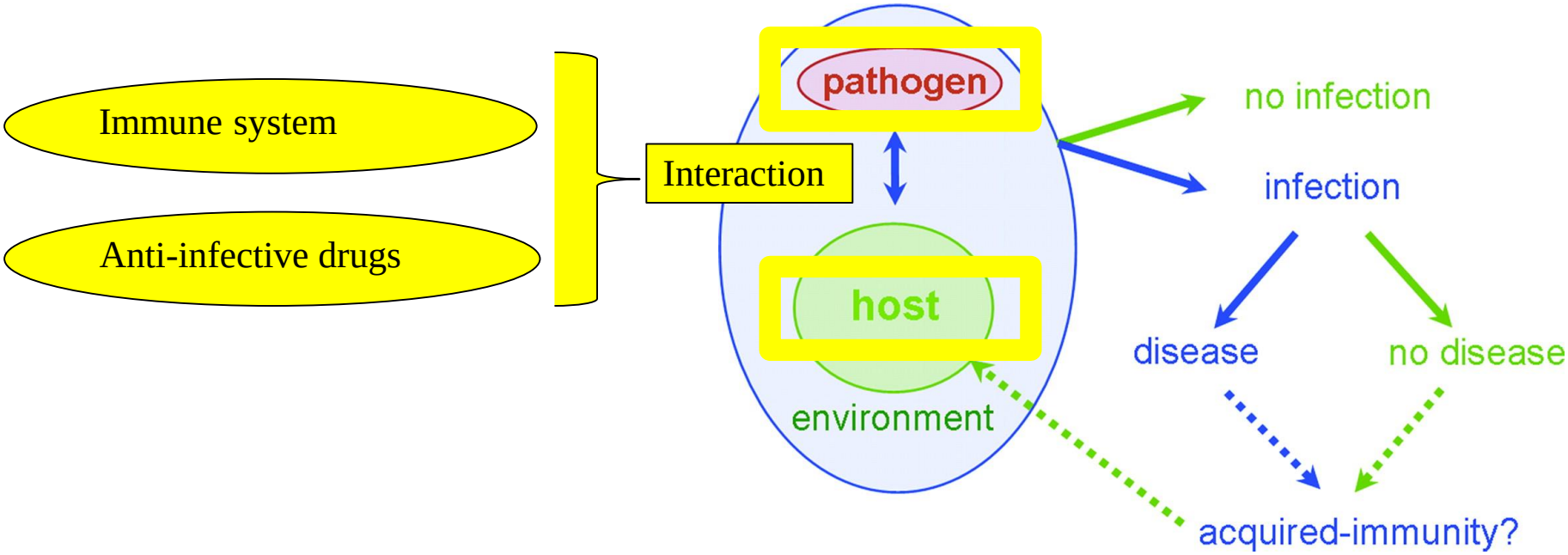
Schematic representation of host-pathogen interactions



IMMUNE SYSTEM

Acquired immunity

Natural

Actively acquired - When the body has already experienced an infection by that pathogen

Passively acquired - Antibodies pass across placenta providing a newborn baby with immunity against disease. Antibodies are also present in breast milk.

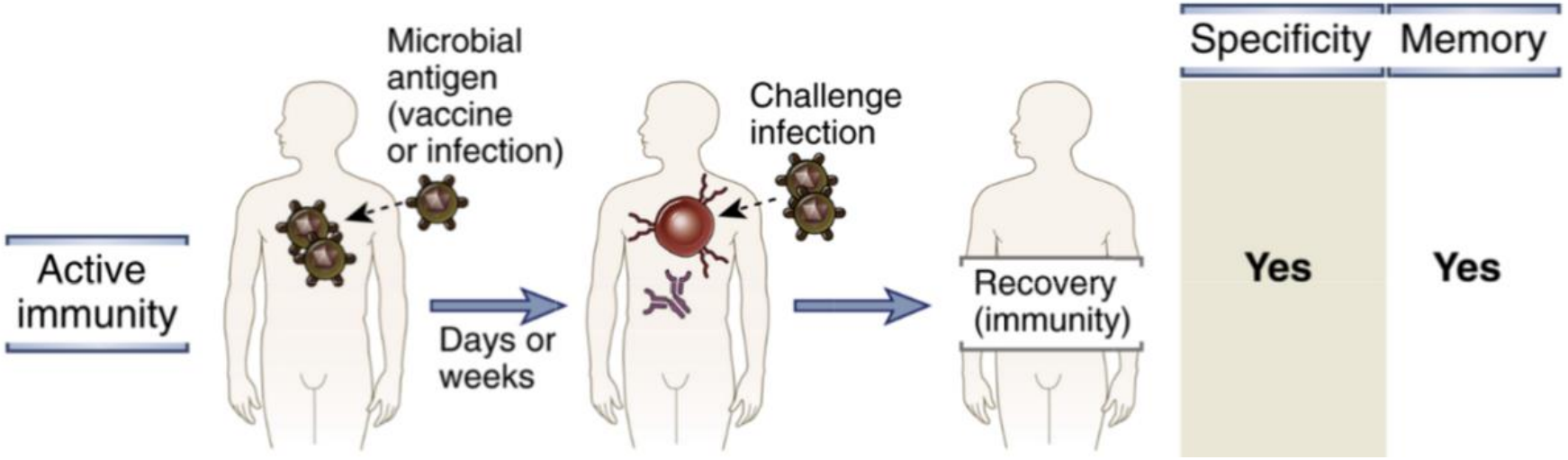
Non natural - induced

Actively acquired – ACTIVE IMMUNIZATION.This is by **vaccination** at a suitable time in the person's life.

Passively acquired – PASSIVE IMMUNIZATION. This is by administrating ready-made **antibodies** which are able to immediately neutralize the viruses

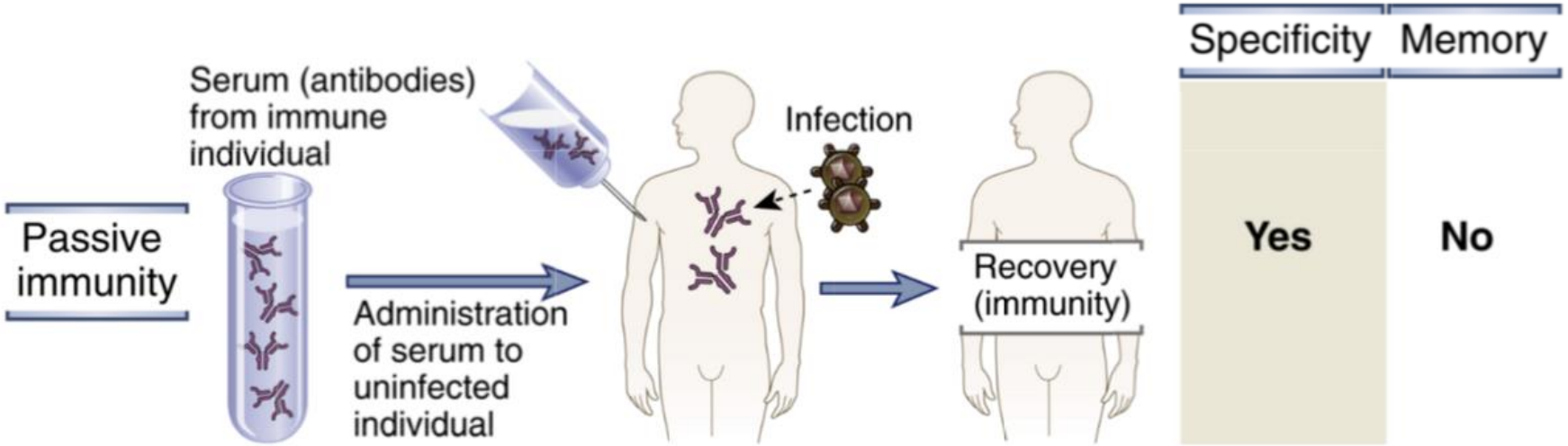
Active immunity (immunoprophylaxis) *Protection conferred*

by person's own immune system, lasts for years or decades



Passive Immunity (immunotherapy) *Protection transferred*

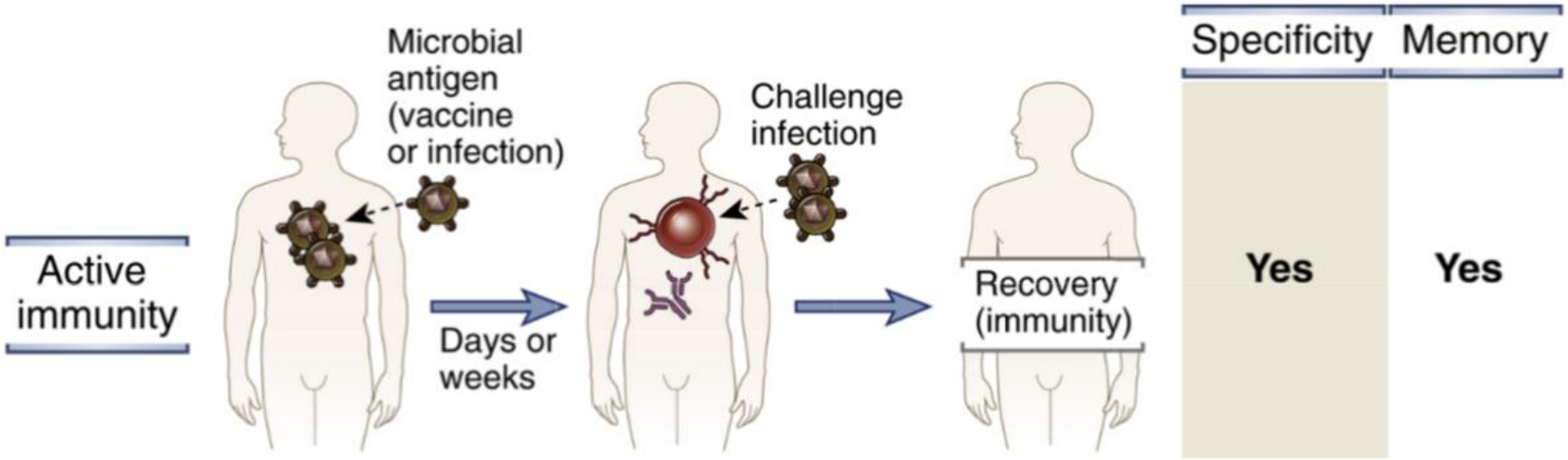
from another person or animal, disappears after two-three weeks



Box 1. **Indications for blood-derived antibodies for infectious diseases with a current American or European Union market authorization[a]**

- Anthrax: treatment of inhaled anthrax.
- Botulism: treatment of botulinum.
- *Clostridium botulinum*: treatment of infant botulism caused by type A or B *C botulinum* in patients < 1 year.
- Cytomegalovirus: prophylaxis of cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas and heart.
- Diphtheria: treatment of diphtheria and rarely as prophylactic of diphtheria in asymptomatic, non-immunized individuals who have been exposed.
- Hepatitis A: protection from hepatitis A in household and other close contacts.
- Hepatitis B: prevention of Hepatitis B recurrence following liver transplantation; treatment of acute exposure to Hepatitis B-containing blood, sexual exposure to infected persons, infants born to infected mothers and household exposure to persons with acute infection.
- Hepatitis C: Prevention of recurrent hepatitis C virus-induced liver disease in liver transplant recipients.
- Measles: postexposure prophylaxis for suspected measles in unvaccinated persons.
- Rabies: postexposure prophylaxis to rabies category III exposure (i.e. single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks; exposure to bat bites or scratches).
- Rubella: prophylaxis of rubella to exposed individuals in early pregnancy.
- *Staphylococcus aureus*: treatment of *S aureus* bacteraemia.
- Tetanus: immediate prophylaxis after tetanus prone injuries in patients not adequately vaccinated, with unknown immunization status, severe deficiency in antibody production or vaccinated patients with high risk wounds.
- Vaccinia: prevention or treatment of vaccinia/smallpox. Treatment and/or modification of conditions which are complications resulting from smallpox vaccination.
- Varicella: prophylaxis against varicella zoster virus infection in at-risk exposed patients.

