Università degli Studi di Padova

Scuola di Scienze

Corso di *Immunologia Farmaceutica*

Anno Accademico 2024-25

Memoria immunologica e vaccinazione

13-05-2025

Edward Jenner
(1749-1823)

Jenner and vaccine development

Jenner's scientific interests were varied, but the importance of his work in vaccination has overshadowed his other results. Early in his career he had begun to observe the phenomena of cowpox, a disease common in the rural parts of the western counties of England, and he was familiar with the belief, current among the peasantry, that a person who had suffered from the cowpox could not take smallpox. Finally, in 1796, he made his first experiment in vaccination, inoculating a boy of eight with cowpox, and, after his recovery, with smallpox; with the result that the boy did not take the latter disease.

Smallpox (Variola): This man's body is covered with lesions from smallpox. A worldwide smallpox vaccination program led to the eradication of the disease in the late 1970s. The global eradication of smallpox ranks as one of the greatest achievements in the history of medicine.

Jenner's success was made possible by antigens shared by cowpox and smallpox

Vaiolo bovino Vaiolo

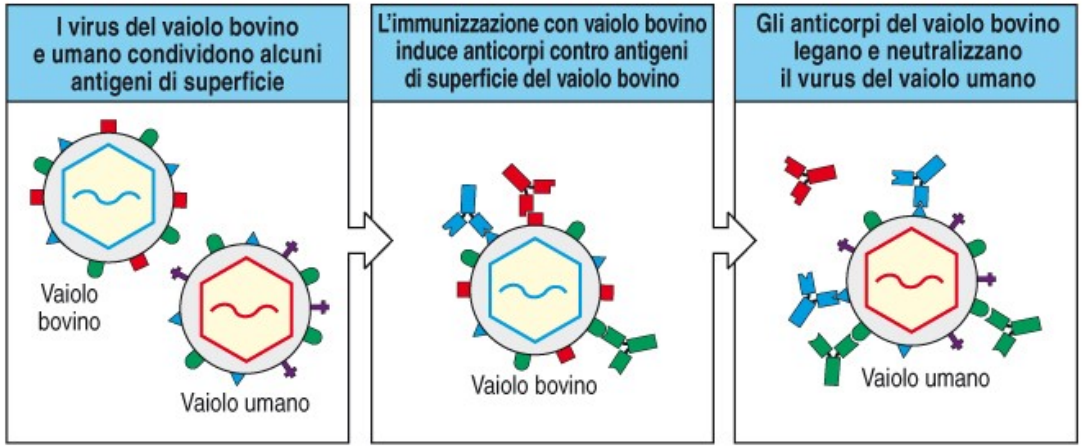


Figura 11.14 La vaccinazione con il virus del vaiolo bovino induce anticorpi neutralizzanti che reagiscono con determinanti antigenici condivisi dal virus del vaiolo umano. Determinanti antigenici condivisi del virus del vaiolo bovino inducono una risposta protettiva delle cellule T anche contro il virus del vaiolo umano (non mostrata qui).

Short story of Vaccinations

- 1796 Jenner : smallpox
- 1805 : napoleonic army vaccinated
- 1840 : vacc. duty for England
- 1885 Pasteur: Rabies
- 1900-1950: diphtheritis, TBC, tetanus

- 1955 : Salk Polio killed
- 1959 : Sabin Polio attenuated

- 1981 : Smallpox eradicated

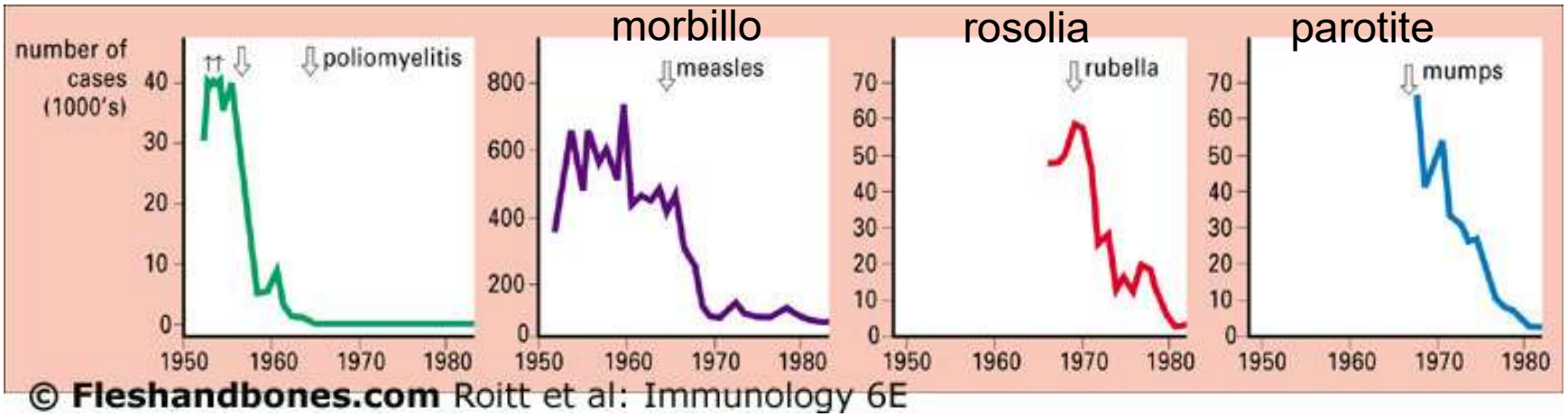
Vaccination is the most effective method for disease prevention

Table 1 | **Reduction of the number of vaccine-preventable diseases in the US**

Disease	Number of cases		
	Maximum	***1997***	***% change***
Diphtheria	206,939	4	99.99
Measles	894,134	138	99.98
Mumps	152,209	683	99.55
Pertussis (whooping cough)	265,269	6,564	97.52
Polio (paralytic)	21,269	0	100.00
Rubella	57,686	181	99.69
Congenital rubella syndrome	20,000*	5	99.98
Tetanus	1,560‡	50	96.79
Influenza (<5 years)	20,000*	165	99.18

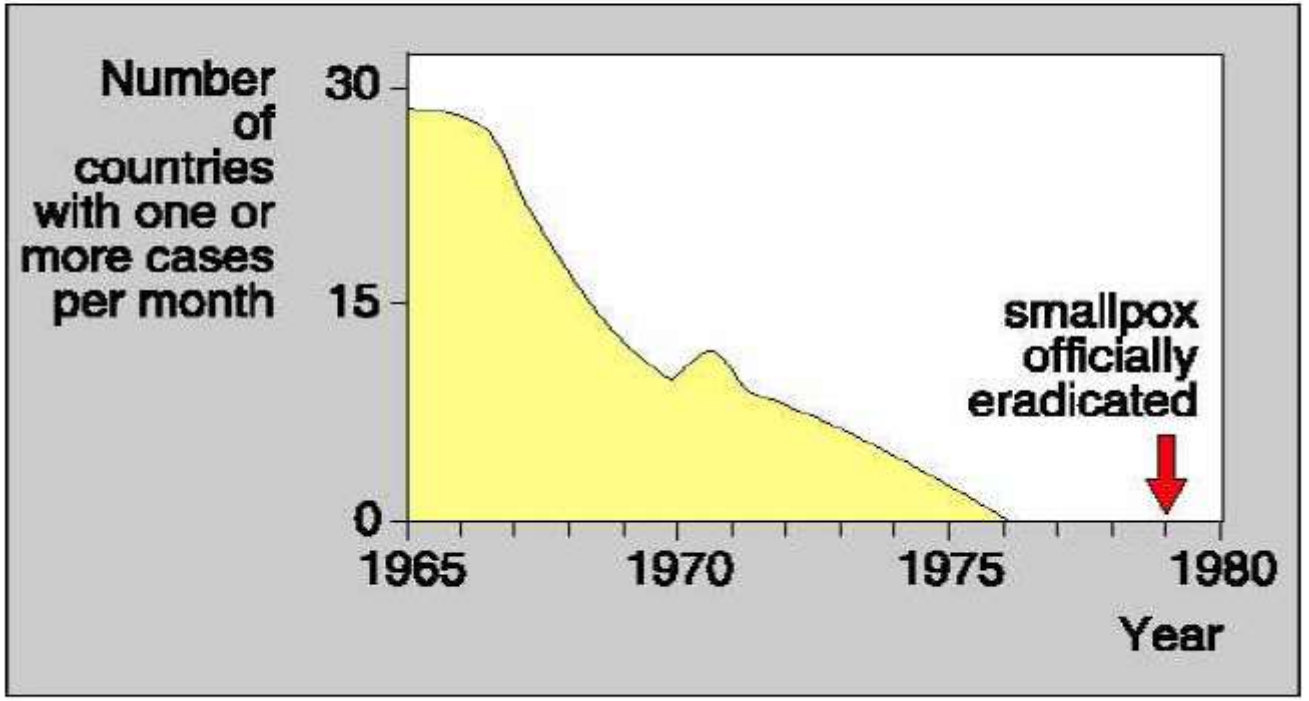
Data taken from REF. 5. * estimated; ‡ mortality.

