Korean Society for Health Promotion and Disease Prevention

2021년 대한임상건강증진학회 춘계학술대회

2021. 5. 30 (일)

코로나백신 우리도 아픈데 어떻게 준비해서 환자들에게 접종해야 할까?

유 병 욱 (순천향의대)

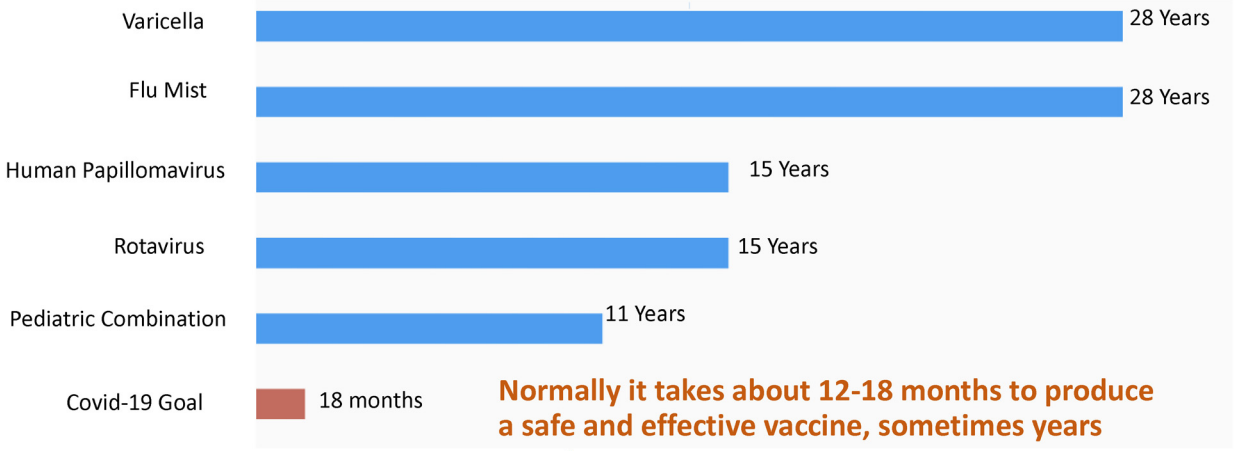
Covid-19 Vaccine Development / Production Status Report

A staggering international effort is underway to rapidly develop an effective vaccine

- More that 135 coronavirus vaccine projects are underway in a wide number of nations and 29 vaccines are now in human trials.

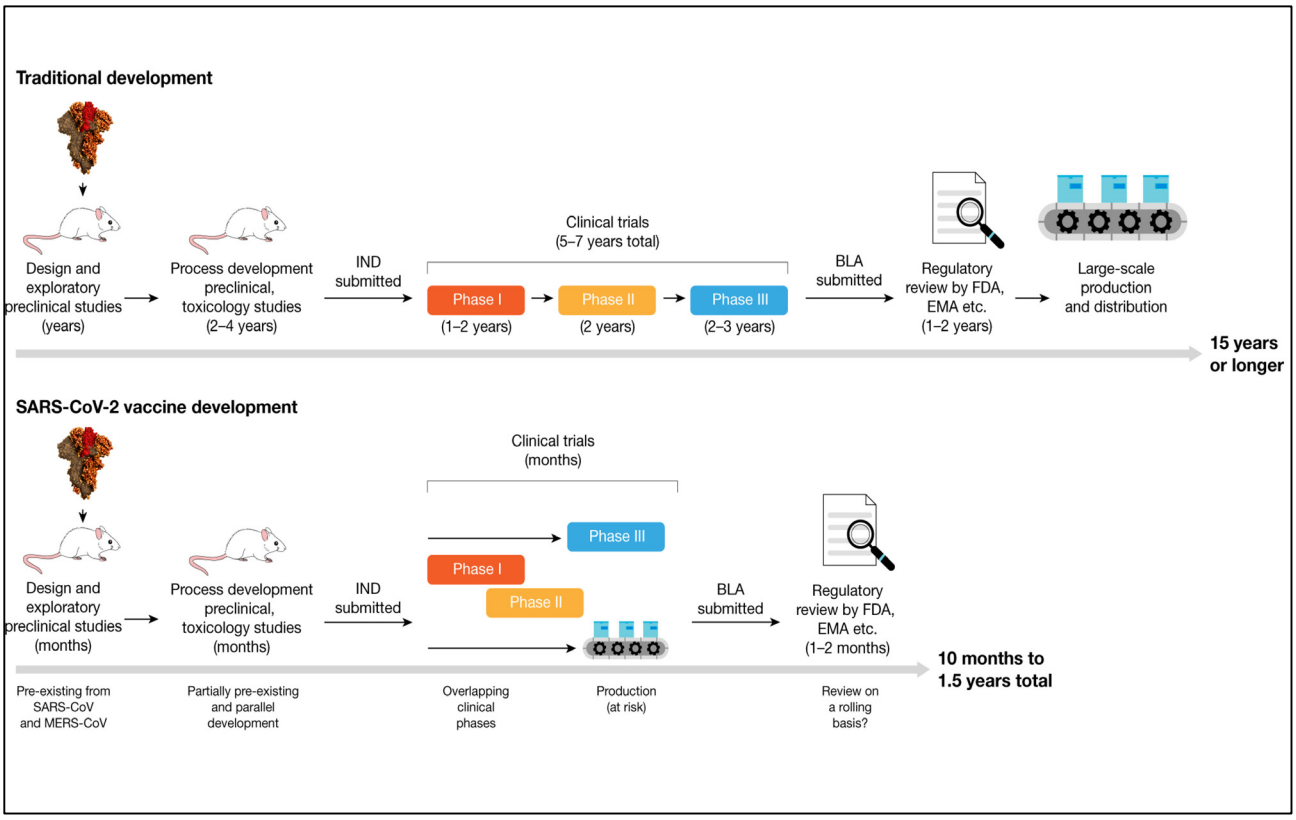
- ✓ Some approaches are well-established and time-tested as it relates to production and manufacturing methods
- ✓ Others are experimenting with novel methods which have yet to result in an approved vaccine

Historical Vaccine Development Times



Normally it takes about 12-18 months to produce a safe and effective vaccine, sometimes years

- ✓ **We're shooting for < 1 year!**
- ✓ **Hyper-accelerated programs may be effective but it's complicated**



The Vaccine Testing Process

- **PRECLINICAL TESTING**: Give the vaccine to **animals**
  - ✓See if it produces an immune response.
- **PHASE I SAFETY TRIALS**: Give the vaccine to a **small number of people**
  - ✓Test safety and dosage
  - ✓Confirm that it stimulates the immune system

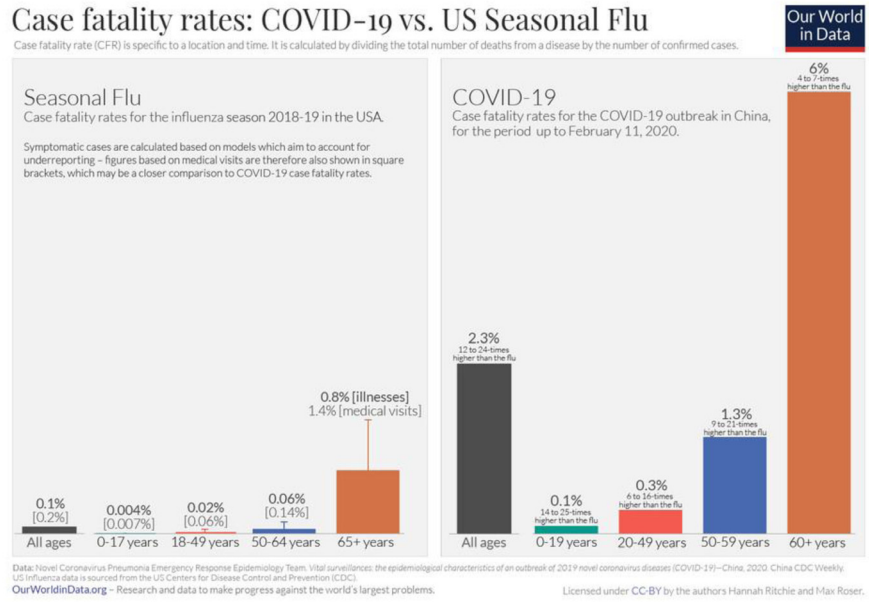
- **PHASE II EXPANDED TRIALS**: Give the vaccine to **hundreds of people of all ages.**
  - ✓Further testing for safety, dosage and stimulation of the immune system.
- **PHASE III EFFICACY TRIALS**:
  - ✓Give the vaccine to **thousands of people** and wait to see how many who are inoculated with the experimental virus v those receiving a placebo become ill.
    - What about hastening the process with purposeful exposure? – controlled human infection models?
- **COMBINED PHASES:** Another way to accelerate vaccine development.
- **APPROVAL**: Regulators review the trial results and decide whether to approve (or not)
  - ✓A vaccine may receive emergency use authorization before getting formal approval

Mortality and Morbidity

Mortality Rates

- More than 6 months into the pandemic the coronavirus killed over one-half million BUT scientists still lack a clear answer to one of the most fundamental questions about the virus. How deadly is it?
- Based on early data China and the United States respectively have case fatality rates of 5.0% and 4.6% respectively
- Some countries have much lower rates, Iceland < 1%, New Zealand and Israel around 2%, but others are much higher, around 14% (Britain). The bottom line is we still don't have a very clear idea as to actual case fatality rates (CFR)
  - ✓Because of likely case underreporting, it's probably much lower, perhaps in the 0.1-0.2% range
  - ✓Hospital treatment varies…some hospitals are just better at critical care than others

Covid-19 Data – Compared to Flu?



mRNA vaccines	
mRNA-1273 (Moderna)	**mRNA-BNT162b2 (BioNTech/Pfizer)**
Moderna/NIAID	Pfizer Inc/BioNTech SE
EUA – For active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals aged ≥ 18 y	EUA – For active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals aged ≥ 16 y
LNP-encapsulated, nucleoside-modified mRNA vaccine	LNP formulated, nucleoside-modified mRNA vaccine

EUA approval of Pfizer and Moderna vaccines

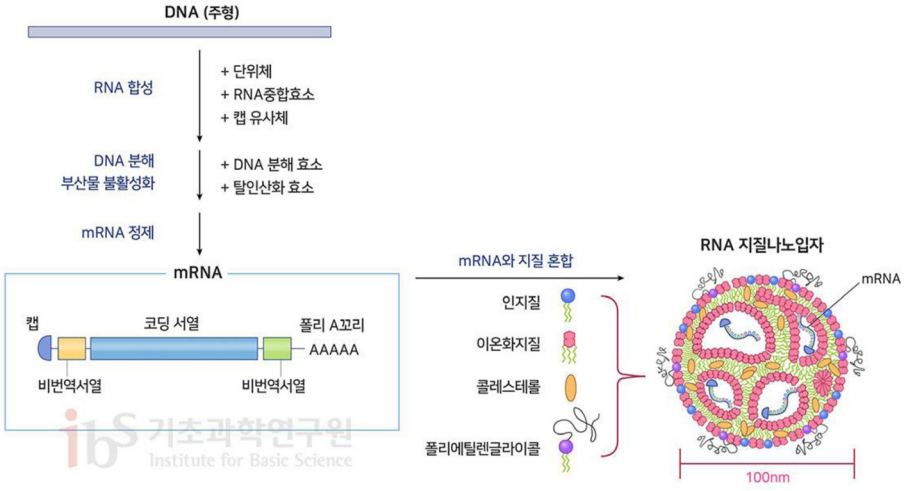
Potential advantages:

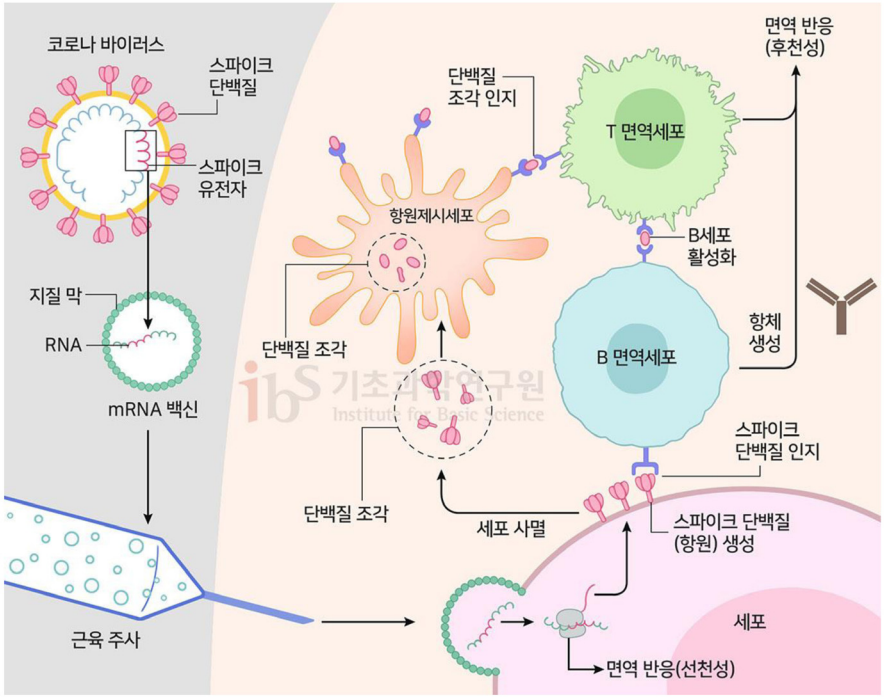
- Safety – mRNA is non-infectious and non-integrating. There is no potential risk of infection or insertional mutagenesis. Additionally, mRNA is rapidly degraded by normal cellular processes.
- Scalable production - engineered production facilitates large-scale vaccine production.
- Potency - capable of generating humoral and cellular immunity.
- Efficacy - structural modifications during engineering improves stability and translation efficacy of mRNA.