Active immunity (immunoprophylaxis) *Protection conferred by person's own immune system, lasts for years or decades*



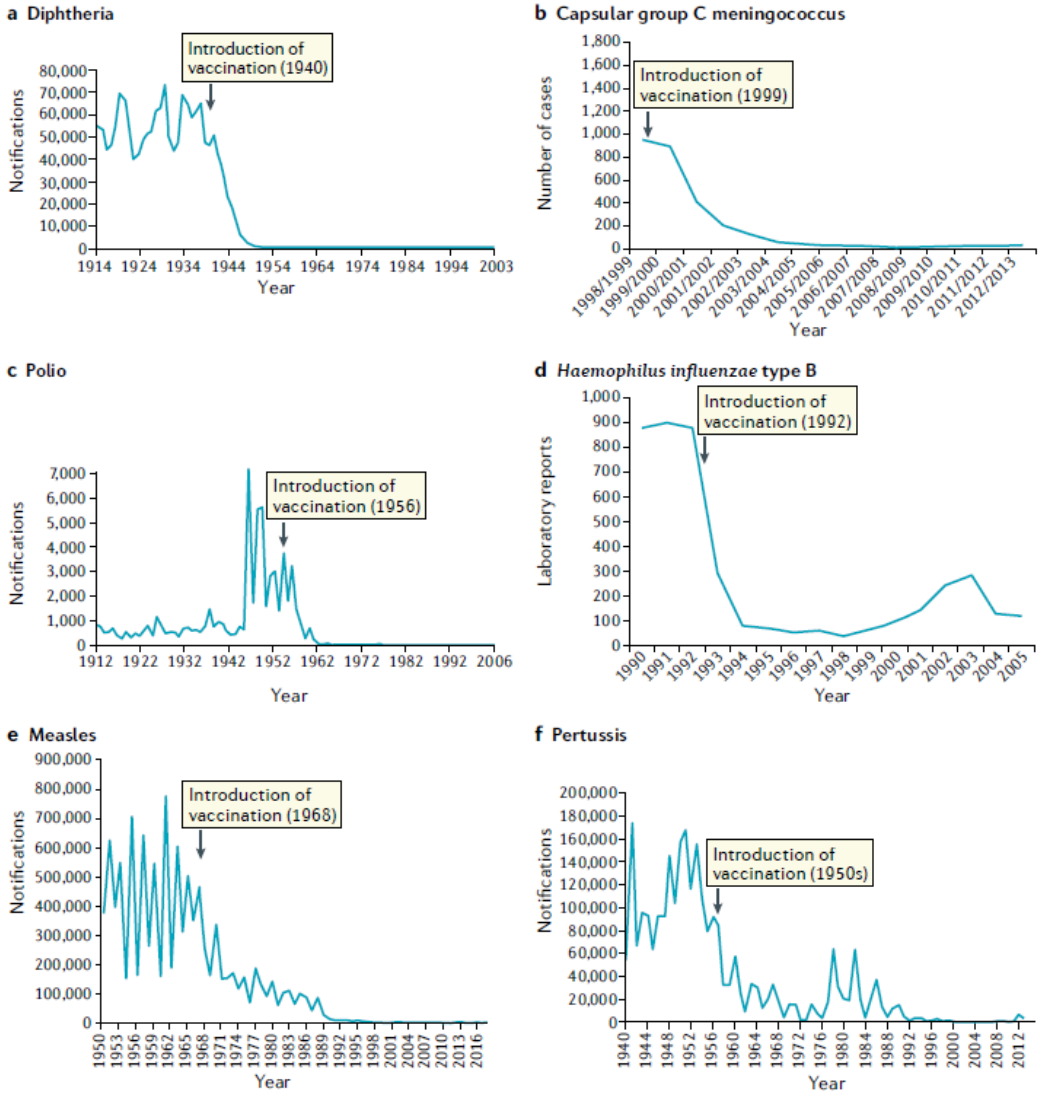
A vaccine is a biological preparation that improves immunity to a particular disease

World Health Organization

……A vaccine typically contains an agent that resembles a disease-causing microorganism ……. The agent stimulates the body's immune system to recognize the agent as foreign, “destroy it, and remember it”, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters…….

Vaccines have proved to be one of the most powerful and effective ways of reducing disease and vaccination is considered the most cost-effective medical intervention ever introduced

The impact of vaccination on selected diseases in the UK



Modificato da: **Stanley Plotkin**

PNAS | **August 26, 2014** | vol. 111 | no. 34

Outline of the development of human vaccines

Empiric development

Rational development

Live attenuated	Killed whole organisms	Purified proteins or polysaccharides	Genetically engineered
18th Century			
Smallpox (1798)			
19th Century			
Rabies (1885)	Typhoid (1896)		
	Cholera (1896)		
	Plague (1897)		
Early 20th Century, first half			
Tuberculosis (bacille Calmette–Guérin) (1927)	Pertussis (1926)	Diphtheria toxoid (1923)	
Yellow fever (1935)	Influenza (1936)	Tetanus toxoid (1926)	
	Rickettsia (1938)		
20th Century, second half			
Polio (oral) (1963)	Polio (injected) (1955)	Anthrax secreted proteins (1970)	Hepatitis B surface antigen recombinant (1986)
Measles (1963)	Rabies (cell culture) (1980)	Meningococcus polysaccharide (1974)	Lyme OspA (1998)
Mumps (1967)	Japanese encephalitis (mouse brain) (1992)	Pneumococcus polysaccharide (1977)	Cholera (recombinant toxin B) (1993)
Rubella (1969)	Tick-borne encephalitis (1981)	*Haemophilus influenzae* type B polysaccharide (1985)	
Adenovirus (1980)	Hepatitis A (1996)	*H.influenzae* type b conjugate (1987)	
Typhoid (*Salmonella* TY21a) (1989)	Cholera (WC-rBS) (1991)	Typhoid (Vi) polysaccharide (1994)	
Varicella (1995)	Meningococcal conjugate (group C) (1999)	Acellular pertussis (1996)	
Rotavirus reassortants (1999)		Hepatitis B (plasma derived) (1981)	
Cholera (attenuated) (1994)			
Cold-adapted influenza (1999)			
21st Century			
Rotavirus (attenuated and new reassortants) (2006)	Japanese encephalitis (2009) (Vero cell)	Pneumococcal conjugates* (heptavalent) (2000)	Human papillomavirus recombinant (quadrivalent) (2006)
Zoster (2006)	Cholera (WC only) (2009)	Meningococcal conjugates* (quadrivalent) (2005)	Human papillomavirus recombinant (bivalent) (2009)
		Pneumococcal conjugates* (13-valent) (2010)	Meningococcal group B proteins (2013)

*Capsular polysaccharide conjugated to carrier proteins.

Rational development

1- ATTENUATION – attenuated vaccines

The idea of attenuation of virulent infections developed slowly over the course of centuries. **It was based on the idea that an agent virulent for animals might be attenuated in humans.** Serial propagation of a pathogen in inhabitual hosts may lead to "attenuation"

Old examples: Jenner's use of an animal poxvirus to prevent smallpox

Cell cultures. In 1948-1949, a revolution happened with the discovery that cells could be cultured in vitro and used as substrates for viral growth. **Passage in cell culture leads to adaptation to growth in that medium,** and the mutants best capable of growth have often lost or modified the genes that allow them to infect and spread within a human host.

More recent examples of attenuation" in vitro in cell culture: measles, rubella, mumps, grown in cell culture

Rational development

2- INACTIVATION inactivated vaccines

Another discovery toward the end of the 19th century was that immunogenicity could be retained if microorganisms were carefully killed by heat or chemical treatment

3- PROTEIN-BASED VACCINES “subunit” vaccines

Some vaccines used today are **purified from microorganism preparation** or generated by growing the viruses in vitro and then breaking up the whole virus with detergents. Then viral protein is purified to serve as the vaccine antigen. Several vaccines consist of partly or fully purified proteins.

Sometimes tha vaccine is a “conjugated “vaccine. Conjugation is a procedure that combines a type of subunit vaccine (with a weak antigen) with a strong antigen (as a carrier) so that the immune system has a stronger response to the weak antigen.