Impact of vaccination on the incidence of some viral diseases



Vaccination has eliminated naturally occuring smallpox and polio is almost eliminated.

Figure 1.1



What is Polio?

•Polio, or poliomyelitis, is a disabling and life-threatening disease caused by the **poliovirus**.
•The virus **spreads from person to person** and can infect a person's spinal cord, causing paralysis.

Transmission

•Poliovirus is very contagious and spreads through person-to-person contact.
•It lives in an infected person's throat and intestines.
Poliovirus only infects people. It enters the body through the mouth and spreads through:
•Contact with the feces of an infected person.
•Droplets from a sneeze or cough of an infected person (less common).

Prevention & Treatment

There are two types of vaccine that can prevent polio:
•**Inactivated poliovirus vaccine (IPV)** (Salk vaccine) given as an injection in the leg or arm, depending on the patient's age.
•**Oral poliovirus vaccine (OPV)** (Sabin vaccine)is still used throughout much of the world.
Polio vaccine protects children by preparing their bodies to fight the poliovirus. Almost all children (99 children out of 100) who get all the recommended doses of the inactivated polio vaccine will be protected from polio.

THE VIRUS

Polio is caused by a human enterovirus called the poliovirus. Polio can interact in its host in two ways:

- Infection not including the central nervous system, which causes a minor illness with mild symptoms
- Infection including the central nervous system, which may cause paralysis

Less than 1% of poliovirus infections result in paralysis. The virus is most often spread by the faecal-oral route. Poliovirus enters through the mouth and multiplies in the intestine. Infected individuals shed poliovirus into the environment for several weeks, where it can spread rapidly through a community, especially in areas of poor sanitation.

Testing for polioviruses

All cases of acute flaccid paralysis (AFP) among children under fifteen years of age are reported and tested for wild poliovirus or vaccine-derived polioviruses within 48 hours of onset. AFP is caused by a range of factors. The Global Polio Laboratory Network tests upwards of 100,000 AFP samples a year, of which a very small portion are positive for poliovirus.

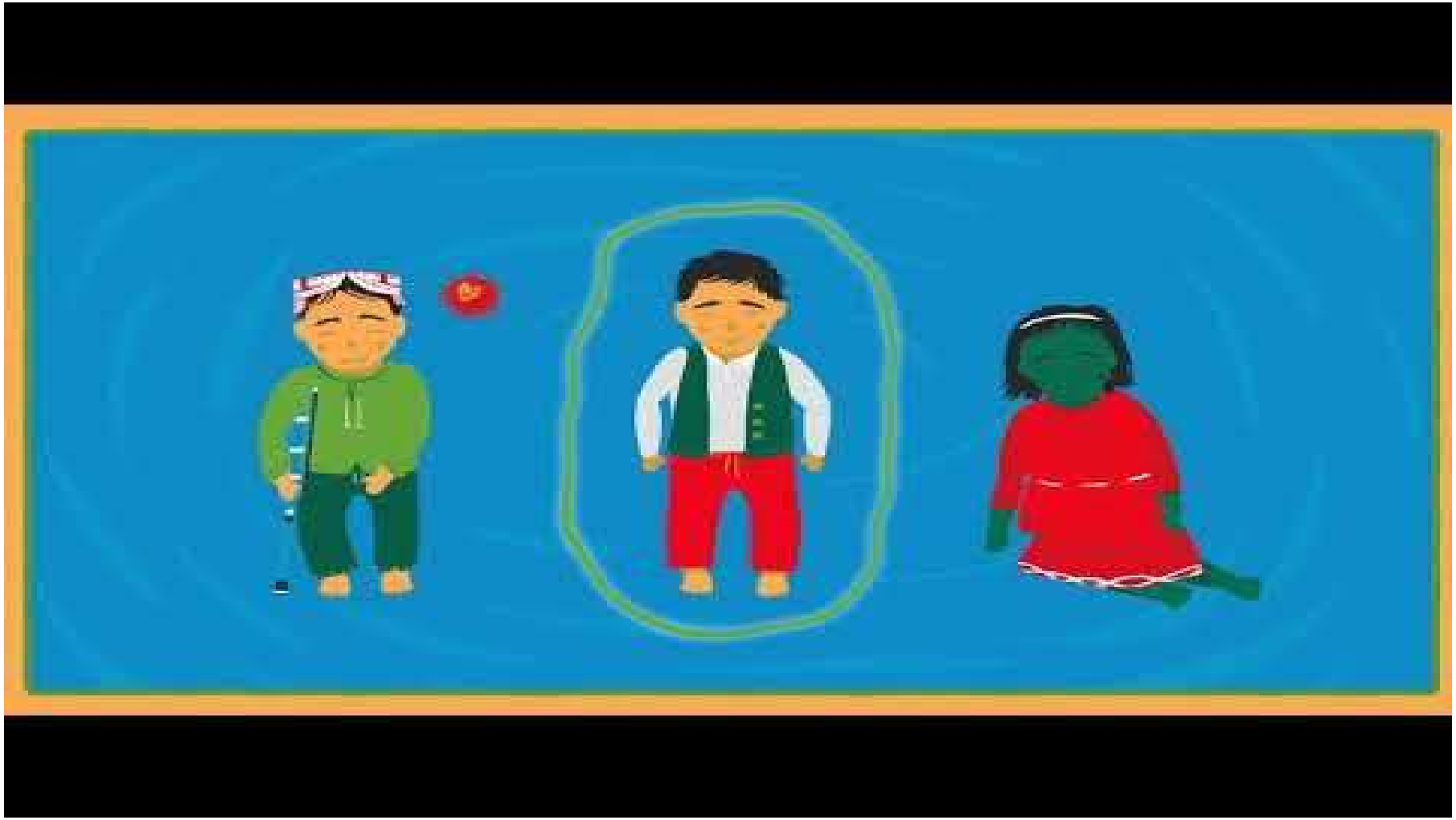
THE VACCINES

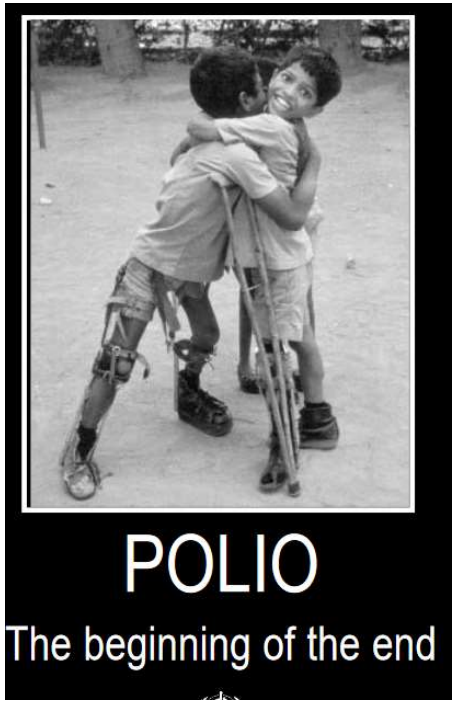
The development of effective vaccines to prevent paralytic polio was one of the major medical breakthroughs of the 20th century. The Global Polio Eradication Initiative uses two types of vaccine to stop polio transmission – inactivated polio vaccine (IPV) and oral polio vaccine (OPV).

If enough people in a community are immunized against polio, the virus will be deprived of susceptible hosts and will die out. High levels of vaccination coverage must be maintained to stop transmission and prevent outbreaks occurring. The Global Polio Eradication Initiative is constantly assessing the optimal use of the different types of vaccine to prevent paralytic polio and stop poliovirus transmission in different areas of the world.

