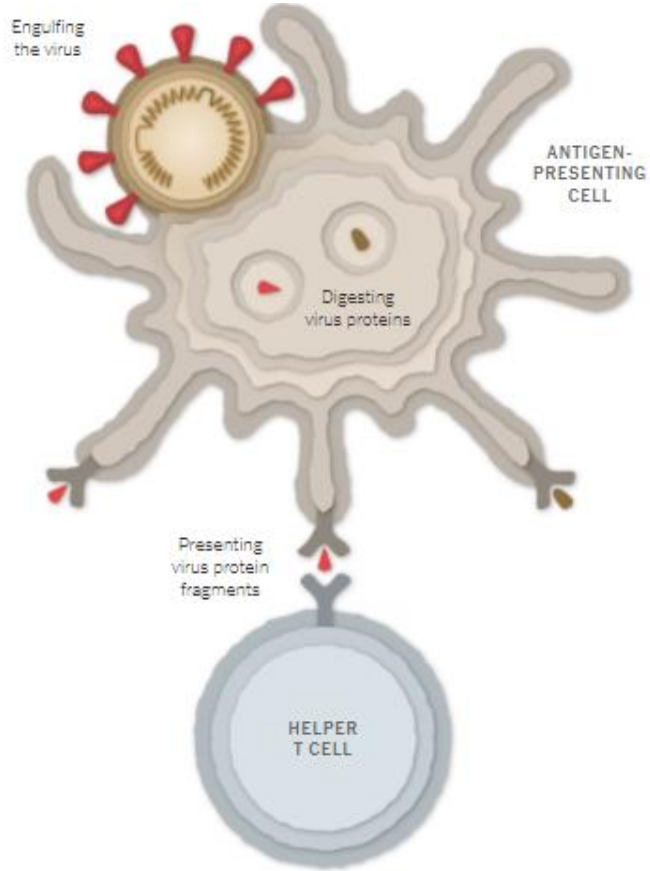
Stopping the Virus

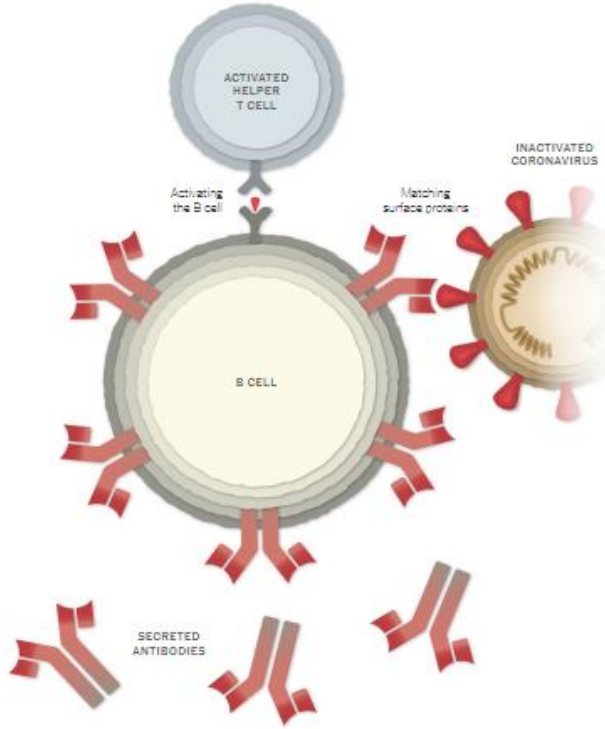
'he antibodies can latch onto coronavirus spikes, mark the virus ɔr destruction and prevent infection by blocking the spikes from ttaching to other cells.



The researchers grew large stocks of the coronavirus in monkey kidney cells. Then they doused the viruses with a chemical called beta-propiolactone. The compound disabled the coronaviruses by bonding to their genes. The inactivated coronaviruses could no longer replicate. But their proteins, including spike, remained intact.