Rational development

2- INACTIVATION inactivated vaccines

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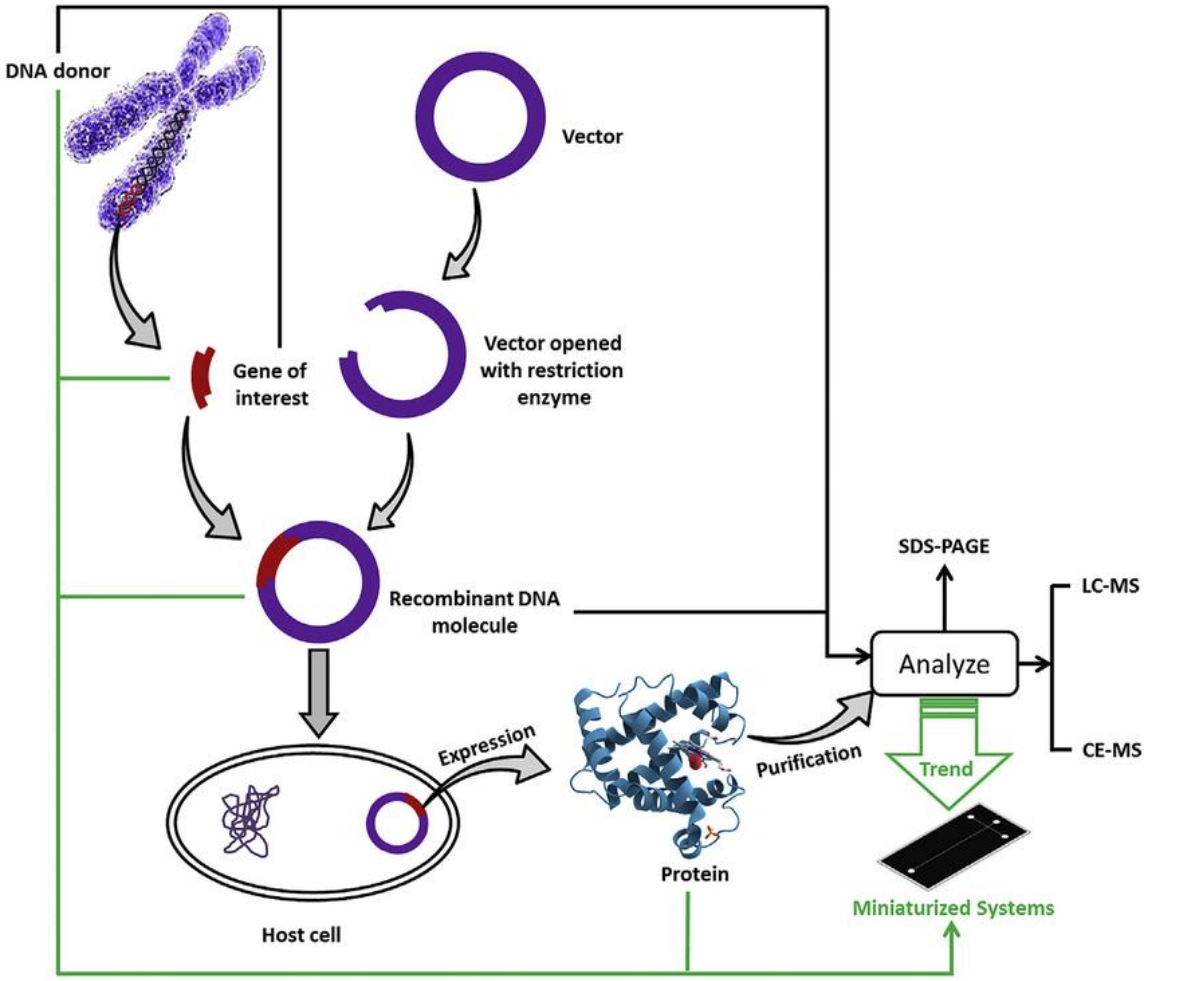
4- GENETIC ENGINEERING

The revolution of genetic engineering toward the end of the 20th century has greatly impacted vaccine development. The first fruit of that revolution was the vaccine against hepatitis B.

Vaccino - Proteine ricombinanti

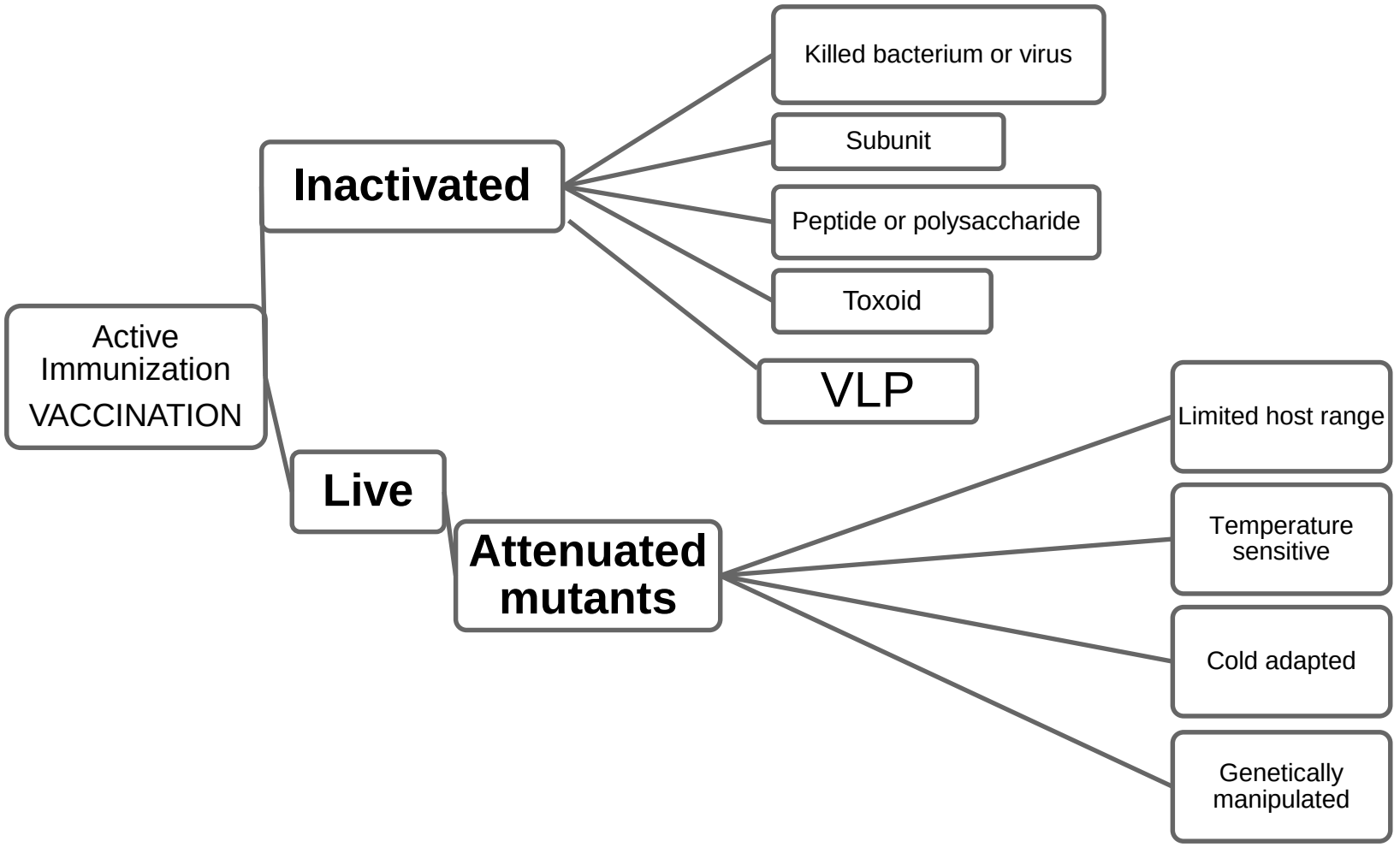
This technique is based on the possibility to allow the cells of the subject to be immunized to directly produce the antigens against which we want to induce an immune response. This is possible using a cDNA encoding the protein of interest carried by a plasmid

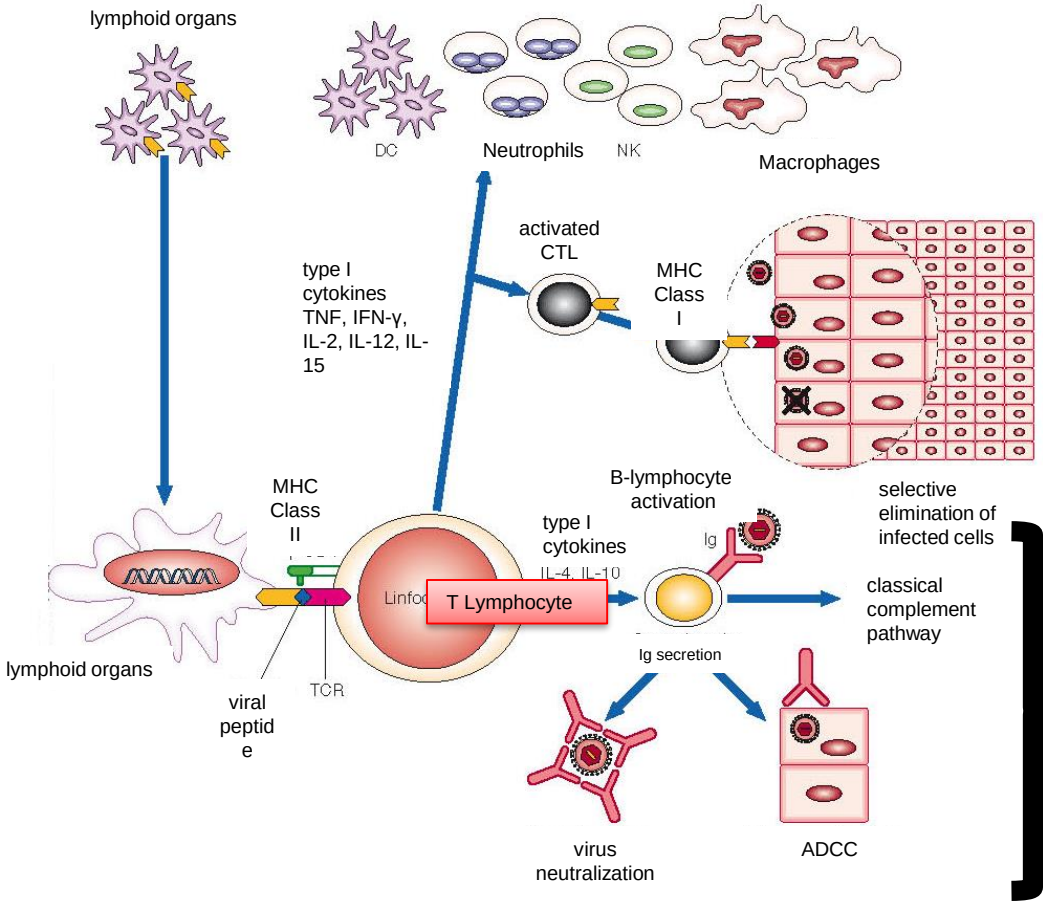


Gianini Morbioli G. et al. Analytica Chimica Acta · September 2016

Strategies for the development of vaccines

PROCEDURE	EXAMPLES
attenuation, inactivation, grown and purification	many
recombinant DNA technology	HBV, HPV
conjugation technology	Haemophilus influenzae B
	Streptococcus pneumoniae (different serotypes)
	Neisseria meningitidis A


Active Immunization
VACCINATION
Inactivated
Killed bacterium or virus
Subunit
Peptide or polysaccharide
Toxoid
VLP
Live
Attenuated mutants
Limited host range
Temperature sensitive
Cold adapted
Genetically manipulated