In 1997 in one week 250.000 of childrens were vaccinated in China, India, Buthan, Pakistan, Bangladesh, Thailandia, Vietnam and Birmania.
«Immunization days» reached about 500 millions of childrens!
Thanks to this effort, polio incidence is less than 1%

https://polioeradication.org/polio-today/polio-prevention/the-vaccines/





POLIO GLOBAL ERADICATION INITIATIVE

Global Polio Eradication Initiative
World Health Organization
Avenue Appia 20,
1211 Geneva 27
Switzerland

DONATE
ACRONYMS
TERMS OF USE
SITEMAP
CONTACT

EVERY LAST CHILD

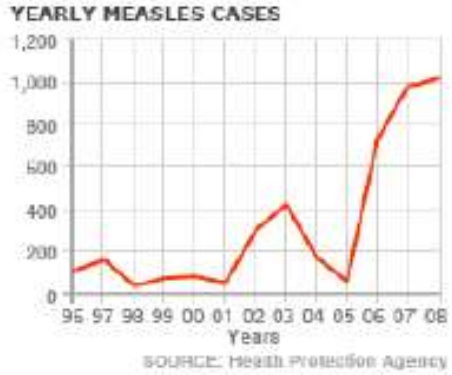
World Health Organization · Rotary · CDC · unicef · Bill & Melinda Gates foundation · Gavi The Vaccine Alliance

https://polioeradication.org/polio-today/polio-prevention/the-vaccines/

Cessation of vaccination can increase disease incidence

Reduced MMR Equals More Measles

Reduced uptake of the MMR vaccine, fueled no doubt by anti-vaccine propaganda, has resulted in a recent **significant increase in Measles in the UK** as shown by the graph on the right. And despite what the anti-vaccine twits will tell you, Measles can be a very serious disease. According to the **CDC**:

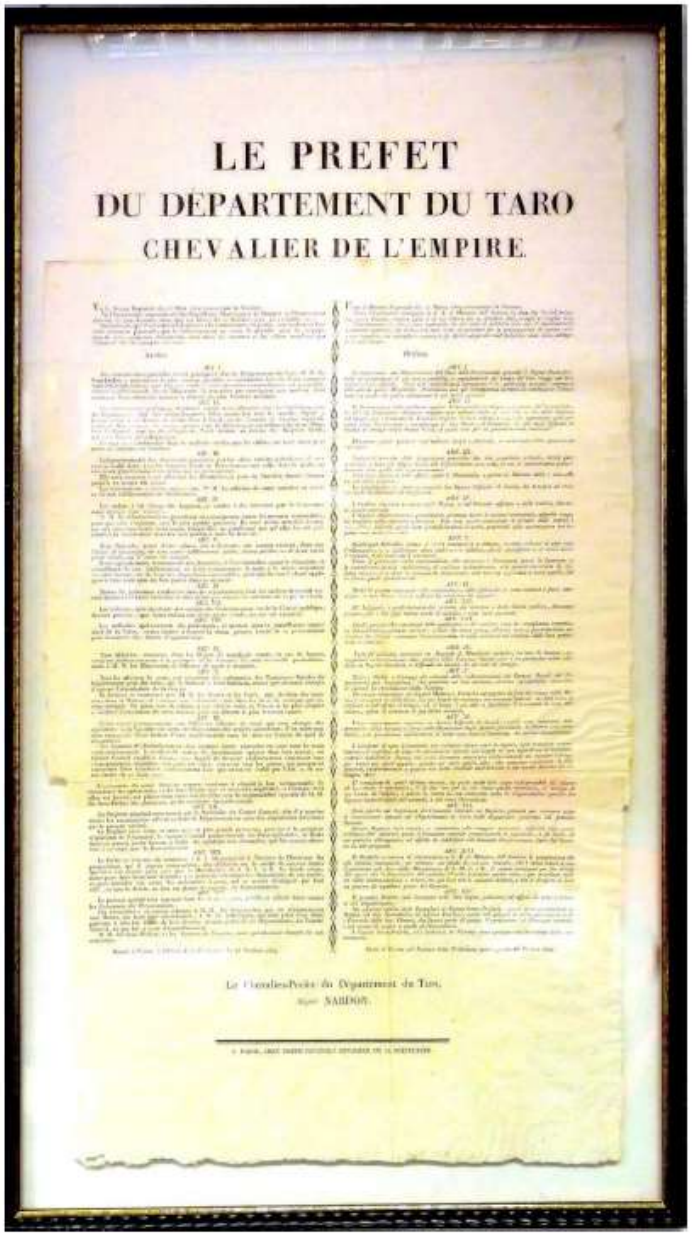


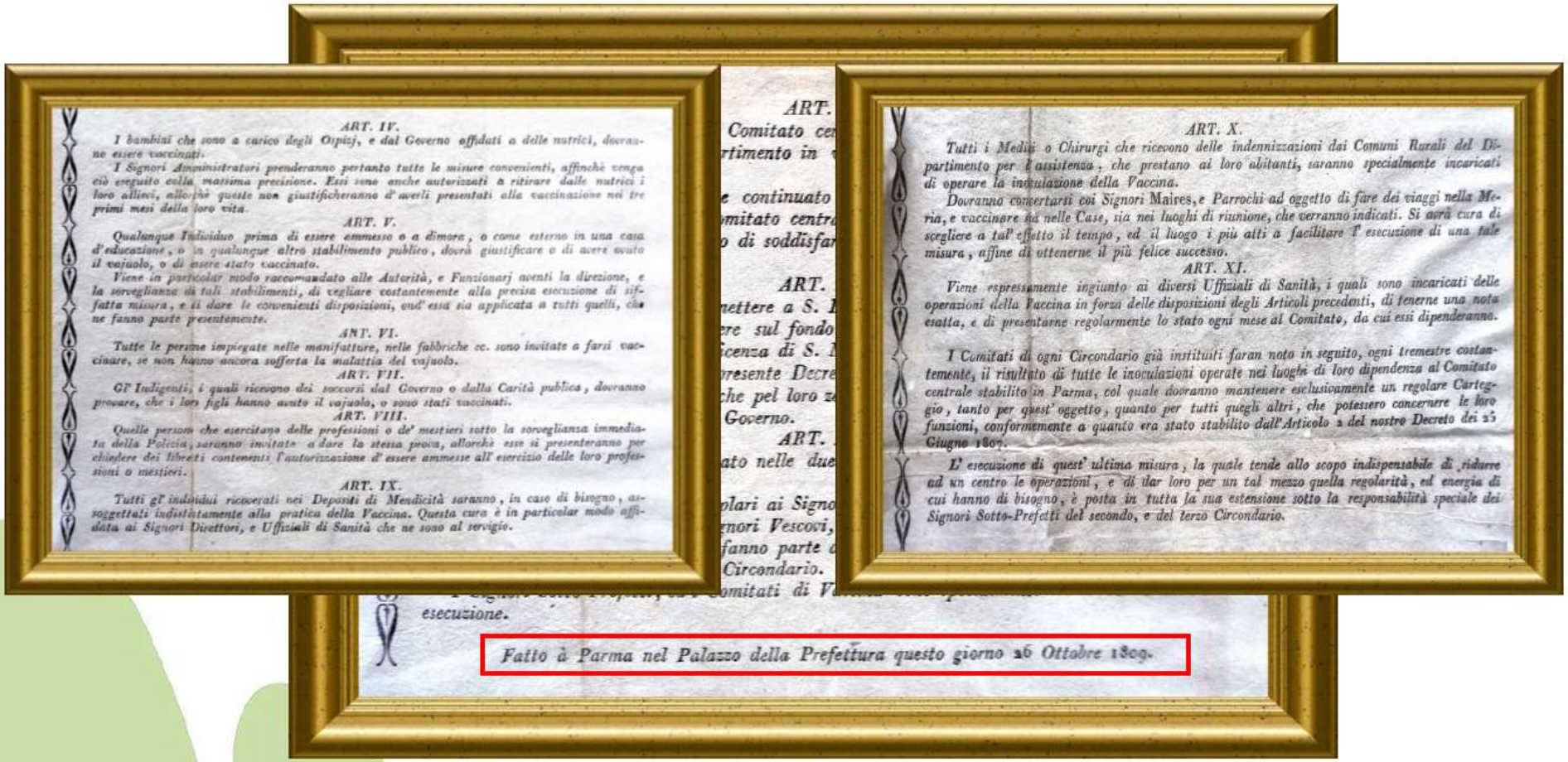
> As many as one out of 20 children with measles gets pneumonia, and about one child in every 1,000 who get measles will develop encephalitis. (This is an inflammation of the brain that can lead to convulsions, and can leave your child deaf or mentally retarded.) For every 1,000 children who get measles, one or two will die from it.

MMR= measles, mumps, and rubella

Una volta era «semplice» organizzare una campagna vaccinale.. La chiamata attiva non era nemmeno necessaria!!

Un unico vaccino e obbligatorio!


LE PREFET
DU DÉPARTEMENT DU TARO
CHEVALIER DE L'EMPIRE



ART. IV.

I bambini che sono a carico degli Ospizj, e dal Governo affidati a delle nutrici, dovranno essere vaccinati.

I Signori Amministratori prenderanno pertanto tutte le misure convenienti, affinchè venga ciò eseguito colla massima precisione. Essi sono anche autorizzati a ritirare dalle nutrici i loro allievi, allorchè queste non giustificheranno d' averli presentati alla vaccinazione nei tre primi mesi della loro vita.

ART. V.

Qualunque Individuo prima di essere ammesso o a dimora, o come esterno in una casa d' educazione, o in qualunque altro stabilimento publico, dovrà giustificare o di avere avuto il vajuolo, o di essere stato vaccinato.

Viene in particolar modo raccomandato alle Autorità, e Funzionarj aventi la direzione, e la sorveglianza di tali stabilimenti, di vegliare costantemente alla precisa esecuzione di siffatta misura, e di dare le convenienti disposizioni, end' essa sia applicata a tutti quelli, che ne fanno parte presentemente.

ART. VI.

Tutte le persone impiegate nelle manifatture, nelle fabbriche ec. sono invitate a farsi vaccinare, se non hanno ancora sofferta la malattia del vajuolo.

ART. VII.