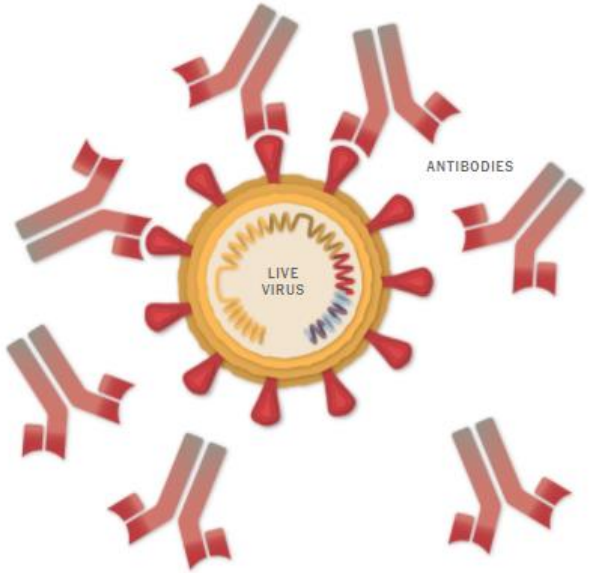






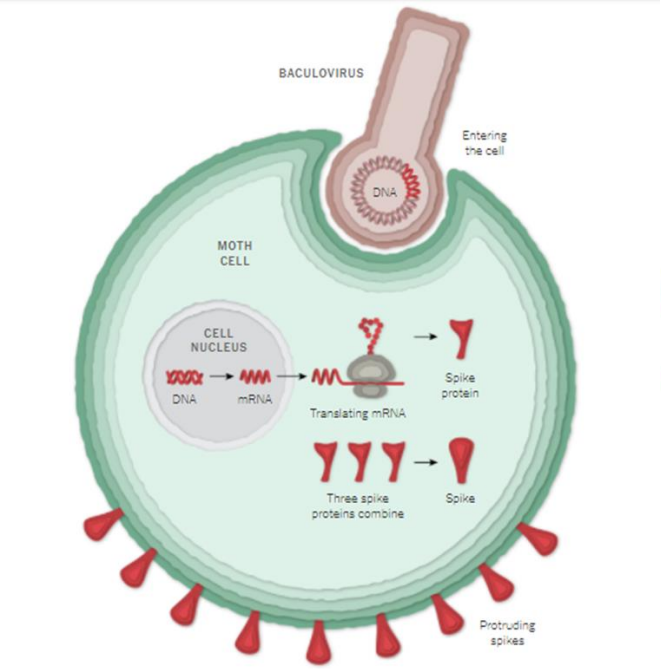
Stopping the Virus

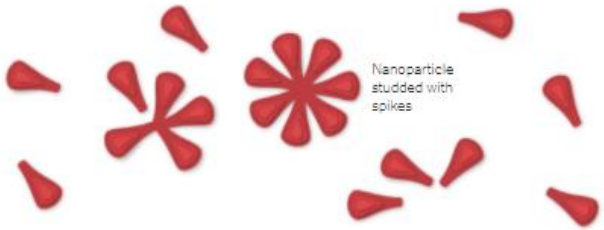
Once vaccinated with CoronaVac, the immune system can respond to an infection of live coronaviruses. B cells produce antibodies that stick to the invaders. Antibodies that target the spike protein can prevent the virus from entering cells. Other kinds of antibodies may block the virus by other means.