Attenuated Vaccines

Inactivated Vaccines

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General Rule

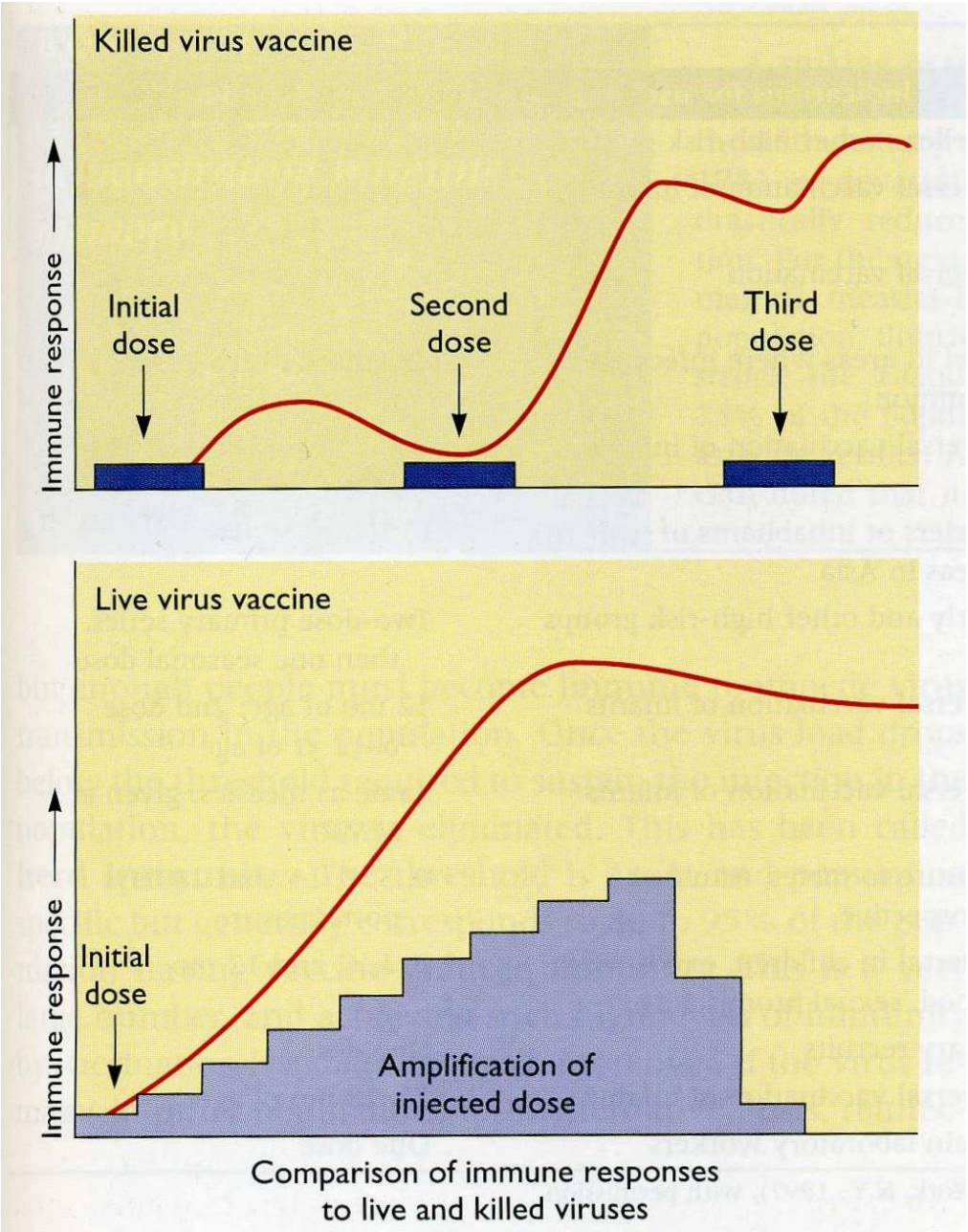


Figure 19.2 Comparison of the predicted immune responses to live and killed viruses used in vaccine protocols.

Further challenges for vaccinologists

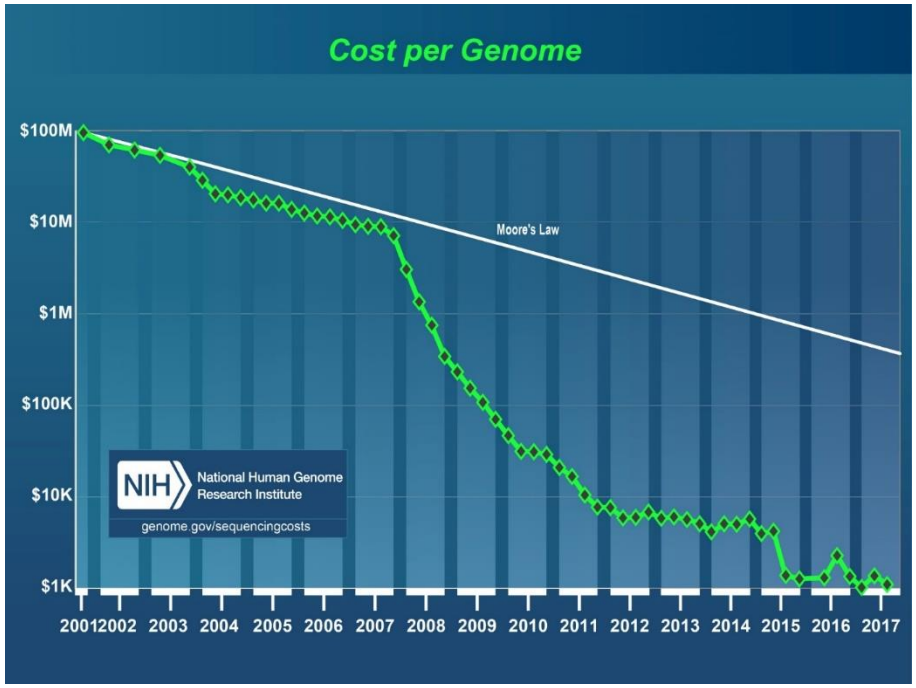
Challenges (examples)	Determinants (examples)	Microorganism (Examples)
Severe infections	No availabilty of curative drugs,	HIV, HCV
Severe infections	Variability of the pathogen	Influenza
Climate changes	Incidence, frequency and distribution of several infection infections	vector-borne diseases, ancient bacteria and viruses
Population growth and urbanization in developing countries	Population density	mosquito-trasmitted diseases, leptospirosis, rabies, etc.
Antibiotic resistance	Hospital acquired infections Misuse of antibiotics	Methicillin-resistant staphyloccocus aureus (MRSA) Pseudomonas aeruginosa Clostridium difficile
Emerging infections	The number of emerging viruses is significantly increasing	Norovirus, SARS-CoV-1, MERS, SARS-CoV-2

Table 1 | Partial list of emerging viral infectious diseases from 1900 to 2020

Year of first description	Name	Deaths	Comments
1918	'Spanish influenza'	In the range of about 50 million to 100 million	1918: H1N1; other pandemics in 1957–1958 (H2N2), 1968 (H3N2) and 2009 (H1N1)
1931	Rift Valley Fever	Overall CFR < 1%; ~50% for hemorrhagic fever	Contact with blood or organs of infected animals and mosquito-borne; several outbreaks in 1977, 1997–1998, 2000–2016
1937	West Nile fever	CFR ~5%	Mosquito-borne; worldwide outbreaks (most recent 1999–2010, USA)
1967	Marburg hemorrhagic fever	~470; very high CFR (24–88%, WHO)	Contact with African green monkey; numerous outbreaks in Africa 1969–2018
1969	Lassa fever	~5,000 deaths annually; CFR 1–2%; Nigerian CFR 25%	Contact with rodents or contaminated food or items; mostly in West Africa (Nigeria 2018)
1969	Acute hemorrhagic conjunctivitis	Rare	First identified in 1969; pandemic in 1981; frequent outbreaks worldwide
1976–2020	Ebola hemorrhagic fever	>15,000; CFR 75%	First identified in 1976; first major outbreak in 2013–2016 in West Africa and in 2018 in Democratic Republic of Congo; 29 regional epidemics in 2020 in West and Central Africa
1981	HIV/AIDS	~37 million	Ongoing pandemic
1996	Avian flu	High CFR (60%)	H5N1 and H7N9 viruses from poultry; several outbreaks worldwide; last outbreak in China in 2018
1999	Nipah fever	<1,000?; very high CFR	Outbreaks in Malaysia, Singapore, Bangladesh and India
2002	SARS	813; CFR ~ 10%	Contained—did not turn into pandemic
2009	H1N1; H7N9 'swine flu'	284,000; CFR 2.9–9%	Pandemic
2012	MERS	935; CFR 34.4%	Major outbreak in 2012–2019; ongoing (camels, humans); detected in 27 countries but mostly in Middle Eastern countries
2014	Chikungunya	Rare	Mosquito-borne
2015	Zika	Unknown	Mosquito-borne
2019–ongoing	COVID-19 (SARS-CoV-2)	>2.3 million; CFR 2–10%; high in elderly and individuals with comorbidities	Pandemic—animal-to-animal, animal-to-human and human-to-human transmission

CFR, case-fatality rate.

Next generation sequencing and the metagenomic revolution



Sequencing technology			
year	time needed	cost	needs
2000	10 years	1 billion US dollars	world-wide teams
2010	10 days	50,000 US dollars	1 laboratory group
now	1 day	1,000 US dollars	

Strategies for the development of new vaccines

Using the computer to rationally design vaccines starting with information present in the genome, without the need to grow the specific microorganisms.