Potential disadvantages:

- Lack of commercial vaccine precedent in humans
- Local and systemic inflammatory responses
- Biodistribution and persistence of the induced antigen expression
- Possible development of autoreactive antibodies
- Toxic effects of any non-native nucleotides and delivery system components

	바이오엔텍-화이자	모더나-NIAID
유효율	95%	94%
1회 투여량	30 마이크로그램	100 마이크로그램
투여 방법	3주 간격 2회 근육 주사	4주 간격 2회 근육 주사
접종 연령	16세 이상	18세 이상
보관 온도	-70도	-20도
부작용	통증, 피로, 두통	통증, 오한, 두통


DNA (주형)
RNA 합성
+ 단위체
+ RNA중합효소
+ 캡 유사체
DNA 분해
부산물 불활성화
+ DNA 분해 효소
+ 탈인산화 효소
mRNA 정제
mRNA
캡
코딩 서열
폴리 A꼬리
AAAAA
비번역서열
비번역서열
mRNA와 지질 혼합
인지질
이온화지질
콜레스테롤
폴리에틸렌글라이콜
RNA 지질나노입자
mRNA
100nm
기초과학연구원
Institute for Basic Science

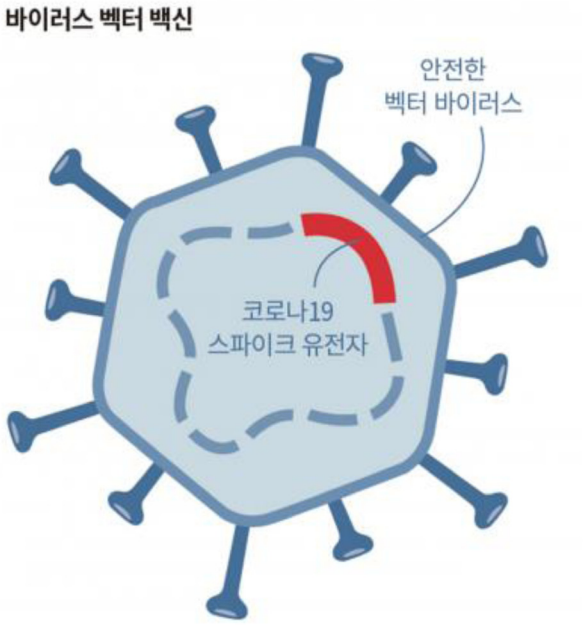

코로나 바이러스
스파이크 단백질
스파이크 유전자
지질 막
RNA
mRNA 백신
근육 주사
단백질 조각 인지
항원제시세포
단백질 조각
단백질 조각
T 면역세포
B세포 활성화
B 면역세포
면역 반응 (후천성)
항체 생성
스파이크 단백질 인지
세포 사멸
스파이크 단백질 (항원) 생성
세포
면역 반응(선천성)
기초과학연구원
Institute for Basic Science

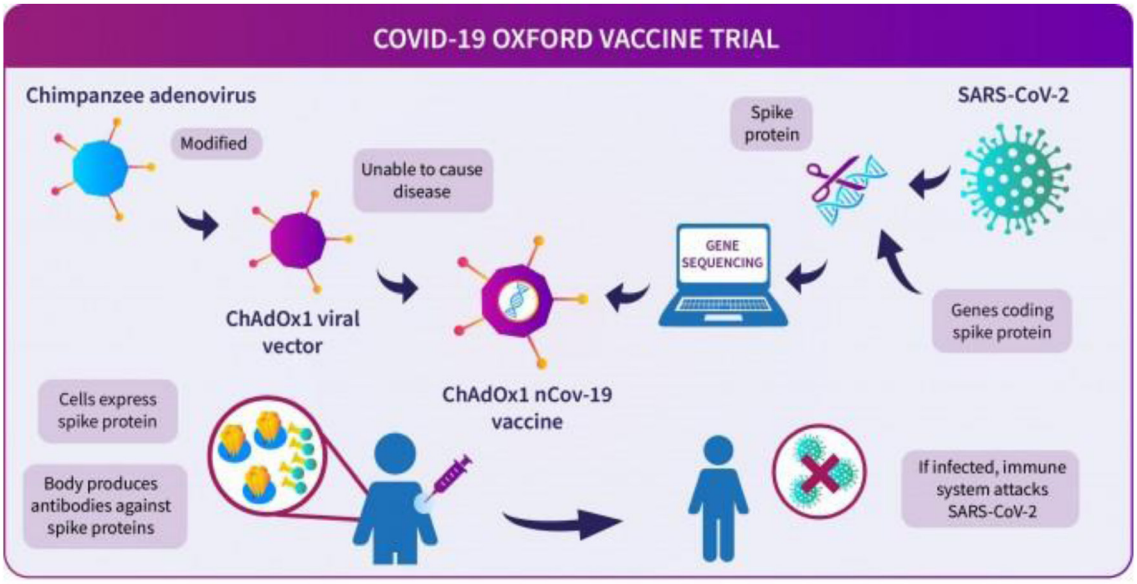
Replication-defective vectored vaccines	
AZD1222 (AstraZeneca)	**JNJ-78436735 (J&J)**
AstraZeneca	Janssen
Investigational	EUA – For active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals aged ≥ 18 y
Recombinant, replication-defective simian adenovirus vector	Recombinant, replication-defective adenovirus type 26 vector leveraging AdVac technology

Potential advantages:

- Stability at refrigerated temperatures
- Experience with platform

Potential advantages:	Potential disadvantages:
• Previous use in immunocompromised populations • Demonstrated immunogenicity in older adults in another disease states (influenza A) • Circumvents existing antivector immunity (novel vector)	• Possibility of pre-existing antivector immunity
Potential disadvantages: • No commercial vaccine precedent in humans	


바이러스 벡터 백신
안전한
벡터 바이러스
코로나19
스파이크 유전자


COVID-19 OXFORD VACCINE TRIAL
Chimpanzee adenovirus
Modified
Unable to cause disease
ChAdOx1 viral vector
ChAdOx1 nCov-19 vaccine
Spike protein
SARS-CoV-2
GENE SEQUENCING
Genes coding spike protein
Cells express spike protein
Body produces antibodies against spike proteins
If infected, immune system attacks SARS-CoV-2

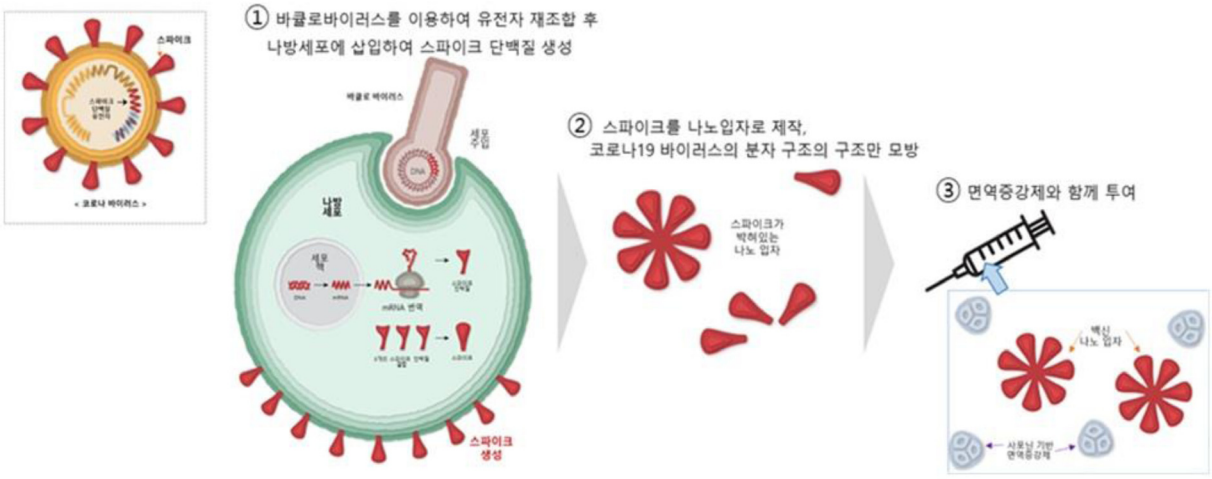
Protein subunit
NVX-CoV2373 (Novavax)
Novavax
Investigational
Recombinant nanoparticle vaccine technology, leveraging Sf9/BV insect cell platform and Matrix-M™ adjuvant technology

Potential advantages:

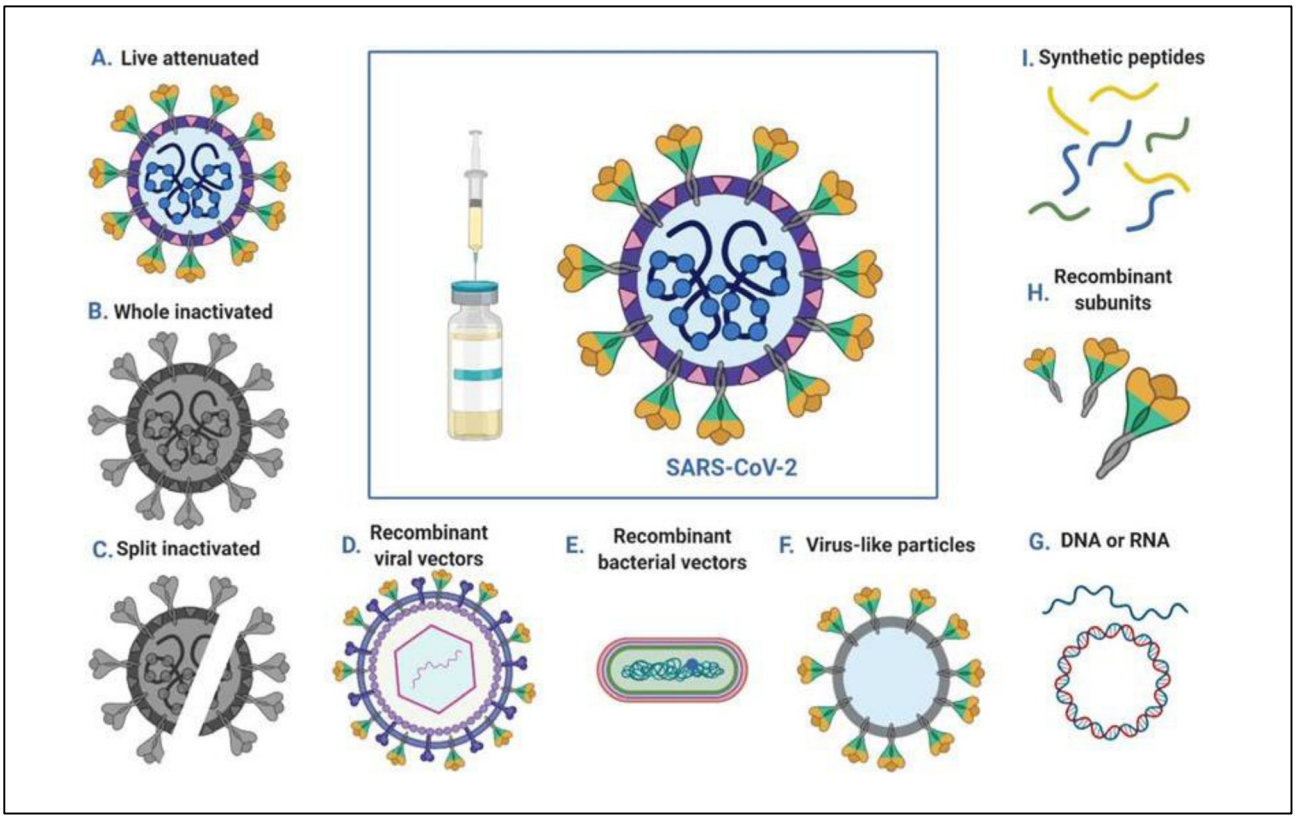
- Safety – non-infectious, non-integrating
- Scalable production – engineered production facilitates large-scale vaccine production
- Potency – capable of generating humoral and cellular immunity
- Adjuvanted –provides enhanced immune response, allowing for vaccine dose-sparing effect