Gl' Indigenti, i quali ricevono dei soccorsi dal Governo o dalla Carità publica, dovranno provare, che i loro figli hanno avuto il vajuolo, o sono stati vaccinati.

ART. VIII.

Quelle persone che esercitano delle professioni o de' mestieri sotto la sorveglianza immediata della Polizia, saranno invitate a dare la stessa prova, allorchè esse si presenteranno per chiedere dei libretti contenenti l'autorizzazione d' essere ammesse all' esercizio delle loro professioni o mestieri.

ART. IX.

Tutti gl' individui ricoverati nei Depositi di Mendicità saranno, in caso di bisogno, assoggettati indistintamente alla pratica della Vaccina. Questa cura è in particolar modo affidata ai Signori Direttori, e Uffiziali di Sanità che ne sono al servigio.

ART. X.

Tutti i Medici o Chirurgi che ricevono delle indennizzazioni dai Comuni Rurali del Dipartimento per l' assistenza, che prestano ai loro abitanti, saranno specialmente incaricati di operare la inoculazione della Vaccina.

Dovranno concertarsi coi Signori Maires, e Parrochi ad oggetto di fare dei viaggi nella Meria, e vaccinare sia nelle Case, sia nei luoghi di riunione, che verranno indicati. Si avrà cura di scegliere a tal' effetto il tempo, ed il luogo i più atti a facilitare l' esecuzione di una tale misura, affine di ottenerne il più felice successo.

ART. XI.

Viene espressamente ingiunto ai diversi Uffiziali di Sanità, i quali sono incaricati delle operazioni della Vaccina in forza delle disposizioni degli Articoli precedenti, di tenerne una nota esatta, e di presentarne regolarmente lo stato ogni mese al Comitato, da cui essi dipenderanno.

I Comitati di ogni Circondario già instituiti faran noto in seguito, ogni tremestre costantemente, il risultato di tutte le inoculazioni operate nei luoghi di loro dipendenza al Comitato centrale stabilito in Parma, col quale dovranno mantenere esclusivamente un regolare Carteggio, tanto per quest' oggetto, quanto per tutti quegli altri, che potessero concernere le loro funzioni, conformemente a quanto era stato stabilito dall' Articolo 2 del nostro Decreto dei 25 Giugno 1807.

L' esecuzione di quest' ultima misura, la quale tende allo scopo indispensabile di ridurre ad un centro le operazioni, e di dar loro per un tal mezzo quella regolarità, ed energia di cui hanno di bisogno, è posta in tutta la sua estensione sotto la responsabilità speciale dei Signori Sotto-Prefetti del secondo, e del terzo Circondario.

esecuzione.

Fatto à Parma nel Palazzo della Prefettura questo giorno 26 Ottobre 1809.

Obbligo vaccinale

1939 ▶ Obbligo **vaccinazione antidifterica**

1966 ▶ Obbligo **vaccinazione antipolio**

1968 ▶ Obbligo **vaccinazione antitetanica**

1981 ▶ Abolizione **vaccinazione antivaiolosa**

1991 ▶ Obbligo **vaccinazione antiepatite B**

Piano Nazionale in fase di approvazione

PIANO NAZIONALE PREVENZIONE VACCINALE - PNPV 2020-2025

Calendario Nazionale Vaccinale per età

	2 mesi	3 mesi	4 mesi	5 mesi	6 mesi	10 mesi	12 mesi	13/14 mesi	5 anni	6 anni	11 anni	12-18 anni	19-59 anni	50-64 anni	60 anni	65 anni	66 anni e più
Esavalente: Difterite, Tetano, Pertosse, Poliomielite, Epatite B, Haemophilus influenzae di tipo b (DTaP-IPV-HBV-Hib)	■		■			■											
Rotavirus (RV)	■	■	1	■													
Pneumococco coniugato (PCV)	■		■			■										■	2
Meningococco B (MenB)	■	■	3	■				■									
Morbillo, Parotite, Rosolia, Varicella (MMRV o MMR+V)							4		■								
Meningococco ACWY (MenACWY)							5					■					
Difterite, Tetano, Pertosse, Poliomielite (DTap-IPV/dTap-IPV)									6			7					
Papillomavirus (HPV)											8						
Difterite, Tetano, Pertosse adulto (dTaP)													9				
Influenza (FLU)					10										11		
Herpes Zoster (HZV)																12	

■ Vaccinazione raccomandata per età

VACCINES

Able to induce specific immune protection against infectious agents

(…and not only)

Among the major successes of Medicine to contrast infectious diseases :

mass protection

eradication

Long experience (Jenner 1796), millions of administered doses, better knowledge of the risk/advantage effects than for many drugs

Principle of vaccination: Immunological memory

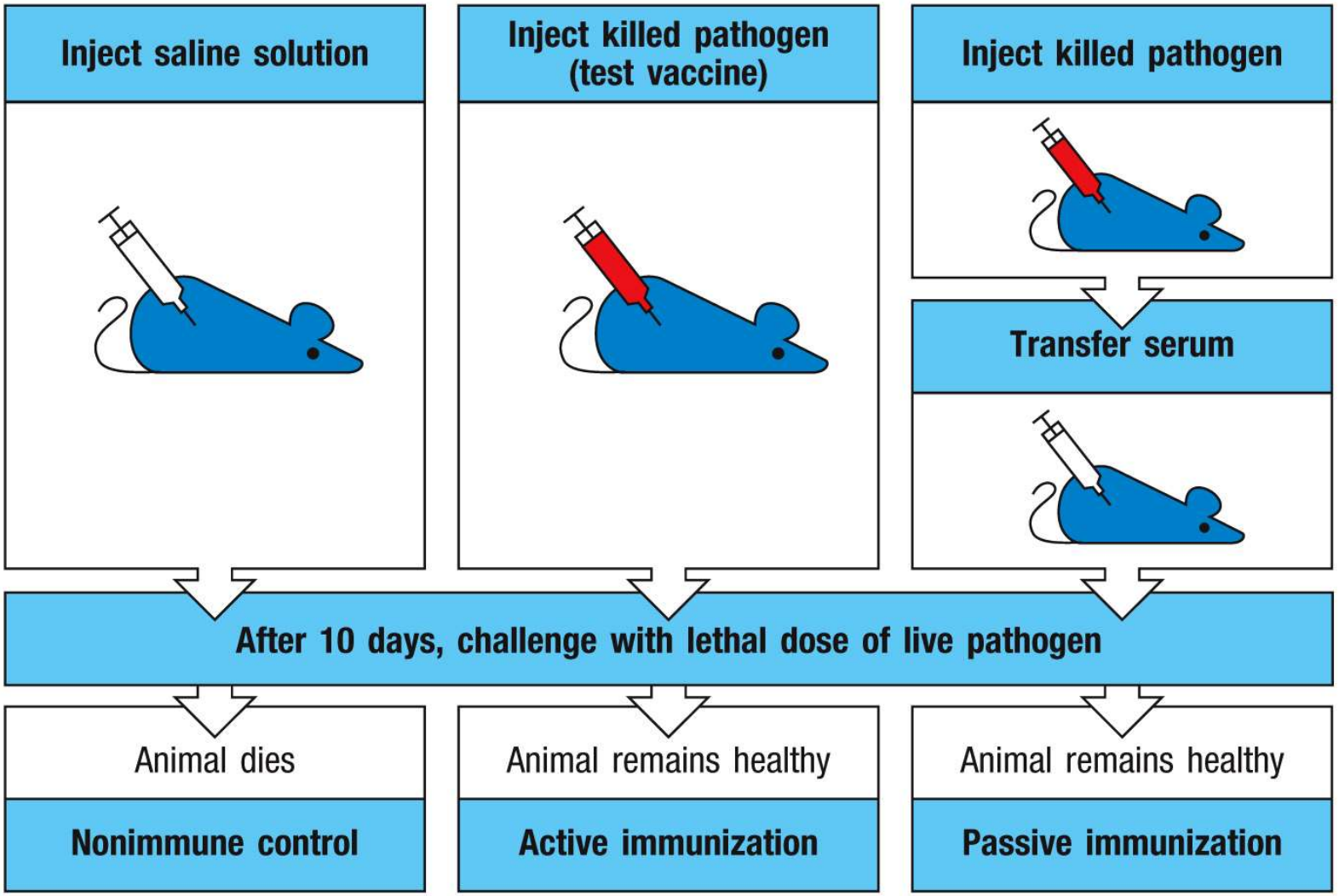


Figure A.40 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Immunological memory