Strategies for the development of vaccines

PROCEDURE	EXAMPLES
growth, isolation, inactivation	many
recombinant DNA technology	HBV, HPV
conjugation technology	Haemophilus influenzae B
	Streptococcus pneumoniae (different serotypes)
	Neisseria meningitidis A
genomics; genome-based approach	**Ebola virus, Influenza virus, SARS-CoV-2**

Vaccini a DNA - vettore adenovirale

Questa tecnica si basa sulla possibilità di far produrre direttamente alle cellule dell'individuo da immunizzare gli antigeni contro i quali si vuol indurre una risposta immunitaria. Questo è possibile utilizzando un cDNA che codifica la proteina di interesse veicolata da un virus non citopatico o difettivo (vettore virale)

A cDNA encoding the protein of interest carried by a non-cytopathic or defective virus (viral vector)

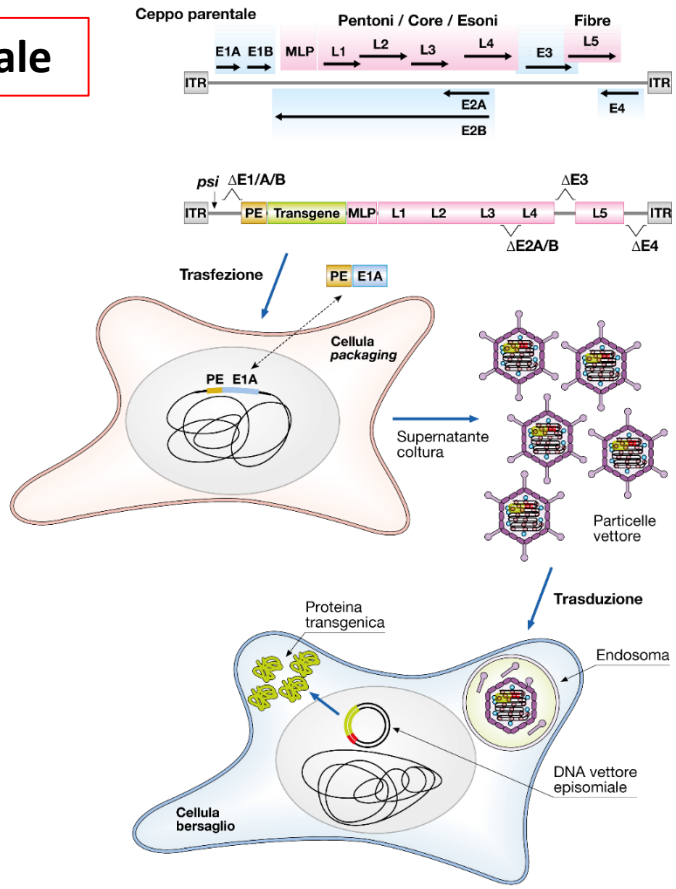
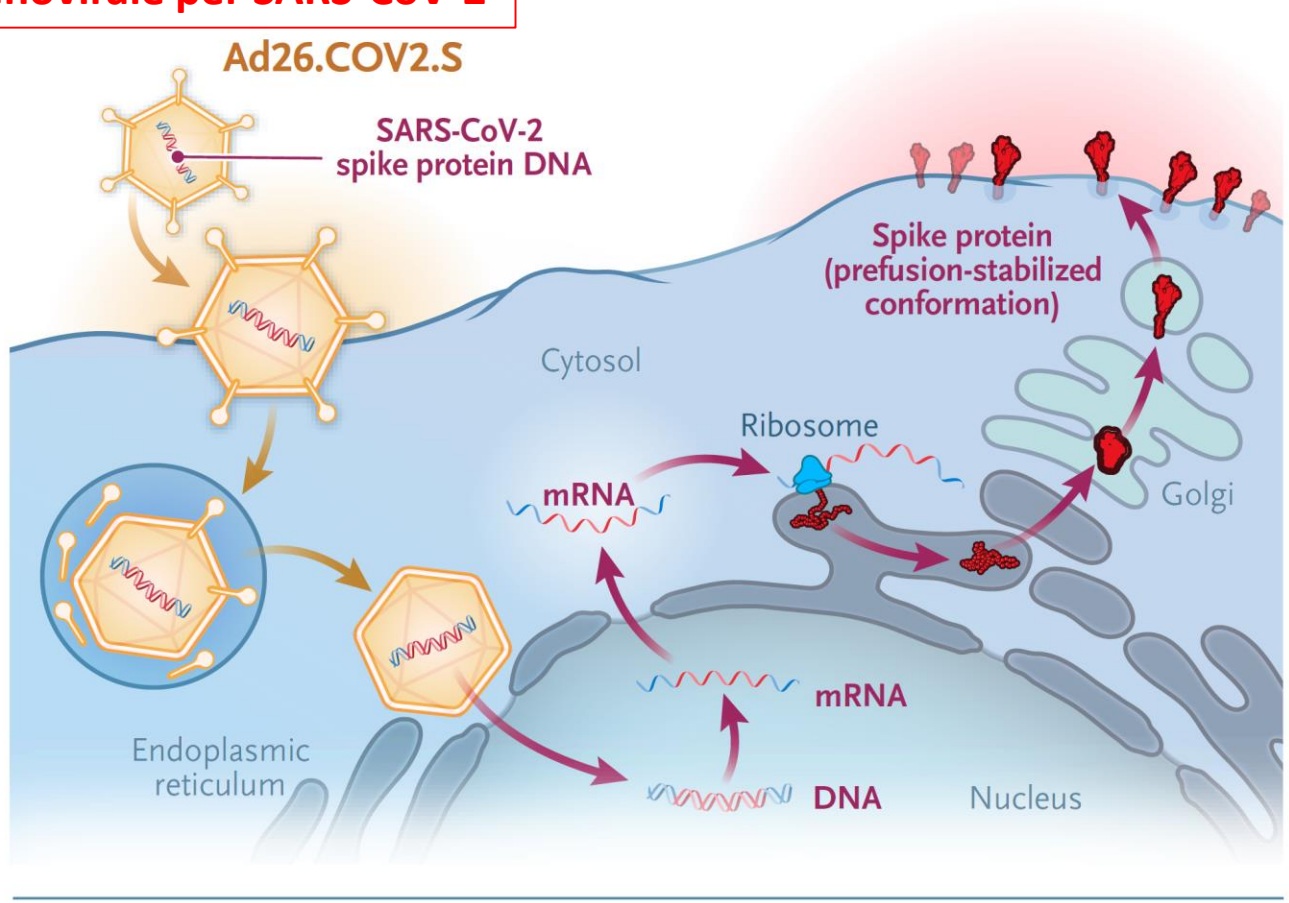


Figura 70.3 **Produzione e trasduzione con vettore adenovirale.**

Vaccini a DNA/vettore adenovirale per SARS-CoV-2

Questa tecnica si basa sulla possibilità di far produrre direttamente alle cellule dell'individuo da immunizzare la proteina S del SARS-CoV-2 contro la quale si vuol indurre una risposta immunitaria. Questo è possibile utilizzando un cDNA che codifica la proteina di interesse veicolata da un adenovirus difettivo.



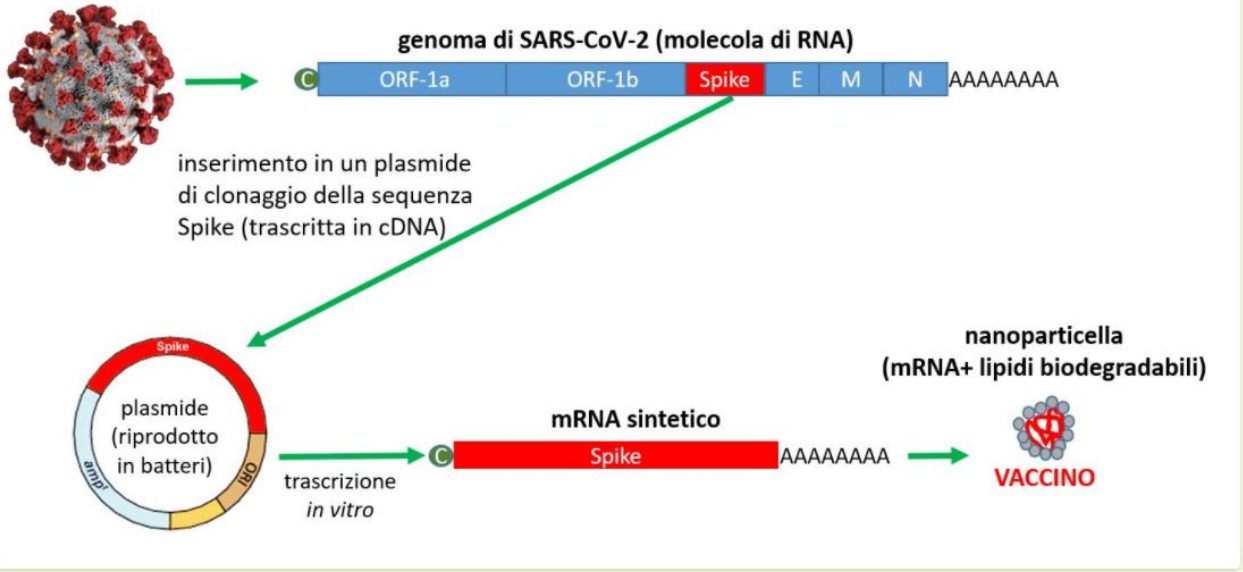
Sadoff J et al. DOI: 10.1056/NEJMoa2101544

A cDNA encoding the S-protein of SARS_CoV-2 carried by a non-cytopathic or defective virus (viral vector)

Vaccini a RNA – SARS-CoV-2 RNA messaggero

Questa tecnica si basa sulla possibilità di far produrre direttamente alle cellule del soggetto vaccinato gli antigeni contro i quali si vuol indurre una risposta immunitaria.

Questo è possibile utilizzando un RNA messaggero corrispondente alla proteina S di SARS-CoV-2 veicolata da un liposoma per far entrare l'RNA nella cellula.



[*Disegno: Ferdinando Di Cunto*]

SARS-CoV-2: Frontiere della ricerca

ZANICHELLI

I **liposomi** sono vescicole con un diametro fra i 25 nm e 1 µm le cui pareti sono composte da colesterolo e lipidi e sono in grado di veicolare al loro *interno* diverse sostanze, ad esempio farmaci o vaccini.
I **virosomi** sono strutture assimilabili ai liposomi che contengono proteine presenti sulla superficie dei virus, sia incapsulate al loro interno sia al loro esterno.

a messenger RNA corresponding to the protein of interest carried by a virosome or liposome to let the RNA enter the cell.

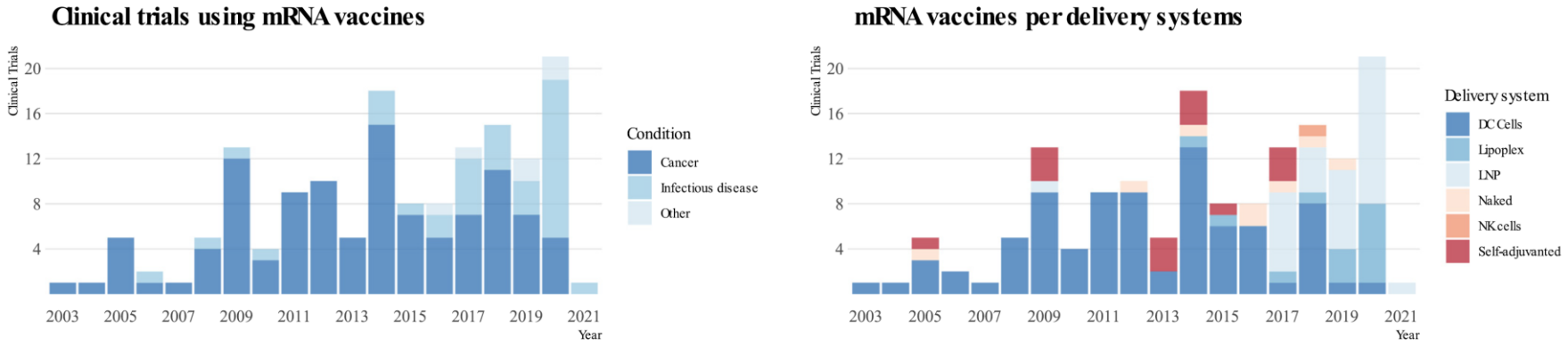


Fig. 2. Breakdown of mRNA vaccines clinical trials filed per year according to disease type (left) and delivery system (right).