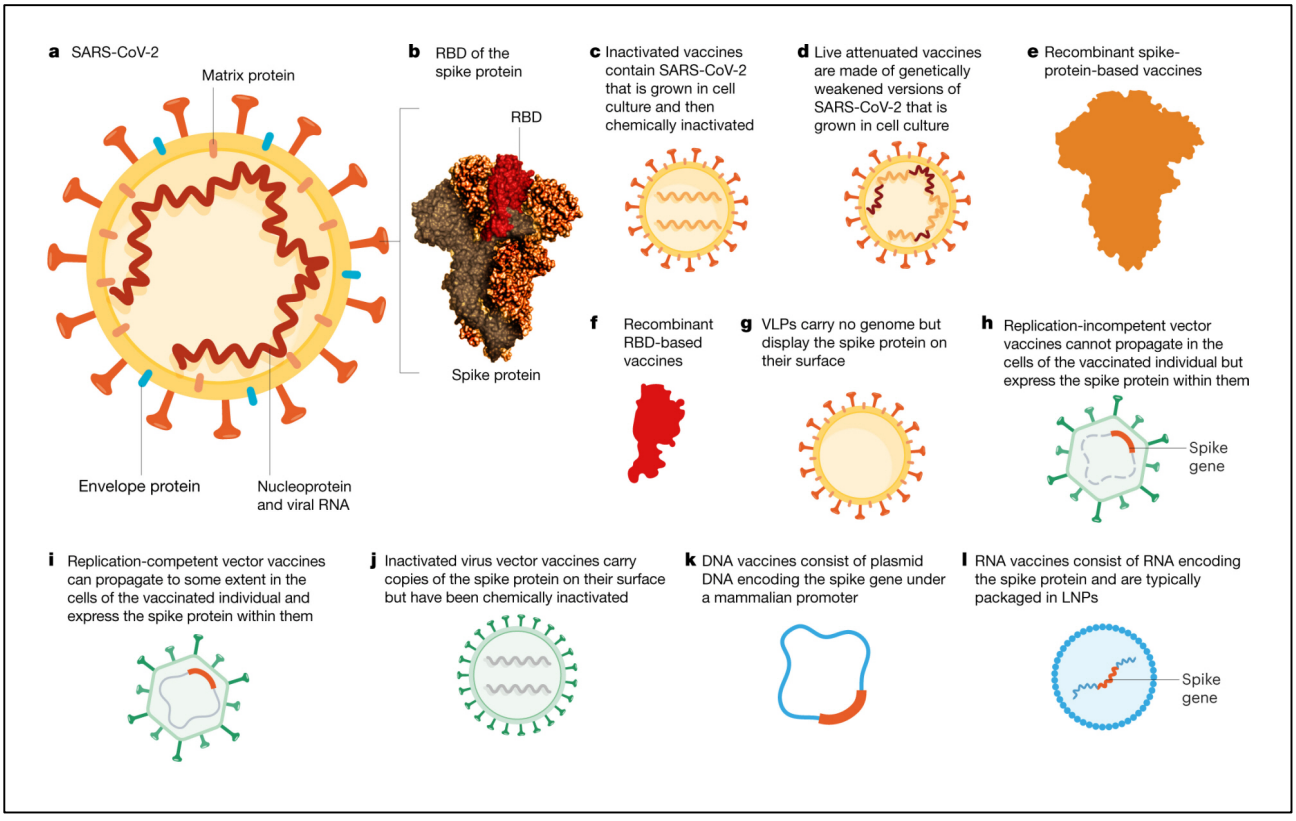
Potential disadvantages:

- Local and systemic inflammatory responses



mRNA vaccines		Replication-defective vectored vaccines		Protein subunit
mRNA-1273 (Moderna)	mRNA-BNT162b2 (BioNTech/Pfizer)	AZD1222 (AstraZeneca)	JNJ-78436735 (J&J)	NVX-CoV2373 (Novavax)
• mRNA encoding for the SARS-CoV-2 spike glycoprotein is delivered to cells in a lipid capsule • Using mRNA, cells manufacture the spike protein (antigen) • Spike protein stimulates the body's immune response and production of antibodies against SARS-CoV-2		DNA sequence for SARS-CoV-2 spike glycoprotein (antigen) is encoded into a human or non-human adenovirus. Upon delivery to the host cell, host cells manufacture the spike protein (antigen), which stimulates the body's immune response. AZD1222 uses a simian adenovirus and JNJ-78436735 uses a human adenovirus with a low prevalence in humans. Due to genetic alterations, adenovirus vectors are unable to replicate (replication-defective) once in the host cell.		Genetic sequence encoding the antigen (spike protein) is cloned into baculovirus and inserted into Sf9 insect cells, where the antigen is produced and subsequently isolated/extracted. Matrix-M adjuvant boosts immune response and enables vaccine dose-sparing by stimulating entry of antigen-presenting cells into the injection site and enhancing B- and T-cell responses


A. Live attenuated
B. Whole inactivated
C. Split inactivated
SARS-CoV-2
I. Synthetic peptides
H. Recombinant subunits
D. Recombinant viral vectors
E. Recombinant bacterial vectors
F. Virus-like particles
G. DNA or RNA

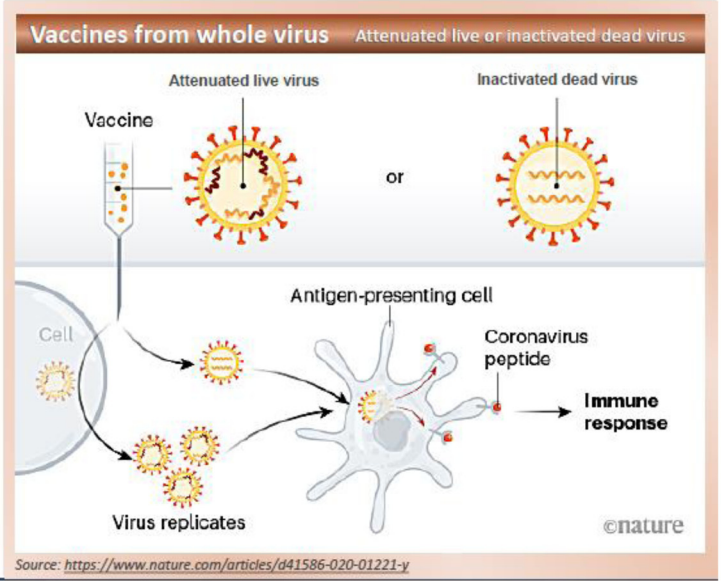

a SARS-CoV-2
Matrix protein
Envelope protein
Nucleoprotein and viral RNA
b RBD of the spike protein
RBD
Spike protein
c Inactivated vaccines contain SARS-CoV-2 that is grown in cell culture and then chemically inactivated
d Live attenuated vaccines are made of genetically weakened versions of SARS-CoV-2 that is grown in cell culture
e Recombinant spike-protein-based vaccines
f Recombinant RBD-based vaccines
g VLPs carry no genome but display the spike protein on their surface
h Replication-incompetent vector vaccines cannot propagate in the cells of the vaccinated individual but express the spike protein within them
Spike gene
i Replication-competent vector vaccines can propagate to some extent in the cells of the vaccinated individual and express the spike protein within them
j Inactivated virus vector vaccines carry copies of the spike protein on their surface but have been chemically inactivated
k DNA vaccines consist of plasmid DNA encoding the spike gene under a mammalian promoter
l RNA vaccines consist of RNA encoding the spike protein and are typically packaged in LNPs
Spike gene

VACCINE DEVELOPMENT — Mechanism of action for types of vaccines

Virus vaccines

- **Virus is selected, modified (weakened) or completely inactivated** so that it will not cause disease

Note:
This illustration shows injectable vaccines. Some vaccines in this category are administered orally

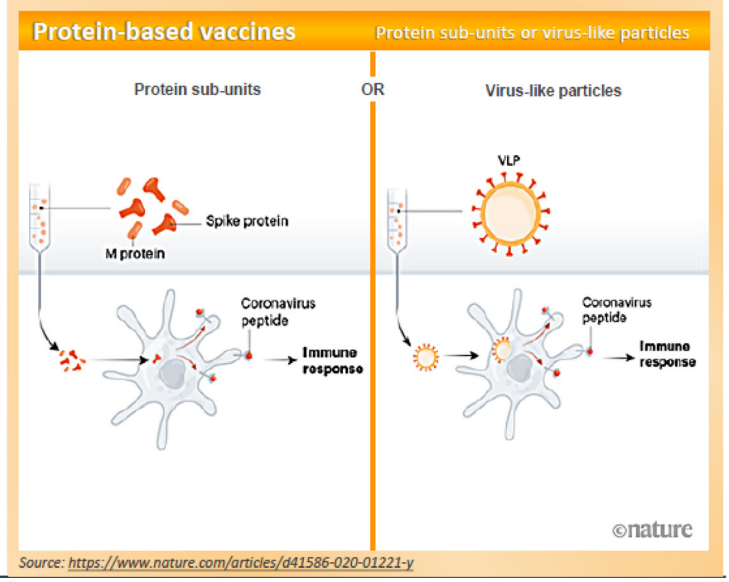


Source: https://www.nature.com/articles/d41586-020-01221-y

VACCINE DEVELOPMENT — Mechanism of action for types of vaccines

Protein-based vaccines

- **A protein is extracted from the virus** (alive or inactivated), purified, and injected as a vaccine
- For coronavirus, this is most commonly the spike protein
- Virus-like particles work in the same way



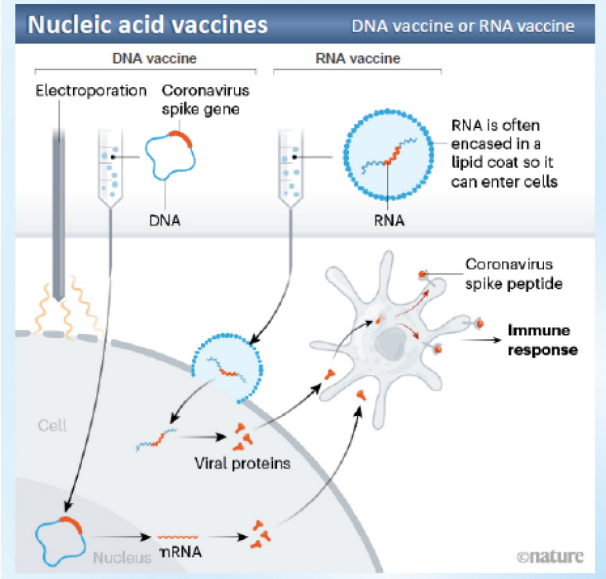
Source: https://www.nature.com/articles/d41586-020-01221-y

VACCINE DEVELOPMENT — Mechanism of action for types of vaccines

Nucleic acid vaccines

- Instead of a virus, a protein antigen, or a virus expressing the protein, **nucleic acid coding for the antigen is injected**
- DNA plasmid: enters nucleus, translated to mRNA for expression of protein
- Or mRNA can be injected. More direct (no translation required) but less stable than DNA
- This is new technology – no other vaccines for human use have used this

Source: https://www.nature.com/articles/d41586-020-01221-y



Vaccine Types

The vaccines portrayed in this report represent the following Vaccine Types.

GENETIC VACCINES

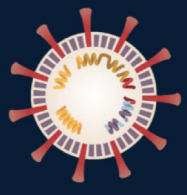
mRNA vaccines are the newest approach. They use genetic material called messenger RNA, a kind of genetic software that instructs cells to make a piece of the coronavirus spike protein. That will get the attention of the immune system. The mRNA is coated in soft fatty lipids to protect it.