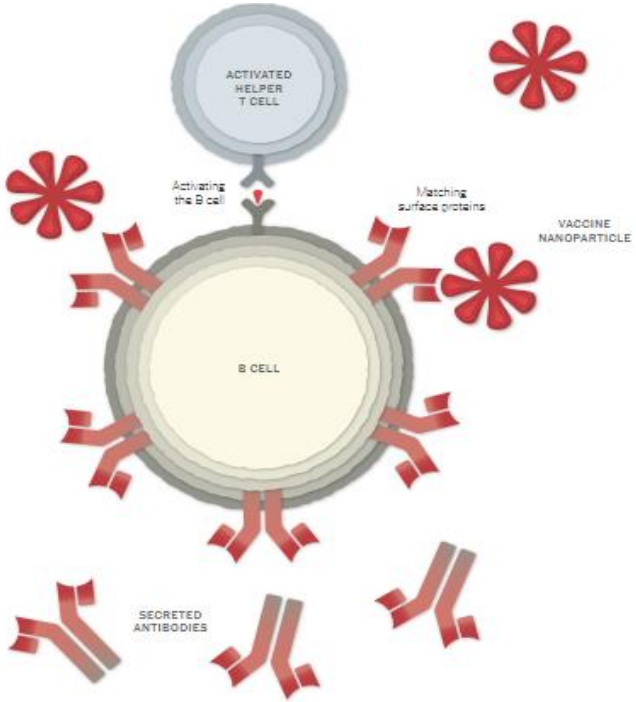


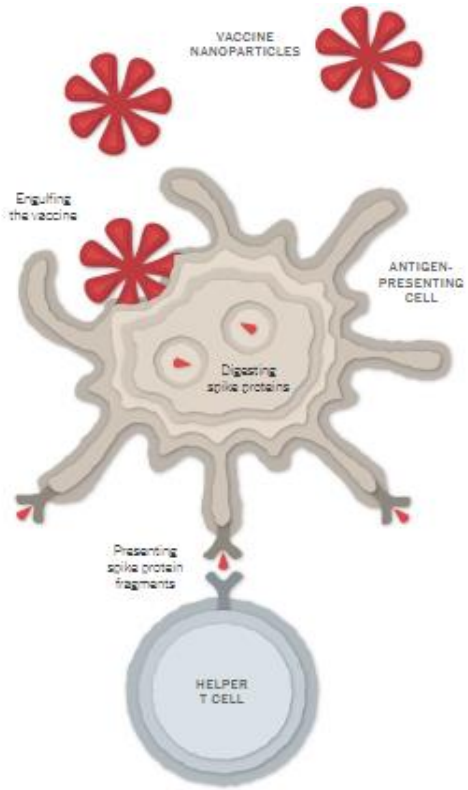
Protein Based

- Insert RNA for spike protein into baculovirus
- Infect Moth cells, and collect spike protein from surface
- Assemble into nanoparticles that mimic coronavirus (but non infectious).
- Inject nano particles into human, and generate antibodies from the Helper T Cells and B Cells









Efficacy of Vaccines to date…

	Doses	Total Sample	Total Endpoints	All Endpoints	"Severe" Infections	Protection Death or Hospitalization
J&J	1	43,783	464	Vaccine 116 Placebo 348	Vaccine 5 Placebo 34	100%
Pfizer	2	43,355	170	Vaccine 8 Placebo 162	Vaccine 1 Placebo 9	100%
Moderna	2	28,207	236	Vaccine 11 Placebo 225	Vaccine 0 Placebo 30*	100%#
Novavax	2	>15,000	62**	Vaccine 6 Placebo 56	Vaccine 0 Placebo 1	100%
Sputnik	2	21,977	76**	Vaccine 16 Placebo 62	Vaccine 0 Placebo 20	100%