Table 4 | **Leading mRNA vaccine developers: research focus, partners and therapeutic platforms**

Institution	mRNA technology	Partners	Indication (disease target)
Argos Biotechnology	mRNA neoantigens (Arcelis platform)	NA	Individualized cancer vaccines, HIV-1
BioNTech RNA Pharmaceuticals GmbH	Nucleoside-modified mRNA (IVAC Mutanome, FixVAC)	Genentech/Roche	Individualized cancer vaccines
		Bayer AG	Veterinary vaccines
CureVac AG	Sequence-optimized, purified mRNA (RNActive, RNArt, RNAdjuvant)	Boehringer Ingelheim GmbH	Cancer vaccines (lung cancer)
		Johnson & Johnson	Viral vaccines
		Sanofi Pasteur	Infectious disease vaccines
		BMGF	Infectious disease vaccines
		IAVI	HIV vaccines
eTheRNA Immunotherapies	Purified mRNA (TriMix)	NA	Cancer (melanoma, breast), viral vaccines (HBV and/or HPV)
GlaxoSmithKline/ Novartis	Self-amplifying mRNA (SAM) (alphavirus replicon)	NA	Infectious disease vaccines
Moderna Therapeutics	Nucleoside-modified mRNA	Merck & Co.	Individualized cancer vaccines, viral vaccines
		BMGF, DARPA, BARDA	Viral vaccines (influenza virus, CMV, HMPV, PIV, chikungunya virus, Zika virus)
University of Pennsylvania	Nucleoside-modified, purified mRNA	NA	Infectious disease vaccines

BARDA, Biomedical Advanced Research and Development Authority; BMGF, Bill & Melinda Gates Foundation; CMV, cytomegalovirus; DARPA, Defense Advanced Research Projects Agency; HBV, hepatitis B virus; HMPV, human metapneumovirus; HPV, human papillomavirus; IAVI, International AIDS Vaccine Initiative; NA, not available; PIV, parainfluenza virus.

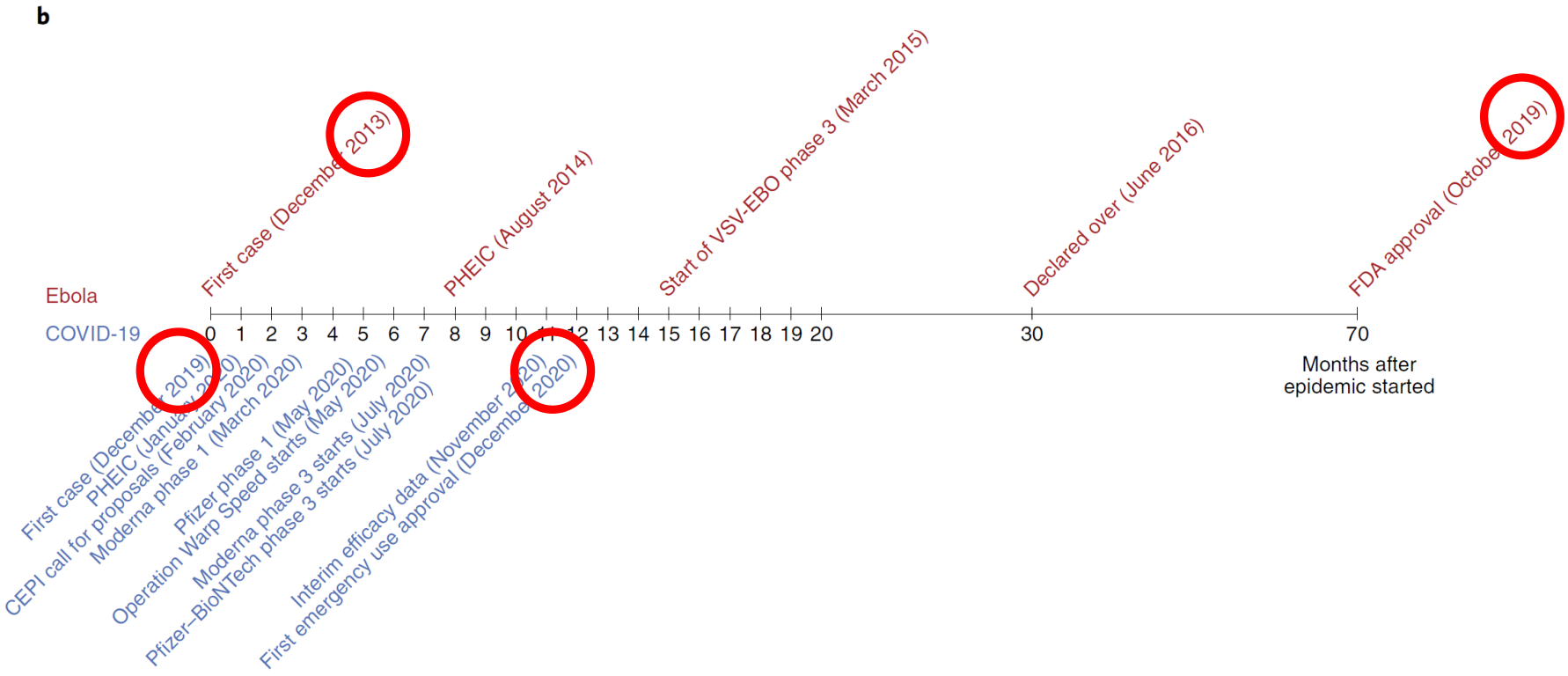
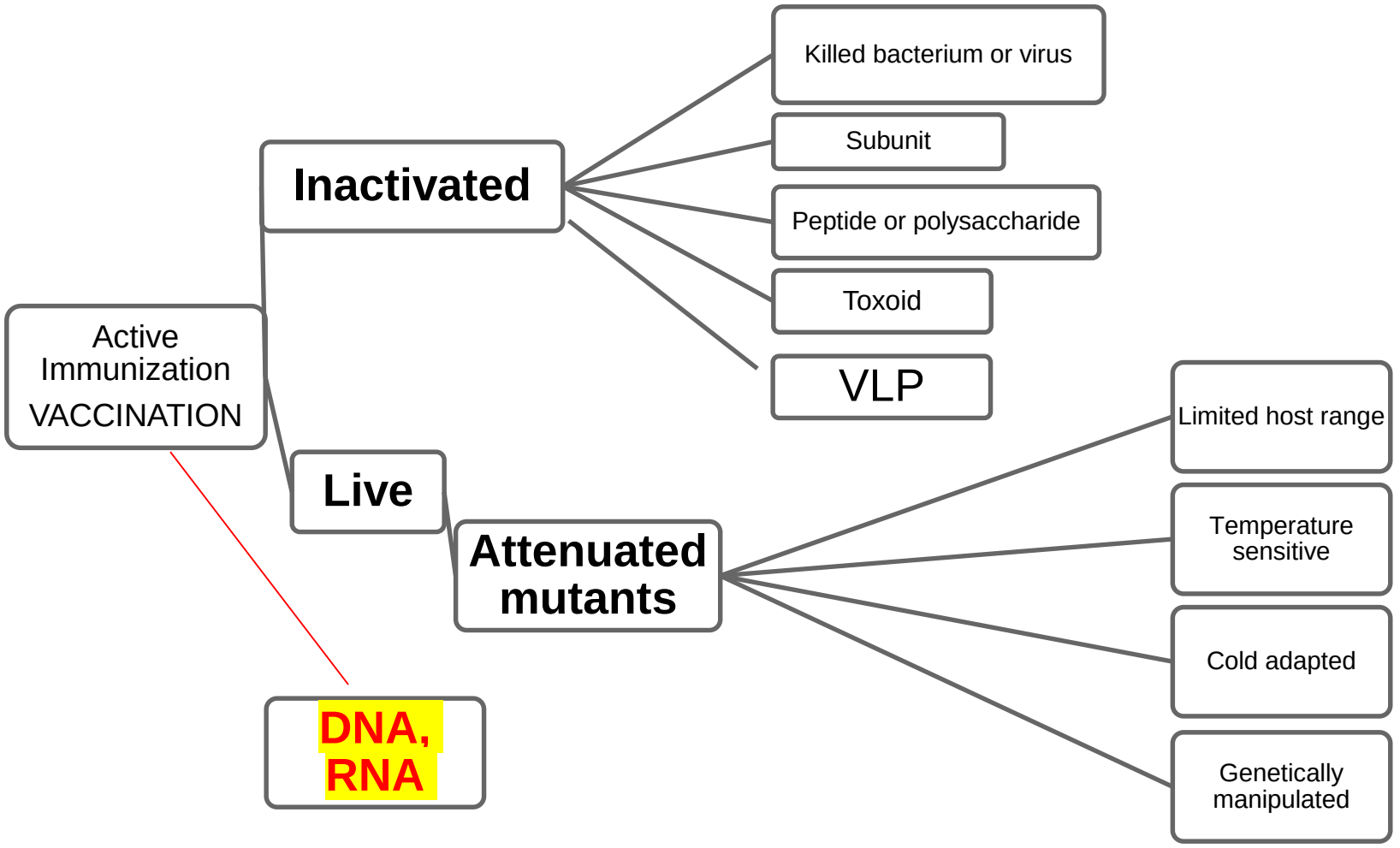
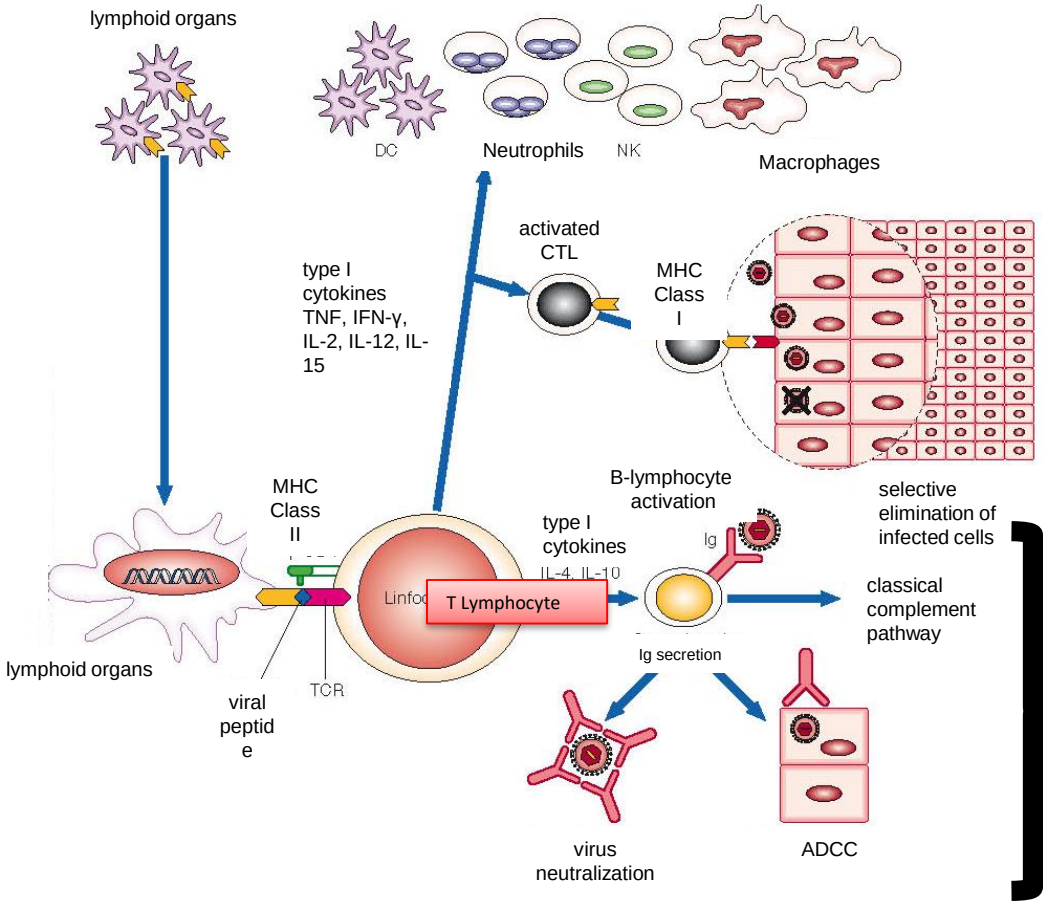