VIRAL VECTOR VACCINES

Vector vaccines use another virus to carry in the genetic instructions to make the spike protein. For coronavirus they all use adenoviruses, a type of common cold virus. They attach to cells and inject DNA that tells the cells to make coronavirus spike protein.

PROTEIN-BASED VACCINES

Protein vaccines just get little pieces of the target virus circulating in the system for the immune system to find and recognize. Instead of using the human body as the vaccine factory, genetically engineered insect viruses are used to infect moths, whose cells then produce the pieces of coronavirus spike protein. These are harvested and made into a vaccine.



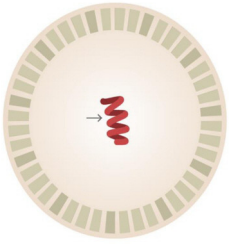
INACTIVATED VACCINES

Whole inactivated virus vaccines take longer to make because batches of the coronavirus must first be grown and then killed using a chemical or heat, and then made into a vaccine that can be injected to elicit an immune response.

IMMUNOGEN	HOW IT WORKS	ADVANTAGE	DISADVANTAGE	EXAMPLE of vaccines
Attenuated live virus	Live virus but doesn't cause disease	Induces same response as natural infection	Not recommended for pregnant women and immunocompromised persons	Measles, rubella, mumps, yellow fever, smallpox (vaccinia)
Whole inactivated virus	Inactivated dead virus	Induces strong antibody response	Requires large quantities of virus	Influenza, rabies hepatitis A
Protein subunit	A protein derived from a pathogen	May have fewer side effects than whole virus (redness, swelling at injection site)	May be poorly immunogenic; complex process	Influenza
Recombinant	Host cell is used to express an antigen	No need to produce the whole virus	May be poorly immunogenic; High cost	Hepatitis B
Peptides	Synthetic produced fragment of an antigen	Rapid development	Poorly immunogenic; High cost	*COVID-19 vaccines in development*
Replicating or non-replicating viral vector	Viral pathogen expressed on a safe virus that doesn't cause disease	Rapid development	Prior exposure to vector virus (eg. adenovirus) may reduce immunogenicity	Ebola
Nucleic acid	DNA or RNA coding for a viral protein	Strong cellular immunity; rapid development	Relatively low antibody response	*COVID-19 vaccines in development*

mRNA Vaccines

Vaccines that use part of the coronavirus´ s genetic code to produce a vaccine

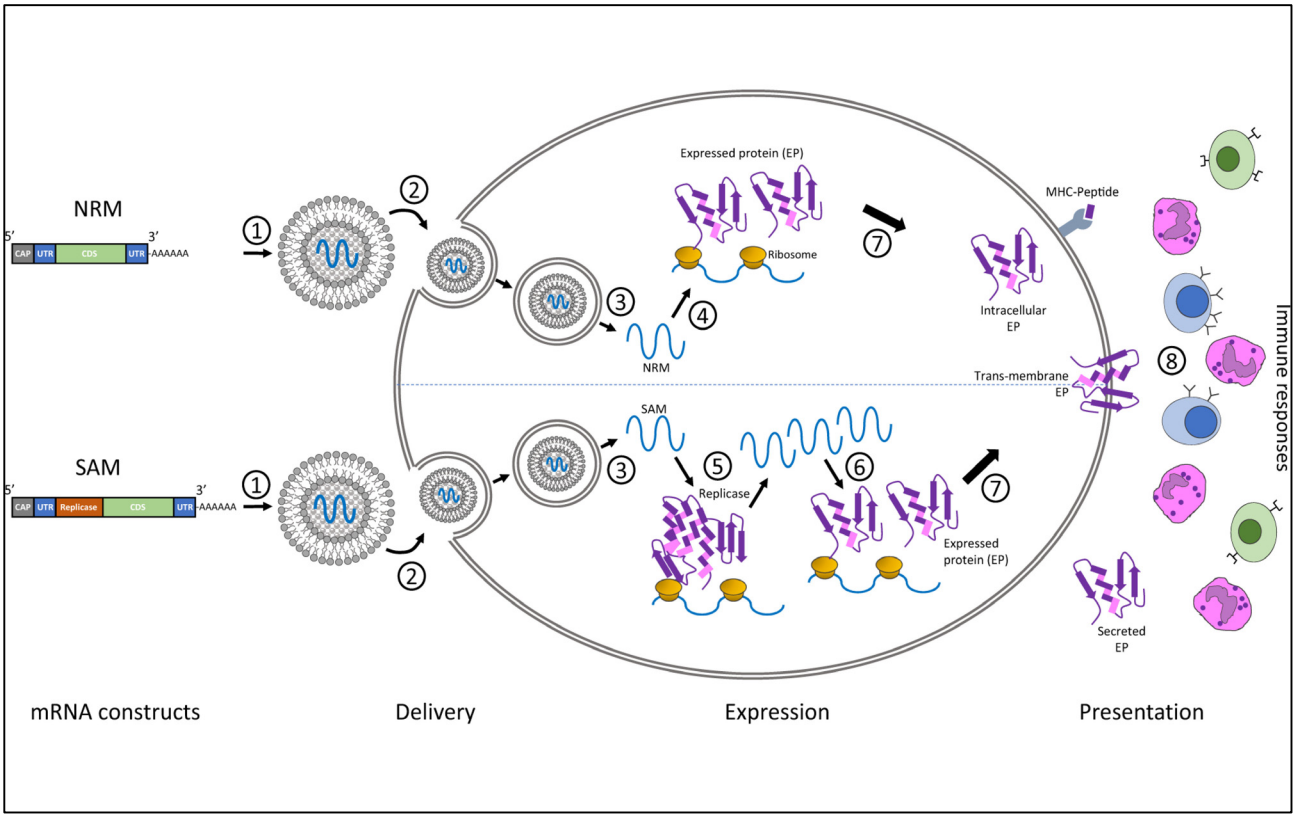


mRNA (Genetic) Vaccines

- Some researchers want to skip DNA and instead deliver messenger RNA (mRNA) into cells.
- Both RNA and DNA vaccines can be produced more quickly than traditional methods.

COMPANIES AND STATUS:

- Moderna and NIH - Phase I,II & III testing $ 972 Million, additional funding for Phase III
- BioNTech & Pfizer - Phase I & II. Moving to Phase III - 2 Billion in BARDA funding
- CureVac - Phase I / 11 trials - 6/15
- Imperial College and Morningside Ventures - Phase I and II trials, self- amplifying RNA
- Sanofio & Translate Bio - Phase II



MODERNA COVID-19 VACCINE

Moderna COVID-19 Vaccine
Storage and Handling Summary

CDC

Basics

- Store vaccine in a freezer or refrigerator. See guidance below for each storage unit.
- Each box contains 10 multidose vials (100 doses).
- Use vaccine vials stored in the refrigerator before removing vials from frozen storage.
- This vaccine does not need to be mixed with a diluent before administration.
- Check and record storage unit temperature each workday. See guidance below for each type of temperature monitoring device. Save storage records for 3 years, unless your jurisdiction requires a longer time period.

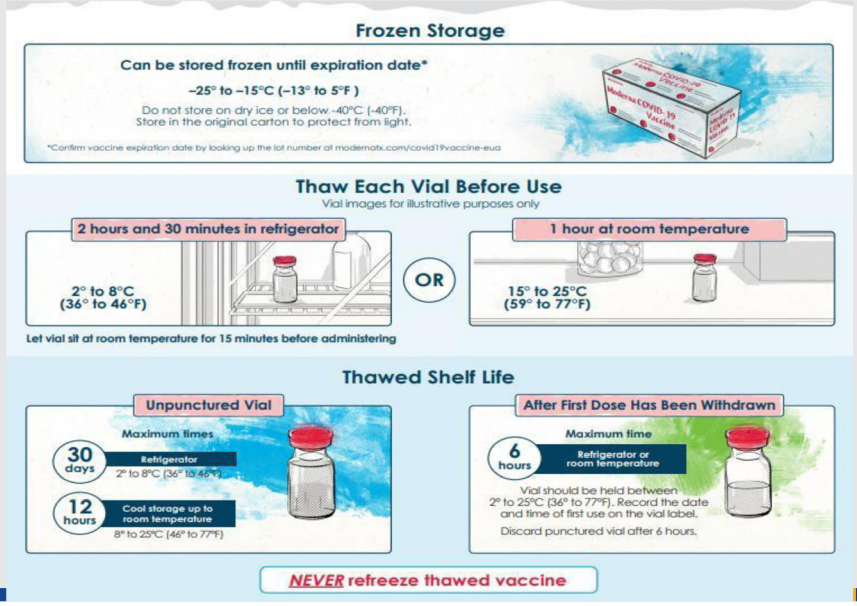
Deliveries

Vaccine

1. The vaccine will arrive frozen between -25°C and -15°C (-13°F and 5°F).
2. Examine the shipment for signs of damage.
3. Open the box and remove TagAlert Temperature Monitor from box (placed in the inner box next to vaccine).
4. Check the TagAlert temperature monitoring device by pressing the blue "start and stop" button.
   - Left arrow points to a **green checkmark:** The vaccine is ready to use. Store the vaccine at proper temperatures immediately.
   - Right arrow points to a **red X:** The numbers 1 and/or 2 will appear in the display. Store the vaccine at proper temperatures and label **DO NOT USE**! Call the phone number indicated in the instructions or your jurisdiction's immunization program **IMMEDIATELY**!

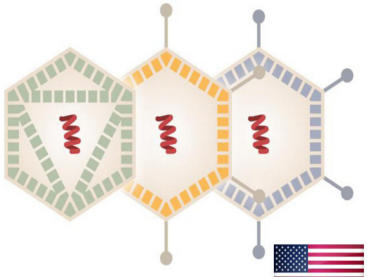
Ancillary Supply Kit

Moderna COVID-19 Vaccine Storage & Handling



Viral Vector Vaccines

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



Vaccines Using Adenovirus

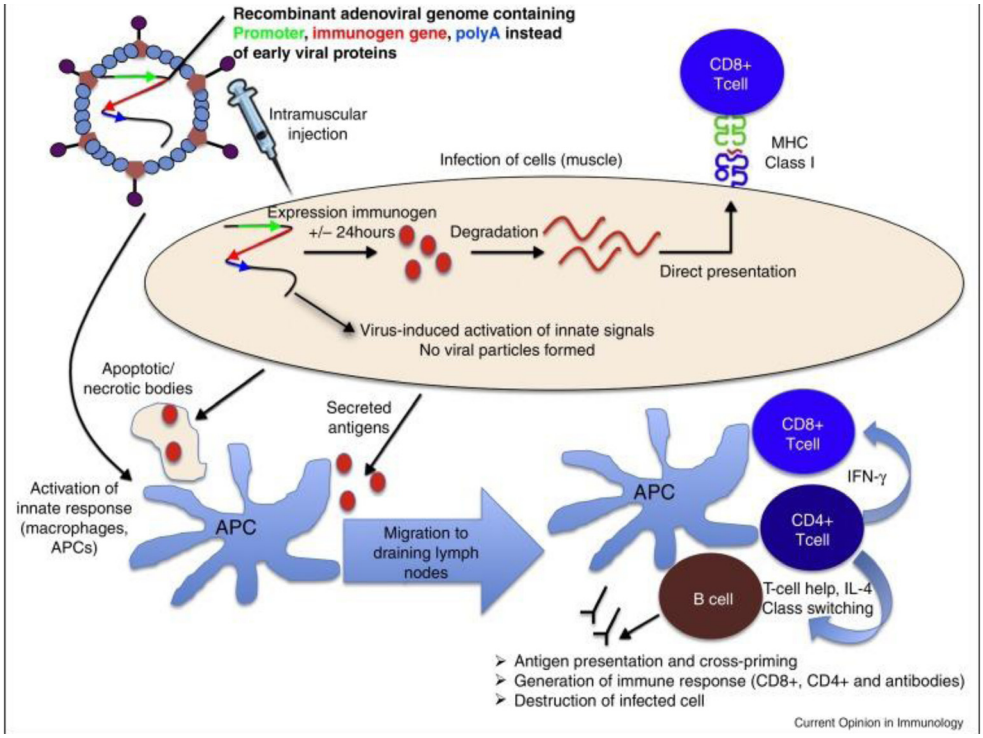
- Adenoviruses viruses are very good at getting into cells
  - ✓Several teams have added the spike protein gene to an adenovirus.
- The adenovirus slips into cells and unloads the gene.
- Because the adenovirus is missing one of its own genes, it cannot replicate and is therefore safe.