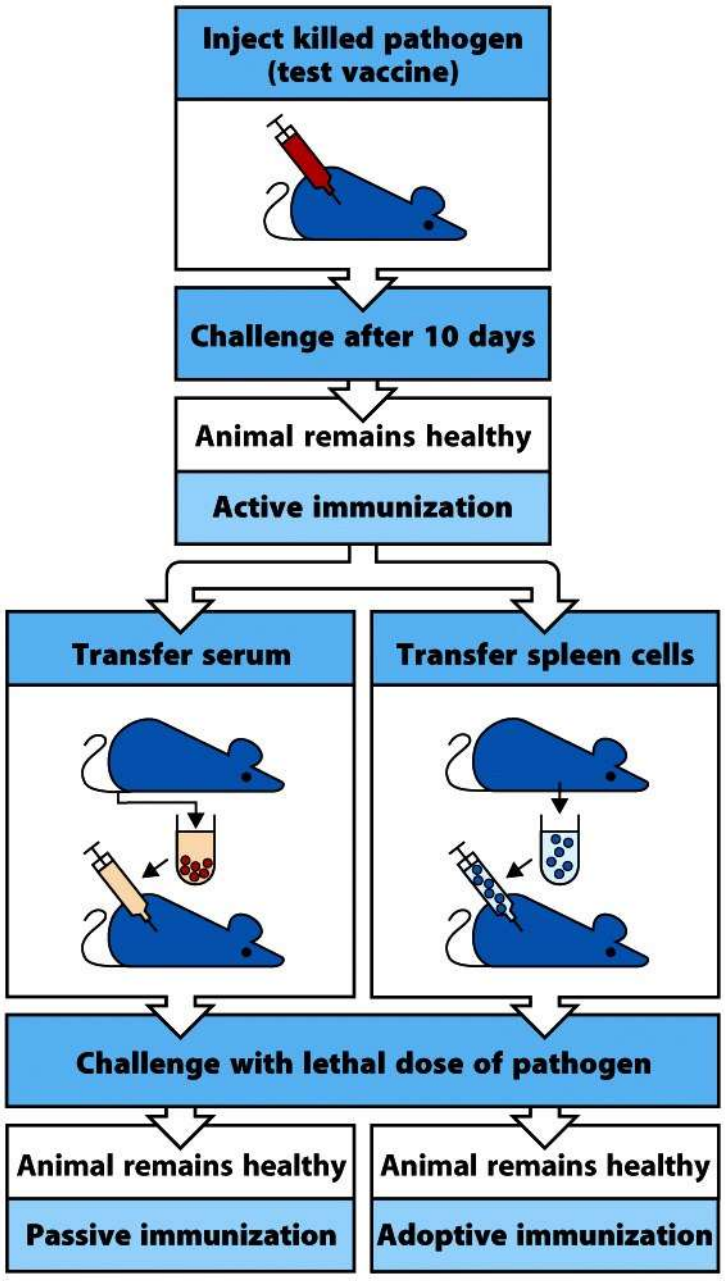


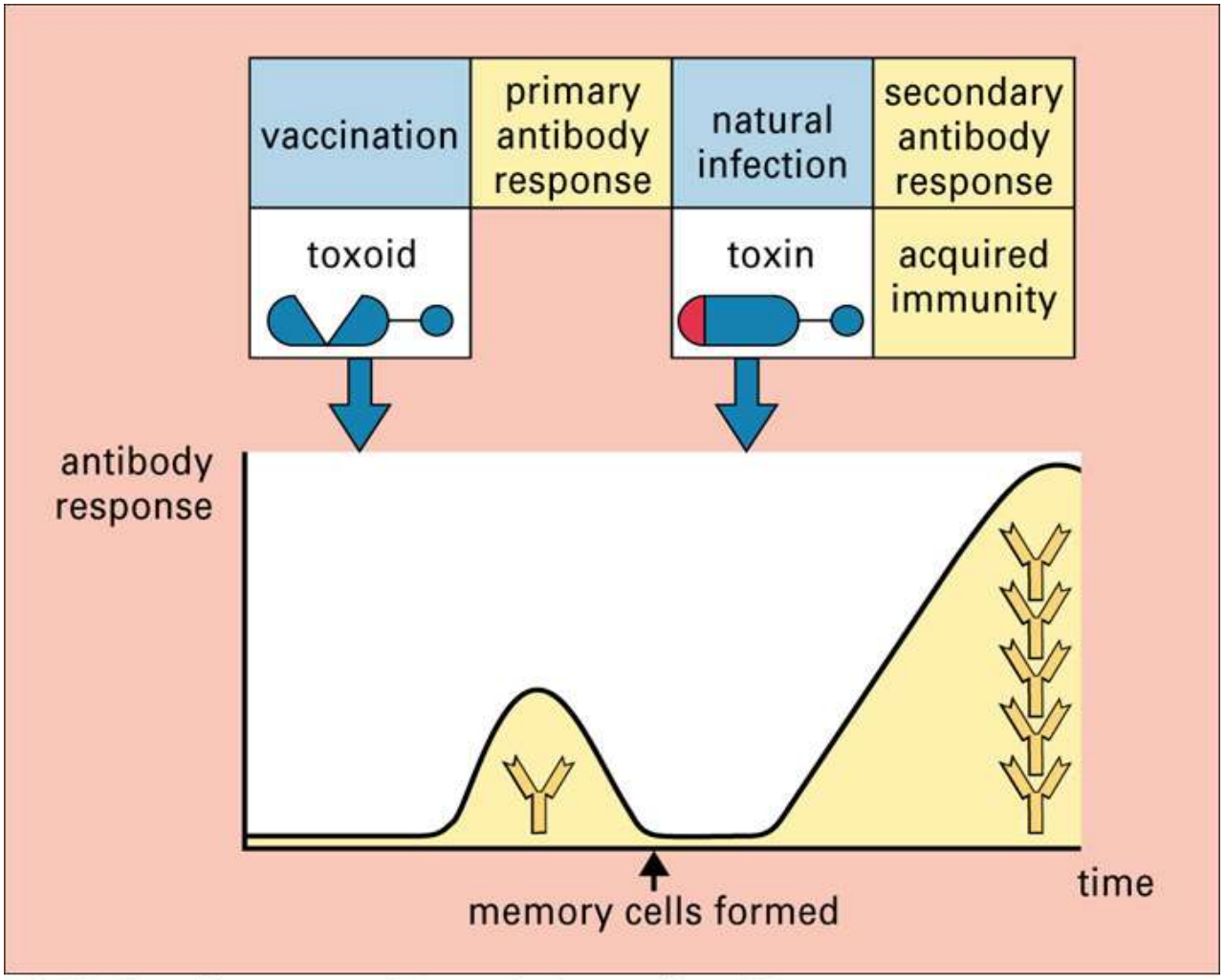
Figure A-42 Immunobiology, 7ed. (© Garland Science 2008)

Naive cells do not confer memory

Effector cells might confer memory by originating memory cells after adoptive transfer but the process is not very efficient (more cells needed since many cells will die)

Memory cells effectively confer memory

Basic principle of vaccination: immunological memory



- Gli anticorpi prodotti durante una risposta immunitaria primaria persistono per diversi mesi e forniscono protezione
- Bassi livelli di anticorpi specifici per il patogeno vengono mantenuti da plasmacellule a lunga vita residenti nel midollo osseo