b
Ebola
COVID-19
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 30 70
Months after epidemic started
First case (December 2013)
PHEIC (August 2014)
Start of VSV-EBO phase 3 (March 2015)
Declared over (June 2016)
FDA approval (October 2019)
First case (December 2019)
PHEIC (January 2020)
CEPI call for proposals (February 2020)
Moderna phase 1 (March 2020)
Pfizer phase 1 (May 2020)
Operation Warp Speed starts (May 2020)
Moderna phase 3 starts (July 2020)
Pfizer–BioNTech phase 3 starts (July 2020)
Interim efficacy data (November 2020)
First emergency use approval (December 2020)

Table 2 | Examples of different vaccine platforms and vaccines currently developed or under development for emerging viral infectious diseases

Vaccine platform	Other specifications	Developed for	Under development or stopped[a] for	Shortcomings and advantages
Live attenuated		Influenza; yellow fever; poliomyelitis	COVID-19; RVF (veterinary and human use) Lassa fever; chikungunya	Biosafety level 3 manufacturing plant for handling dangerous viruses
Whole inactivated	With or without adjuvant	Influenza; poliomyelitis; COVID-19	SARS[a]; Zika; RVF (veterinary use); chikungunya	Biosafety level 3 manufacturing plant for dangerous viruses; needs adjuvant; HPB regimens possible
DNA	Electroporation; adjuvant		SARS[a]; MERS; Zika; Lassa fever; COVID-19	Poorly immunogenic; electroporation requires device; difficult use for rollout; HPB regimens possible
mRNA		COVID-19	Lassa fever; disease X	Rapidly adaptable to new emerging viruses; HPB regimens possible; ultracold chain currently unpractical for large-scale use in resource-limited settings
Recombinant vectors				
Nonreplicating				
Ad5			COVID-19	Preexisting immunity to Ad5
ChAd3			Ebola	Cell-line-produced; adaptable construct to emerging virus in 5–6 months; HPB regimens possible
ChAdOx1		COVID-19	MERS; RVF; Lassa fever; Nipah; Zika; chikungunya	
Ad26		Ebola; COVID-19		
Live attenuated				
MVA		Ebola	MERS	
VSV		Ebola	COVID-19[a]; Lassa fever; Nipah	
Measles			MERS; Lassa fever; Nipah; chikungunya; COVID-19[a]	
Protein based				Requires more time to adapt to new emerging viruses; likely needs adjuvant; HPB regimens possible
Virus-like particle	With adjuvant	COVID-19	COVID-19	
Monomer; dimer; trimer	With adjuvant		COVID-19; RFV; Nipah	
Molecular clamp	With adjuvant		Influenza; MERS; COVID-19[a]	

[a]Vaccine development stopped.


Active Immunization
VACCINATION
Inactivated
Killed bacterium or virus
Subunit
Peptide or polysaccharide
Toxoid
VLP
Live
Attenuated mutants
Limited host range
Temperature sensitive
Cold adapted
Genetically manipulated
DNA, RNA



Attenuated Vaccines

Inactivated Vaccines , Subunit, DNA, RNA

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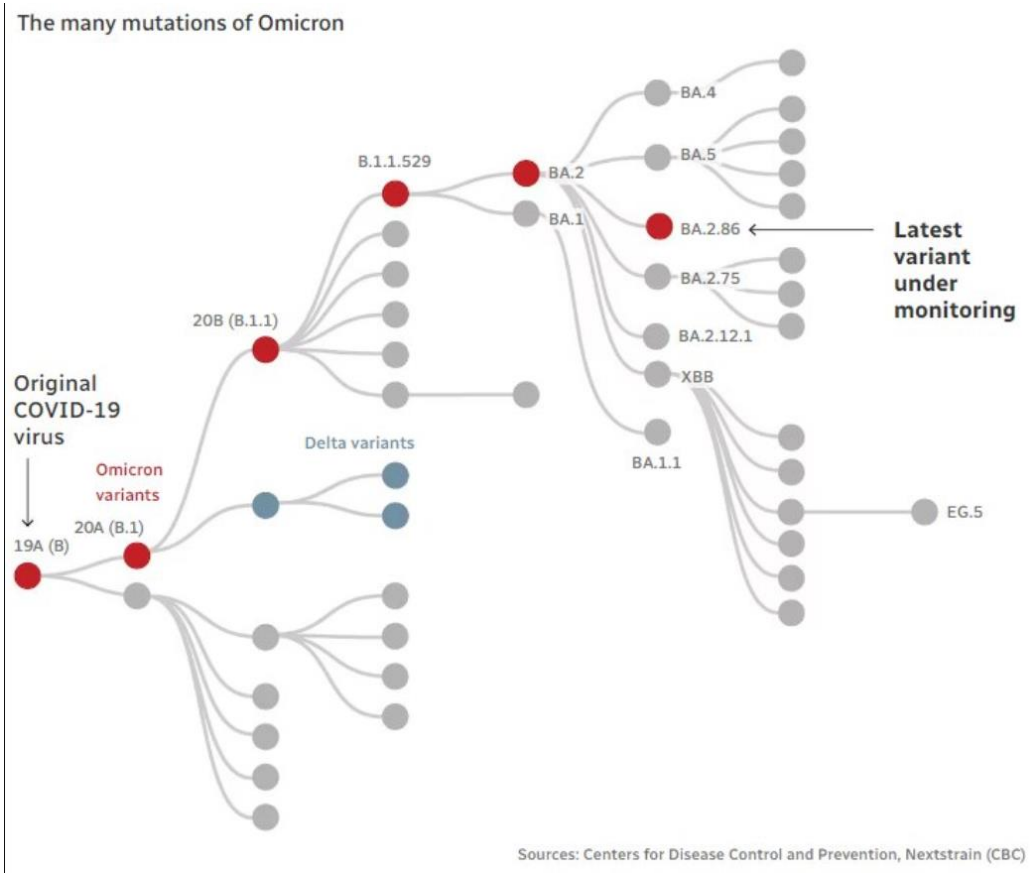
Viral Vaccines

Virus	Vaccines Components	Who Should Receive Vaccinations
Polio, inactivated	Trivalent (Salk vaccine)	Children
Attenuated polio	Live (oral polio vaccine, Sabin vaccine)	Children
Measles	Attenuated	Children
Mumps	Attenuated	Children
Rubella	Attenuated	Children
Varicella-zoster	Attenuated	Children
Rotavirus	Human-bovine hybrids Attenuated	Infants
Human papilloma-virus	VLP	Girls aged 9-26 yr
Influenza	Inactivated Attenuated (nasal spray)	Children, adults, especially medical personnel, and the elderly 2-50 yr
Hepatitis B	Subunit (VLP)	Newborns, health care workers, high risk groups (e.g. sexually promiscuous, intravenous drug users)
Hepatitis A	Inactivated	Children, child care workers, travelers to endemic areas, Native Americans and Alaskans
Adenovirus	Attenuated	Military personnel
Yellow fever	Attenuated	Travelers at risk to exposure, military personnel
Rabies	Inactivated	Anyone exposed to virus Preexposure: veterinarians, animal handlers
Smallpox	Live vaccinia virus	Protection from bioterrorism, military
Japanese encephalitis	Inactivated	Travelers at risk to exposure

Advantages and Disadvantages of Live versus Inactivated Vaccines

Property	Live	Inactivated, "Subunit", DNA, RNA
Route of administration	Natural or injection	Injection
Dose of virus, cost	Low	High
Number of doses, amount	Single, low	Multiple, high
Need for adjuvant	No	Yes
Duration of immunity	Long-term	Short-term
Antibody response	IgG, IgA	IgG
Cell-mediated immune response	Good	Poor
Potential lability	Yes	No
Interference	Occasional	None
Side effects	Occasional mild symptoms	Rare
Reversion to virulence	Rarely	None

Modified From Murray et al Medical Microbiology Elsevier 2016



BA.2.86 Variant- September 2023

BA.2.86 Variant hyper-mutated variant has shown up in many places now. To date, the BA.2.86 variant has been detected in Israel, Denmark (3 individuals), the UK, the US (2 individuals, one coming back from Japan), and South Africa (2 individuals). It has also been detected in wastewater in 1 region in Switzerland (2% level), along with wastewater detection in Ohio and in Thailand. It's safe say that BA.2.86's presence is widespread across the world at this point.