EXAMPLES:

- Several virus vector vaccines have been used to vaccinate animals against rabies and distemper.
- Johnson & Johnson has developed HIV and Ebola vaccines using an adenovirus.

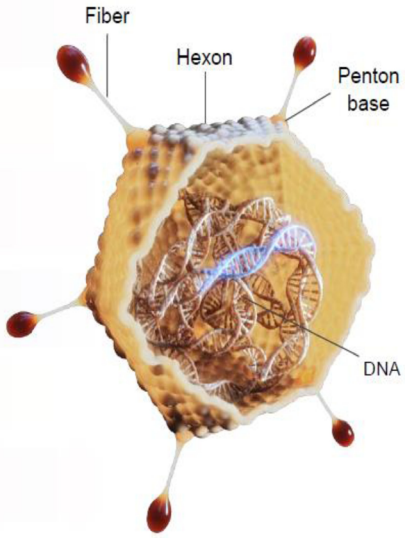
COMPANIES and STATUS:

- Johnson & Johnson & Janssen (a Johnson & Johnson Co.) – Adenovirus Ad26 – 456 Million in BARDA finding
- University of Oxford & Astra Zeneca – Phase II / III England ; Phase III Brazil and South Africa – AZD 1222 – 1.2. Billion in BARDA funding
- CanSino and the Chinese Academy of Military Science (AMS) – Phase II / III Trials, Adenovirus Ad5-nCoV – First approved vaccine but for limited use – results relatively weak



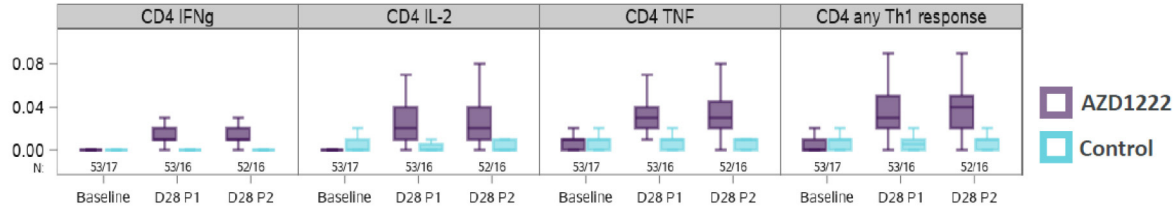
AZD1222: The Technology

- Non-replicating chimp adenovirus-vectored vaccine expressing nCoV-19 spike[1]
- Non-replicating due to E1 (and E3) gene deletion[2]
- Chimp adenovirus avoids issues with pre-existing immunity to human adenoviruses[2]
- Vaccine antigen encoded in the viral genome – not a structural part of the virion[3]
- Induces strong B- and T-cell responses after a single vaccination[1]
- Prior to April 2020, 12 Phase I studies, 330 subjects vaccinated
- Dose is 5 x 10^{10} viral particles (vp) as an IM injection, 0.5 ml[1]

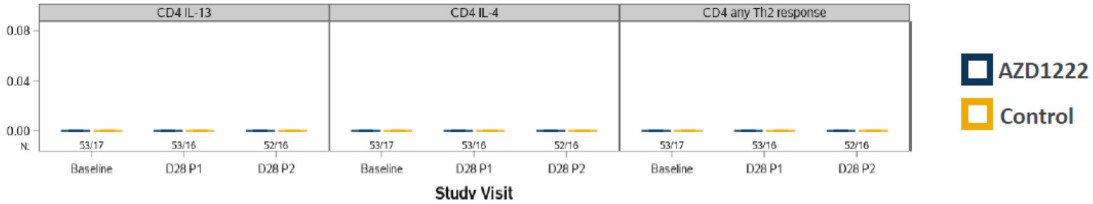


AZD1222 Induced A Robust Th1 Biased T-Cell Response In COV001 And COV002 Participants

Th1 cytokines were induced following stimulation with overlapping SARS-CoV-2 peptides



Limited Th2 cytokines were induced following stimulation with overlapping SARS-CoV-2 peptides



D28 P1 = Day 28 post 1st Dose, D28 P2 = Day 28 post 2nd Dose. Boxplots display the median and 1st and 3rd quartiles. Th1 data result indicates percentage of CD69+ cells expressing IFNγ, IL-2, TNFα (or any Th1 cytokine) after stimulation with SARS-CoV-2 S1 peptide pool (similar results were seen with S2 peptide pool). Th2 data result indicates percentage of CD69+ cells expressing IL-4, IL-13 (or either Th2 cytokine). Background percentage was subtracted from the stimulated percentage prior to analysis. Stimulated percentages less than the background percentage were set to 0%.

10

Exploratory analysis, Unpublished results

Across Four Studies, AZD1222 Exhibited A Favorable Safety Profile

Across all four studies, SAEs occurred in 168 participants (<1%)
79 of whom received AZD1222 (0.7%) and 89 of whom received MenACWY or saline control (0.8%)

There were 175 SAEs, of which 4 were considered possibly related to intervention (either the experimental vaccine or the control)

AZD1222 group
- **Pyrexia:** 2 days after dose 1; treated with paracetamol and resolved the same day
- **Transverse myelitis:** 14 days after dose 2

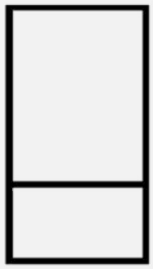
Control group
- **Autoimmune hemolytic anemia:** 10 days after MenACWY
- **Transverse myelitis**: 2 months after first control dose

Solicited Adverse Events, the majority usually resolved within a few days of vaccination.
- Reactogenicity; the most frequently reported AEs were mild to moderate in severity including injection site tenderness (>60%); injection site pain, headache, fatigue (>50%); myalgia, malaise (>40%); pyrexia, chills (>30%); and arthralgia, nausea (>20%).
- Generally milder and reported less frequently after second dose and in older adults (≥65 years old)

MenACWY = meningococcal group A, C, W, and Y conjugate vaccine; SAE = severe adverse event.

AZD1222 Storage And Administration

Storage



Refrigerator
- Store in refrigerator (2 to 8°C)
- Shelf life = 6 months
- Do not freeze
- Keep vials in outer carton to protect from light

Administration

Multi-dose Vial
- After first puncture cumulatively store up to 6 hours at room temperature or up to 48 hours at 2-8°C with total storage time not to exceed 48 hours.
- No dilution or reconstitution

22

Safety and Efficacy of Janssen COVID-19 vaccines:
Data from Phase III clinical trial

6

Summary of the Available Evidence:
Vaccine Efficacy

- The clinical trial demonstrated efficacy against symptomatic, laboratory-confirmed COVID-19. The overall efficacy was **66.3%** (95% CI: 59.9%, 71.8%).
- For COVID-19 associated hospitalization, 31 events occurred, 29 in the placebo group, 2 in the vaccine group. Vaccine efficacy against hospitalization was **93%** (95% CI: 71%, 98%).
- For all-cause deaths, 5 occurred in the vaccine group and 20 in the placebo group. Vaccine efficacy against all-cause death was **75%** (95% CI: 33%, 91%)

7

Summary of the Available Evidence:
Vaccine Efficacy

- **Higher** efficacy against **severe** outcomes than for any symptomatic COVID-19*
  - VE against **deaths** due to COVID-19**: 100%**
- Efficacy estimates for severe outcomes **assessed ≥28 days** post vaccination were **higher**: **83.5%** for severe disease†, **100%** for hospitalization
- Efficacy against severe disease† remained high across world regions (**73-82%***), suggesting protection against severe illness with variant strains

†**Definition:** Respiratory Rate ≥ 30, Heart Rate ≥125, SpO2≤ 93% on room air at sea level or PaO2/FIO2< 300 mm Hg; OR respiratory failure or Acute Respiratory Distress Syndrome (ARDS), defined as needing high-flow oxygen, non-invasive or mechanical ventilation, or ECMO; OR evidence of shock (systolic blood pressure <90mmHg, diastolic BP<60mmHg or requiring vasopressors); OR significant acute renal, hepatic or neurologic dysfunction; OR admission to an intensive care unit or death

*Assessed ≥ 14 days post vaccination

10

Summary of the Evidence:
All authorized COVID-19 vaccines

- No trials compared efficacy between vaccines in the **same** study at the **same** time
  - All Phase 3 trials differed by calendar time and geography
  - Vaccines were tested against different circulating variants and in settings with different background incidence
- All authorized COVID-19 vaccines demonstrated efficacy (range 65 to 95%) against symptomatic lab-confirmed COVID-19
- All authorized COVID-19 vaccines demonstrated **high** efficacy (≥89%) against COVID-19 severe enough to require **hospitalization**
- In the vaccine trials, **no** participants who received a COVID-19 vaccine **died** from COVID-19
  - The Moderna and Janssen trials each had COVID-19 deaths in the placebo arm

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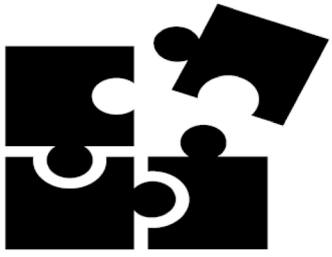
Janssen COVID-19 Vaccine
How does it best fit?

Characteristics of the vaccine

- 1 dose
- Transport, and storage (x3m) at 2-8°C
- No diluent/reconstitution necessary



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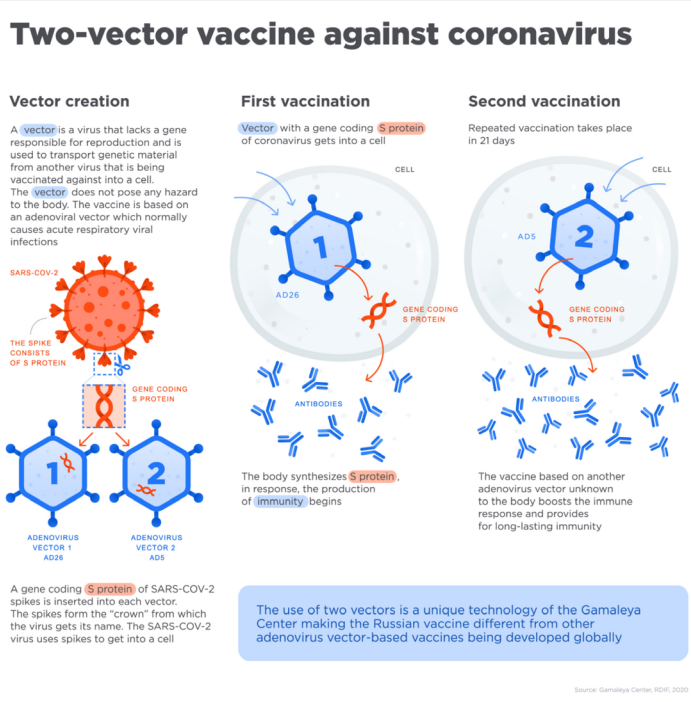
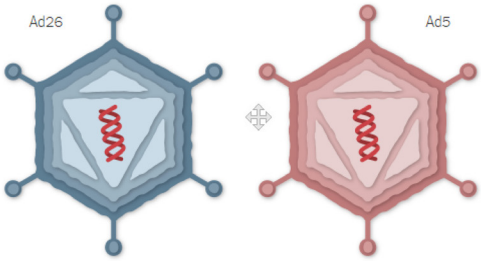
Sputnik V



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.

