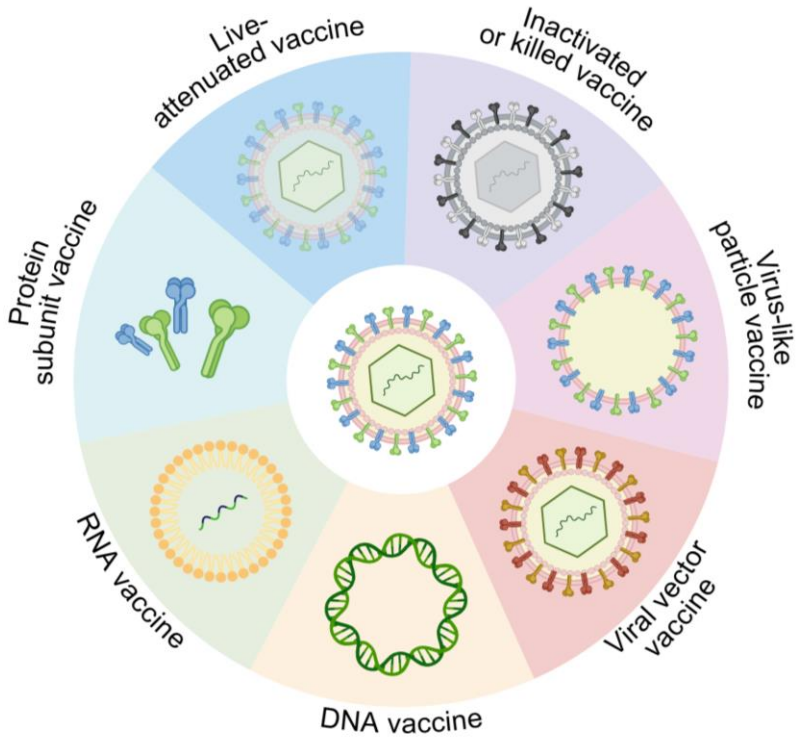


Vaccines as countermeasure against viral pathogens:

The history of vaccination

Vaccine platforms

Main licensed viral vaccines

Technologies applied to viral threats

How we measure the immune response in a lab

Vaccination as a countermeasure against viruses with epidemic and pandemic potential

Immunization is a global health success story, saving millions of lives every year. Vaccines reduce risks of getting a disease by working with your body's natural defenses to build protection. When you get a vaccine, your immune system responds.

We now have vaccines to prevent more than 30 life-threatening diseases and infections, helping people of all ages live longer, healthier lives. Immunization currently prevents 3.5 million to 5 million deaths every year from diseases like diphtheria, tetanus, pertussis (whooping cough), influenza and measles.

Immunization is key to primary health care, an indisputable human right, and one of the best health investments money can buy. Vaccines are also critical to the prevention and control of infectious disease outbreaks. They underpin global health security and are a vital tool in the battle against antimicrobial resistance.

The COVID-19 pandemic strained health systems, resulting in dramatic setbacks. The most recent data for diphtheria-pertussis-tetanus (DTP) immunization coverage underscores the need for ongoing catch-up, recovery and system-strengthening.

Measles, because of its high transmissibility, quickly exposes immunity. In 2024, the routine first dose of measles vaccine was missed by 20.6 million children – far from the 2019 level of 19.3 million children.

World Health Organization

https://www.who.int/health-topics/vaccines-and-immunization#tab=tab_1

PRINCIPLES *Vaccines*

- Following an initial encounter with a pathogen, memory immune cells are established; reexposure to the same pathogen reawakens these memory cells to control the infection and prevent disease.
- The goal of vaccination is to trigger an immune response more rapidly and with less harm than a natural infection.
- Smallpox virus, which caused infections that killed, crippled, or disfigured more than 1 in 20 of all humans who ever lived, is the only human virus to be eradicated.
- Viral candidates for eradication must possess two essential features: the infectious cycle must take place in a single host, and infection (or vaccination) must induce lifelong immunity.
- Vaccination can be active (the host makes its own response to a viral preparation) or passive (components of the immune response are obtained from an appropriate donor or donors and injected directly into the patient).
- To be effective, a vaccine must induce protective immunity in a fraction of the population that is sufficient to impede person-to-person transmission, a concept called herd immunity.
- Active vaccination can occur by administration of virus preparations that have been inactivated or attenuated or by delivery of individual immunogenic proteins or recombinant DNA vectors that encode them.
- Inactivated virus particles or purified proteins often do not induce the same immune response as attenuated preparations, unless mixed with adjuvants that stimulate the early inflammatory response.
- The failure to develop a human immunodeficiency virus vaccine can be explained by both the biology of this virus and its interaction with the host immune system.

What do we want from a Vaccine

We want a vaccine to be:

Safe: no adverse outcome (we measure Reactogenicity and adverse events)

Immunogenic: induce Immune response (we measure Immunogenicity)

Effective in preventing the disease

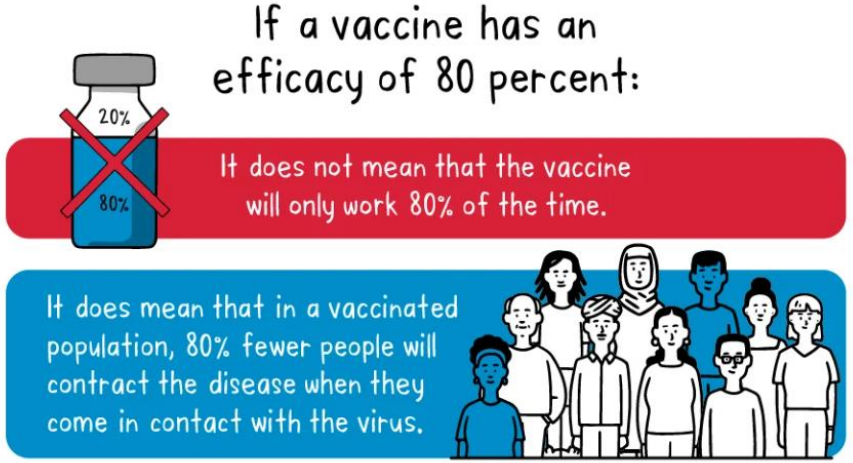
Offer long-lasting protection, ideally conferring lifelong immunity

We Look for a correlate of protection to link immune response to effectiveness

Vaccine efficacy is measured in controlled clinical trials. It is based on how many people who got vaccinated developed the 'outcome of interest' (usually disease) compared with how many people who got the placebo (dummy vaccine) developed the same outcome.

Vaccine efficacy tells us how much the vaccine lowers the risk of the outcome (e.g., getting sick) in a trial setting. For example, if a vaccine has an efficacy rate of 80%, it means that the vaccinated group had an 80% lower risk of developing disease than the unvaccinated group (those who received the placebo).

Effectiveness is a real-life measure, Efficacy is a measure in clinical trials



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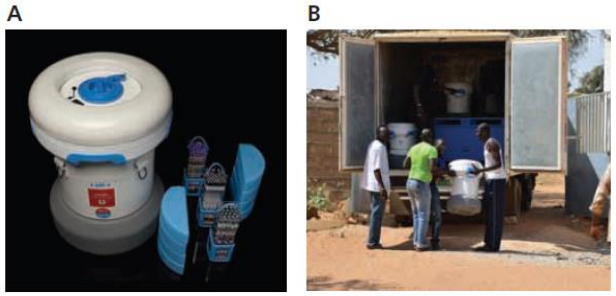
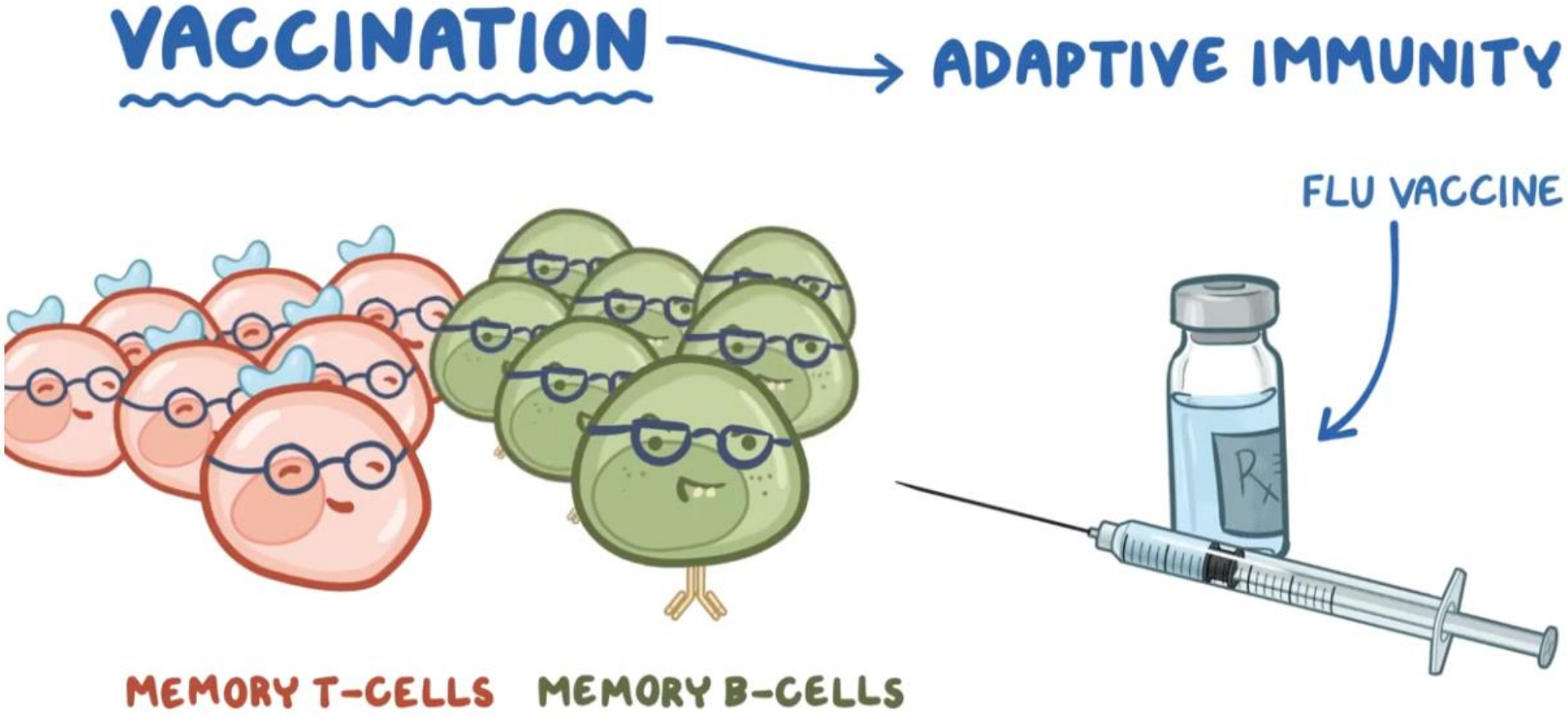
We look for a correlate of protection to link immune response to effectiveness

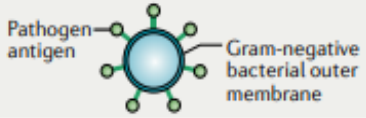
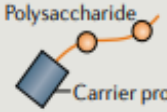
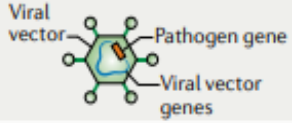
Practical: stability, ease of administration, and cost must be considered.

Figure 8.7 Vaccine thermoses. Development of novel chambers that keep vaccines cold for extended periods without electricity may revolutionize the efficacy of delivery of some attenuated vaccines for which the cold chain must be maintained. Credit: Intellectual Ventures.



What do we want from a Vaccine



Type of vaccine		Licensed vaccines using this technology	First introduced
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)
Toxoid		Diphtheria, tetanus	1923 (diphtheria)
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	1970 (anthrax)
Virus-like particle		Human papillomavirus	1986 (hepatitis B)
Outer membrane vesicle		Group B meningococcal	1987 (group B meningococcal)
Protein–polysaccharide conjugate		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid	1987 (*H. influenzae* type b)
Viral vectored		Ebola	2019 (Ebola)
Nucleic acid vaccine		SARS-CoV-2	2020 (SARS-CoV-2)

The majority of the vaccines used currently to combat infectious diseases can be broadly divided into three categories: live-attenuated; inactivated; protein subunits/polysaccharides

Despite the success of these established vaccine platforms, they have failed against immune-evading pathogens such as HIV, malaria, and tuberculosis.

In other cases, such as influenza and COVID-19, vaccines require annual or seasonal updates to combat rapidly arising mutations and vary substantially in efficacy year to year.

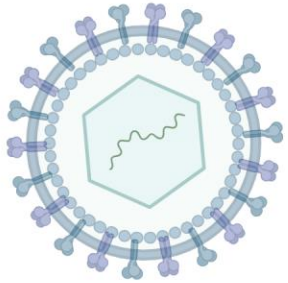
Finally, these vaccine modalities take years to decades to develop, thereby limiting their ability to combat outbreaks caused by **rapidly emerging and re-emerging pathogens**.

The need to overcome these limitations of traditional vaccine platforms has contributed to an increasing interest in the development of novel vaccine technologies against infectious diseases

Pollard AJ and Bijker EM Nat rev imm 2021; Gupta A et al. Nat rev drug discovery 2024

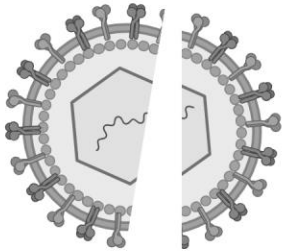
Approaches to **Viral Vaccine Development**

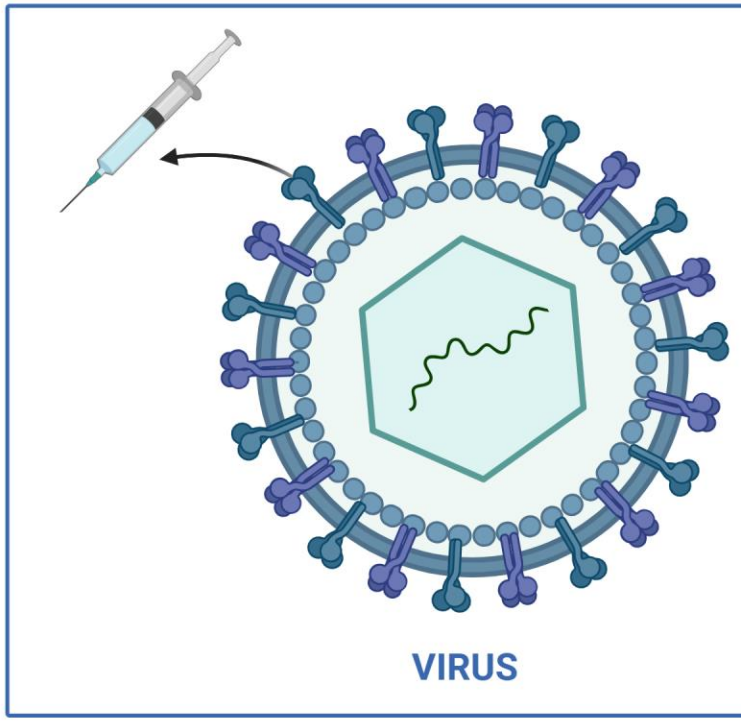
a. Live attenuated



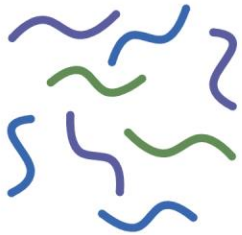
b. Whole inactivated

c. Split inactivated

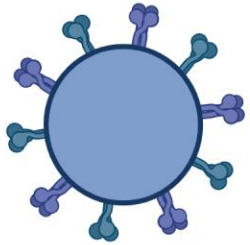




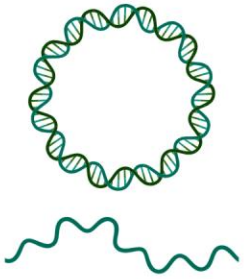
d. Synthetic peptides



e. Virus-like particles

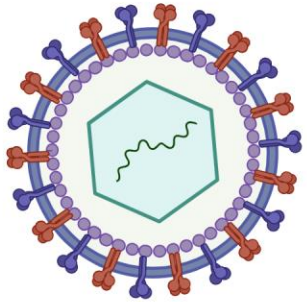


f. DNA or RNA

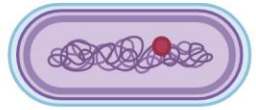


g. Recombinant subunits

i. Recombinant viral vectors



h. Recombinant bacterial vectors



Vaccine components

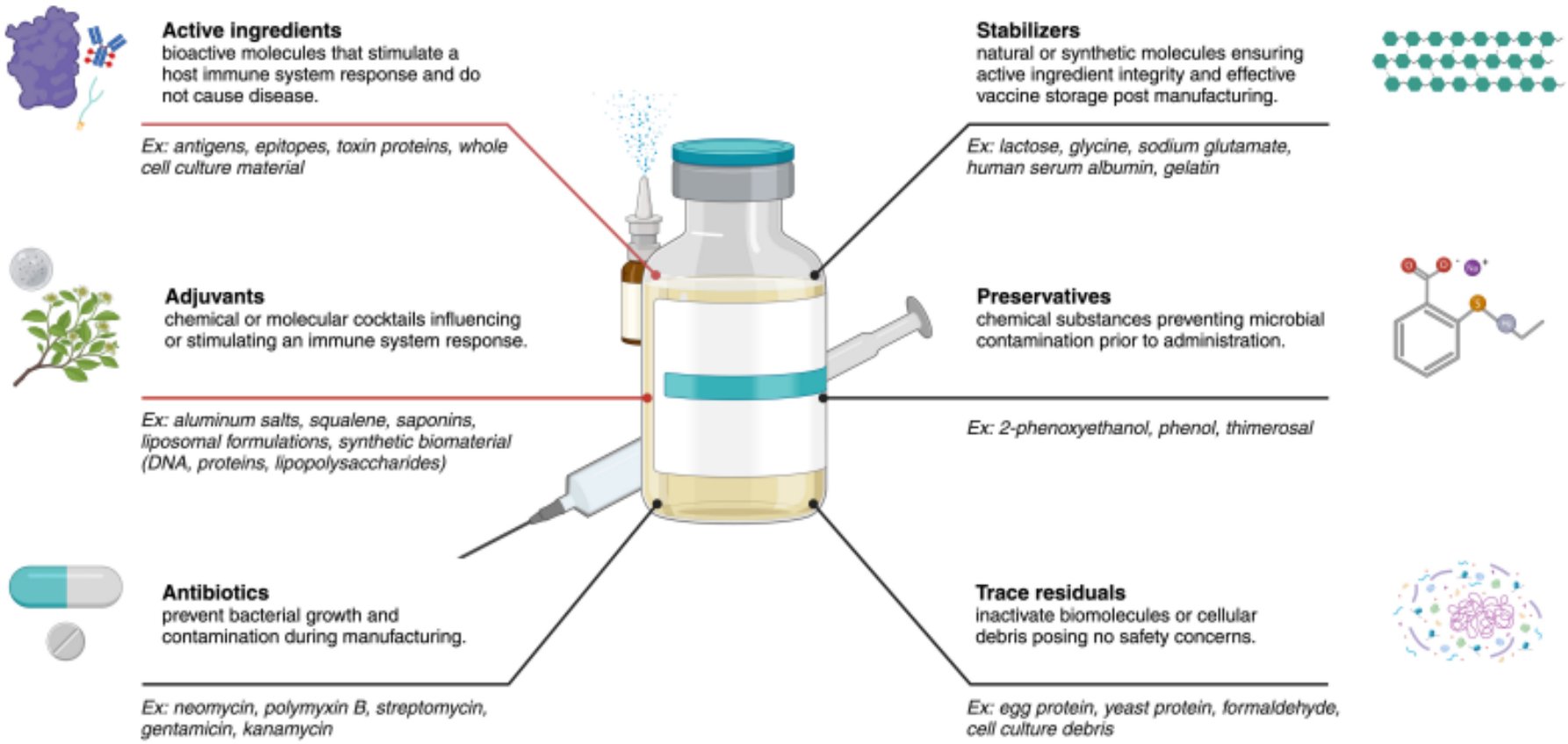


FIGURE 3

Common vaccine components (antigen, adjuvant, and delivery system) representing specific roles these ingredients play in the overall design of a given vaccine product for enhancing protection against an emerging infectious disease. Red lines indicate the two main contributors having a direct influence on vaccine efficacy and immune systems responses, where flexible combinations of these two ingredients enable improved vaccine efficacy and effectiveness depending on the optimal technology platform selected. The optimal combination of these components is crucial for developing safe and effective vaccines that elicit robust and long-lasting immune protection. Created using BioRender.com.