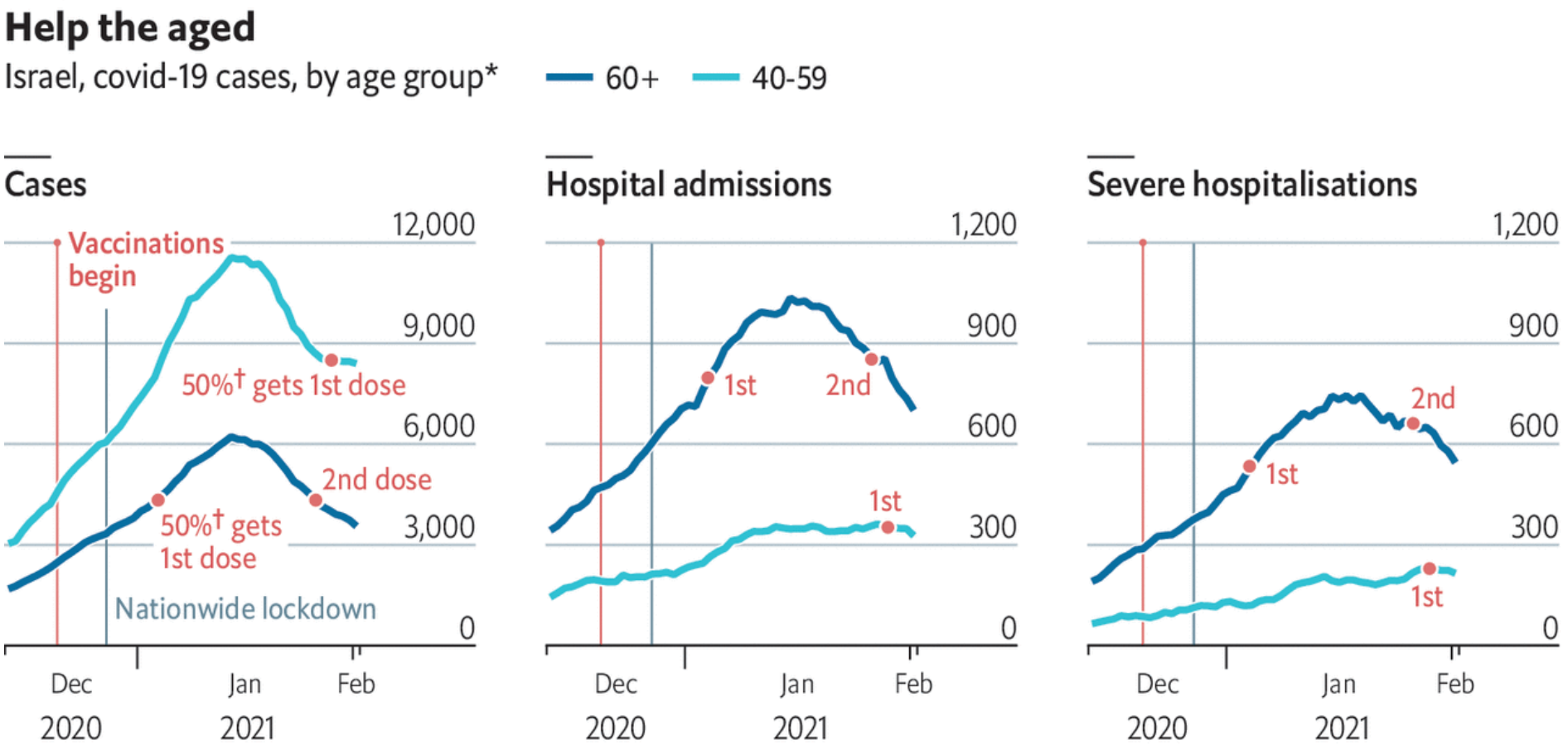
* 1 death, ^after 28 days, 23 events in placebo and 0 in vaccine group, **interim analysis; # 1 patient in vaccine arm hospitalized after 1st dose; Astra Zeneca not included due to admixture of multiple trials and dose regimens, await large US trial results

COVID-19 Vaccine Efficacy

	Gam-COVID-Vac (Sputnik V) [1]	Sinovac CoronaVac Brazil [2]	Sinovac CoronaVac Turkey [2]	Sinovac Indonesia [1]
Study population	n=21,977 3:1 >18 y.o.	n= 9,614 18-59; >60 yo (n=362) high risk HCWs	*n*= 7,374 18-59 yo HCWs and gen pop	*n*= 1,620 18-59 yo, healthy
VE prevention symptomatic COVID	**91.6%** (85·6–95·2) >60 yrs old: **91·8%** (67·1–98·3)	**Overall 50.4%** (CI 35.26-61.98)	**91.25%** (71.25-97.34%)	**65.3%** (16.9-85.5)
VE Prevention of moderate/ Severe COVID	**100%** (94·4–100·0)	**Mild to Moderate** **77.96%** (CI 46.15-90.4) **Severe 100%** (95.4-100)		
VE across age, sex, race, ethnicity underlying medical conditions	**≥87%**			

[1] Logunov et al. The Lancet S0140-6736(21)00191-4; [2] on file (unpublished)