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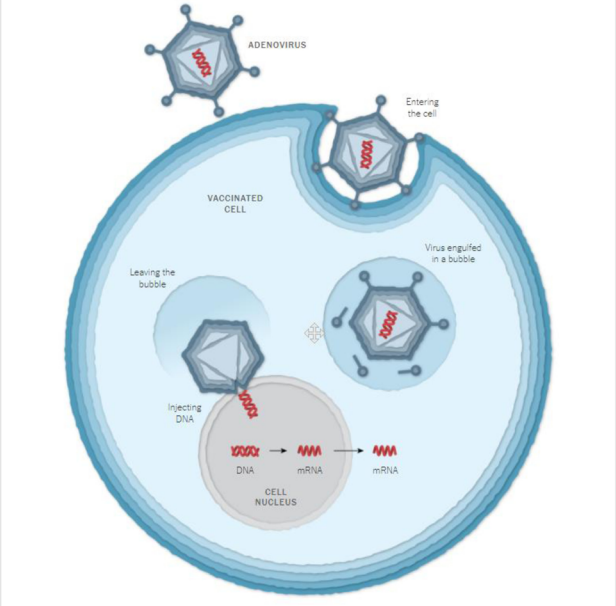
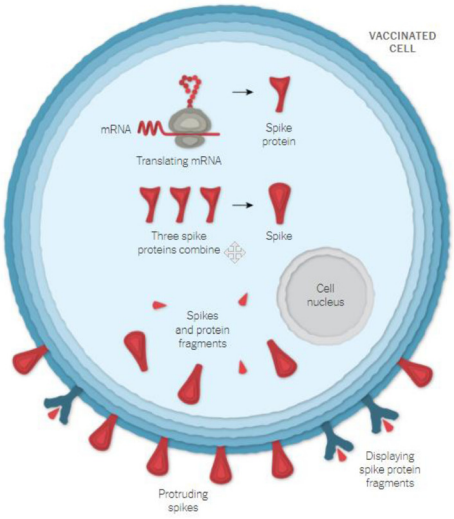


47

Building Spike Proteins

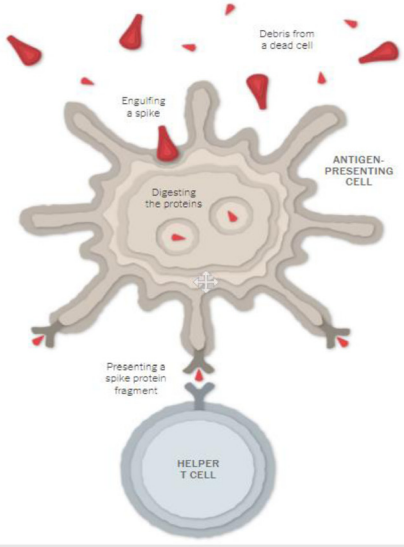
The mRNA leaves the nucleus, and the cell's molecules read its sequence and begin assembling spike proteins.



48

Spotting the Intruder

When a vaccinated cell dies, the debris contains spike proteins and protein fragments that can then be taken up by a type of immune cell called an antigen-presenting cell.



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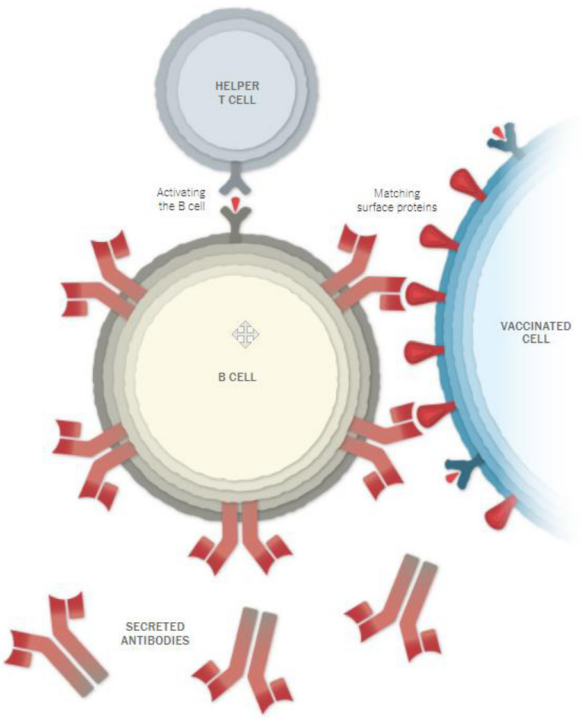

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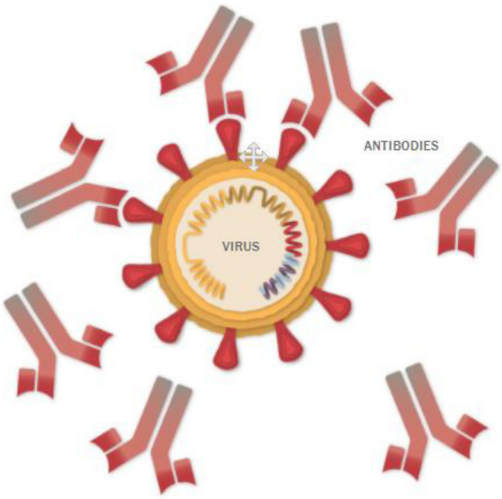
Stopping the Virus

The antibodies can latch onto coronavirus spikes, mark the virus for destruction and prevent infection by blocking the spikes from attaching to other cells.



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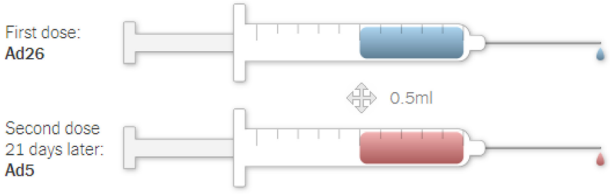
Two Doses

Some researchers worry that our immune systems could respond to an adenovirus vaccine by making antibodies against it, which would render a second dose ineffective. To avoid this, the Russian researchers used one type of adenovirus, Ad26, for the first dose, and another, Ad5, for the second.



Adenovirus-based vaccines for Covid-19 are more rugged than the mRNA vaccines from Pfizer and Moderna. DNA is not as fragile as RNA, and the adenovirus's tough protein coat helps protect the genetic material inside. As a result, Sputnik V can be refrigerated and does not require very low storage temperatures.

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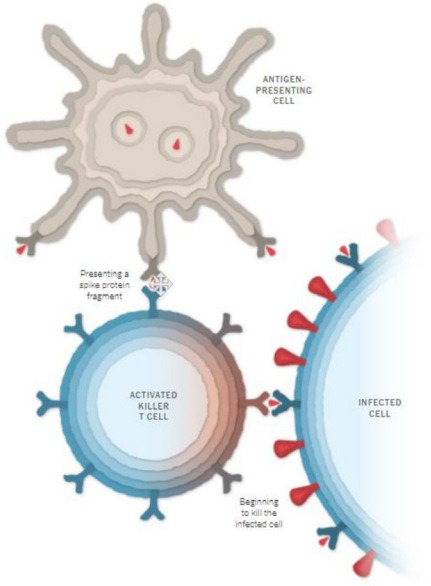
Killing Infected Cells

The antigen-presenting cells can also activate another type of immune cell called a killer T cell to seek out and destroy any coronavirus-infected cells that display the spike protein fragments on their surfaces.



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NEJM Journal Watch

SPECIALTIES & TOPICS | NEWS | BLOGS | CME | SPECIAL FEATURES | ARCHIVES/PDFs

MEDICAL NEWS | PHYSICIAN'S FIRST WATCH

February 2, 2021

"Sputnik V" Vaccine Found Over 90% Effective Against COVID-19

By Joe Elia

Edited by David G. Fairchild, MD, MPH, and Lorenzo Di Francesco, MD, FACP, FHM

A Russian vaccine against COVID-19 — Gam-COVID-Vac (dubbed "Sputnik V") — shows 92% efficacy in interim results from a phase 3 trial reported in *The Lancet*.

The two-dose vaccine uses replication-deficient adenoviruses to deliver a SARS-CoV-2 glycoprotein as the antigenic stimulus. Doses are administered at 21-day intervals, and the vaccine may be stored in normal freezers. The Moscow-based, placebo-controlled trial enlisted some 22,000 SARS-CoV-2–negative adults, about 20,000 of whom had no protocol violations and were included in the analysis.

Starting at day 21, the day of the booster shot, 0.1% of vaccine recipients were diagnosed with COVID-19, versus 1.3% of placebo recipients (16 of 15,000 vaccine recipients vs. 62 of 4900 placebo recipients).

The authors report that, since federal approval in August 2020, more than 2 million doses of Gam-COVID-Vac have been administered to the Russian public — largely to at-risk groups.

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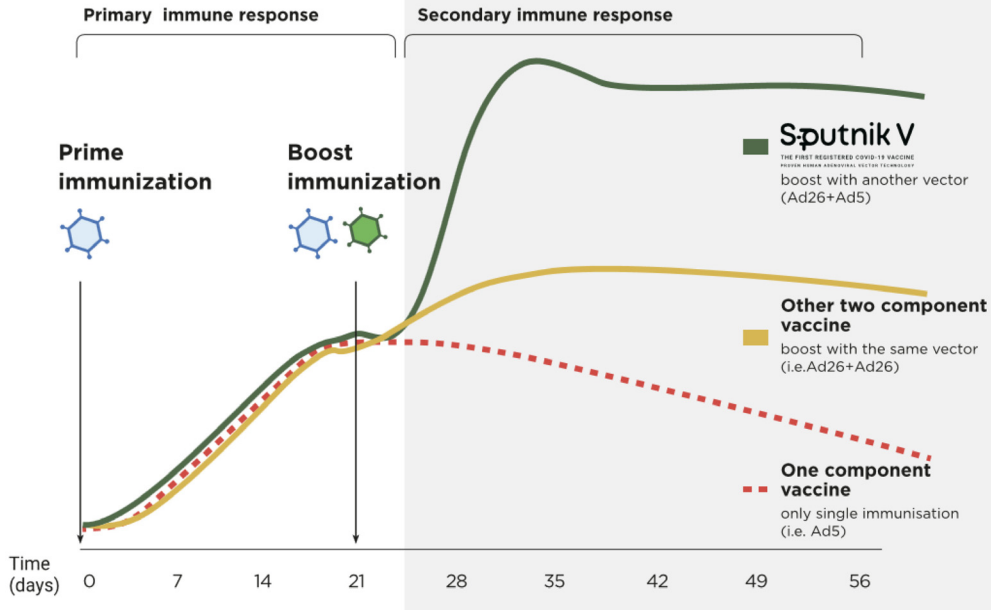
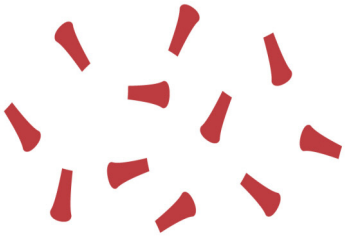


55

Protein– Subunit Based Vaccines

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



Recombinant Vaccines

- **Microscopic particles carrying fragments of coronavirus proteins.**
- **Particles that contain pieces of viral proteins. They can't cause disease because they are not actual viruses, but they can still show the immune system what coronavirus proteins look like**

EXAMPLES:

This category includes some vaccines for shingles and hepatitis B

COMPANIES and STATUS:

- **Novavax - Phase I / II Trials underway, Phase III this Fall - 1.6 Billon in BARDA funding**
- **Medicago - Phase I**

- **Sanofi & GlaxoSmithKline - 2.1 Billion in BARDA Funding = Phase II by year's-end**

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Executive summary

- Novavax has a prefusion, stable recombinant SARS-CoV-2 Spike protein nanoparticle vaccine candidate (NVX-CoV2373) that has been highly immunogenic in mice and nonhuman primates
- Novavax is employing a mature vaccine platform to address the current COVID 19 pandemic
- Novavax is initiating a single protocol (Phase 1 and 2) this month with key data delivered Q3 and into Q4
- NVX-CoV2373 can be scaled up rapidly to produce up to 100M doses by year end and continue to scale throughout 2021
- NVX-CoV2373 could potentially be deployed under emergency use authorization by the end of 2020 pending positive safety and immune data

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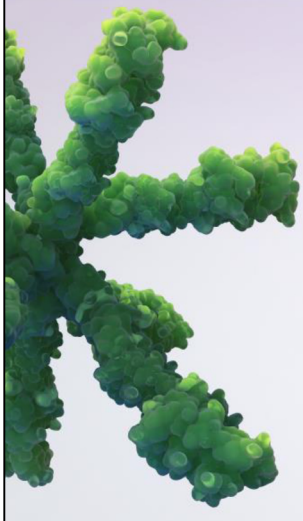
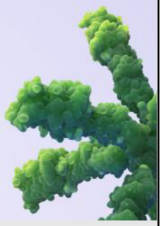


RECOMBINANT NANOPARTICLE ADVANTAGES

Ability to tailor our vaccines to key components of pathogens to enhance functional immunity and lead to better protection against infection and disease.

Select genetic sequences to encode vaccine antigens



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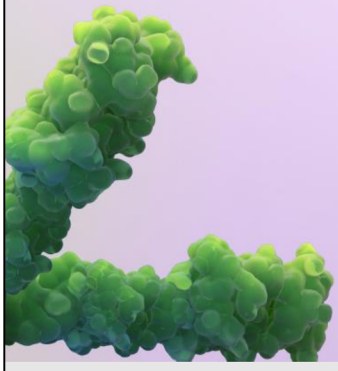
RECOMBINANT NANOPARTICLE ADVANTAGES

Promote superior immunogenicity and better functional immunity via our Sf9/BV insect cell platform to efficiently express large antigens and particles.