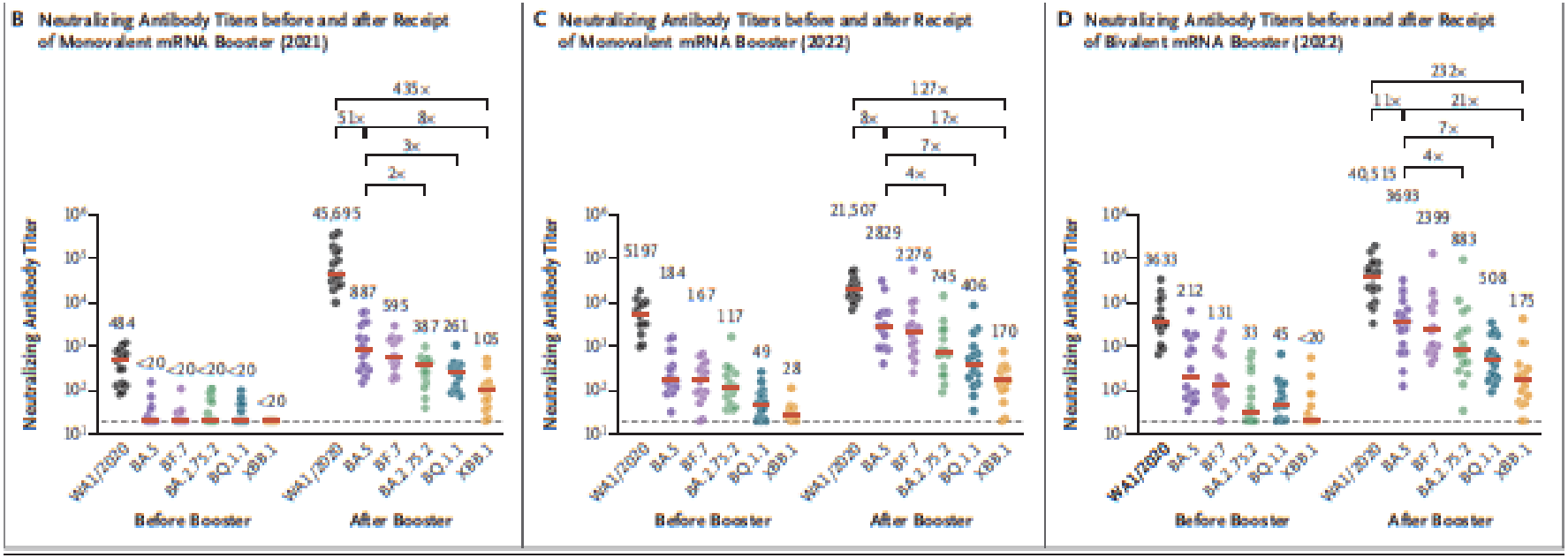
BA.2.86 has probably been circulating in a region of the world with poor viral surveillance and
has now been repeatedly exported to other places in the world

The lineage seems to be descended from an Omicron subvariant called BA.2, which caused large case spikes in early 2022. However, the BA.2.86 spike protein carries 34 changes relative to BA.2. Large numbers of spike mutations have been observed in people with long-term SARS-CoV-2 infections, and it is likely that BA.2.86 emerged from one such chronic infection

Substantial Neutralization Escape by SARS-CoV-2 Omicron Variants BQ.1.1 and XBB.1

Jessica Miller,

N ENGL J MED 388;7 NEJM.ORG FEBRUARY 16, 2023



BQ.1.1 and XBB.1 variants escaped neutralizing antibodies substantially more effectively than the BA.5 variant by factors of 7 and 17, respectively, after monovalent mRNA boosting and by factors of 7 and 21, respectively, after bivalent mRNA boosting

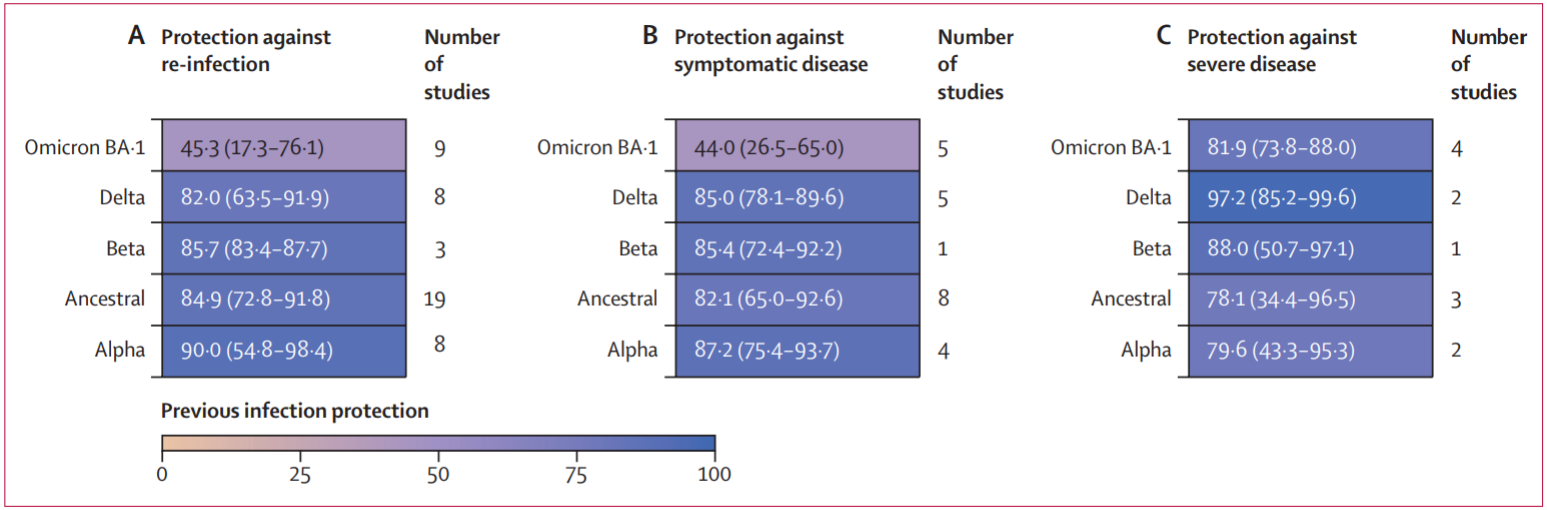
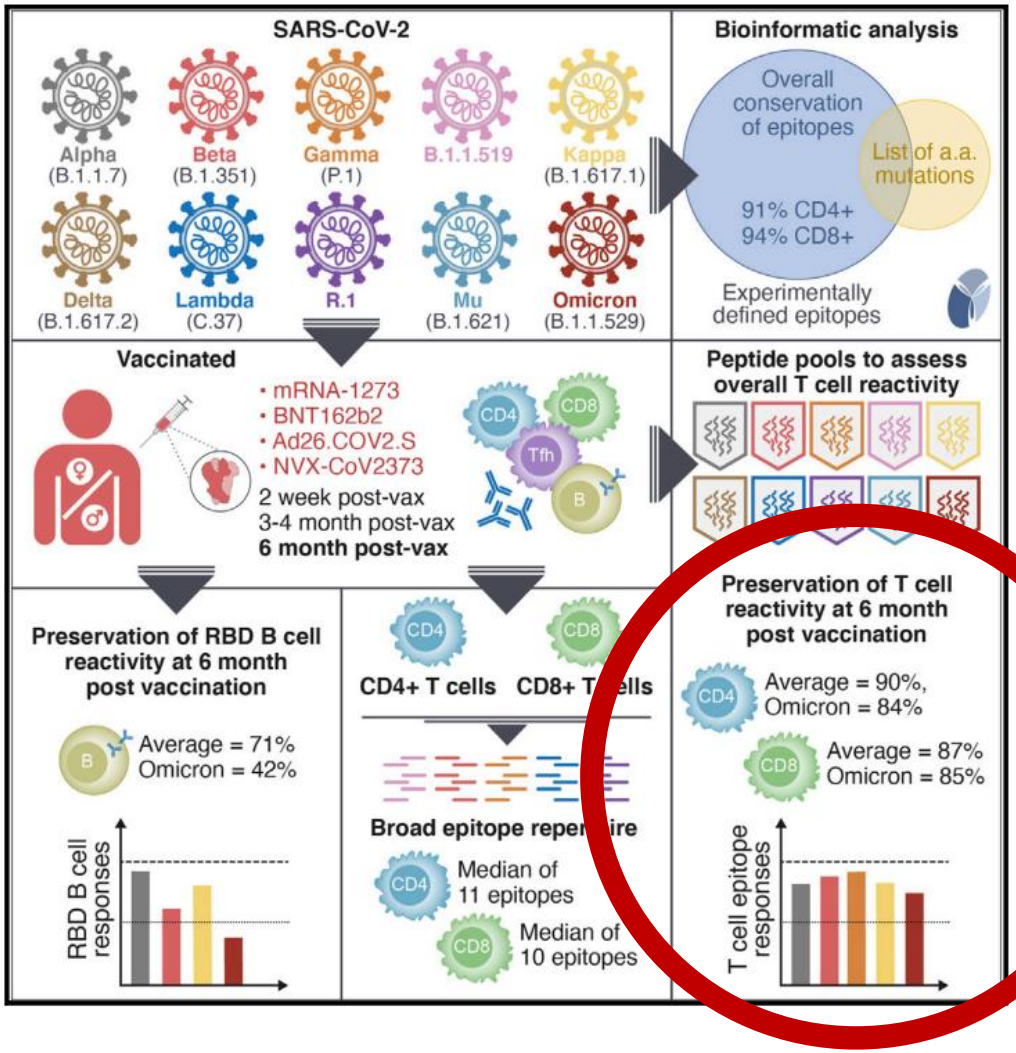


Figure 2: **Pooled estimate of protection from past SARS-CoV-2 infection against re-infection, symptomatic disease, and severe disease by variant, and number of included studies in each meta-analysis estimate**

Data are pooled estimate (95% uncertainty interval). Estimates of protection against re-infection (A), symptomatic disease (B), and severe disease (C).



- T cells of vaccinees recognize SARS-CoV-2 variants, including Omicron
- RBD memory B cells' recognition of Omicron is reduced

Human memory T cells induced by SARS-CoV-2 vaccines maintain the ability to recognize viral variants, including the Omicron variant.

CellPress

Tarke et al., 2022, Cell *185*, 847–859
March 3, 2022 © 2022 Elsevier Inc.
https://doi.org/10.1016/j.cell.2022.01.015

Vaccination against infectious diseases: challenges

- Are broadly neutralizing antibodies an absolute necessity?
- We do not know how to generate long-lasting protective antibodies at mucosal surfaces
- There are multiple viral serotypes/genotypes and antigenic variation requires constant updating of vaccine formulations;
- For some infectious diseases, **no validated immunological correlates of immunity (protective or pathological) do exist**

The ‘best’ vaccine

Any effort to rank the vaccines must take into account their reported effectiveness, but also:

- their ability to fend off emerging viral variants
- the durability of the protection they offer
- the logistics of deploying them
- the supply and cost issues