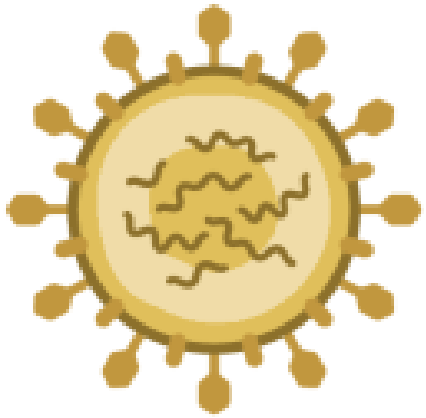
Why Vaccine Diversity Matters

Multiple platforms ensure we're prepared for diverse threats—whether a fast-spreading pandemic or a slow-evolving endemic virus.

Moreover, combining technologies (e.g., protein boosts after mRNA priming) could enhance protection against complex pathogens.

The platform, route of administration, additional vaccine components, and delivery systems, all together contribute to the safety and immunogenicity of a vaccine for a particular target population

Attenuated virus vaccine



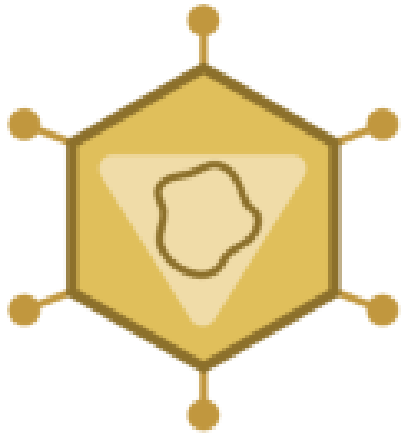
Pros

- Long-term immunological memory
- Mimics virus infection

Cons

- Possibility of virus revertant
- Contraindicated for immunocompromised people

Viral vector vaccine



Pros

- Replication-defective
- Robust immune responses including cytotoxic T cell responses

Cons

- Require a high biological safety level
- Pre-existing acquired immunity against the vector

Subunit vaccine

Pros

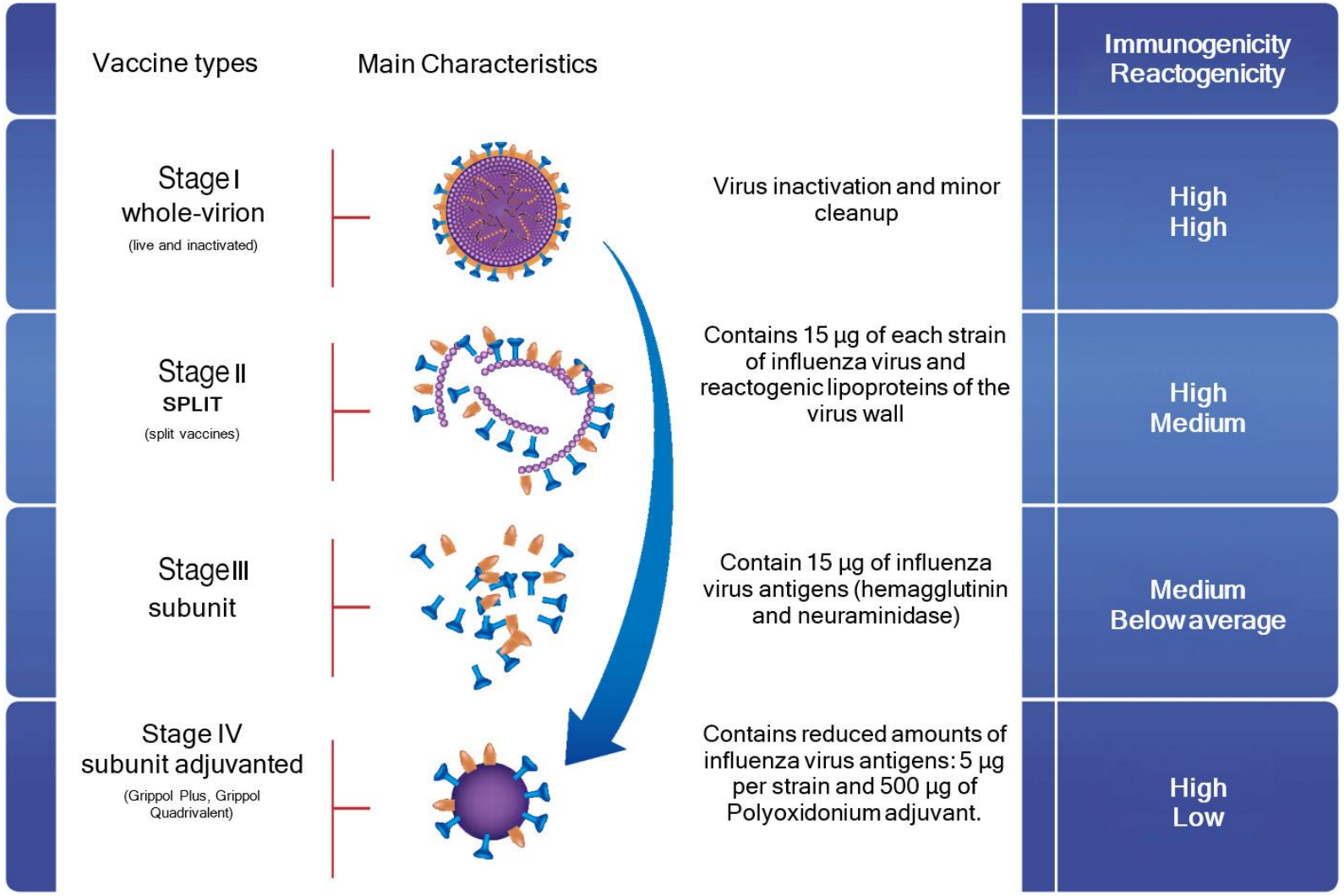
- Use of purified antigen
- Humoral responses against specific components of pathogen

Cons

- Necessity for adjuvant
- Generally requires booster immunization
- Vaccine delivery across the mucosal barrier

Improvement of influenza vaccine manufacturing technology

Vaccine safety is increasing with each generation.



Different platforms exists for Influenza vaccine from 1st to 4th generation.

How to choose?

Target population is the key, e.g.:

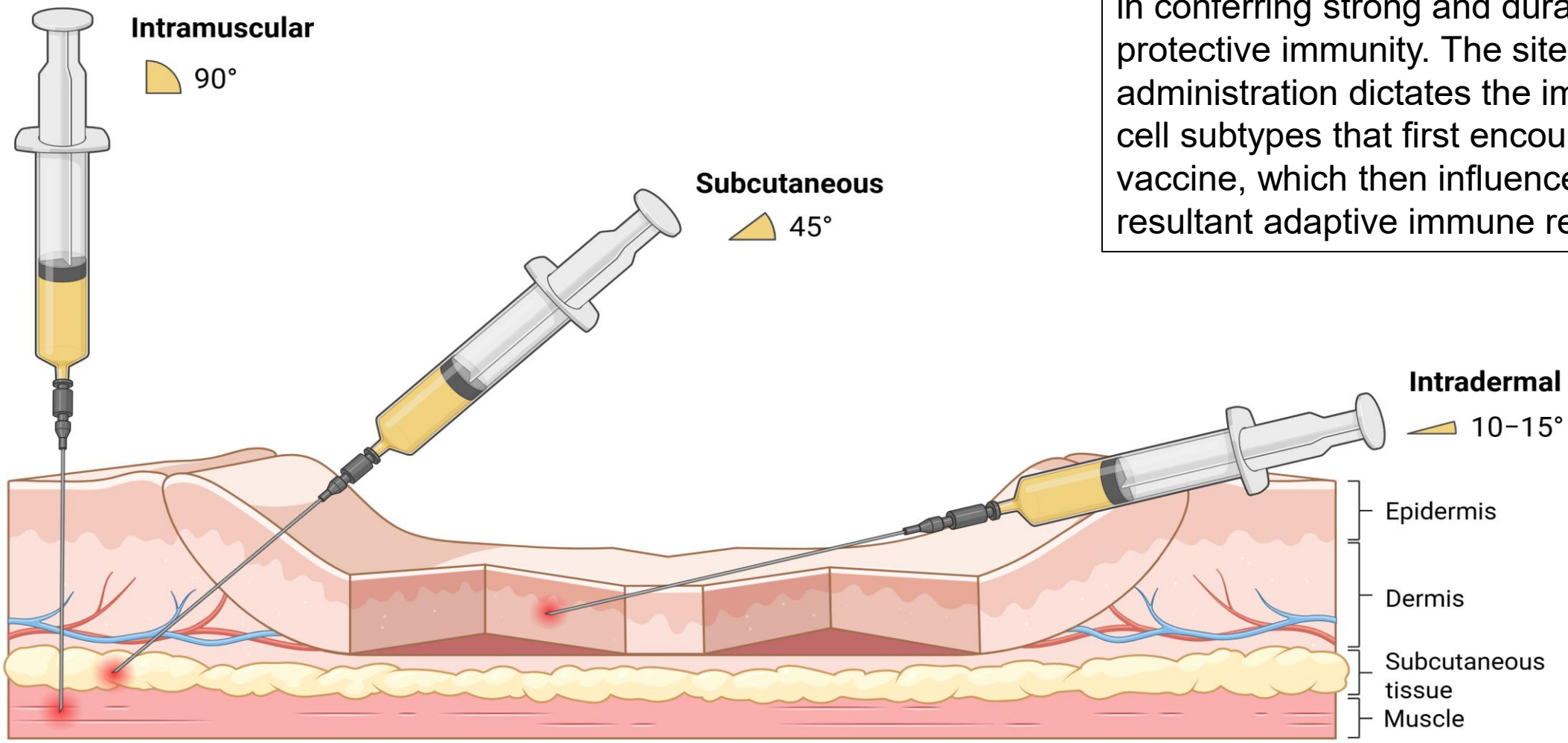
Nasal administration less invasive for children

Inactivated to be chosen for fragile people

And…
The availability

Main Routes of administration

Administration route plays a major role in conferring strong and durable protective immunity. The site of administration dictates the immune cell subtypes that first encounter the vaccine, which then influence the resultant adaptive immune response



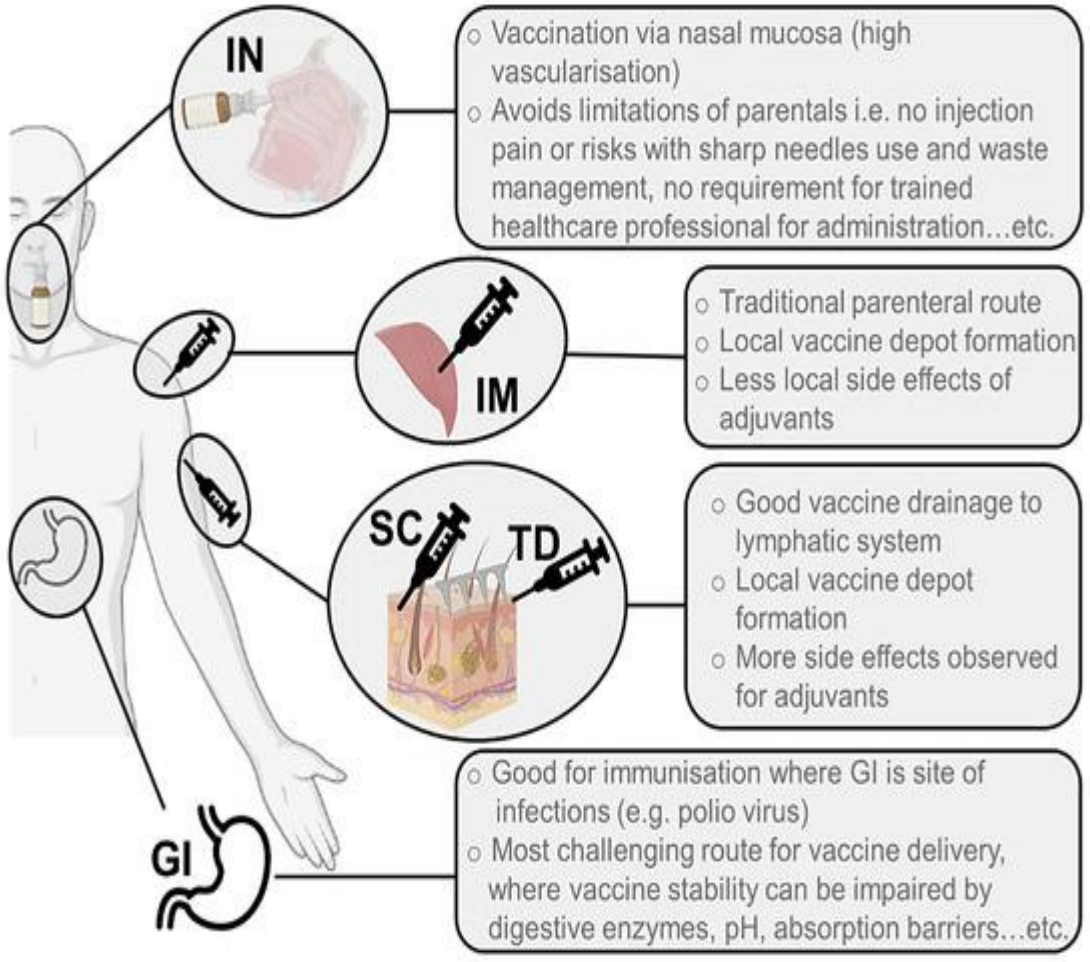
Main Routes of administration

- Most clinically approved vaccines are administered intramuscularly (IM) or subcutaneously (SC), as these injection routes are well-established and these tissues contain a large number of innate immune cells.

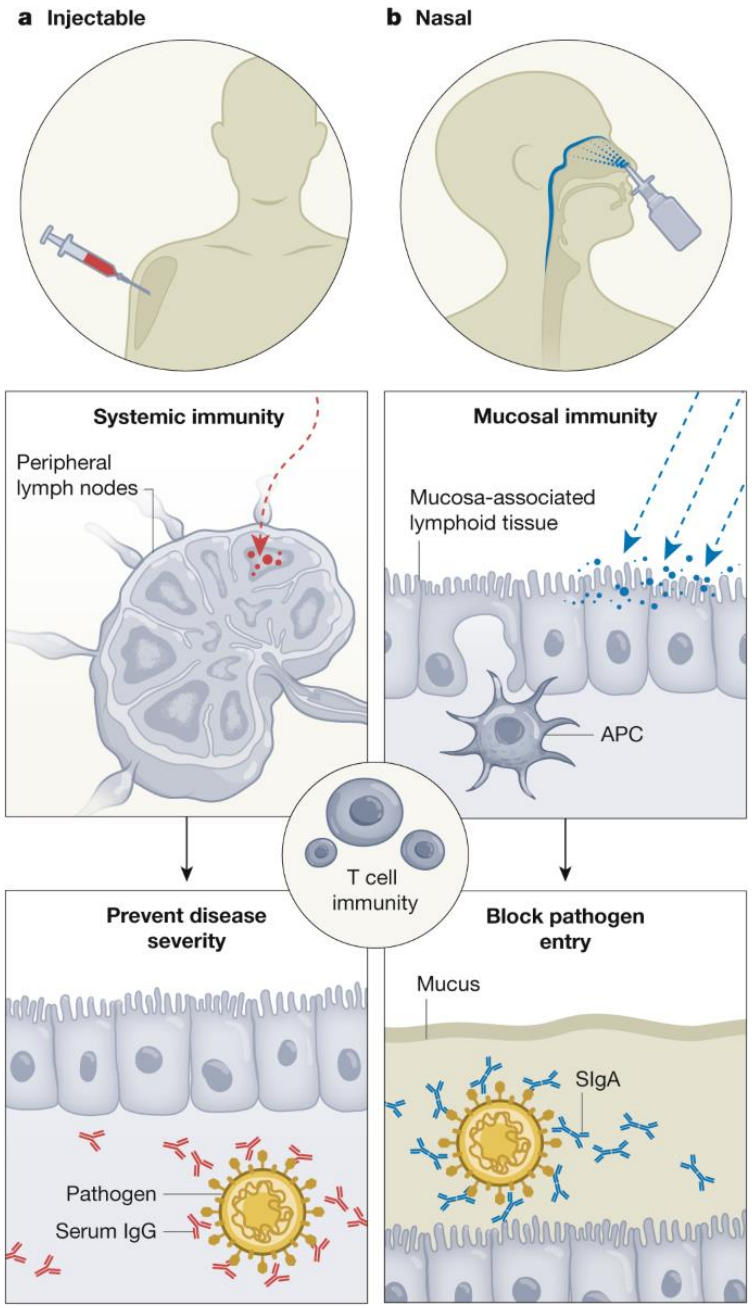
- Oral (GI) administered vaccines also exists.

- Other administration routes are emerging:

transdermal (TD) and respiratory (IN) administration routes expose the vaccine to a higher number of innate immune cells in skin and mucosa, respectively



Cordeiro AS et al.doi.org/10.3390/pharmaceutics13122091



Review

Nasal vaccines for respiratory infections

https://doi.org/10.1038/s41586-025-08910-6

Hiroshi Kiyono[1,2,3,4] ✉ & Peter B. Ernst[1,2,3,5] ✉

Received: 28 May 2024

a, Currently, most vaccinations are administered by injection, which effectively stimulates systemic immunity and leads to the induction of pathogen-specific serum IgG neutralizing antibodies and T cell immunity, resulting in control of the severity of infectious diseases. However, they are generally less effective in inducing antigen-specific immune responses on mucosal surfaces and thus may not provide adequate protective immunity at the site of pathogen invasion.

b, By contrast, nasal vaccines effectively stimulate the mucosal immune system to produce pathogen-specific sIgA antibodies and systemic (serum IgG) immunity, which together, provide broad protection to the host.

Because most infections are initiated at the mucosal surfaces, mucosal vaccination is considered a means to induce broad protection against infection.

Route of administration and Reactogenicity

Administration of vaccines to different tissues, may impact the reactogenicity profile and safety of vaccines. They can also result in dose sparing!!!!

1) In a clinical study evaluating mRNA vaccines against influenza:
Immunity: intradermal (ID) > intramuscular (IM), adverse events: ID >IM.