Genes are cloned into baculovirus (BV)

60

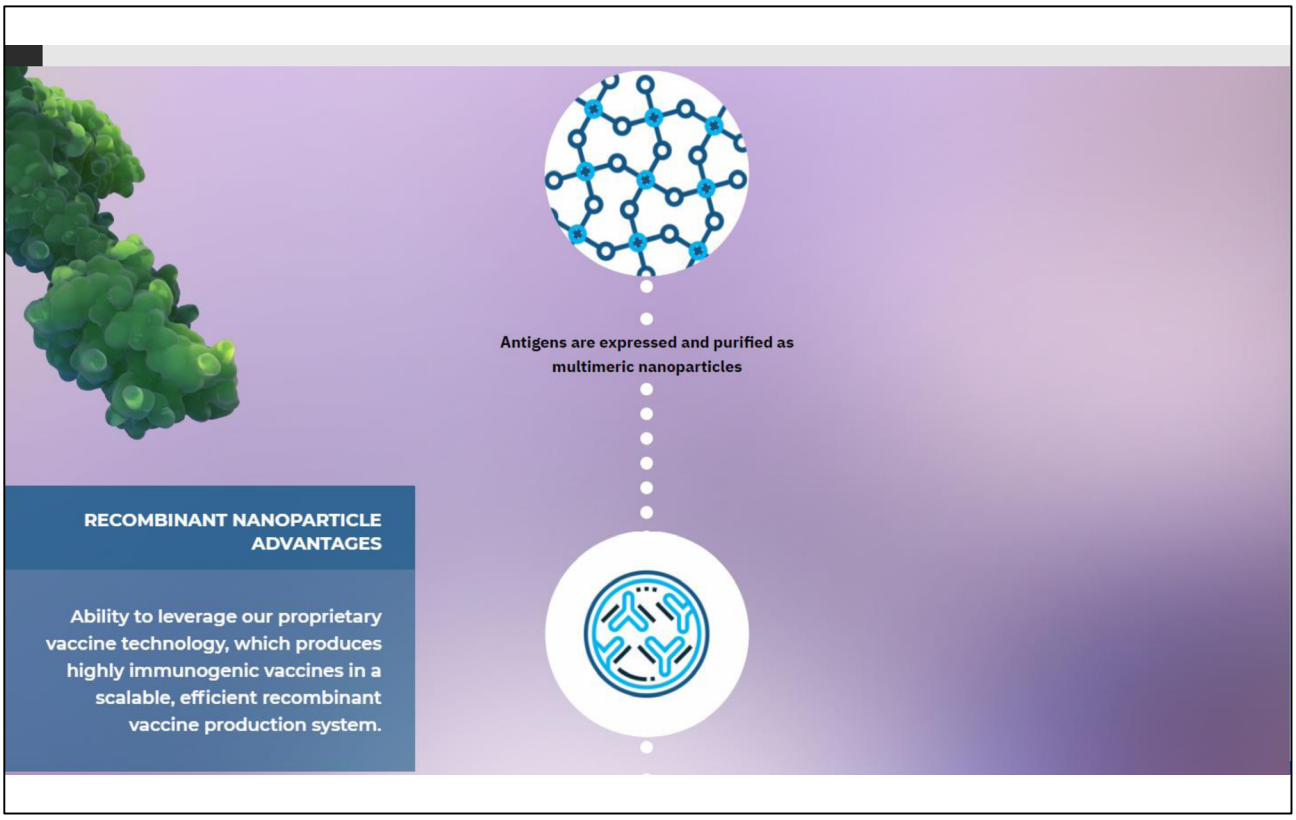


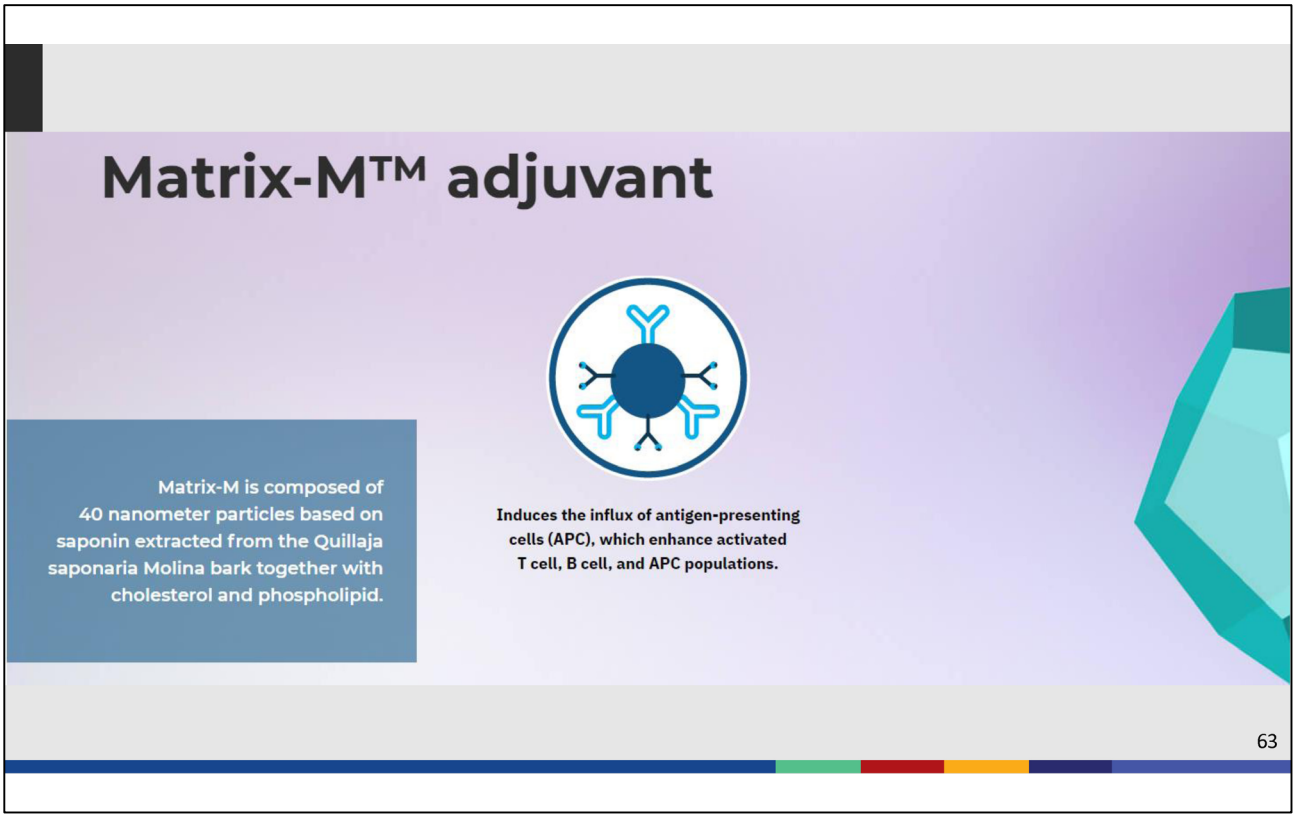
BV infects Sf9 insect cells

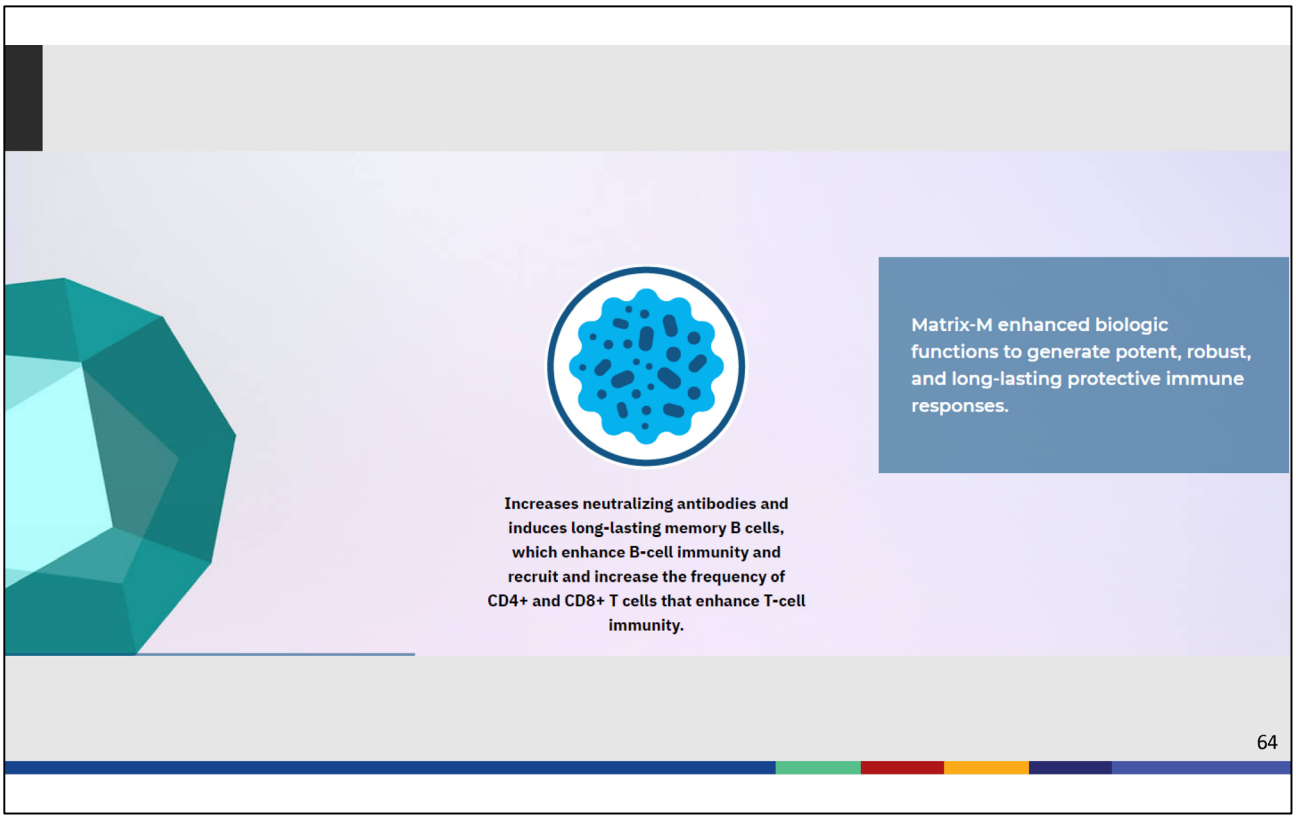
RECOMBINANT NANOPARTICLE ADVANTAGES

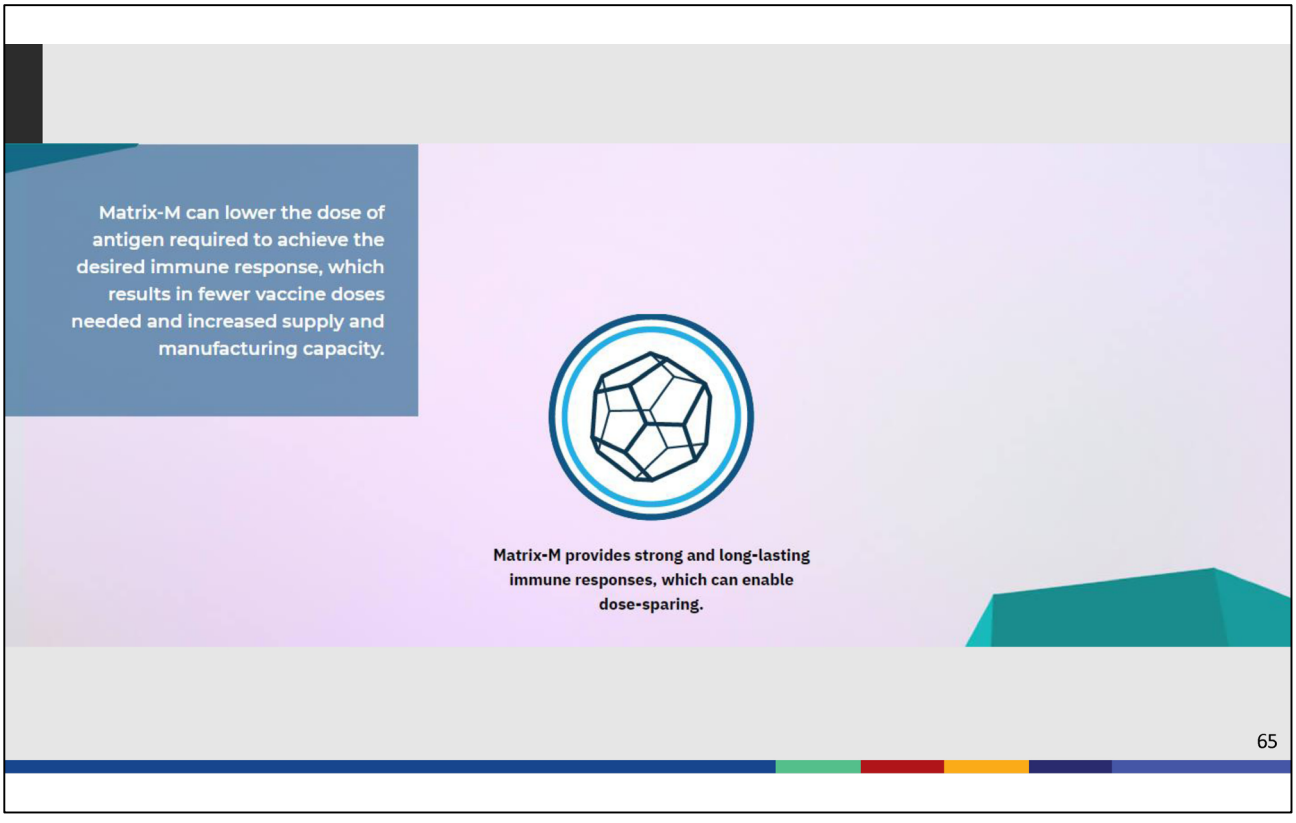
Ability to manufacture and produce proteins that are properly folded and modified, which can be critical for functional, protective immunity.