Principles of Vaccination

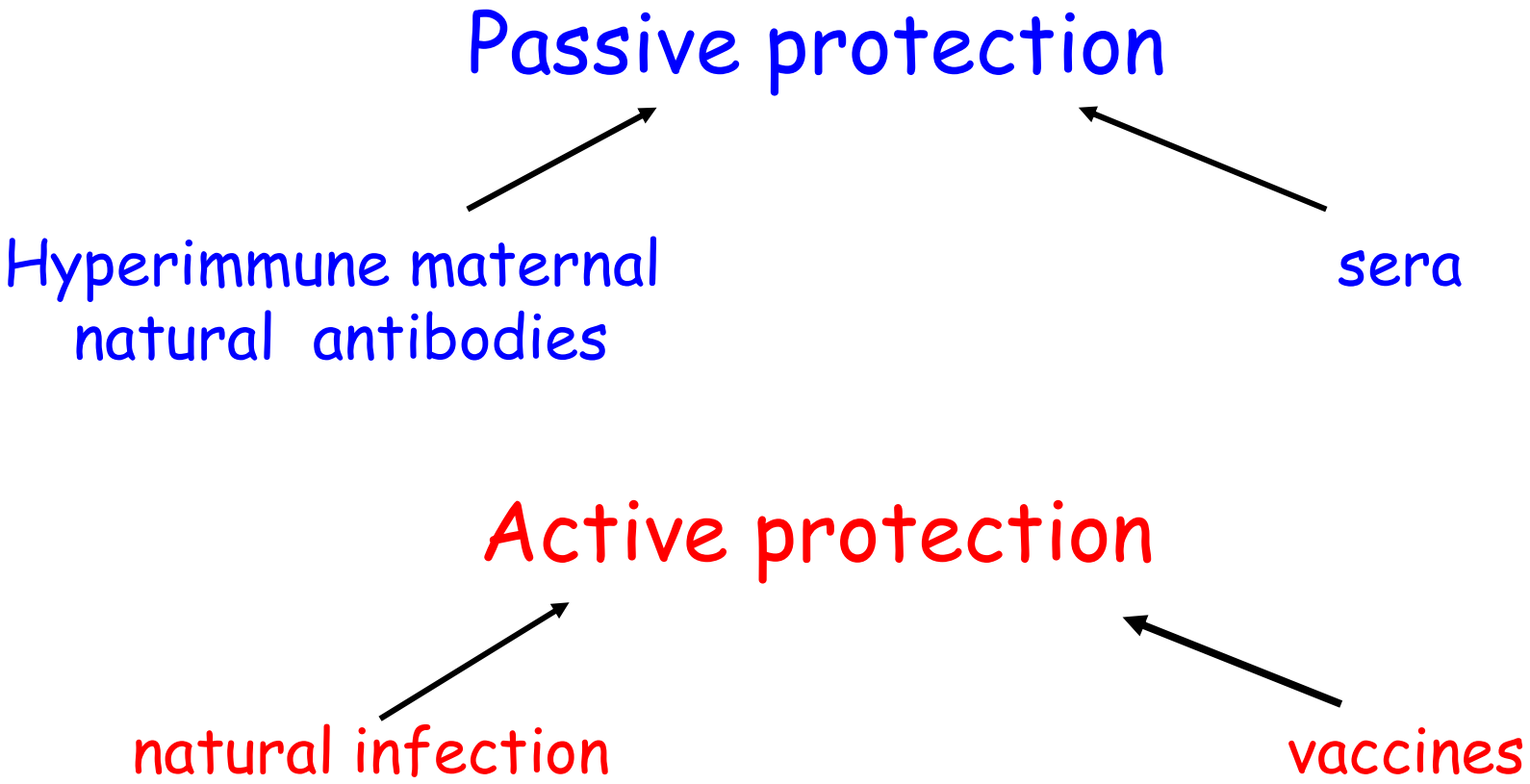
Active Immunity

- Protection produced by the person's own immune system
- Usually permanent

Passive Immunity

- Protection transferred from another person or animal as antibody
- Temporary protection that wanes with time

Acquisition of Immunity



Passive Immunization

(rapid but of short duration: 4-6 weeks)

Product	Source	Protection
Normal Immunoglobulins of human origin	Pool of unselected donors	Ipo/agammaglob Hepatitis A
Hyperimmune Immunoglobulins	Immunized or convalescent donors with high specific antibody titer	Measles, Parotitis (mumps), Rubella, Chicken pox, B Hepatitis, Rabies, Diphtheria, Tetanus, Pertussis
Heterologous sera	Animals (horse, ox) immunized with specific antigens	Botulism, gaseous Gangrene, snake Poisons

Different types of immunization

Passive Immunization

-- direct transfer of protective antibodies

-- no immunological memory

Active Immunization

-- activation of immune response

-- immunological memory

Therapeutic Immunization

-- treat existing disease

Examples of Passive Immunotherapies

Disease	Agent
Black widow spider bite	Horse antivenin
Botulism	Horse antitoxin
Diphtheria	Horse antitoxin
Hepatitis A and B	Pooled human immune gamma globulin
Measles	Pooled human immune gamma globulin
Rabies	Pooled human immune gamma globulin
Snake bite	Horse antivenin
Tetanus	Pooled human immune gamma globulin or horse antitoxin

from Kuby Immunology 4th ed Table 18-2

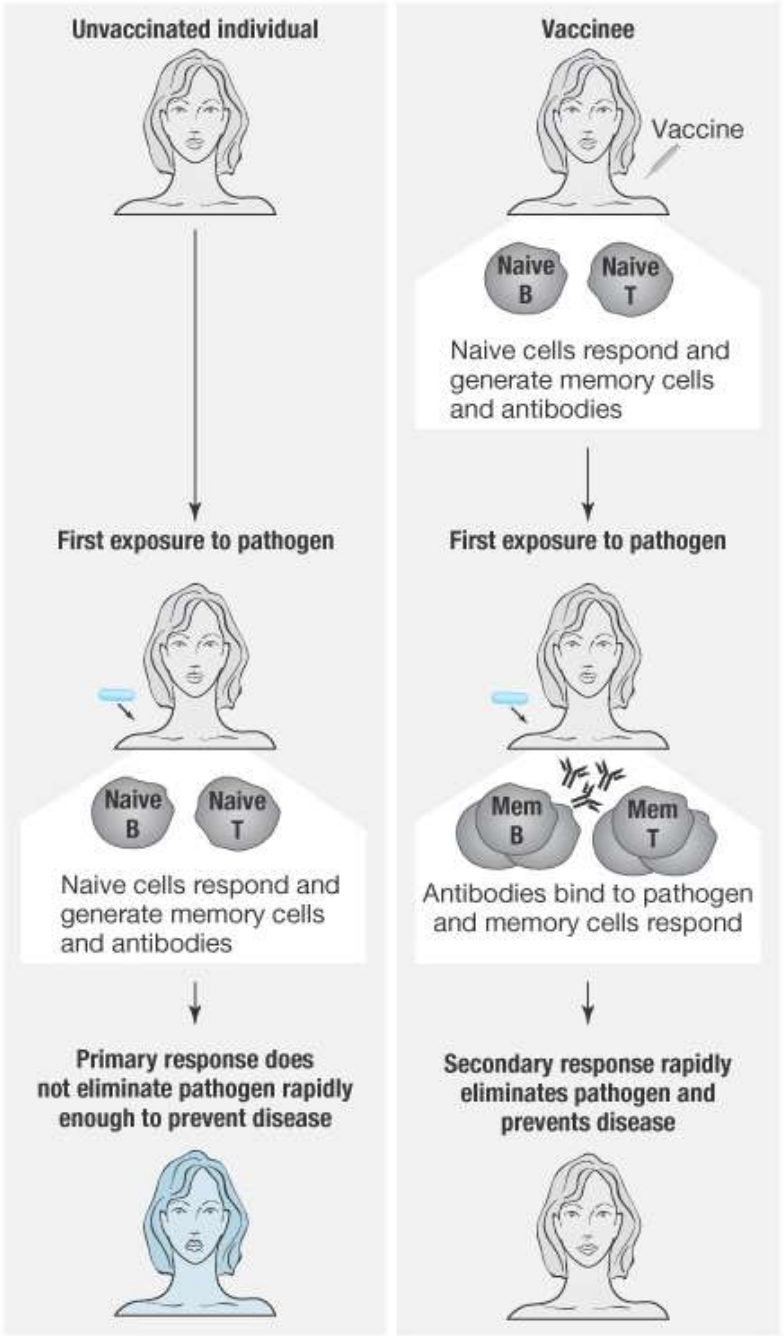
Active Vaccination: What are some important considerations in the design of vaccines?

Characteristics of pathogen & disease

- Intra- vs extra-cellular
- short or long incubation
- acute or chronic disease
- Antigenic stability
- route of infection

Characteristics of vaccine

- efficacy
- appropriate response
- booster
- safety
- stability, cost



Active Immunization

(slow but prolonged)