2) COVID-19 mRNA-1273 compared with IM administration, ID administration offers dose-sparing and an enhanced safety profile

3) Vaccination against monkeypox with MVA-BN, similar adverse events comparing SC vs ID, but dose-sparing with ID (1/5 of the SC dose)

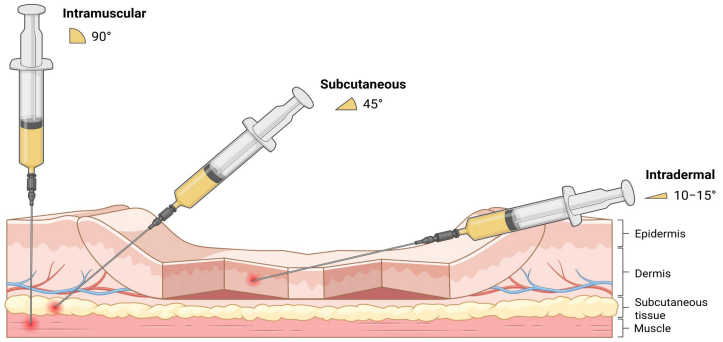


Figure 8.2 Irrational fears of the effects of vaccines. Some believed that vaccination using a virus that infected cows would cause cow-like features to appear in the recipient. The preponderance of data suggests this is not the case.

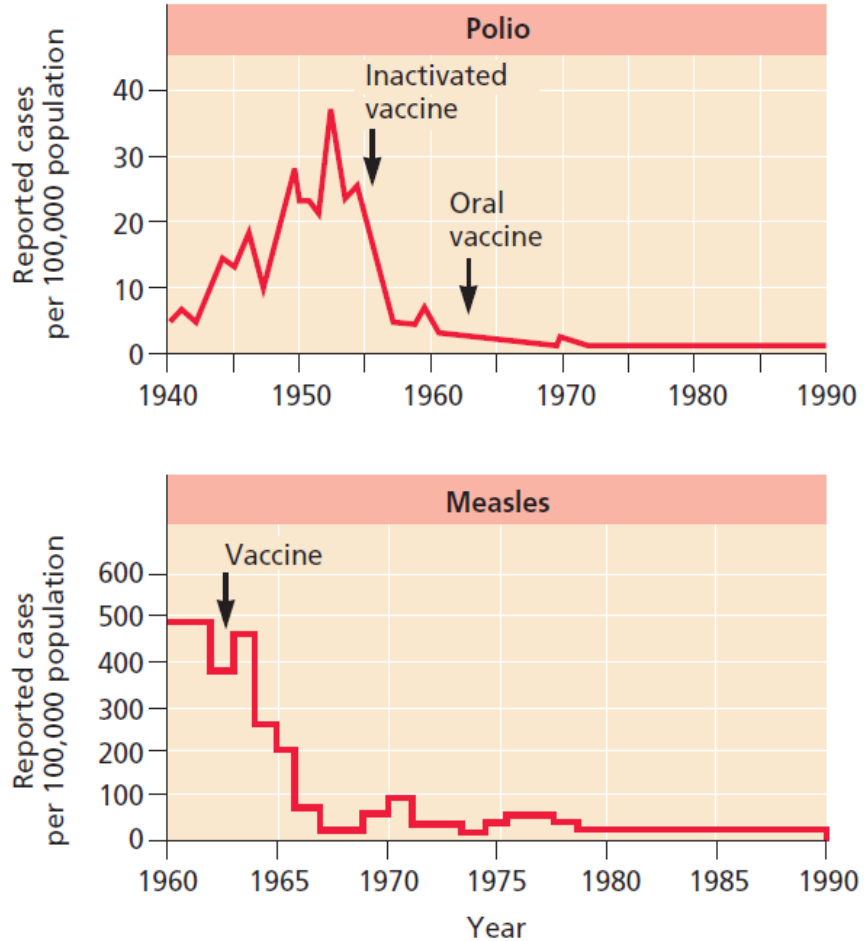
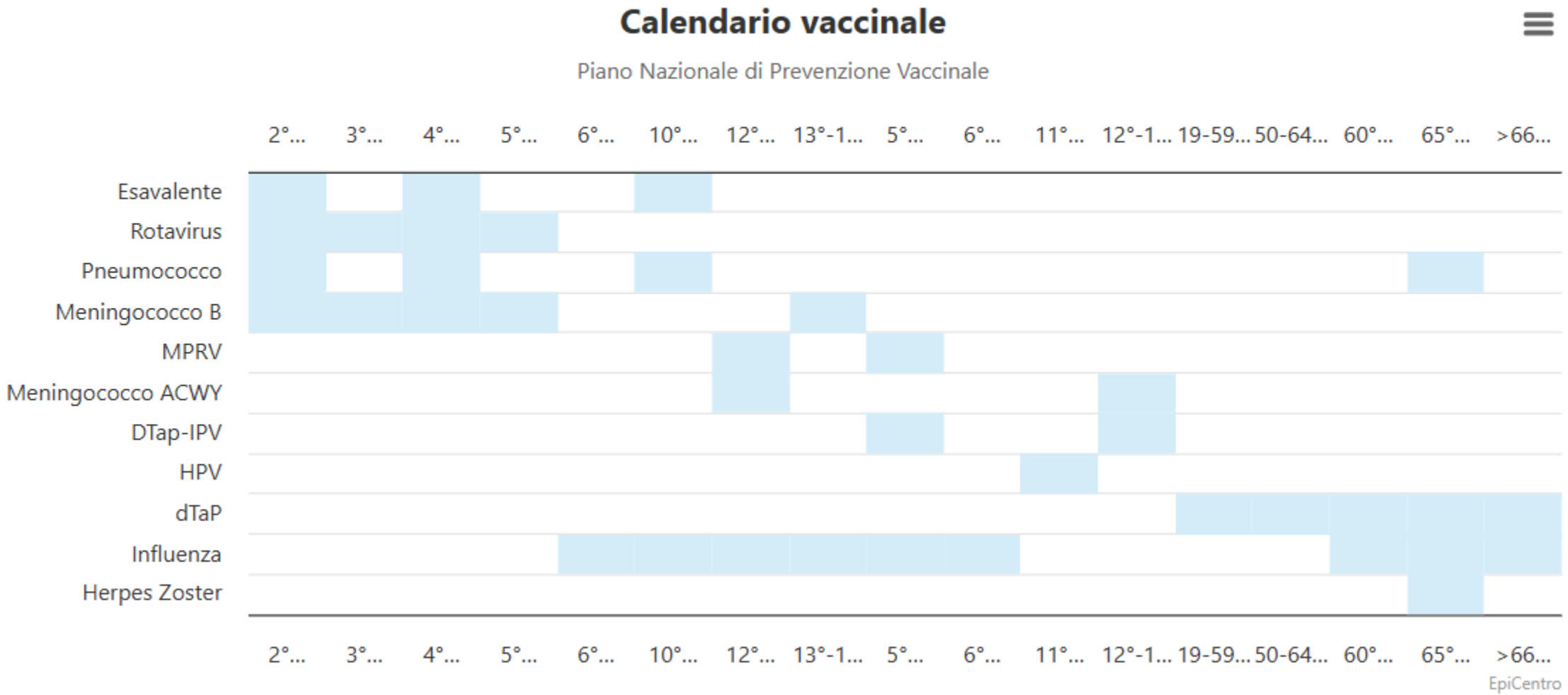


Figure 8.1 Profiles of successful vaccination campaigns. The number of reported cases of poliovirus (top) and measles virus (bottom) infection in the United States has been greatly reduced after massive vaccination programs. Adapted from C. A. Janeway, Jr., et al., *Immunobiology: the Immune System in Health and Disease* (Current Biology Limited, Garland Publishing Inc., New York, NY, 2001), with permission.

Tabella calendario vaccinale



Vaccino esavalente (DTPa/IPV/Ep B/Hib):difterite, tetano, pertosse, polio, epatite B, *Haemophilus influenzae* tipo b
Morbillo, Parotite, Rosolia, Varicella (MPRV)

Polio Vaccine

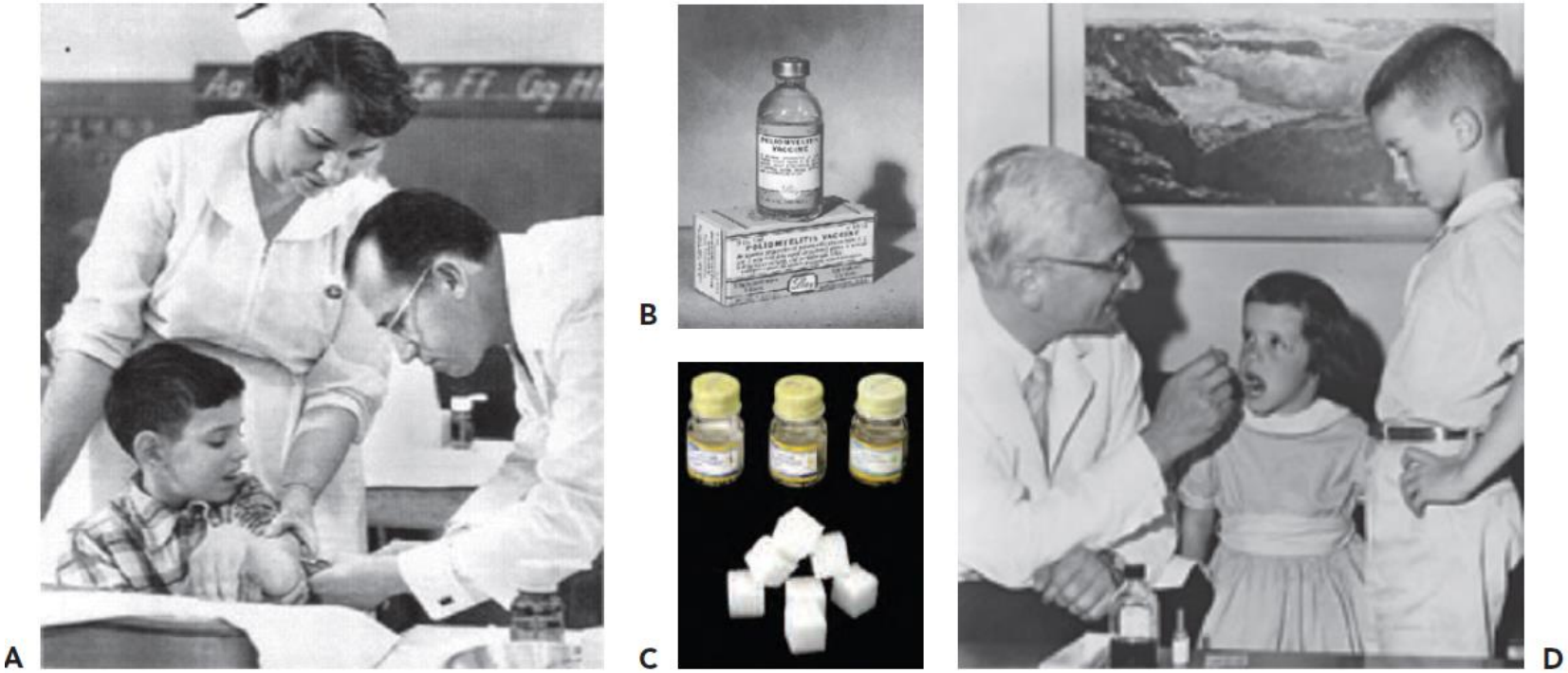


FIGURE 14.1. Polio vaccine development. The development of vaccines for polio brought the process of vaccine development into the public eye and was the first licensed vaccine that relied on mammalian cell culture. Jonas Salk **(A)** spearheaded the development of the inactivated polio vaccine **(B)**. The development of the oral polio vaccine **(C)** was headed by Albert Sabin **(D)**. These two vaccines are still in use today and over the past 50 years have nearly eliminated poliovirus, making the goal of global eradication feasible. (**A,** © AP Wide World Photos; **C** and **D** courtesy Hauck Center for the Albert B. Sabin Archives, Henry R. Winkler Center for the History of the Health Professions, University of Cincinnati.)

Polio Vaccine

A breakthrough occurred in 1949, when poliovirus was successfully cultivated in human tissue by John Enders, Thomas Weller and Frederick Robbins at Boston Children's Hospital. Their pioneering work was recognized with the 1954 Nobel Prize.

Not long afterwards, in the early 1950s, the first successful vaccine was created by US physician Jonas Salk. Salk tested his experimental killed-virus vaccine on himself and his family in 1953, and a year later on 1.6 million children in Canada, Finland and the USA.

The results were announced on 12 April 1955, and Salk's inactivated polio vaccine **(IPV)** was licensed on the same day.

In a 1955 interview, when asked who owned the patent for IPV, he replied: "Well, the people, I would say. There is no patent. Could you patent the sun?"

https://www.who.int/news-room/spotlight/history-of-vaccination/history-of-polio-vaccination

Polio Vaccine

A second type of polio vaccine, the oral polio vaccine **(OPV)** was developed by physician and microbiologist Albert Sabin.
Sabin's vaccine was live-attenuated (using the virus in weakened form) and could be given orally, as drops or on a sugar cube. **This method mimics natural infection more closely, activating both systemic immunity and local intestinal immunity**

Trials carried out in the Soviet Union, on 20 000 children in 1958 and 10 million children in 1959, and in Czechoslovakia, on over 110 000 children from 1958 to 1959, proved the vaccine was safe and effective.
Independent review of the trials for the World Health Organization by United States specialist Dorothy Horstmann endorsed their findings – a crucial validation in the time of the Cold War.

https://www.who.int/news-room/spotlight/history-of-vaccination/history-of-polio-vaccination

Polio Vaccine

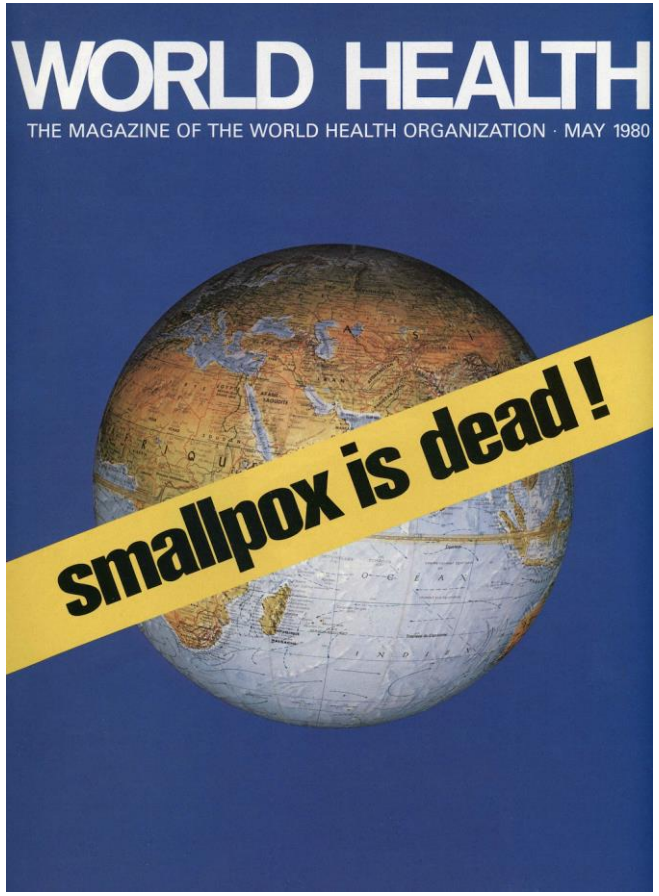
Pros and Cons of Each Vaccine
Both vaccines have their pros and cons worth considering:

- **Safety:** IPV is regarded as safer because there's no risk of vaccine-derived paralytic poliomyelitis (VDPV), a rare condition associated with OPV where weakened viruses revert to virulence under certain conditions.
- **Cost:** Generally speaking, OPV is less expensive than IPV due to lower production costs; this makes it particularly appealing for mass immunization campaigns in low-resource settings.
- **Accessibility:** While both vaccines require careful handling—especially IPV which needs cold chain storage—OPVs ease administration since they don't require needles or syringes.

While IPV protected the vaccinated child, it did not stop the poliovirus from spreading between children.
OPV, on the other hand, interrupted the chain of transmission, meaning that this was a powerful vaccine to stop polio outbreaks in their tracks.

https://www.who.int/news-room/spotlight/history-of-vaccination/history-of-polio-vaccination

Smallpox (Variola virus) vaccination



Edward Jenner tested the hypothesis that infection with cowpox could protect a person from smallpox infection.
Cowpox is an uncommon illness in cattle, usually mild, that can be spread from a cow to humans via sores on the cow. During an infection, dairy workers may have pustules on their hands

First-generation vaccines grown on the skin of live animals were widely distributed in the 1950s–1970s to eradicate smallpox.

Second-generation vaccines were grown in chorioallantoic membrane or cell cultures for greater purity, and they were used in some areas during the smallpox eradication campaign.

Third-generation vaccines are based on attenuated strains of vaccinia and saw limited use prior to the eradication of smallpox

https://www.who.int/news-room/spotlight/history-of-vaccination/history-of-smallpox-vaccination

https://pmc.ncbi.nlm.nih.gov/articles/PMC1200696/

HBV vaccine and correlate of protection

In 2019, the World Health Organization (WHO) estimated that hepatitis B (HBV) infections resulted in 820,000 deaths globally, mostly from cirrhosis and hepatocellular carcinoma, with 296 million people living with chronic disease and 1.5 million new infections each year.

In Italy, the incidence rate of acute HBV cases decreased from 5 per 100,000 inhabitants in 1990 to 2 per 100,000 ten years later. In 2021, only 89 new cases were reported, with an incidence of 0.18 per 100,000 inhabitants

Hepatitis B infection acquired in adulthood leads to chronic hepatitis in less than 5% of cases, whereas infection in infancy and early childhood leads to chronic hepatitis in about 95% of cases. This is the basis for strengthening and prioritizing infant and childhood vaccination.