Israel Experience to Date

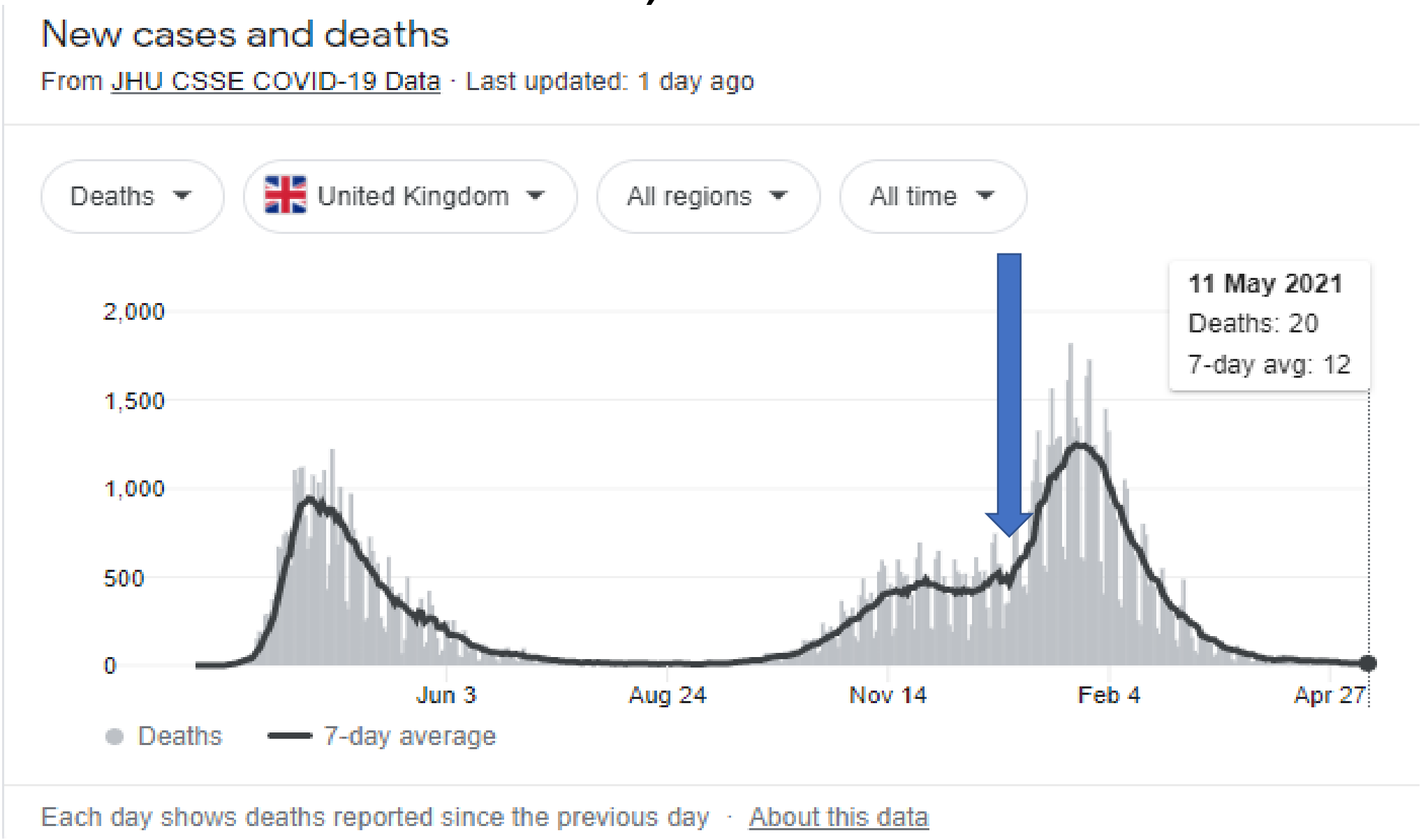


Source: Eran Segal, Hagai Rossman, Smadar Shilo, Tomer Meir, Weizmann Institute of Science, Malka Gorfine, Tel-Aviv University, Uri Shalit, Technion

*Seven-day rolling total †50% of age group received first/second dose of Pfizer-BioNTech vaccine

The Economist

Deaths in the UK, Vaccine Roll Out



Side Effect Profile to date…

Common side effects

On the arm where you got the shot:

- Pain
- Redness
- Swelling

Throughout the rest of your body:

- Tiredness
- Headache
- Muscle pain
- Chills
- Fever
- Nausea

- Anaphylaxis is RARE, particularly for the PEG lipid that coats mRNA
- Safety protocols include readiness to deal with severe allergic reactions
- Allergic reactions (including severe allergic reactions) not related to vaccines (COVID-19 or other vaccines) or injectable therapies, such as allergic reactions related to food, pet, venom, or environmental allergies, or allergies to oral medications (including the oral equivalents of injectable medications), are **not** a contraindication or precaution to COVID-19 vaccination.