VACCINES

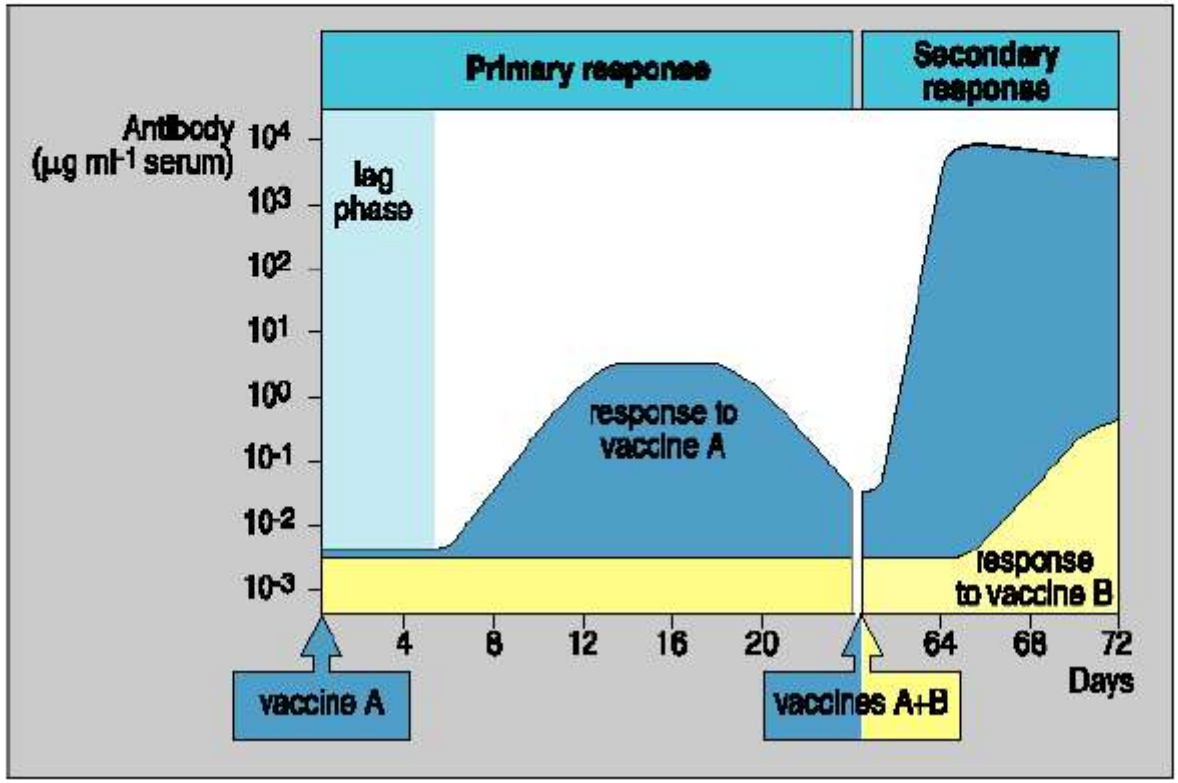
Caratteristiche di un buon vaccino

Features of effective vaccines	
Safe	Vaccine must not itself cause illness or death
Protective	Vaccine must protect against illness resulting from exposure to live pathogen
Gives sustained protection	Protection against illness must last for several years
Induces neutralizing antibody	Some pathogens (such as polio virus) infect cells that cannot be replaced (e.g., neurons). Neutralizing antibody is essential to prevent infection of such cells
Induces protective T cells	Some pathogens, particularly intracellular, are more effectively dealt with by cell-mediated responses
Practical considerations	Low cost per dose Biological stability Ease of administration Few side-effects

Figure 16.23 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Humoral responses are specifically enhanced upon reexposure to the same (priming) antigen. This secondary response shows memory to the initial antigen.

Figure 1.26



Vaccination is an attempt to generate immunological memory without disease pathology

- Memory is induced through immune recognition of vaccine antigens.
- Immune memory allows an accelerated humoral and cellular responses if the vaccine antigen is re-encountered.
- Immune recognition leads to:
    - Neutralization of the infectious agent before it can enter cells
    - Destruction of infected cells before they multiply
    - Suppression of the spread of the infectious agent to other cells

Mechanism of vaccine mediated protection:

- Produce B and T cell memory without disease
- B cell memory in the form of quiescent antigen specific recirculating cells.
- B cell memory in the form of long-lived antibody secreting cells residing in the bone marrow
- T (CD4) cells in the form of recirculating and bone marrow sequestered quiescent cells

Principles of Vaccination

Antigen

- A live or inactivated substance (e.g., protein, polysaccharide, mRNA) capable of producing an immune response

Passive Immunity

- Transfer of antibody produced by one human or other animal to another
- Transplacental most important source in infancy
- Temporary protection

Sources of Passive Immunity

- Almost all blood or blood products
- Homologous pooled human antibody (immune globulin)
- Homologous human hyperimmune globulin
- Heterologous hyperimmune serum (antitoxin)

The 5 types of vaccine

- **Live attenuated** vaccine
- **Inactivated/killed** vaccine
- **Toxoid** vaccine
- **Subunit** vaccine
- **DNA/mRNA** vaccines

WHICH VACCINES….

TYPE	ADVANTAGES	DISADVANTAGES
Inactivated	No virulence Rare controindications Thermostability No interference with other vaccines	Multiple doses Antigen amounts Elevated cost Immunity duration No mucosal response
Attenuated	Single dose Antigen amounts Low cost Immunity duration IgG and IgA response Cellular response	Virulentation More side effects Thermolability Interference with other vaccines
Antigenic fragments	Absence of useless antigens	Difficulty in preparation Low efficacy in infants

Live attenuated vaccines

- First to be developed
- Based on pathogens that were previously **attenuated** in laboratory (i.e. by heating or in vitro culture)
- Capable of replicating in vaccinated individuals > optimal immune response
- Since they are based on attenuated pathogens, they do not cause disease in immunocompetent individuals
  > not suitable for immunocompromised individuals

Live attenuated vaccines

Bacterial

Tuberculosis (BCG, *Mycobacterium tuberculosis*)

Only vaccine available (~1920)
New ongoing research
Not part of Italian vaccination schedule

Important issue: safety

Viral

Poliomyelitis (OPV, Oral Polio Vaccine, *Poliovirus)*

Measles, Mumps, Rubella, Varicella (MMRV)*

Yellow fever

Rotavirus (recommended)

Part of Italian vaccination schedule

*Morbillo, Orecchioni, Rosolia, Varicella

Inactivated vaccines

- Based on pathogens that were previously **inactivated** in laboratory

- **Not** capable of replicating in vaccinated individuals
  > weaker immune response than live vaccines, multiple vaccinations are required to achieve protection
  > higher stability and safety profile compared to live vaccines

Inactivated vaccines

Bacterial

Pertussis (wP, *Bordella pertussis*)

Replaced by aP, a subunit vaccine

Viral

Poliomyelitis (IPV, Inactivated Polio Vaccine, *Poliovirus)*

Hepatitis A (HAV)

Part of Italian vaccination schedule

Also the seasonal influenza vaccines are inactivated vaccines

Inactivated Vaccines

- Cannot replicate
- Generally not as effective as live vaccines
- Generally require 3-5 doses
- Immune response mostly humoral
- Antibody titer diminishes with time

Inactivated Vaccines

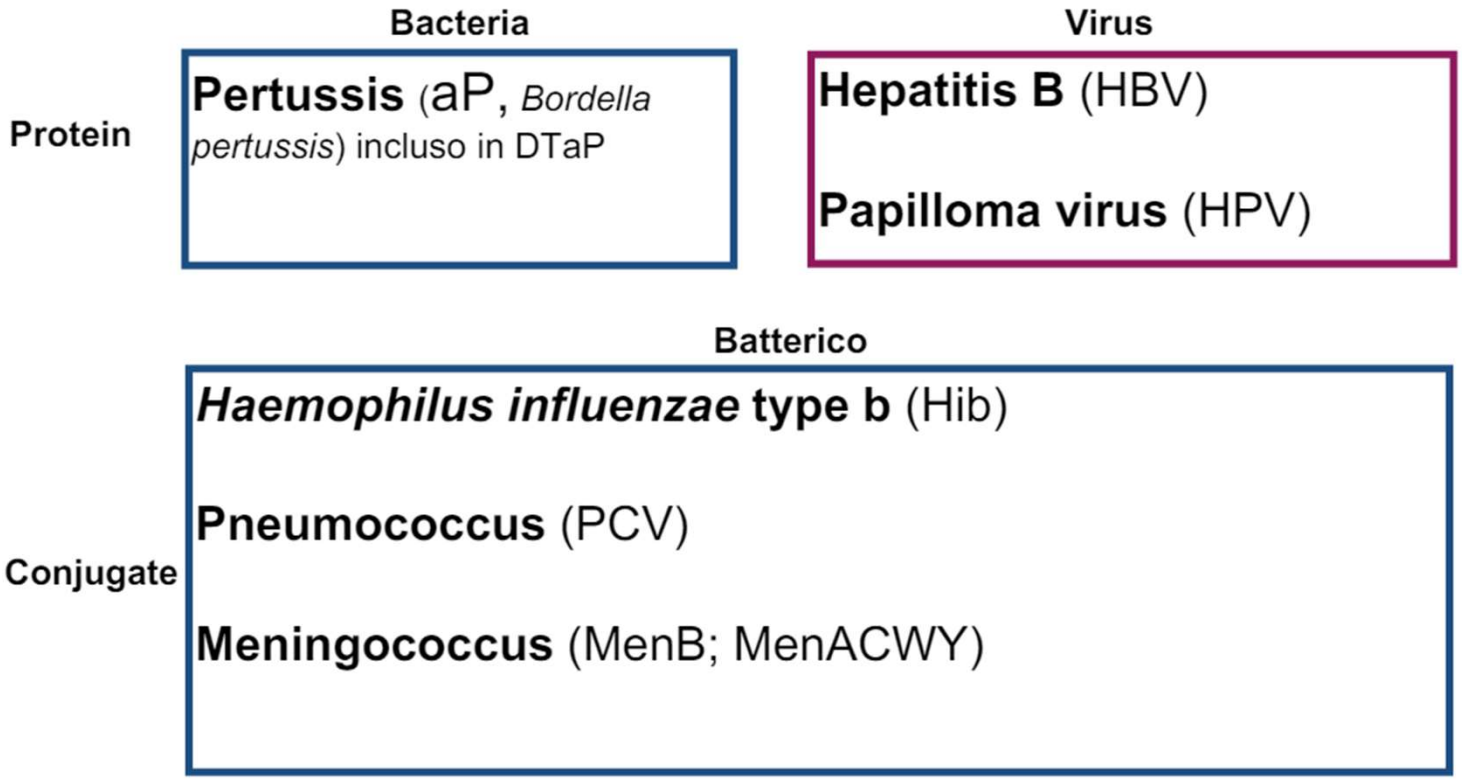
Fractional vaccines

- Subunit — hepatitis B, influenza, acellular pertussis, (Lyme)
- Toxoid — diphtheria, tetanus