HBV vaccine and correlate of protection

Since the HBsAg synthesized in bacteria is not able to properly assemble as particles similar to those in natural infection in human, the expression of the S gene was tried in eukaryotic systems. The HBsAg synthesized in the yeast Saccharomyces cerevisiae is able to assemble into particles similar to the 22-nm particles produced in human

TABLE 1. Definitions of terms used in this article

Term	Definition
Correlate	An immune response that is responsible for and statistically interrelated with protection
Absolute correlate	A specific level of response highly correlated with protection; a threshold
Relative correlate	A level of response variably correlated with protection
Cocorrelate	One of two or more factors that correlate with protection in alternative, additive, or synergistic ways
Surrogate	An immune response that substitutes for the true immunologic correlate of protection, which may be unknown or not easily measurable

Vaccine-efficacy studies and immunological standards have defined an anti-HBsAg titer ≥ 10 mIU/ml as protective against HBV

Main Vaccines against EID

Virus	Vaccine platform	Licensed	Use	Disease
Yellow Fever	Attenuated	Yes	Human	Fever/Haemorragic fever
Tick Borne Encephalitis	Inactivated	Yes	Human	Fever/Encephalitis-Meningitis
Japanese Encephalitis	Inactivated (or attenuated*)	Yes	Human	Fever/Encephalitis-Meningitis
Dengue	Attenuated	Yes	Human	Fever/Haemorragic fever
Chikungunya	VLP	Yes	Human	Fever/Joint pain
Ebola	Vector	Yes	Human	Haemorragic Fever
Monkeypox	Vaccinia Virus based Attenuated and non replicating	Yes	Human	Skin lesions with complications in Immunocmpromised individuals
SARS-CoV-2	Vector/Subunit/mRNA	Yes	Human	Respiratory Syndrome
Influenza	Multiple platforms	Yes	Human	Respiratory Syndrome
Avian Influenza	Subunit/Split Vaccines	Yes**	Human	Respiratory Syndrome
Avian Influenza	Inactivated/Vector	Yes	Veterinary	Respiratory Syndrome
West Nile	Inactivated/Vector	Yes	Veterinary	Fever/Encephalitis-Meningitis
Rift Valley Fever	Inactivated/Attenuated	Yes	Veterinary	Fever/Haemorragic fever
Hendra	Subunit	Yes	Veterinary	Respiratory or Neurological syndrome
Zika	Inact/Att/mRNA/Vector/DNA	Phase I/II	Human	Fever/Congenital syndrome
Lassa	DNA/Vector	Phase I/II	Human	Haemorragic Fever
Marburg	Vector	PhaseI/II	Human	Haemorragic Fever
MERS-CoV	Vector	Phase I	Human	Respiratory Syndrome
Crimea-Congo Haemorragic fever	Multiple Platforms/Vector	Preclinical/Phase I	Human	Haemorragic Fever

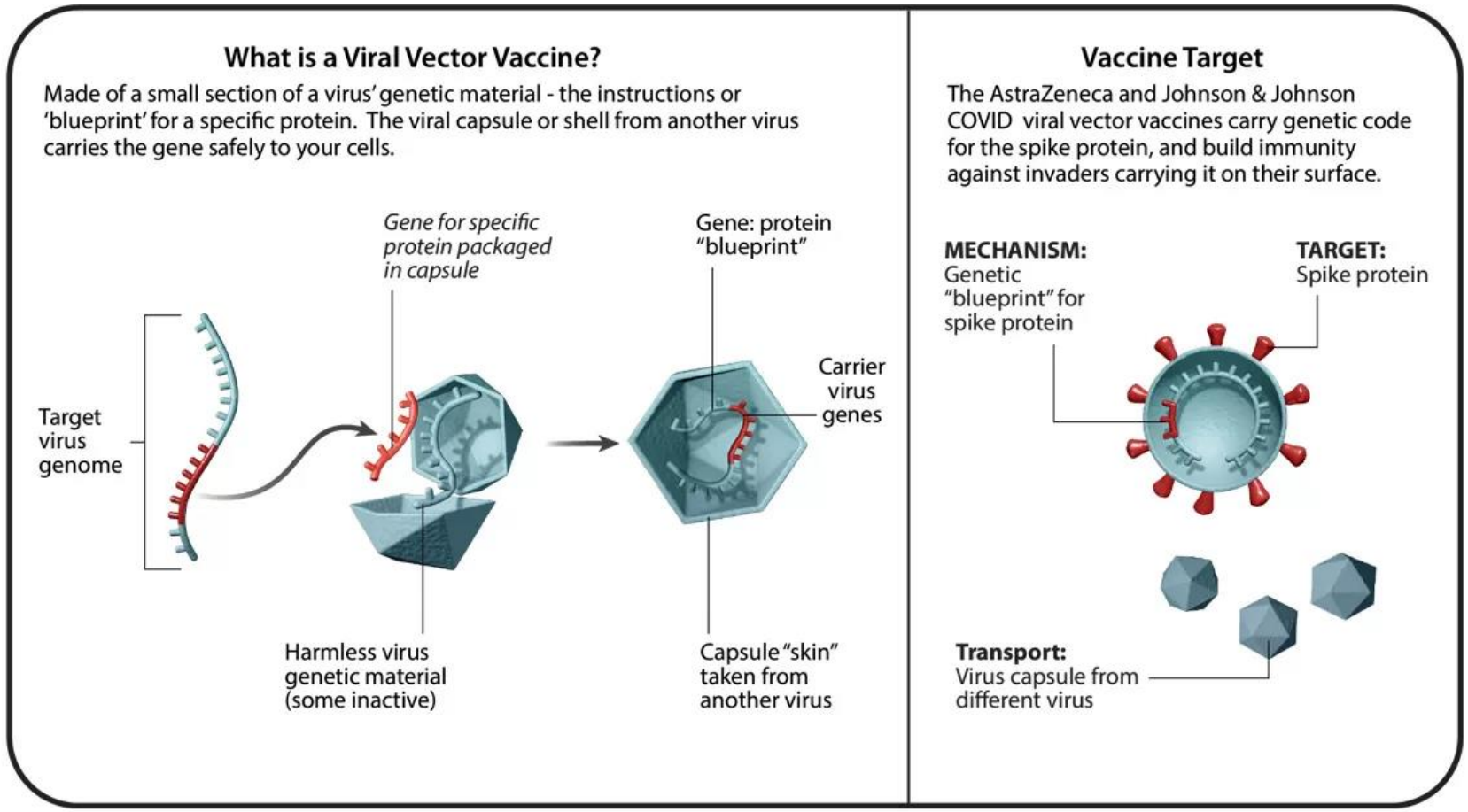
*not licensed in EU and US

**H5 strains, limited to People in contact with livestock and HCW

EID: Emerging Infectious diseases

Viral vector vaccines

Viral vector vaccines use a harmless virus to deliver to the hosts cells the genetic code of the antigen you want the immune system to fight.

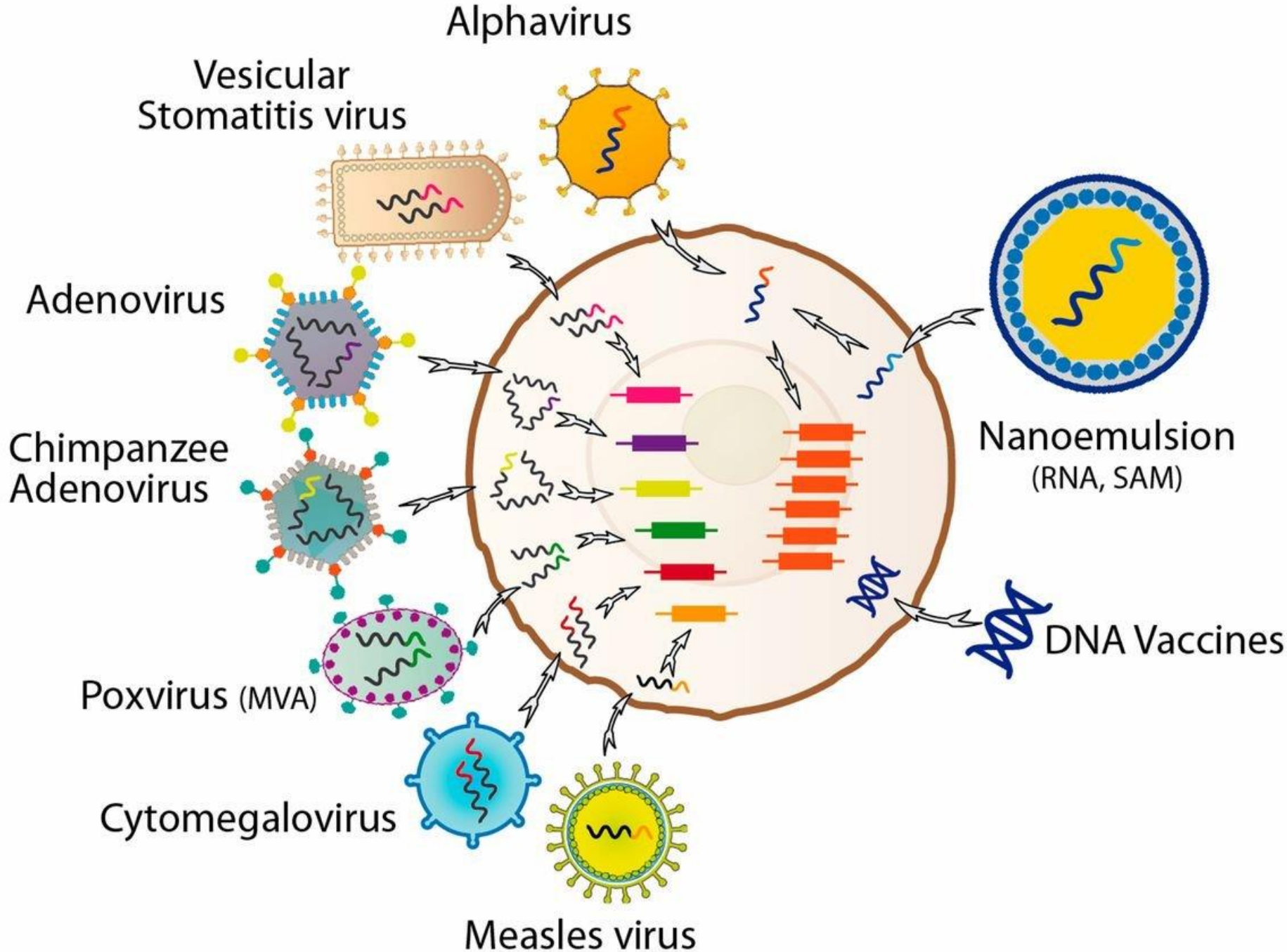


Examples: Ebola vaccine, COVID-19 vaccine

We can develop immunity against the vector…

VIRAL VECTORS

FULLY SYNTHETIC VACCINES



Viral vector vaccines

Pre-existing immunity, particularly relevant for Adenovirus 5 (Ad5) and other common adenovirus serotypes, can significantly lower vaccine immunogenicity by neutralizing the vector before it delivers its payload.

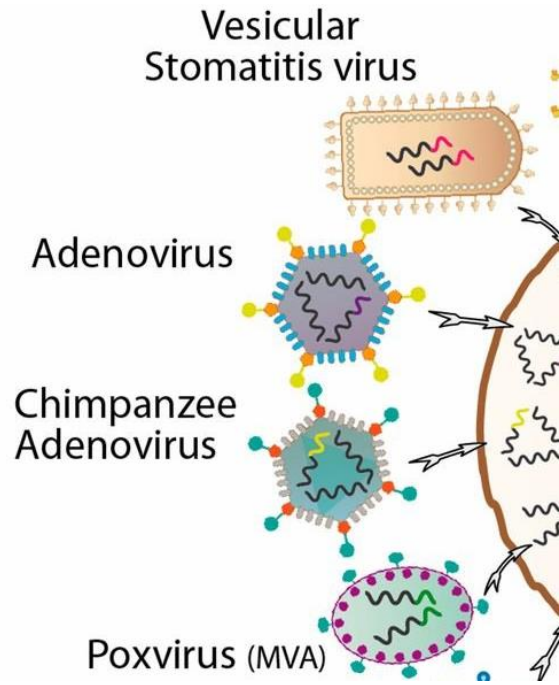
This challenge is circumvented in multiple ways:

•Using alternative serotypes (Ad26, Ad35, or simian adenoviruses)

•Adopting heterologous prime-boost regimens

•Employing poxvirus, VSV, or other unrelated vectors

•Engineering chimeric capsids with novel antigenic surfaces



Some COVID-19 vaccines are based on Adenoviral vectors
Oxford–AstraZeneca vaccine uses the modified chimpanzee adenovirus ChAdOx1
Sputnik V uses human adenovirus serotype 26 for the first shot, and serotype 5 for the second.
Janssen vaccine uses serotype 26

Ebola Vaccines

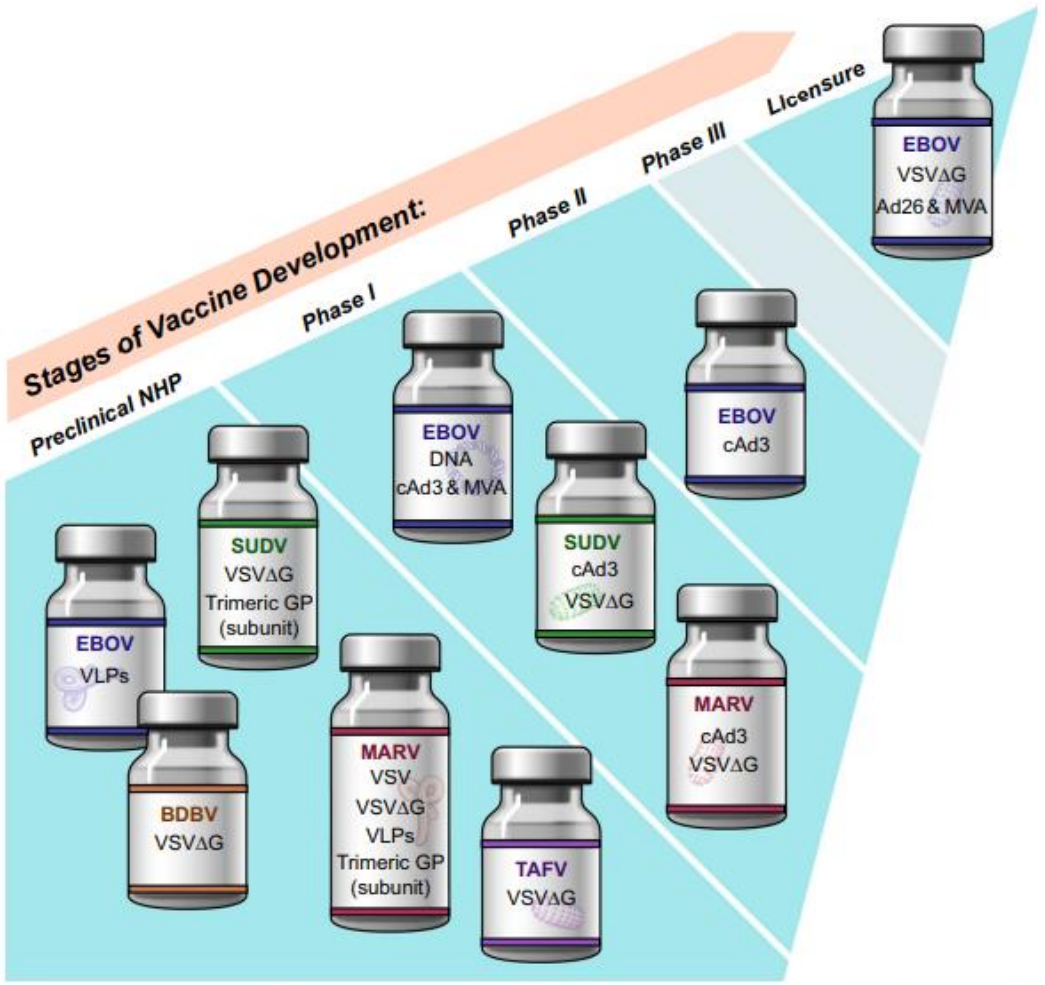


Fig. 1 | Development stages of filovirus vaccines in the USA. The cartoon indicates the development stages of different filovirus vaccines. C

Ervebo (rVSVΔG-ZEBOV-GP, live attenuated VSV with Ebola Zaire GP) was licensed in 2019 by the EMA and FDA and prequalified by WHO. The vaccine is safe and protective against the species Zaire ebolavirus. It is recommended by the Strategic Advisory Group of Experts (SAGE) on Immunization as part as a broader set of **Ebola outbreak response tools**. (>18years)

In May 2020, authorisation to a second new vaccine delivered in 2 doses called **Zabdeno** (Ad26.ZEBOV-GP) and **Mvabea** (MVA-BN-Filo: GP Zaire, Sudan, Tai Forest and Marburg) for individuals 1 year and older.

The vaccine is delivered in **2 doses**: Zabdeno is administered first and Mvabea is given approximately 8 weeks later as a second dose. This prophylactic 2-dose regimen is therefore not suitable for an outbreak response where immediate protection is necessary.

MVA Modified Vaccinia Ankara; EMA European Medicines Agency; FDA Food and Drug Administration in the US

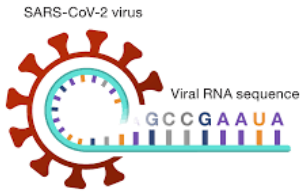
Nucleic Acid vaccines

Advantages:

The development and manufacture are simple and fast, and can be rapidly scaled up in manufacturing

The absence of infectious agents in the production process also clears out the concern of incomplete virus deactivation or purification

The genetic sequence of nucleic acid vaccines can be easily modified, making them adaptable to emerging infectious diseases and rapidly evolving pathogens

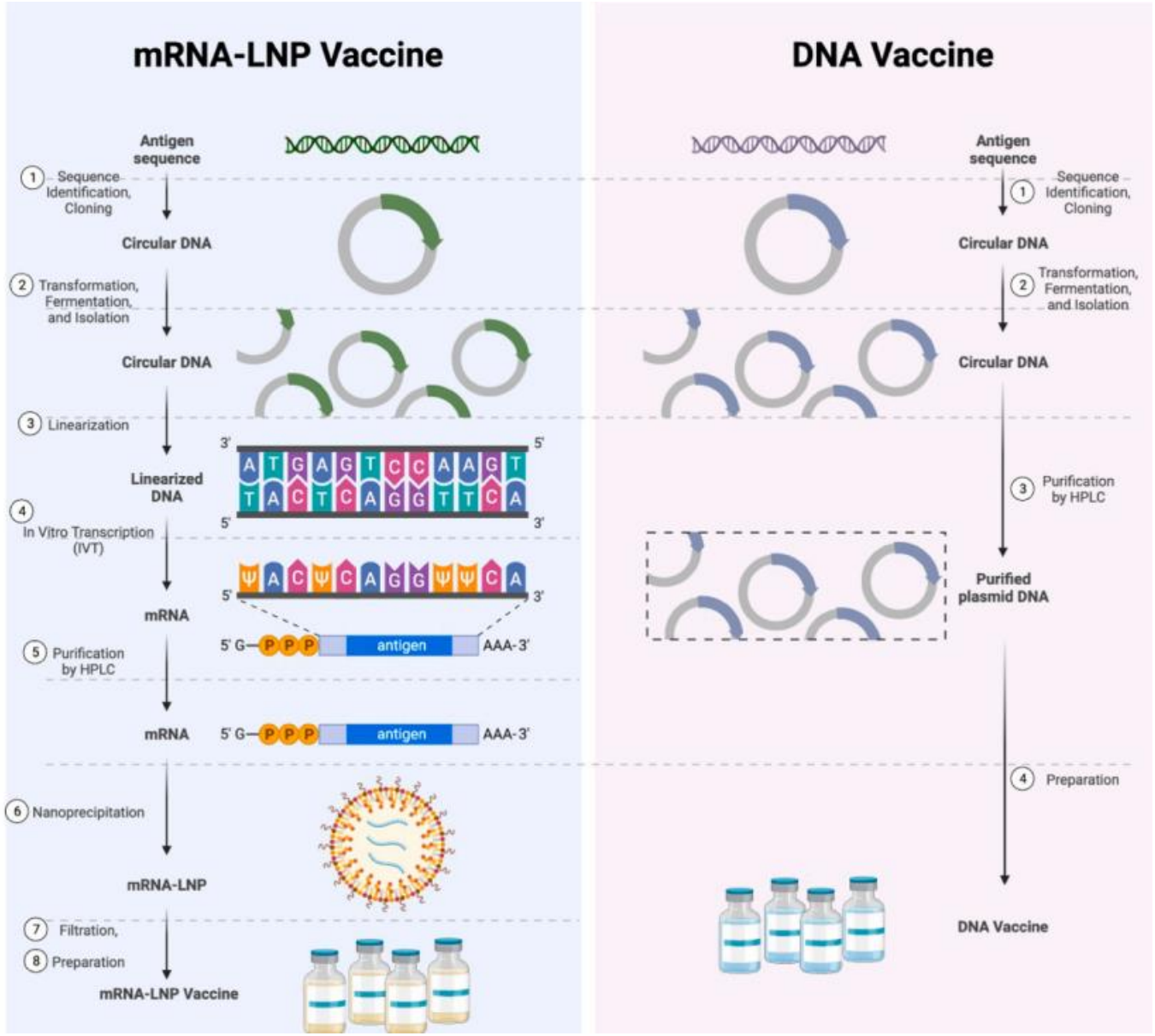


Nucleic Acid vaccines

Both mRNA and DNA vaccines need to be delivered into cells for antigen expression (cytosol and nucleus, respectively).