CDC recommends the following observation periods after COVID-19 vaccination:

30 minutes: History of an immediate allergic reaction of any severity to a vaccine or injectable therapy

People with a contraindication to a different type of COVID-19 vaccine (for example, people with a contraindication to mRNA COVID-19 vaccines who receive Janssen viral vector vaccine should be observed for 30 minutes following Janssen vaccination).History of anaphylaxis due to any cause

15 minutes: All other people

Summary of Safety Data

	Pfizer BNT162b2 [1]	Moderna M1273 [2]	Astra Zeneca-Oxford AZD-1222 [3]	Gam-COVID-Vac (Sputnik V) [1]	Sinovac CoronaVac Brazil
Dose and interval	2 doses, 30 µg, 0.3 ml each: 3 weeks apart	2 doses , 100 µg, 0.5 ml): 1 month apart	2 doses, SD/SD 1-3 months apart	2 doses, 0.5 ml 3 weeks interval rAd26, rAd5	2 doses , 600 SD, 2 weeks apart
Solicited Local reactions	Pain at injection site Redness and swelling	Pain at injection site Redness, swelling , LAP	Pain at injection site tenderness	flu-like illness, injection site reactions	Pain at injection site Redness, swelling
Solicited Systemic reactions	Fatigue, headache, muscle pain chills, joint pain	Fatigue, headache, myalgia, chills, joint pain	Fatigue, headache, feverishness, and myalgia	headache asthenia	Headache, fatigue , myalgia
Severity	mild or moderate, less common and milder in older adults	mild or moderate, less common and milder in older adults	Mild to moderate	Grade 1 or mild 94%	mild or moderate, less common and milder in older adults
Severe Adverse Events	shoulder injury, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, NO DEATHS related to vaccine	Hypersensitivity reaction NO DEATHS	NO DEATHS related to vaccine	full AE data, will be provided later, publication NO Vaccine related Deaths	None reported NO DEATHS related to vaccine

ADVANTAGES AND DISADVANTAGES OF VIRAL VECTOR-BASED VACCINES

- Well-established technology
- Strong immune response
- Immune response involves B cells and T cells
- Previous exposure to the vector could reduce effectiveness
- Relatively complex to manufacture

ADVANTAGES AND DISADVANTAGES OF NUCLEIC ACID VACCINES

- Immune response involves B cells and T cells
- No live components, so no risk of the vaccine triggering disease
- Relatively easy to manufacture
- Some RNA vaccines require ultra-cold storage
- Never been licensed in humans
- Booster shots may be required

ADVANTAGES AND DISADVANTAGES OF INACTIVATED VIRUS VACCINES

- Well-established technology
- Suitable for people with compromised immune systems
- No live components, so no risk of the vaccine triggering disease
- Relatively simple to manufacture
- Relatively stable
- Booster shots may be required

ADVANTAGES AND DISADVANTAGES OF PROTEIN SUBUNIT VACCINES

- Well-established technology
- Suitable for people with compromised immune systems
- No live components, so no risk of the vaccine triggering disease
- Relatively stable
- Relatively complex to manufacture
- Adjuvants and booster shots may be required
- Determining the best antigen combination takes time

Vaccination Centers Rolling Out Programs

Health Care Workers Priority, Senior Citizens, co-morbids now

Protecting Ourselves

- Physical Distancing remains Key
- Reduce Exposure as much as possible
  - Duration
  - Dose
- Open Air vs Closed spaces
- Use of Facemasks / Face Shields
- Reduce Talking during meals, elevator rides
- Frequent washing of hands with soap and water
- Disinfectants such as >60% alcohol
- Control of Hypertension, kidneys Diabetes, coronary artery disease/ atherosclerosis