61


Antigens are expressed and purified as multimeric nanoparticles
RECOMBINANT NANOPARTICLE ADVANTAGES
Ability to leverage our proprietary vaccine technology, which produces highly immunogenic vaccines in a scalable, efficient recombinant vaccine production system.


Matrix-M™ adjuvant
Induces the influx of antigen-presenting cells (APC), which enhance activated T cell, B cell, and APC populations.
Matrix-M is composed of 40 nanometer particles based on saponin extracted from the Quillaja saponaria Molina bark together with cholesterol and phospholipid.
63


Matrix-M enhanced biologic functions to generate potent, robust, and long-lasting protective immune responses.
Increases neutralizing antibodies and induces long-lasting memory B cells, which enhance B-cell immunity and recruit and increase the frequency of CD4+ and CD8+ T cells that enhance T-cell immunity.
64

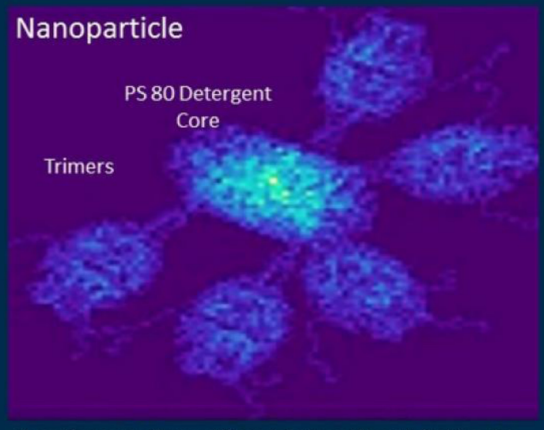

Matrix-M can lower the dose of antigen required to achieve the desired immune response, which results in fewer vaccine doses needed and increased supply and manufacturing capacity.
Matrix-M provides strong and long-lasting immune responses, which can enable dose-sparing.
65

Recombinant Protein Nanoparticles

Platform technology: previous experience allows directional confidence in early development

Engineered for immunogenicity, stability and productivity

SARS-CoV-2 Spike protein structure critical for protection, characterization tools well developed



Susan Krueger, et al Structural Characterization and Atomistic Modeling of a Respiratory Syncytial Virus Fusion Glycoprotein Nanoparticle Vaccine, ACS Nano

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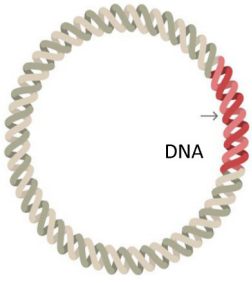
DNA Genetic Vaccines

Vaccines that use part of the coronavirus's genetic code.



DNA (Genetic) Vaccines

- Some experimental coronavirus vaccines deliver genetic instructions for building a viral protein. The protein then stimulates the immune system to make antibodies.
- The cells read the viral gene, make a copy in a molecule (messenger RNA), and then use mRNA to assemble viral proteins.
- The immune system detects the proteins and mounts defenses against the corona virus

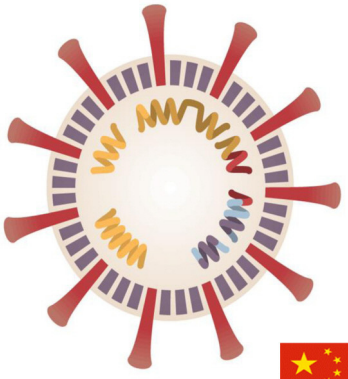
EXAMPLES: There are no approved DNA vaccines for use in humans. Some have been approved for veterinary cases such as canine melanoma and West Nile virus in horses.

COMPANIES and STATUS:

- Inovio - Now Phase I, Phase II / III started in July
- Zydus Cadila (India) - Phase I complete, will start Phase II
- AnGee (Japan) - Phase I / II

Inactivated and Live Attenuated Whole Virus Vaccines

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



Inactivated and Live Attenuated Vaccines

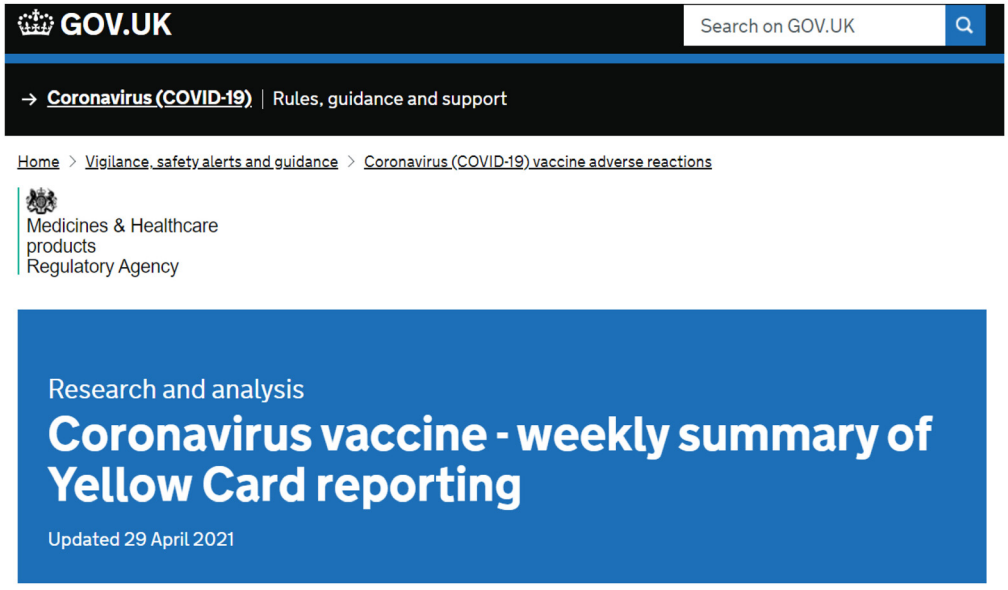
- Most vaccines today incorporate an inactivated or weakened virus not able to cause disease. When immune cells encounter them, they make antibodies.
- Making these vaccines means growing viruses…and lots of them, in chicken eggs with other vaccines growing in tanks full of floating cells. This production methodology can take months to produce batches of new vaccines

EXAMPLES:

Conventional vaccines for influenza, chickenpox, measles, mumps and rubella all fall into this category.

COMPANIES and STATUS:

- Sinovac Biotech – Phase III trials
- Sinopharm and Wuhan Institute – Beginning Phase III Trials in June
- Chinese Academy of Military Medical Science Phase II



Blood clots with concurrent low platelets

The MHRA has undertaken a thorough review into UK reports of an extremely rare specific type of blood clot in the brain, known as cerebral venous sinus thrombosis (CVST) occurring together with low levels of platelets (thrombocytopenia) following vaccination with the COVID-19 Vaccine AstraZeneca. It is also considering other blood clotting cases (thromboembolic events) alongside low platelet levels.

On the basis of this ongoing scientific review, it has concluded that the evidence of a link with COVID-19 Vaccine AstraZeneca is stronger, but more work is still needed. An announcement on 7 April 2021 gave information about cases received up to 31 March 2021. In this report (page 13) we provide updated information on cases received up to 21 April 2021. Our advice remains unchanged.

Anyone who experienced cerebral or other major blood clots occurring with low levels of platelets after their first vaccine dose of COVID-19 Vaccine AstraZeneca should not have their second dose. Anyone who did not have these side effects should come forward for their second dose when invited.

The MHRA recently confirmed that the evidence to date does not suggest that the COVID-19 Vaccine AstraZeneca causes venous thromboembolism without a low platelet count.

If you experience any of the following from around 4 days after vaccination you should seek medical advice urgently:

Conclusion

- Vaccines are the best way to protect people from Covid-19 and have already saved thousands of lives. Everyone should continue to get their vaccination when asked to do so unless specifically advised otherwise.
- As with all vaccines and medicines, the safety of COVID-19 vaccines is being continuously monitored .
- Cases of an extremely rare specific type of blood clot with low blood platelets continue to be investigated.

Further information on the type of suspected adverse reactions (ADRs) reported for the COVID-19 mRNA Pfizer/BioNTech vaccine, the COVID-19 Oxford University/AstraZeneca vaccine and the COVID-19 Moderna vaccine is provided in Annex 1. It is important to read the attached guidance notes to ensure appropriate interpretation of the data.

Selected Adverse Events Reported after COVID-19 Vaccination

Updated Apr. 27, 2021 Languages Print

Johnson & Johnson's Janssen COVID-19 Vaccine: CDC and FDA have recommended that use of Johnson & Johnson's Janssen (J&J/Janssen) COVID-19 Vaccine resume in the United States, effective April 23, 2021. However, women younger than 50 years old especially should be aware of the rare risk of blood clots with low platelets after vaccination, and that other COVID-19 vaccines are available where this risk has not been seen. If you received a J&J/Janssen vaccine, here is what you need to know. Read the CDC/FDA statement.

J&J/Janssen Updates

Safety of COVID-19 Vaccines

Results from monitoring efforts are reassuring. Some people have no side effects. Many people have reported only mild side effects after COVID-19 vaccination.

Is the Vaccine Safe?

Reports of death after COVID-19 vaccination

To date, Vaccine Adverse Event Reporting System (VAERS) has not detected patterns in cause of death that would indicate a safety problem with COVID-19 vaccines.

- FDA requires vaccination providers to report any death after COVID-19 vaccination to VAERS.
- Reports of death to VAERS following vaccination do not necessarily mean the vaccine caused the death.
- CDC follows up on any report of death to request additional information and learn more about what occurred and to determine whether the death was a result of the vaccine or unrelated.
- CDC, FDA, and other federal partners will continue to monitor the safety of COVID-19 vaccines.

Over 230 million doses of COVID-19 vaccines were administered in the United States from December 14, 2020, through April 26, 2021. During this time, VAERS received 3,848 reports of death (0.0017%) among people who received a COVID-19 vaccine. CDC and FDA physicians review each case report of death as soon as notified and CDC requests medical records to further assess reports. **A review of available clinical information including death certificates, autopsy, and medical records revealed no evidence that vaccination contributed to patient deaths.** CDC and FDA will continue to investigate reports of adverse events, including deaths, reported to VAERS.

How does the risk of serious side-effects from the AstraZeneca vaccine compare with other risks?

Chance in a million of...	25-year-old	55-year-old
serious harm due to vaccine side-effects	11 in a million	4 in a million
dying with coronavirus	23 in a million	800 in a million
dying due to an accident or injury	110 in a million	180 in a million
dying in a road accident	38 in a million	23 in a million
being hit by lightning this year	1 in a million	1 in a million

Figures show the chance of dying with coronavirus since the start of the pandemic. Figures for accidents and car crash fatalities are for 2018

Source: Winton Centre for Risk and Evidence Communication BBC