Naked DNA alone has been used as vaccines in many clinical trials, and proved to be useful, although further improvement in the delivery efficiency and immunogenicity of naked DNA vaccines is necessary to broaden their applications.

Vs



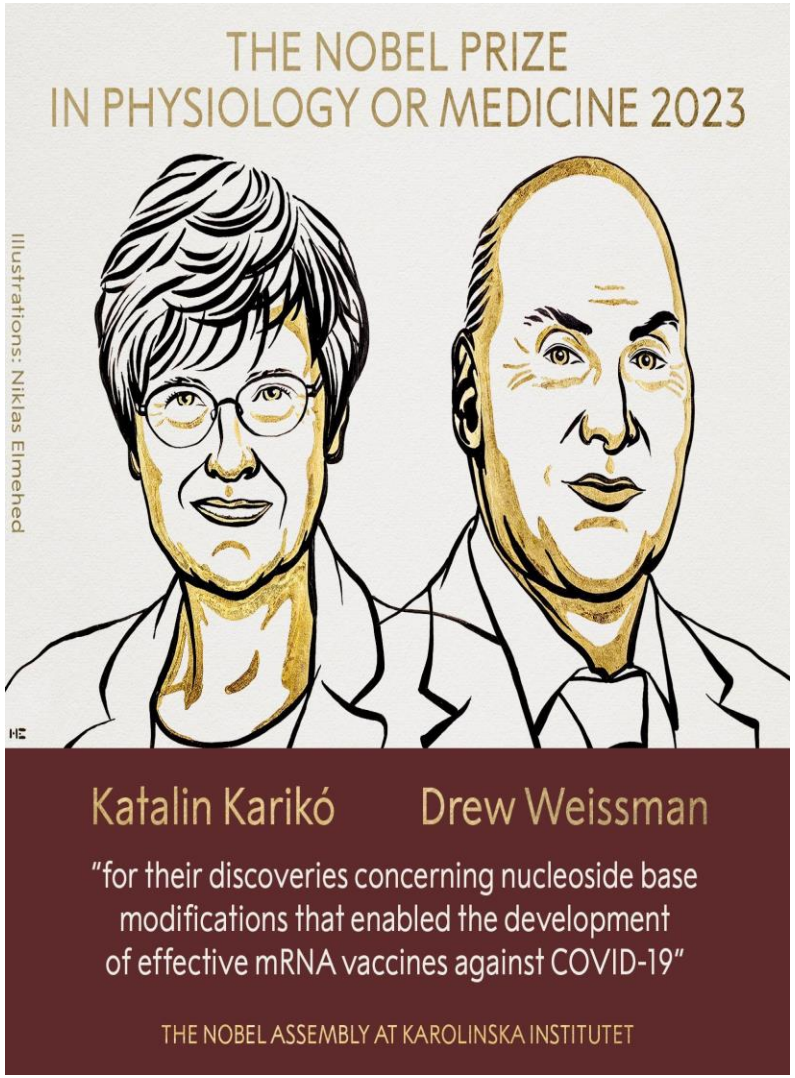
Vs

Faster production process, longer stability, and no need for cold chain in the case of DNA vaccines

No concern for integration in Host DNA, optimized delivery, and higher immunogenicity (so far) for mRNA vaccines

DNA vaccines are licensed for veterinary use

The mRNA Revolution

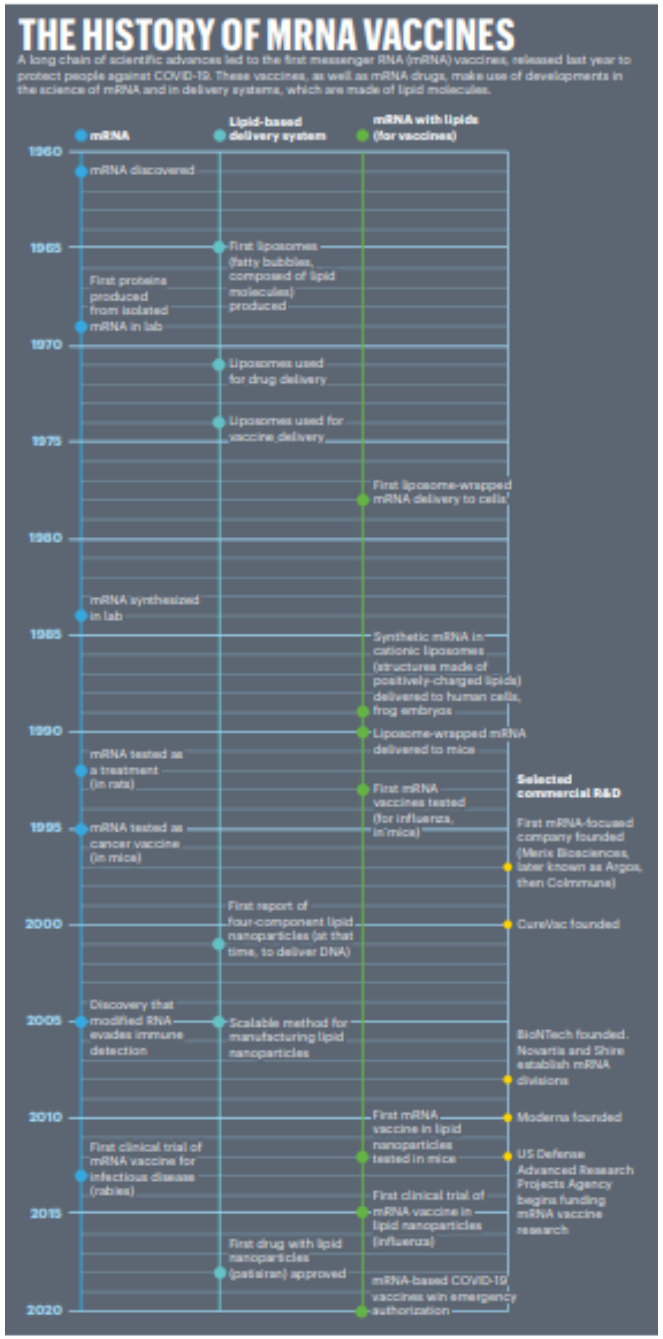


Feature

Pieter Cullis founded firms that pioneered using lipid nanoparticles to shuttle mRNA into cells.

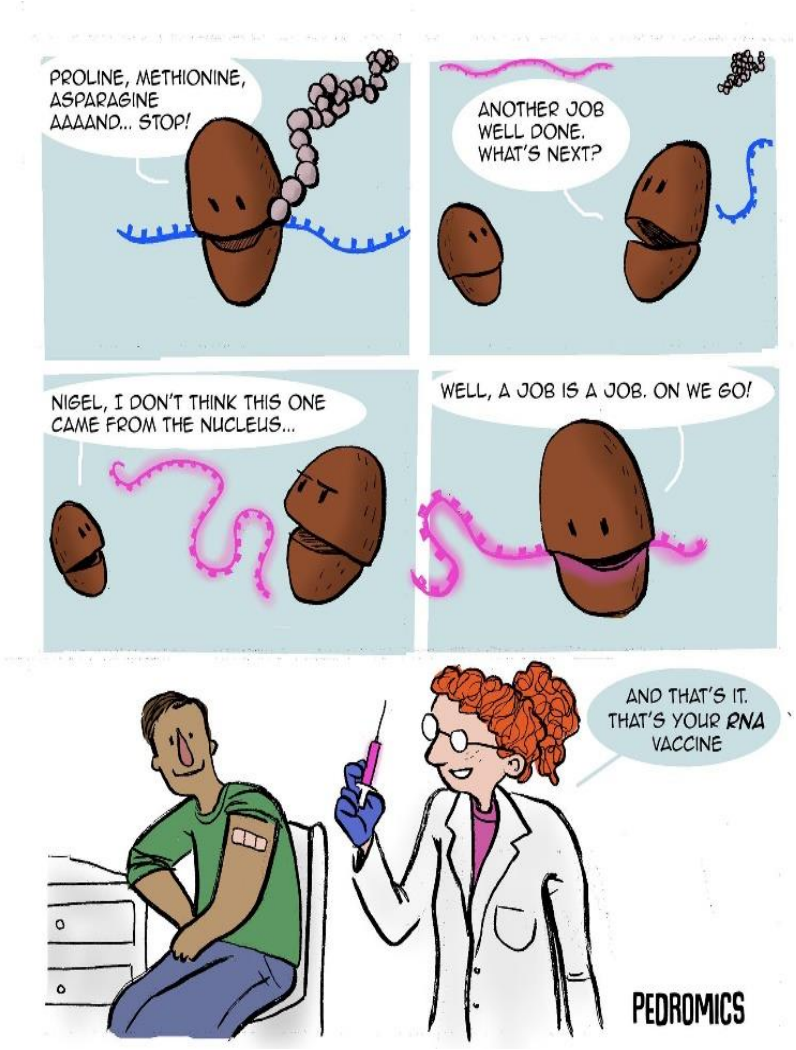
THE TANGLED HISTORY OF MRNA VACCINES

Hundreds of scientists had worked on mRNA vaccines for decades before the coronavirus pandemic brought a breakthrough. **By Elie Dolgin**



| Nature | Vol 597 | 16 September 2021

The mRNA Revolution

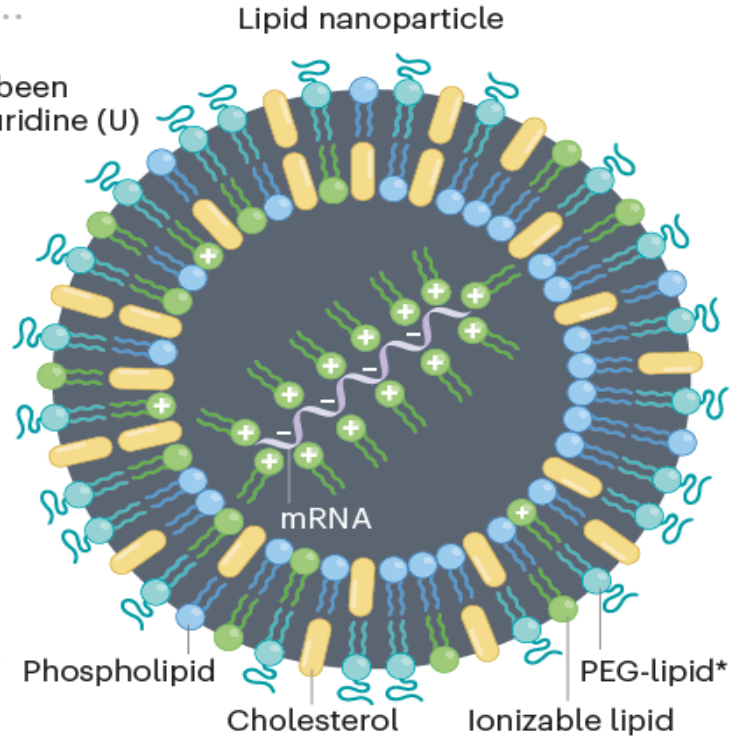


INSIDE AN MRNA COVID VACCINE

COVID-19 vaccines made from messenger RNA use lipid nanoparticles — bubbles of fats — to carry the molecules into cells. The mRNA contains the code for cells to produce the 'spike' protein that the coronavirus SARS-CoV-2 uses to enter cells. Here are key innovations in the design of these vaccines.

The vaccines made by Moderna and Pfizer–BioNTech use mRNA that has been chemically modified to replace the uridine (U) nucleotide with pseudouridine (Ψ). This change is thought to stop the immune system reacting to the introduced mRNA.

To help the body mount an effective immune response to later SARS-CoV-2 infections, the mRNA sequence is adapted to stabilize the spike protein in the shape it uses when fusing with human cells.



The fatty nanoparticle around the mRNA is made of four types of lipid molecule. One of these is 'ionizable': in the vaccine, many of these molecules have a positive charge and cling to negatively charged mRNA, but they lose that charge in the more alkaline conditions of the bloodstream, reducing toxicity in the body.

*Lipid attached to polyethylene glycol

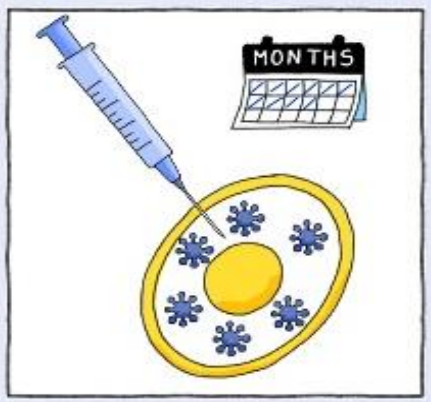
©nature

Benefits: “It is a very powerful technique to be able to create a lot of a vaccine fast. The benefit is that the technology is very adaptable. We can potentially go in and change the mRNA in the formulation to target a new antigen and can make a lot of high-quality vaccine material relatively quickly.”

Production Time

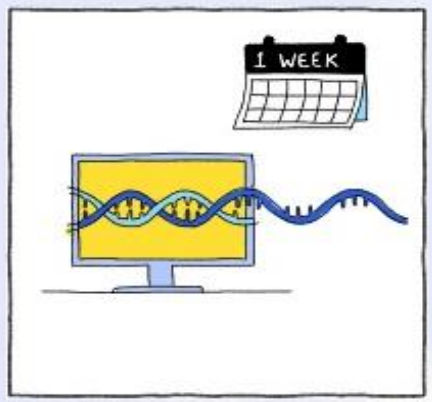
Conventional Vaccines

Most vaccines against viral diseases are made from viruses grown in chicken eggs or mammalian cells. The complex process of collecting the virus, adapting it to grow in the lab and shipping the vaccines around the world can take months. For emerging viruses, for which a new vaccine is needed as quickly as possible, these steps may be slower than some newer technologies like mRNA.



RNA Vaccines

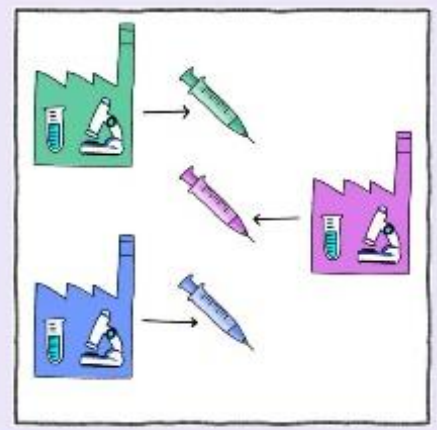
The mRNA (which encodes one or more antigens of the infectious agent) is made from a DNA template in the lab. The DNA can be synthesized from a digital sequence that can be sent across the world in an instant by a computer. Currently it takes about a week to generate an experimental batch of an mRNA vaccine.



Flexibility

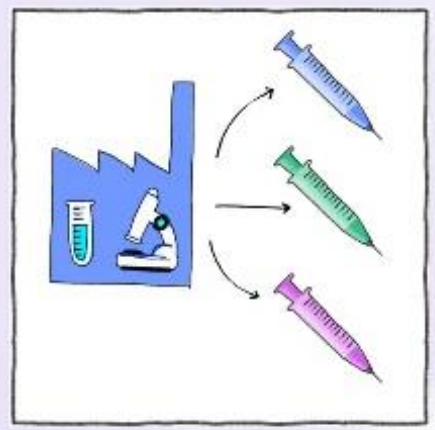
Conventional Vaccines

Each new vaccine requires a bespoke production process, including complex purification and testing.



RNA Vaccines

The production process for RNA vaccines can be scaled and standardized. This can enable replacement of the sequence encoding the target protein of interest for a new vaccine, with minimal changes to the vaccine production process.



Plasmid DNA vaccines

Relatively **low manufacturing cost**, easy production processes, high stability, and a good safety profile

Specific motifs on the DNA construct can induce immunostimulatory effects

Temperature stable and cold chain free, which are important advantages over approved RNA and vector vaccines for delivery to resource-limited settings.

The primary obstacle lies in the absence of an optimal delivery system, which significantly hampers the immunogenicity of DNA vaccines

pDNA vaccines

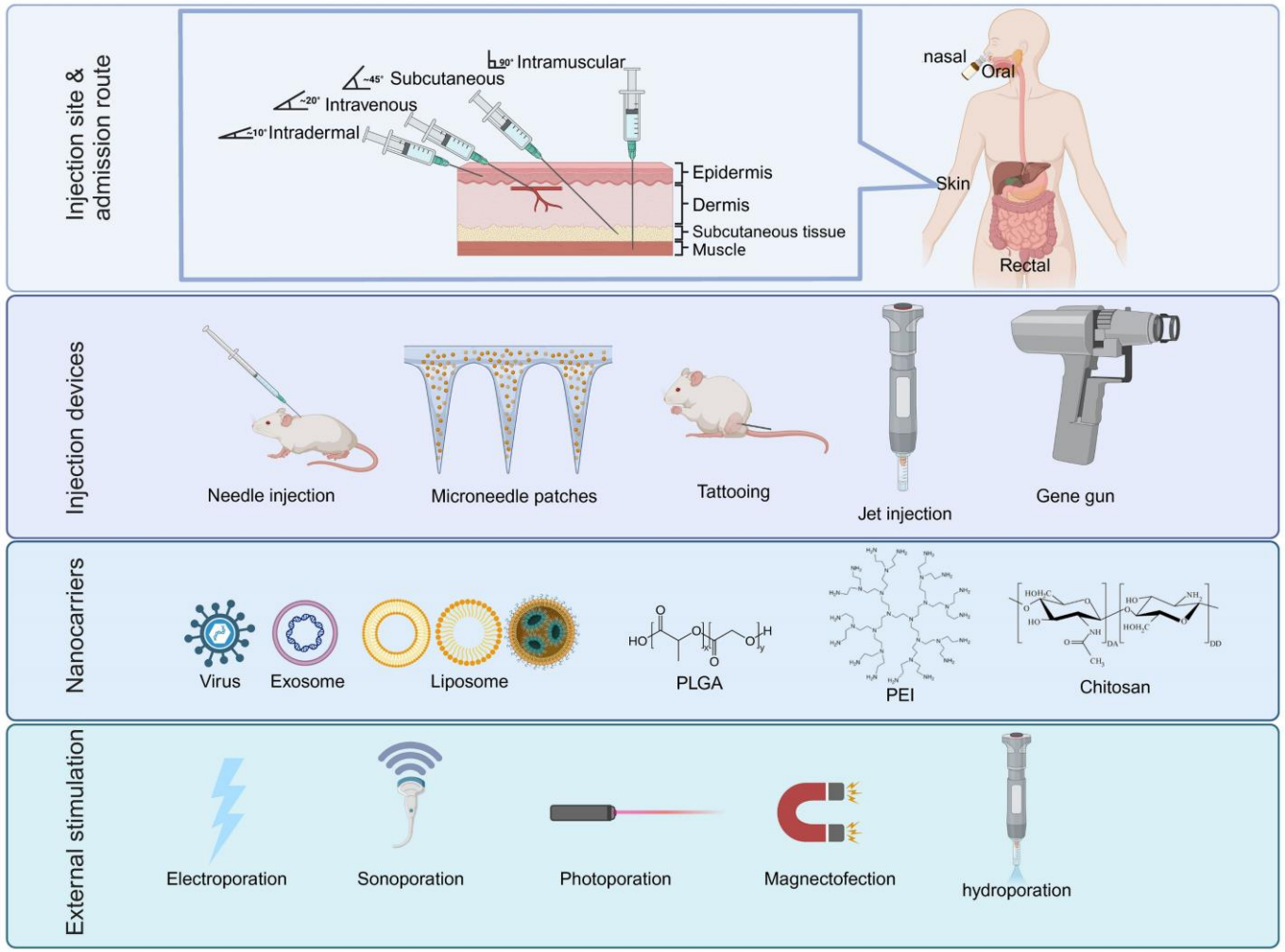
There is a theoretical possibility that this DNA could integrate into the host genome, potentially leading to unintended genetic changes.

DNA vaccines are designed to minimize the risk of genetic integration. The DNA used in vaccines is typically in the form of a circular plasmid , which is different from the linear chromosomes found in the host genome.

Furthermore, the amount of DNA delivered by a DNA vaccine is usually very small, reducing the likelihood of integration.

However, it is important to continue monitoring and conducting research on DNA vaccines to ensure their safety.
Regulatory authorities have specific guidelines and requirements in place to assess the safety and potential for genetic integration of DNA vaccines during their development and approval processes

pDNA vaccines



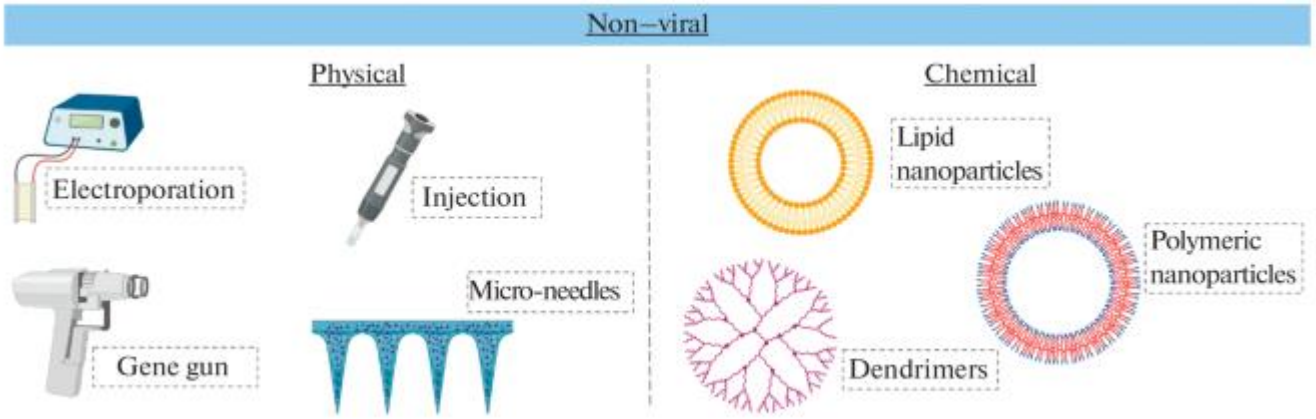
PLGA, poly D,L-lactic-co-glycolic acid; PEI, Polyethylenimine.

The main components of various DNA delivery systems. DNA vaccines generally have four different components that can enhance immunity through high throughput gene delivery to the target cells:

a) Injection site/admission route,
b) injection instrument,
c) nanocarriers with adjuvants,
d) external stimulations for temporary cell permeabilization.

Nanocarriers can protect DNA from nuclease degradation, ensure its long-term stable circulation in the bloodstream, and facilitate targeted tissue aggregation

Front. Immunol. Sec. Vaccines and Molecular Therapeutics Volume 15 – 2024 https://doi.org/10.3389/fimmu.2024.1332939



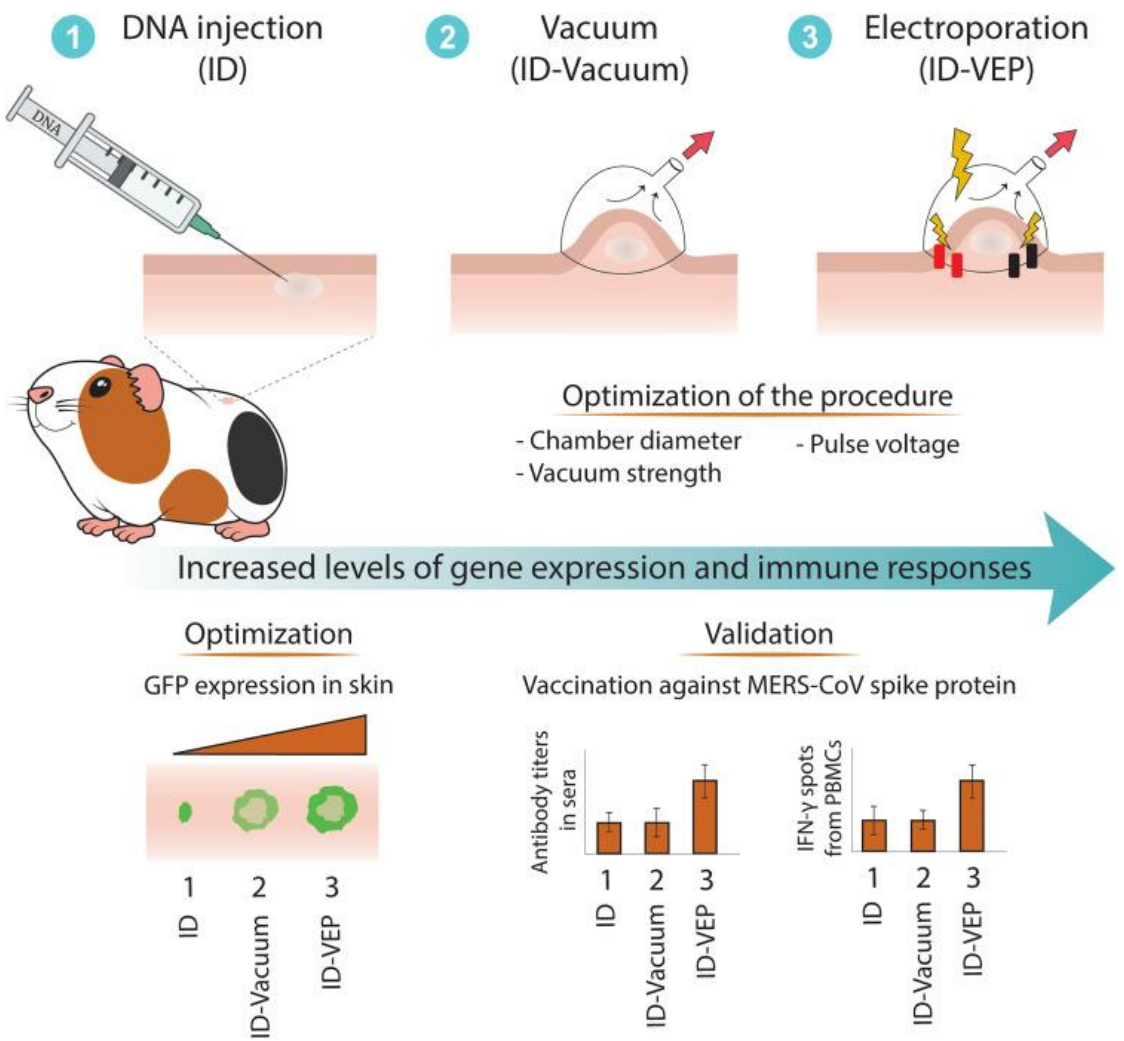
Injection of DNA plasmid into the skeletal muscle followed by a short electrical stimulation—referred to as electro-gene transfer (EGT) or electroporation (EP)—enhances DNA uptake and gene expression by several hundred-fold leading to improved antigen expression and a local and transient tissue damage favoring inflammatory cell recruitment and cytokine production at the injection site.

Molecular Therapy
Nucleic Acids
Original Article

Intradermal DNA vaccine delivery using vacuum-controlled, needle-free electroporation

Alison Generotti,[1] Ryne Contreras,[1] Brenden Zounes,[1] Eric Schade,[1] Andrea Kemme,[1] Yatish Rane,[2] Xinggang Liu,[1] Dustin Elwood,[1] Katherine Schultheis,[1] Jeremy Marston,[2] Jay McCoy,[1] Kate Broderick,[1] and Paul Fisher[1]

Negative pressure was shown to independently enhance transfection and synergized with EP delivery by immobilizing a fixed volume of skin securely against the electrodes lining the EP chamber. This technique provides a reliable, repeatable platform to perform non-invasive EP, and the impact of negative pressure on skin tissue and its interaction with electroporation merits continued research.



What do we want from a Vaccine

We want a vaccine to be:

Safe: no adverse outcome (we measure Reactogenicity)

Immunogenic: induce Immune response (we measure Immunogenicity)

Effective in preventing the disease

Offer long-lasting protection, ideally conferring lifelong immunity

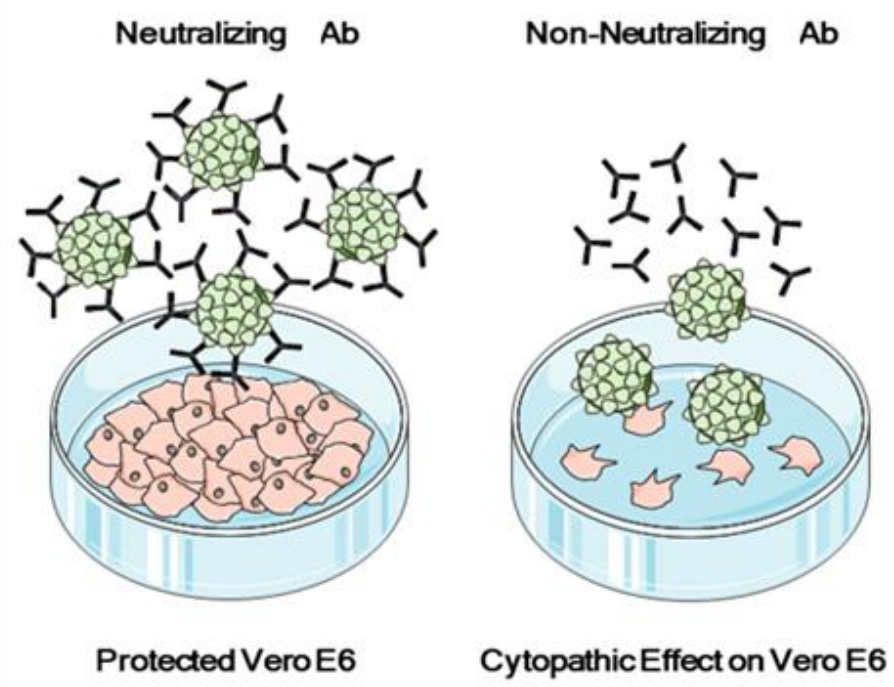
We Look for a correlate of protection to link immune response to effectiveness

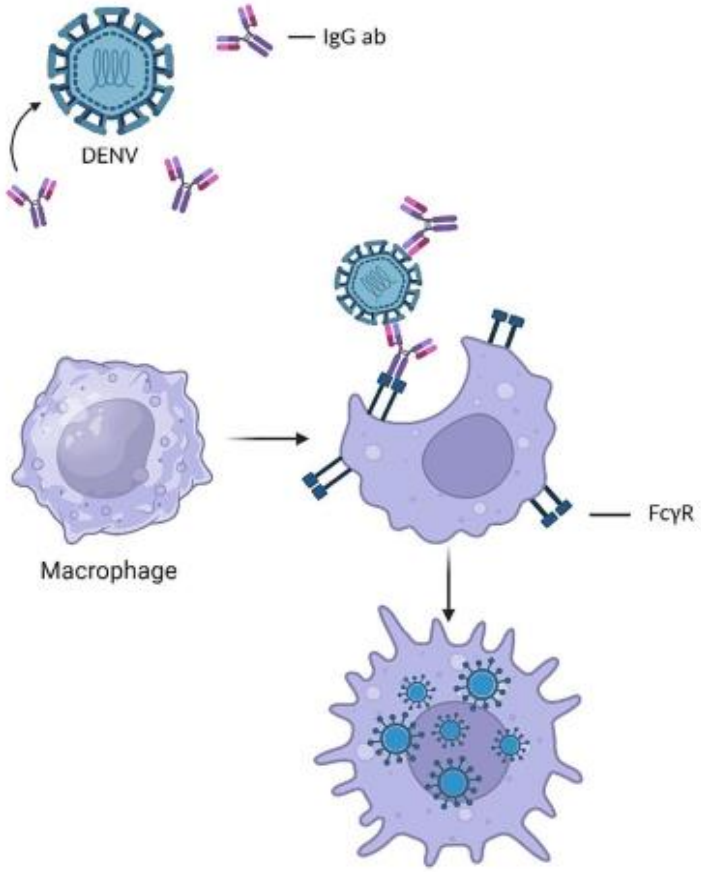
Box 2 | Vaccine-induced side effects and safety concerns

Reactogenicity – Physical manifestations of inflammation post-vaccination resulting in local pain, redness, swelling or systemic flu-like symptoms, such as fever, chills and myalgia, are known as reactogenicity. Reactogenicity can be classified into local and systemic, depending on the symptoms[204]. Vaccine components can activate the innate immune system through pattern recognition receptors on local/circulating immune cells and resident stromal cells, which, upon activation, can bring about the production of different mediators (for example, chemokines, cytokines and others) that contribute to reactogenicity. Infiltration of neutrophils, monocytes and lymphocytes at the site of injection, and cell recruitment from blood, can be attributed to local reactogenicity characterized by pain, redness (erythema) and swelling. Systemic reactogenicity is believed to be caused by high levels of secretion of pro-inflammatory signalling molecules, leading to systemic circulation. These signalling molecules include chemokines (CCL2 and CXL9), cytokines (IL-1b, IL-6, IFN-γ and TNFs), lipid mediators (prostaglandins-E2), complement components and vasodilators[310,311]. These molecules can interact with peripheral nociceptive receptors and the central nervous system, leading to reactogenic symptoms such as fever and pain[312]. Additionally, genetics, dose, and age may all play a role in the severity of reactogenicity[313]. Occasionally, vaccine administration may lead to rare but serious adverse events, including myocarditis, Guillain–Barré syndrome, Bell's palsy and thrombocytopenia syndrome. Additionally, some individuals may experience rare hypersensitivity reactions, such as severe anaphylaxis, throat swelling or respiratory issues, which necessitate immediate medical attention. Given the challenges of linking rare adverse events to specific vaccine components in smaller clinical trials, larger trials and post-licensure data should be meticulously analysed and monitored, with appropriate controls in place[204].

Vaccine-associated enhancement of diseases – An important safety concern for vaccines is the potential risk of enhanced disease upon subsequent infection through antibody-dependent enhancement or vaccine-associated enhanced respiratory disease (VAERD)[7]. Vaccines that elicit weakly neutralizing titres of antibodies can cause antibody-dependent enhancement due to Fcg receptor (FcgR)-mediated cellular uptake or other Fc-mediated effector functions[308,314,315]. For instance, Dengue viruses bind with cross-reactive antibodies that promote infection in FcgR-bearing cells such as macrophages[316]. In some cases, immune complexes of non-neutralizing antibodies and pathogens are deposited in host tissues, resulting in complement-mediated inflammation[317]. As previously mentioned, disease enhancement is associated with vaccines that elicit T helper 2 cell-biased responses. For instance, VAERD was observed in a clinical trial after children were vaccinated with a formalin-inactivated respiratory syncytial virus vaccine[318,319]. Although immunological mechanisms for VAERD are not explicitly defined, this phenomenon was attributed to the deposition of immune complexes in the lungs due to infiltration by neutrophils and eosinophils, indicating an excessively T helper 2 cell-biased cellular response[320,321].

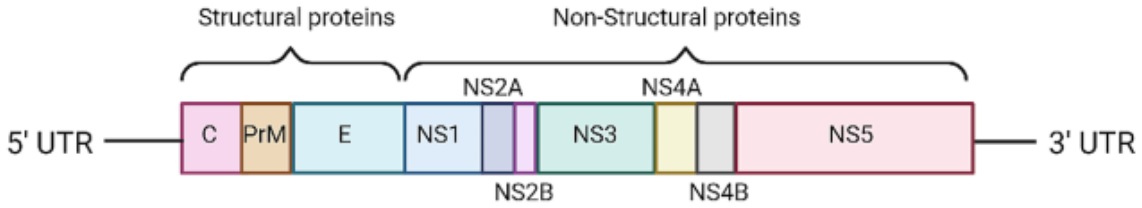
Neutralization vs ADE



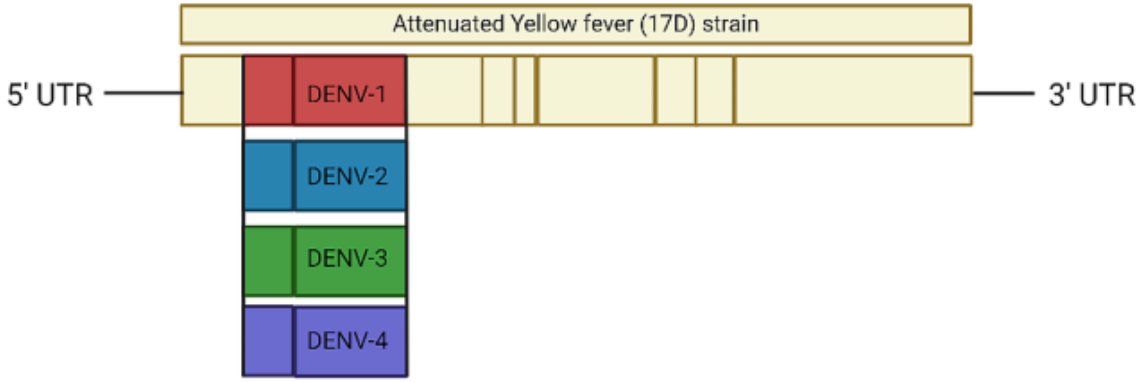


An important factor associated with increased severity of a dengue infection is **antibody-dependent enhancement (ADE).** ADE may also cause increased disease severity in vaccinated people. This process is mediated by cross-reactive, non-neutralizing antibodies or antibodies in non-neutralizing concentrations

A. Dengue virus (DENV) genome



B. Dengvaxia



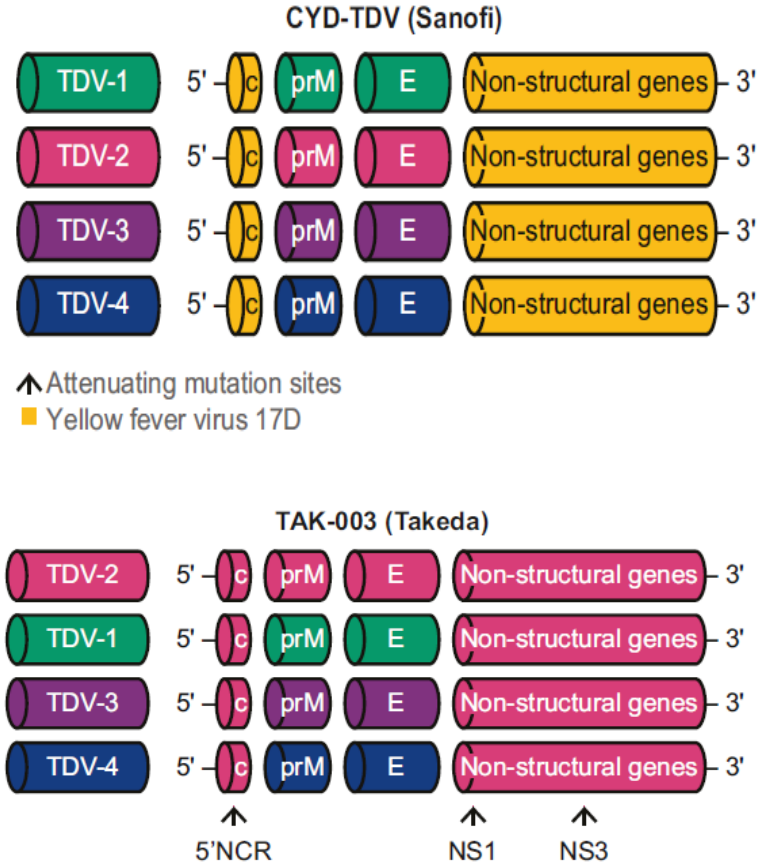
Dengvaxia (Sanofi Pasteur) is a tetravalent attenuated chimeric yellow fever vaccine (2015). It incorporates pre-membrane (prM) and envelope (E) genes from each DENV serotype into a backbone existing of non-structural (NS) genes of yellow-fever virus . Although the vaccine initially seemed to provide reasonable protection against dengue-related hospitalization after 2 years, the risk of severe dengue was found to be higher in vaccinated children who were seronegative at baseline.

A possible cause of the increased amount of Severe Dengue may be the usage of a yellow fever backbone.
NS-1 is a major pathogenic part of DENV.
Dengvaxia does not result in the production of antibodies against dengue NS1, but instead to yellow fever NS1.
These yellow fever NS1 antibodies might bind to dengue NS1 but not neutralize dengue NS1.
Therefore, these yellow fever NS1 antigens hypothetically could play a role in ADE development.

Aynekulu Mersha, D.G. *et al.* . *Trop Dis Travel Med Vaccines* **10**, 22 (2024)

Dengue Vaccines

A primary and central challenge is achieving balanced and long-lasting protection against all four serotypes



Dengvaxia CYD-TDV licensed as secondary prevention after laboratory-confirmed previous dengue infection for individuals aged 6–16 years (FDA) and 6–45 years (EMA) or in areas with high (> 80%) seroprevalence (its used is limited). *Sanofi subsequently announced a halt in production of CYD-TDV in 2024 due to low uptake likely because of the need for pre-vaccination screening.*

The need remains for a vaccine that is well tolerated and efficacious and can be used regardless of recipients' previous dengue exposure.

The EMA has authorized the use of Qdenga (TAK-003) in >4 yo, regardless of serostatus.
Although vaccine-enhanced disease has not been demonstrated, several European countries maintain a cautious policy.

Fig. 1 | Genetic structure of the TAK-003, CYD-TDV, and Butantan-DV vaccine strains. *C* capsid, *DV* dengue vaccine, *E* envelope, *NS* nonstructural protein, *prM* pre-membrane, *TDV 1/2/3/4* dengue serotype 1/2/3/4 strain.

https://doi.org/10.1038/s41541-025-01366-9

The TAK-003 story: key decisions that shaped development of a tetravalent dengue vaccine

Ian Escudero[1] ✉, Dieter Gniel[2], Shibadas Biswal[1], Eckhardt Petri[2], Gonzalo Perez[1], Mayuri Sharma[1], John Weil[2] & Derek Wallace[1]

Development considerations	Key observations and decisions
Vaccine type and composition	• Live attenuated approach selected • Single DENV-2 backbone with chimeric DENV-1, -3, and -4 components chosen for balance between immunogenicity and reactogenicity
Degree of vaccine virus attenuation	• Attenuation achieved via 3 mutations in DENV-2 PDK-53 backbone (5'NC-57, NS1, NS3) • Comprehensive assessment of association between vaccination and occurrence of dengue-like syndrome was performed • Level of attenuation is sufficient and vaccination with TAK-003 is not associated with dengue-like syndrome
Risk of reversion	• Genetic stability thoroughly assessed, no evidence of reversion for 2 of the 3 attenuations mutations, with very low levels of reversion seen for the 5′NC-57 loci • Reversion of any of the attenuation loci to a phenotype like the wild-type DENV-2 virus required reversions in at least 2 of the 3 loci • Risk of reversion is low and even in rare instances of a single locus reversion, the vaccine maintains the attenuated phenotype
Transmission potential	• Each of the individual vaccine components exhibits a lower transmission rate compared with the corresponding wild-type DENV serotype • TAK-003 and its components demonstrated incompetent or defective replication, infection, transmission, and dissemination in *Ae. Aegypti* and *Ae. Albopictus* mosquitoes • TAK-003 is unlikely to be transmitted by either the primary or secondary vectors
Dosing schedule	• Higher tetravalent seropositivity rate observed when a second dose of the vaccine was given after 3 months compared with a 1-dose schedule in baseline seronegative individuals • A schedule consisting of a 2-dose regimen, administered at Months 0 and 3, was selected to advance to phase 3 clinical trials

Experience with other flaviviruses found that using an LAV approach was successful for YF and Japanese encephalitis (JE) viruses. Therefore, a **live-attenuated approach** was selected for TAK-003.

DENV-2 was chosen as backbone:
i) in early studies, live-attenuated DENV-2 component elicited high rates of seroconversion in seronegative human volunteers, with minimal signs or symptoms of dengue;
ii) DENV-2 higher risk of severe secondary infection
iii) DENV-2 higher pooled mortality

Unlikely transmitted by vectors

...

https://doi.org/10.1038/s41541-025-01366-9

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Pivotal trial study design	• Study was designed in compliance with the WHO guidelines on vaccine development • Multi-country study was chosen to ensure heterogeneity of dengue epidemiology and flavivirus exposure • An age range of 4–16 was chosen to reflect the pathophysiology of dengue to ensure high enough incidence of febrile illness to assess vaccine efficacy • Baseline blood samples taken to allow stratification of data by baseline serostatus

The pivotal phase 3 Tetravalent Immunization against Dengue Efficacy Study (TIDES) investigated TAK-003 in >20,000 children aged 4 to 16 in 8 dengue-endemic countries in Latin America (Brazil, Colombia, Panama, Dominican Republic, and Nicaragua) and Asia (Philippines, Thailand, and Sri Lanka).

A multi-country study to ensure heterogeneity of dengue epidemiology (circulating serotypes) and flavivirus exposure (JE/YF vaccination or Zika infection).
To enable the assessment of the efficacy of TAK-003 against all 4 serotypes and the impact of flavivirus exposure on the safety and efficacy of the vaccine

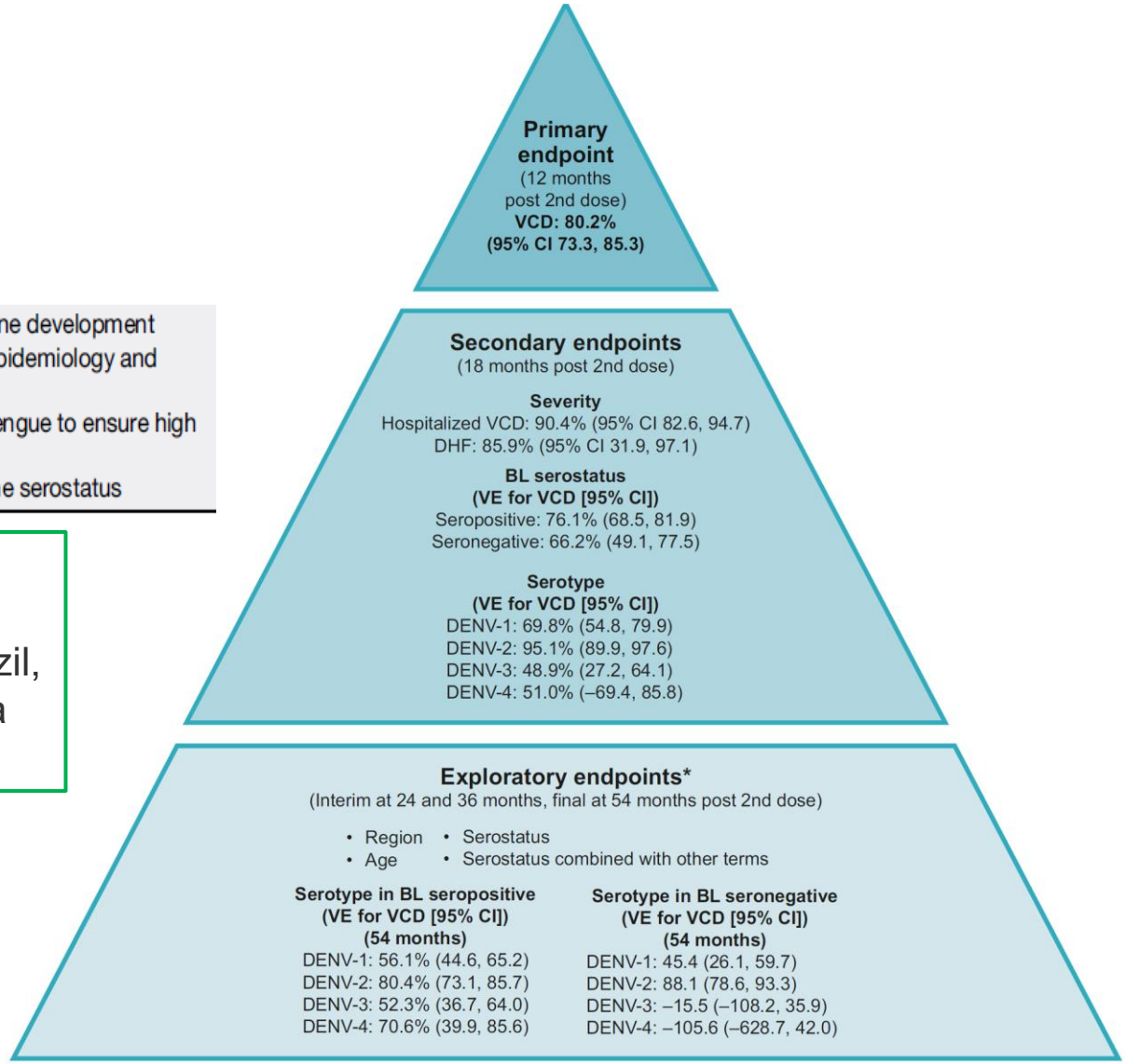


Fig. 2 | Overview of Tetravalent Immunization against Dengue Efficacy Study (TIDES) efficacy endpoints. Baseline seronegative – baseline reciprocal neutralizing titer of <10 for all 4 dengue serotypes as determined by MNT 50% assay. Baseline seropositive – baseline reciprocal neutralizing titer of ≥10 for at least one dengue serotype as determined by MNT 50% assay. *Not powered to support definitive conclusions due to low number of observations. These analyses are descriptive only. *BL* baseline, *CI* confidence interval, *DENV* dengue virus, *DHF* dengue hemorrhagic fever, *MNT* microneutralization test, *VCD* virologically confirmed dengue, *VE* vaccine efficacy.

Dati di immunogenicità per i soggetti di età compresa tra 18 e 60 anni provenienti da aree non endemiche

L'immunogenicità di Qdenga negli adulti di età compresa tra 18 e 60 anni è stata valutata in DEN-304, uno studio di Fase 3, in doppio cieco, randomizzato, controllato con placebo, in un Paese non endemico (USA). Le GMTs post-dose 2 sono riportate nella **Tabella 7**.

Tabella 7: GMTs degli anticorpi neutralizzanti la dengue nello studio DEN-304 (set per protocollo)

	Sieropositività al basale*		Sieronegatività al basale*	
	Pre-vaccinazione N = 68	1 mese post-dose 2 N = 67	Pre-vaccinazione N = 379	1 mese post-dose 2 N = 367
DENV-1				
GMT	13,9	365,1	5,0	268,1
IC al 95%	(9,5; 20,4)	(233,0; 572,1)	NS**	(226,3; 317,8)
DENV-2				
GMT	31,8	3 098,0	5,0	2 956,9
IC al 95%	(22,5; 44,8)	(2 233,4; 4 297,2)	NS**	(2 635,9; 3 316,9)
DENV-3				
GMT	7,4	185,7	5,0	128,9
IC al 95%	(5,7; 9,6)	(129,0; 267,1)	NS**	(112,4; 147,8)
DENV-4				
GMT	7,4	229,6	5,0	137,4
IC al 95%	(5,5; 9,9)	(150,0; 351,3)	NS**	(121,9; 155,0)

N: numero di soggetti valutati; DENV: virus dengue; GMT: medie geometriche dei titoli; IC: intervallo di confidenza; NS: non stimata

* Dati aggregati dai lotti 1, 2 e 3 di vaccino tetravalente per la dengue

** Tutti i soggetti presentavano valori GMT inferiori al LLOD (10), di conseguenza sono stati riportati come 5 con nessun valore IC

Dati di immunogenicità nelle aree endemiche, per i soggetti di età compresa tra 4 e 16 anni

Nello studio DEN-301, nei soggetti di età compresa tra 4 e 16 anni, al basale, le medie geometriche dei titoli (GMTs) per stato sierologico della dengue, sono riportate nella **Tabella 6**.

Tabella 6: Nello studio DEN-301, immunogenicità per stato sierologico della dengue, al basale (set per protocollo per l'immunogenicità)[a]

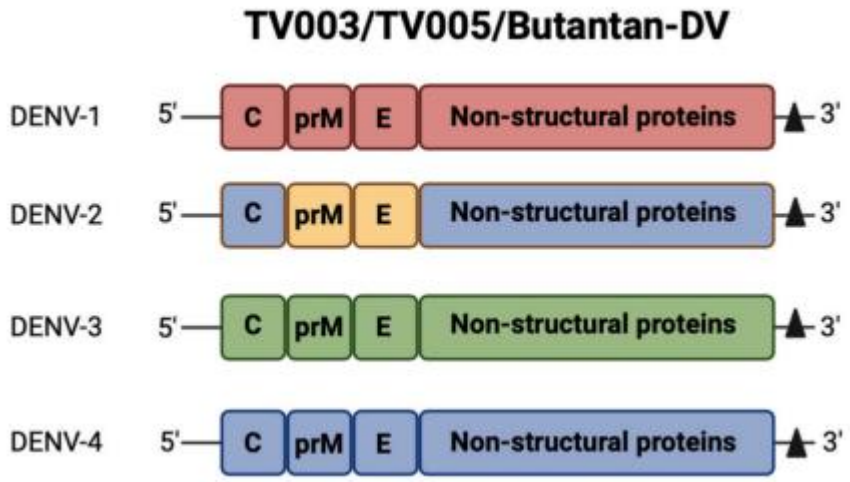
	Sieropositività al basale		Sieronegatività al basale	
	Pre-vaccinazione N = 1 816*	1 mese dopo la dose 2 N = 1 621	Pre-vaccinazione N = 702	1 mese dopo la dose 2 N = 641
DENV-1				
GMT	411,3	2 115,2	5,0	184,2
IC al 95%	(366,0; 462,2)	(1 957,0; 2 286,3)	NS**	(168,6; 201,3)
DENV-2				
GMT	753,1	4 897,4	5,0	1 729,9
IC al 95%	(681,0; 832,8)	(4 645,8; 5 162,5)	NS**	(1 613,7; 1 854,6)
DENV-3				
GMT	357,7	1 761,0	5,0	228,0
IC al 95%	(321,3; 398,3)	(1 645,9; 1 884,1)	NS**	(211,6; 245,7)
DENV-4				
GMT	218,4	1.129,4	5,0	143,9
IC al 95%	(198,1; 240,8)	(1 066,3; 1 196,2)	NS**	(133,6; 155,1)

N: numero di soggetti valutati; DENV: virus dengue; GMT: medie geometriche dei titoli; IC: intervallo di confidenza; NS: non stimata

[a] Il sottoinsieme di immunogenicità era un sottogruppo di soggetti selezionati in modo casuale e il set per protocollo per l'immunogenicità era l'insieme dei soggetti di quel sottogruppo che appartenevano anche al set per protocollo

* Per DENV-2 e DENV-3: N = 1 815

** Tutti i soggetti presentavano valori GMT inferiori al LLOD (10), di conseguenza sono stati riportati come 5 con nessun valore IC



Butantan Institute, NIH and Merck (MSD) reported the initial results of the Butantan-DV (TV003/TV005) vaccine, from the phase III clinical trial conducted in Brazil with over 16,000 enrollees (2 to 59 years of age) followed for 2 years (during prevalent DENV-1 and 2 circulation).
Attenuation through the deletion of 30 and 31 contiguous nt within the 3'UTR of wt DENV-1, -4, and DENV- 3, respectively. DENV-2 the prM and E in DENV-4

	DENV-1	DENV-2	DENV-3	DENV-4
	Overall efficacy (VE against symptomatic VCD)##			
Dengvaxia® (DEN-YF17D)	50.3%	42.3%	74%	77%
Qdenga® (TAK-003)	73.7%	97.7%	62.6%	inconclusive
Butantan-DV (TV003/TV005)	89.5%	69.6%	Not available	Not available

npj Vaccines
https://doi.org/10.1038/s41541-026-01400-4
Article in Press

From promise to pitfalls: immunological lessons from dengue vaccines and their implications

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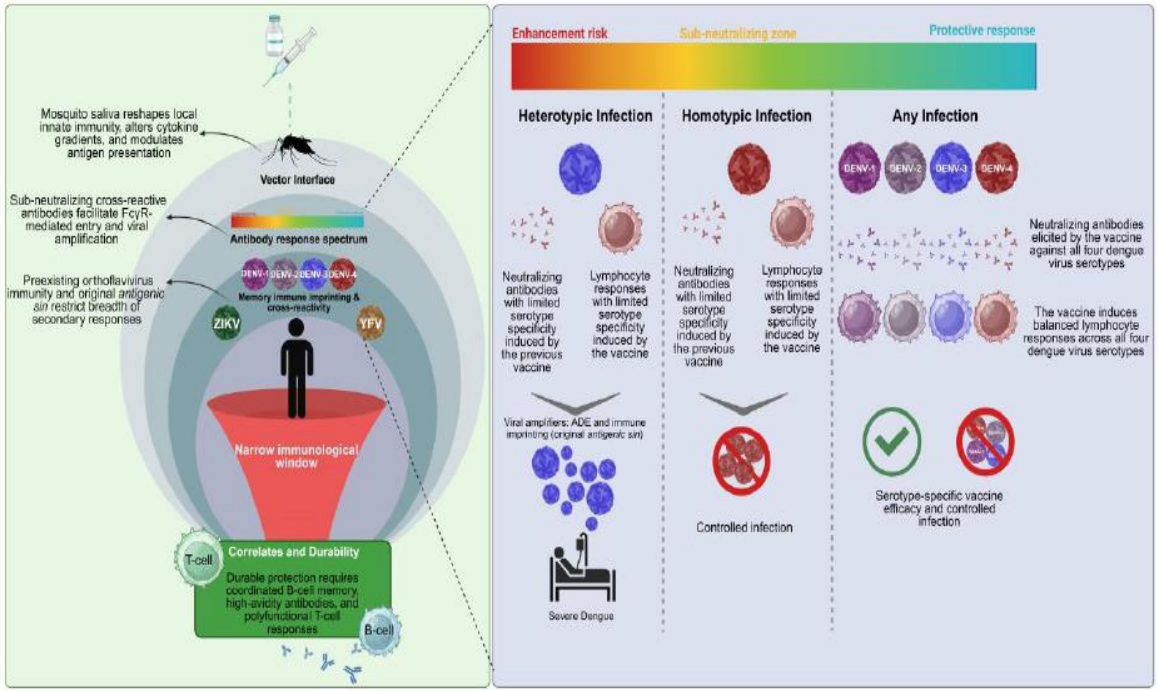

Figure 1. Bottlenecks in dengue vaccinology: the narrow window between protection and enhancement. This

- *In Italia la dengue non è endemica, pertanto la vaccinazione non è indicata per la popolazione generale. Tuttavia, essa rappresenta uno strumento di prevenzione opportuno per i soggetti che si recano in aree a rischio.*
- *Il vaccino può essere somministrato a tutti i soggetti di età ≥ 4 anni, sia sieropositivi che sieronegativi, senza necessità di test sierologico preventivo.*
- *La vaccinazione non è raccomandata in modo routinario per tutti i viaggiatori.*
- *Restano fondamentali le misure di protezione personale (utilizzo di abiti coprenti e chiari, zanzariere, repellenti cutanei e insetticidi per abiti e ambienti), che costituiscono la prima linea di difesa contro la trasmissione della dengue.*
- *La vaccinazione è particolarmente raccomandata per i viaggiatori diretti in aree endemiche o in zone con epidemia in corso, indipendentemente dalla durata del soggiorno.*
- *L'efficacia del vaccino è maggiore nei soggetti già sieropositivi, che presentano anche un rischio più elevato di forme gravi in caso di reinfezione; in questi soggetti la vaccinazione assume un ulteriore valore protettivo.*
- *Le iniziali preoccupazioni teoriche sull'uso nei soggetti sieronegativi, derivate dall'esperienza con il precedente vaccino CYD-TDV e legate al possibile rischio di dengue grave in seguito a infezione da sierotipo 3 o 4, non hanno trovato conferma nella pratica clinica. Dopo quasi sette anni di monitoraggio e milioni di dosi somministrate in Paesi endemici e non endemici, non risultano segnalazioni in letteratura di eventi avversi riconducibili a tale problematica.*
- *Qualora non fosse possibile completare il ciclo vaccinale di due dosi prima della partenza, è comunque raccomandata la somministrazione della prima dose, considerando che la protezione inizia dopo circa due settimane e informando il viaggiatore di tale tempistica.*
- *La seconda dose, se non somministrata prima del viaggio, va effettuata non prima di 3 mesi e preferibilmente entro 12 mesi dalla prima.*
- *Le controindicazioni sono quelle previste per tutti i vaccini vivi attenuati.*

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Rio de Janeiro begins dengue vaccination campaign with vaccine from the Butantan Institute.

Published on 24/02/2026 - 11:05 | Updated

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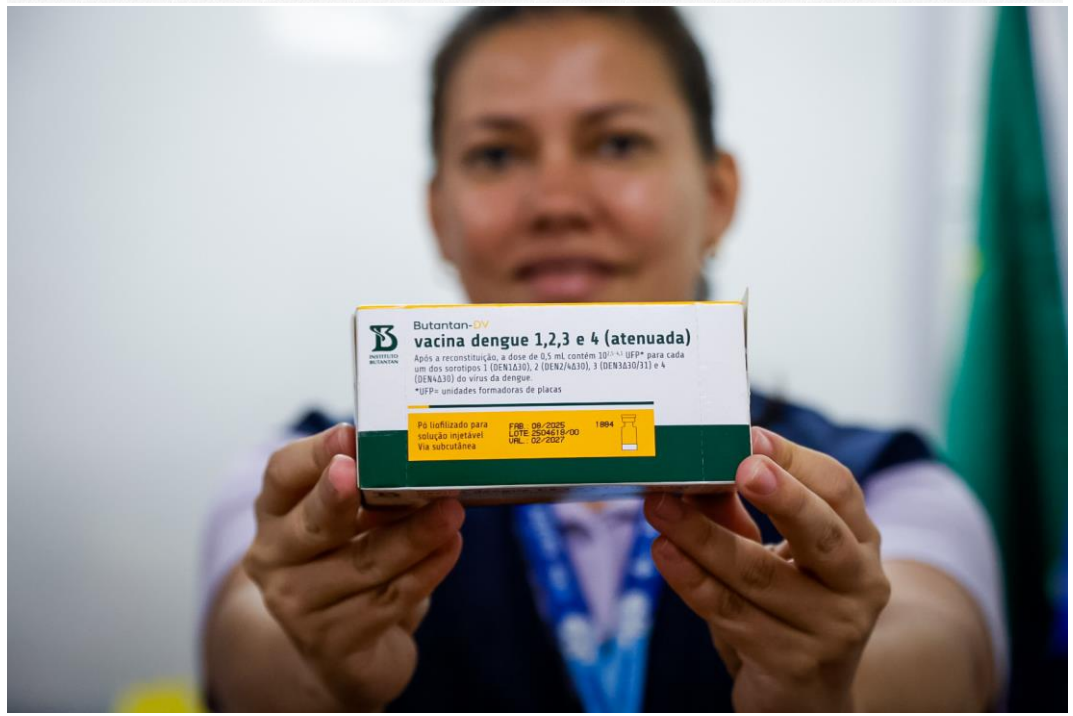
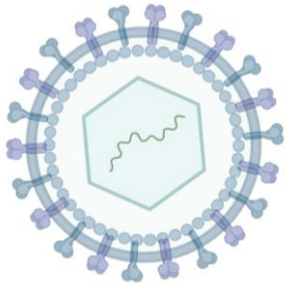


Chikungunya Vaccines

Live attenuated



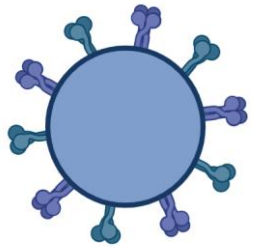
Non disponibile

Table 1 Product characteristics and administration information for live attenuated and virus-like particle chikungunya vaccines

	Live attenuated chikungunya vaccine (CHIK-LA)	Virus-like particle chikungunya vaccine (CHIK-VLP)
Trade name	IXCHIQ	VIMKUNYA
Manufacturer	Valneva	Bavarian Nordic
Age group	≥12 or ≥ 18 years[a]	≥12 years
Vaccine type	Live attenuated vaccine with attenuation based on a 61 amino acid deletion in non-structural protein 3	Recombinant vaccine with three structural proteins that assemble into virus-like particles which resemble live chikungunya virus but have no genetic material and so are non-replicating
Virus strain	East Central South African genotype, La Réunion strain 2006-OPY1	West African genotype, Senegal strain 37997[b]
Adjuvant	None	Aluminium hydroxide
Presentation	Lyophilized antigen and sterile water diluent for reconstitution	Pre-filled syringe
Dose	0.5 mL	0.8 mL
Route	Intramuscular	Intramuscular
Schedule	1 dose	1 dose
Booster dose	Need for booster not determined	Need for booster not determined
Storage	35°F–46°F (2°C–8°C)	36°F–46°F (2°C–8°C)[c]
Co-administration with other vaccines	No data available[d]	No data available[e]

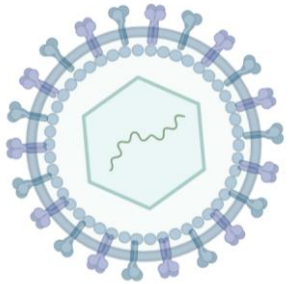
[a]Refer to relevant regulatory authority for age indication in each country; in the United States CHIK-LA was licensed for ≥18 years at the time of the licence suspension. [b]The virus-like particles consist of capsid protein and envelope proteins E1 and E2 derived from this strain. [c]CHIK-VLP may be held at room temperature (up to 77°F or 25°C) for up to 2 hours after removal from refrigerator. [d]Best practice immunization guidelines in the United States indicate ≥2 live vaccines should be administered simultaneously or ≥ 28 days apart, and a non-live vaccine may be administered simultaneously or at any interval before or after a live vaccine (https://www.cdc.gov/vaccines/hcp/imz-best-practices/timing-spacing-immunobiologics.html) [e]Best practice immunization guidelines in the United States indicate that non-live vaccines can be administered simultaneously or at any interval before or after a different non-live or live vaccine (https://www.cdc.gov/vaccines/hcp/imz-best-practices/timing-spacing-immunobiologics.html)

Virus-like particles



Utilizza strutture ricombinanti (proteine C, E1 ed E2) di un ceppo CHIKV del lignaggio dell'Africa occidentale

Live attenuated



Chikungunya Vaccines

Reactions 2098, p2 - 21 Feb 2026

IXCHIQ Chikungunya vaccine contraindication updated

Following the completion of a safety review and the recommendations of the Commission on Human Medicines (CHM), the IXCHIQ Chikungunya vaccine is no longer indicated for adults over the age of 60 years, and is contraindicated in all individuals with hypertension, cardiovascular disease, diabetes mellitus, and/or chronic kidney disease, advises the UK Medicines and Healthcare products Regulatory Agency (MHRA).

This change follows very rare fatal reactions and other serious adverse reactions reported globally last year. In addition, the CHM have advised that the IXCHIQ vaccine should be given no later than 30 days prior to travel, says the MHRA.Healthcare professionals are advised that strict adherence to contraindications and precautions is essential to reduce the risk of very rare but potentially fatal adverse reactions. In addition, a comprehensive benefit risk assessment must be conducted prior to vaccination by a healthcare professional trained in the benefit risk assessment of live vaccines.

Patients who have received the vaccine should be advised to seek emergency medical attention if they develop signs or symptoms associated with viraemia, including arthralgia, or neurological symptoms which may indicate encephalitis, said the MHRA.

Product information will be updated to reflect these changes.

MHRA. IXCHIQ Chikungunya vaccine: updates to restrictions of use following safety review Internet Document : 11 Feb 2026. Available from: URL: https://www.gov.uk/drug-safety-update/ixchiq-chikungunya-vaccine-updates-to-restrictions-of-use-following-safety-review 803921397

	Total	
	n/N	(%)
Seroresponse rate[b,c]		
7 days	4/251	(2)
28 days	263/266	(99)
6 months	233/242	(96)
1 year	356/360	(99)
2 years	306/316	(97)
3 years	268/278	(96)

Adverse events[d]		
Injection site, solicited	463/3082	(15)
Injection site reported by > 10%		
Tenderness	328/3082	(11)
Systemic, solicited	1553/3082	(50)
Systemic reported by > 10%		
Headache	973/3082	(32)
Fatigue	879/3082	(29)
Myalgia	737/3082	(24)
Arthralgia	529/3082	(17)
Fever ≥38.0°C/100.4°F	415/3082	(13)
Nausea	345/3082	(11)
CLAR[e]	361/3082	(12)
Severe[f]	48/3082	(2)
Prolonged[g]	14/3082	(<1)

Radiocor

Borsa Parigi: -2% Valneva, ritira richiesta autorizzazione vaccino in Usa

20 gennaio 2026

(Il Sole 24 Ore Radiocor) - Milano, 20 gen - Valneva sotto pressione alla Borsa di Parigi, dopo il ritiro volontario delle domande di autorizzazione all'immissione in commercio e sperimentazione clinica negli Stati Uniti per Ixchiq, il suo vaccino contro la chikungunya. Il titolo della biotech francese specializzata nei vaccini e' arrivato a perdere oltre il 6% nella mattinata, ma ha ridotto la flessione nel pomeriggio e ora il calo e' del 2% a 4,13 euro. La decisione di ritirare le richieste Usa fa seguito alla sospensione dell'autorizzazione all'immissione in commercio del vaccino da parte della Food and Drug Administration (Fda) statunitense lo scorso agosto, ha spiegato l'
informazi
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attivamen

La FDA sospende il vaccino Ixchiq di Valneva contro il virus chikungunya negli Stati Uniti

Pubblicato il 25/08/2025 alle 08:04

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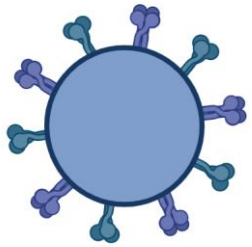
Condividi

VALNEVA +3,53% BAVARIAN NORDIC A/S +0,10%

L'agenzia americana del farmaco (FDA) ha deciso di sospendere con effetto immediato il vaccino Ixchiq, sviluppato dalla società francese Valneva, contro il virus chikungunya. La decisione segue la segnalazione di quattro casi di gravi effetti collaterali, come comunicato in una nota stampa.

Tre delle persone colpite avevano un'età compresa tra i 70 e gli 82 anni; la più anziana ha dovuto trascorrere due giorni in ospedale. Un ulteriore caso riguarda una persona di 55 anni che ha manifestato reazioni avverse dopo la somministrazione del vaccino.

Virus-like particles



Chikungunya Vaccines

Table 3 Summary of key immunogenicity and safety data from the two pivotal phase 3 clinical trials of virus-like particle chikungunya vaccine in adolescents and adults aged 12–64 years and adults aged ≥65 years[a]

	12–64 years		≥65 years	
	n/N	(%)	n/N	(%)
Seroresponse rate[b]				
7 days	1169/2510	(47)	Not measured	
14 days	2355/2434	(97)	149/181	(82)
21 days	2503/2559	(98)	165/189	(87)
6 months	1967/2301	(85)	139/184	(76)
Adverse events[c]				
Injection site, solicited	661/2765	(24)	11/205	(5)
Injection site reported by > 10%			No events[d]	
Pain	656/2764	(24)		
Systemic, solicited	891/2765	(32)	22/205	(11)
Systemic reported by > 10%			No events[d]	
Fatigue	551/2764	(20)		
Headache	498/2765	(18)		
Myalgia	486/2764	(18)		
New onset or worsening arthralgia[e]	3/2790	(<1)	0/205	(0)

Indicazioni alla vaccinazione contro il virus Chikungunya
Il vaccino contro CHIKV dovrebbe essere preso in considerazione/raccomandato per:

- Viaggiatori diretti in aree con focolai attivi
- Viaggiatori a più alto rischio (es. malattie croniche o gravi, età avanzata)
- Viaggiatori diretti in paesi in cui si è verificata trasmissione locale di CHIKV negli ultimi 5 anni
- Personale di laboratorio che maneggia il virus
- Donne in gravidanza che non possano per alcune motivo posporre il viaggio in area a rischio

Non si ritiene opportuno porre un limite temporale rispetto alla durata del viaggio poiché l'evento che conduce all'infezione (la puntura della zanzara) può verificarsi in qualsiasi momento a partire dall'arrivo nel paese di destinazione.
Si raccomanda di vaccinare almeno 14 giorni prima della potenziale esposizione al CHIKV.

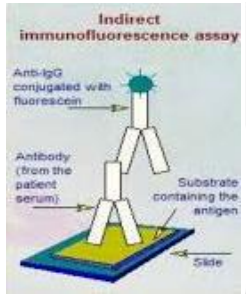
I gruppi a più alto rischio di sviluppare malattia grave[11-17] includono:

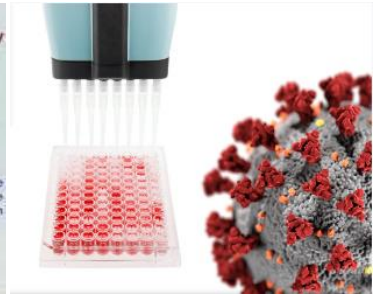
- Neonati nel primo anno di vita
- Adulti di età superiore ai 65 anni (in questo gruppo, l'artralgia può progredire in artrite reumatoide cronica)
- Persone con malattie croniche (ad esempio, diabete e malattie cardiovascolari, neurologiche o respiratorie)
- Donne in gravidanza: la trasmissione *intra partum* è stata osservata in donne affette dalla malattia nelle ultime settimane prima del parto.
- Pazienti immunocompromessi
- Sebbene non sia stato chiaramente stabilito, il sesso femminile è un fattore di rischio per lo sviluppo di artrite cronica post-CHIKV[18].

La vaccinazione non è indicata nei soggetti con una storia documentata di infezione da CHIKV. Tuttavia, non vi è alcuna controindicazione alla somministrazione del vaccino se lo stato sierologico non è noto, poiché il test delle IgG non deve essere considerato un prerequisito per il processo decisionale.

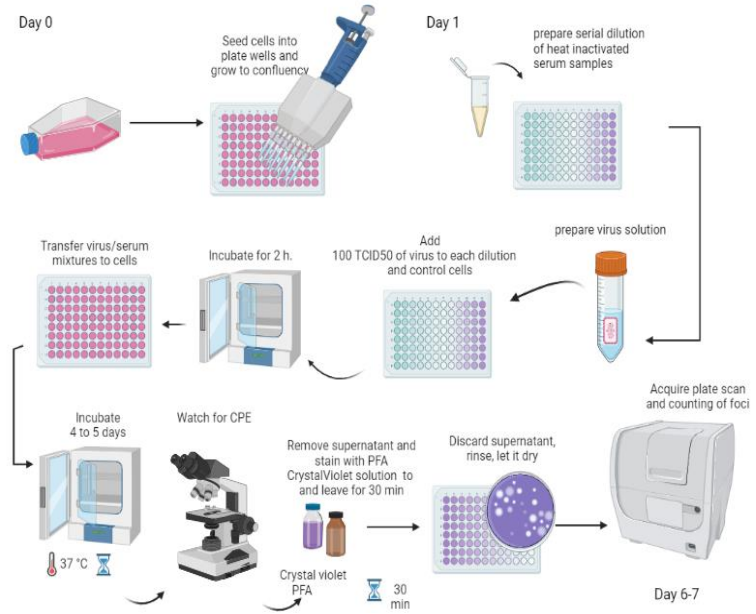
Vaccine response: Immunogenicity

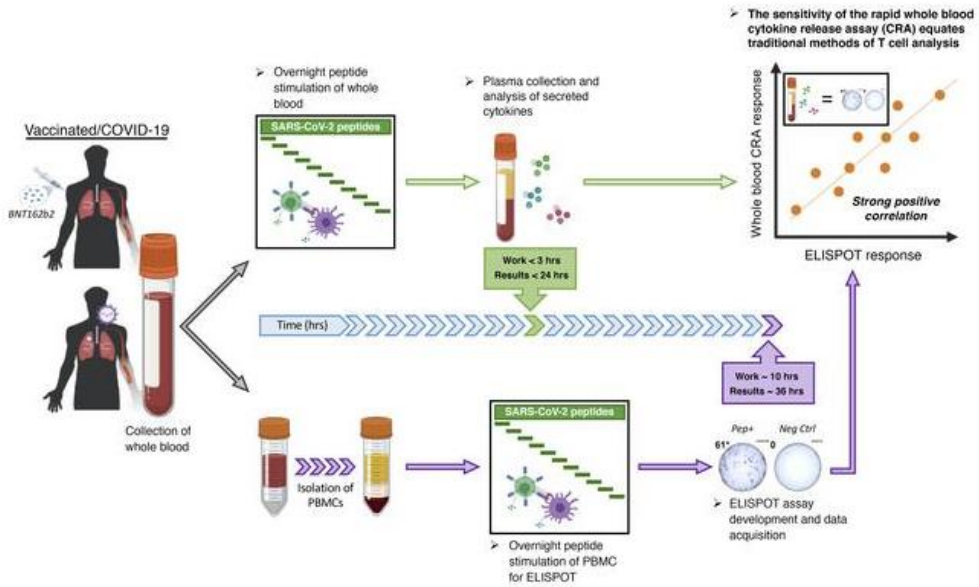
IFA ELISA CLIA/CMIA

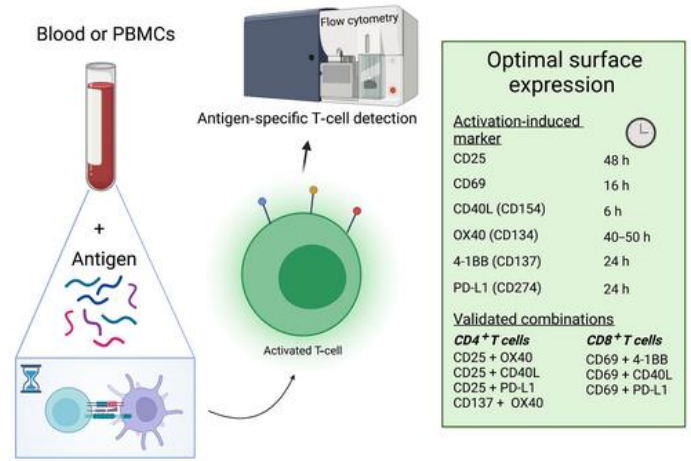




Neutralization assays (MNA, PRNT50)







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