Toxin-based vaccines

organism	vaccine	remarks
Clostridium tetani	inactivated toxin (formalin)	3 doses, alum-precipitated; boost every 10 years
Corynebacterium diphtheriae		usually given with tetanus
Vibrio cholerae	toxin, B subunit	sometimes combined with whole killed organisms
Clostridium perfringens	inactivated toxin (formalin)	for newborn lambs

Subunit vaccines



Polysaccharide Vaccines

Pure polysaccharide

- pneumococcal
- meningococcal
- *Salmonella* Typhi (Vi)

Conjugate polysaccharide

- *Haemophilus influenzae* type b
- pneumococcal

Vaccini contro batteri patogeni capsulati

- Molti batteri patogeni possiedono un capsula esterna composta da polisaccaridi (es. *S. pneumoniae, N. meningitidis, H. influenzae, E. coli*…)
- La capsula previene la fissazione del complemento per via alternativa
- Solo se si formano anticorpi che si legano alla capsula si ha la fissazione del complemento, che elimina i batteri
- L'obiettivo della vaccinazione contro tali batteri è quello di produrre anticorpi capaci di fissare il complemento che si leghino alla capsula

Pure Polysaccharide Vaccines

- Not consistently immunogenic in children <2 years of age
- No booster response
- Antibody with less functional activity
- Immunogenicity improved by conjugation

Vaccini coniugati a proteine: Effetto aptene-carrier

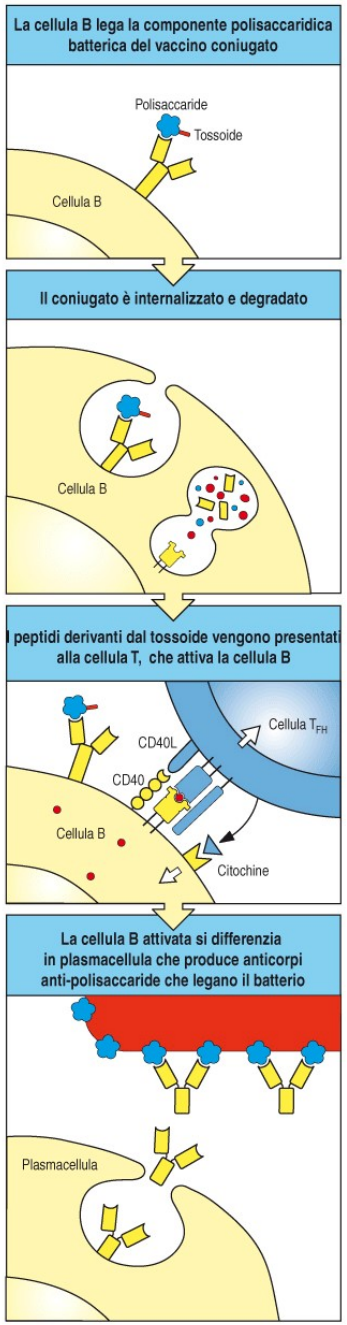


Figura 11.20 Complessi molecolari riconosciuti da cellule B e cellule T rendono i vaccini efficaci. Il primo pannello mostra l'immunoglobulina di superficie di una cellula B vergine che lega un epitopo polisaccaridico di un vaccino costituito da un polisaccaride di *Haemophilus* (blu) coniugato al tossoide tetanico (rosso). Ciò comporta l'endocitosi mediata da recettori del coniugato e la sua degradazione in endosomi e lisosomi, come mostrato nel secondo pannello. Peptidi derivati dalla degradazione della parte del tossoide tetanico del coniugato sono legati da molecole MHC di classe II e presentati sulla superficie della cellula B. Nel terzo pannello, il recettore di una cellula T_{FH} riconosce il complesso peptide:MHC. Questo induce la cellula T a secernere citochine che attivano le cellule B, che si differenziano in plasmacellule, che producono anticorpi protettivi contro il polisaccaride di *Haemophilus* (quarto pannello).

Safety problems associated to vaccines

type of vaccine	potential safety problems	examples
attenuated vaccines	reversion to wild type	especially polio Types 2 and 3
	severe disease in immunodeficient patients	vaccinia, BCG, measles
	persistent infection	varicella-zoster
	hypersensitivity to viral antigens	measles
	hypersensitivity to egg antigens	measles, mumps
killed vaccines	vaccine not killed	polio accidents in the past
	yeast contaminant	hepatitis B
	contamination with animal viruses	polio
	contamination with endotoxin	pertussis

Figura 11.25 Malattie per le quali sono disponibili vaccini. Non tutti questi vaccini sono ugualmente efficaci e non tutti sono usati di routine.

Vaccini disponibili per malattie infettive nell'uomo			
Malattie batteriche	**Tipi di vaccini**	**Malattie virali**	**Tipi di vaccini**
Difterite (*Corynebacterium diphtheriae*)	Tossoide	Febbre gialla	Virus attenuato
Tetano (*Clostridium tetani*)	Tossoide	Morbillo	Virus attenuato
Pertosse (*Bordetella pertussis*)	Batteri uccisi. Vaccino a subunità composto da tossoide della pertosse	Parotite	Virus attenuato
Febbre paratifoide (*Salmonella paratyphi*)	Batteri uccisi	Rosolia	Virus attenuato
Tifo epidemico (*Rickettsia prowazekii*)	Batteri uccisi	Poliomielite	Virus attenuato (Sabin) o virus ucciso (Salk)
Colera (*Vibrio cholerae*)	Batteri uccisi o estratto cellulare	Varicella	Virus attenuato
Peste (*Yersinia pestis*)	Batteri uccisi o estratto cellulare	Influenza	Virus inattivato
Tubercolosi (*Mycobacterium tuberculosis*)	Ceppo bovino attenuato di *Mycobacterium tuberculosis* (BCG)	Rabbia	Virus inattivato (umano) Virus attenuato (cani e altri animali) Virus vaccinico vivo ricombinante (animali)
Febbre tifoide (*Salmonella typhi*)	Vaccino a subunità polisaccaridiche Vaccino orale vivo attenuato	Epatite A	Vaccino a subunità (antigene dell'epatite ricombinante)
Meningite (*Neisseria meningitidis*)	Polisaccaride capsulare purificato	Epatite B	Vaccino a subunità (antigene dell'epatite ricombinante)
Polmonite batterica (*Streptococcus pneumoniae*)	Polisaccaride capsulare purificato Polisaccaride coniugato a proteina	Papillomavirus umano	Vaccino a subunità (proteine di rivestimento del virus)
Meningite (*Haemophilus influenzae*)	Polisaccaride di *H. influenzae* coniugato a proteina	Rotavirus	Virus attenuato Virus vivo ricombinante

ADJUVANTS:
substances added to vaccines to increase their immunonogenicity

Mechanism of action:

- Immunomodulation: modifying the cytokine network by selection of Th sub-populations
- Presentation: mantaining the conformational integrity of Ag. An appropriate presentation influences Ab production e.g.: neutralizing Ab, affinity and immune response duration
- CTL induction: favouring the Ag binding to MHC-I and stability of MHC-I/Ag complex
- APC uptake: forming multimolecular Ag aggregates
- "Storage" effect: short or long term

Adiuvanti				
Anno di licenza	**Nome**	**Classe**	**Composizione**	**Bersaglio del vaccino**
1924	Allume	Sale minerale	Fosfato o idrossido di alluminio	Molte malattie infettive
1997	MF59	Emulsione di olio in acqua	Squalene, polisorbato 80, sorbitano trioleato	Influenza
2000	Virosomi	Liposomi	Lipidi, emoagglutinina	Influenza, epatite A
2005	AS04	Agonisti di TLR4 allume-assorbito	Idrossido di alluminio, lipide A monofosforilato	Epatite B, papilloma umano
2009	AS03	Emulsione di olio in acqua	Squalene, polisorbato 80, α-tocoferolo	Influenza
In via di sviluppo	CpG 7909	Agonista di TLR9	Nucleotidi CpG	
	Imidazochinoloni	Agonista di TLR7 e TLR8	Piccole molecole	
	PolyIC	Agonista di TLR3	Analoghi dell'RNA a doppio filamento	
	Pam3Cys	Agonista di TLR2	Lipopeptide	
	Flagellina	Agonista di TLR5	Proteina batterica legata all'antigene	

Figura 11.21 Alcuni adiuvanti usati nei vaccini umani.

Inghilterra: più di 5000 casi di parotite nel 2019. Mai così tanti da dieci anni a questa parte.

a cura di **Andrea Siddu**

pubblicata il 18/02/2020 **aggiornata il 18/02/2020**

Il numero di casi di parotite che si sono registrati in Inghilterra nel 2019 è salito al livello più alto degli ultimi dieci anni: 5042 casi confermati in laboratorio (nel 2018 erano 1066). Secondo il Public Health England il numero sembra destinato ad aumentare nel 2020; sono infatti 546 i casi confermati già nel mese di gennaio 2020, rispetto ai 191 dello stesso periodo del 2019.

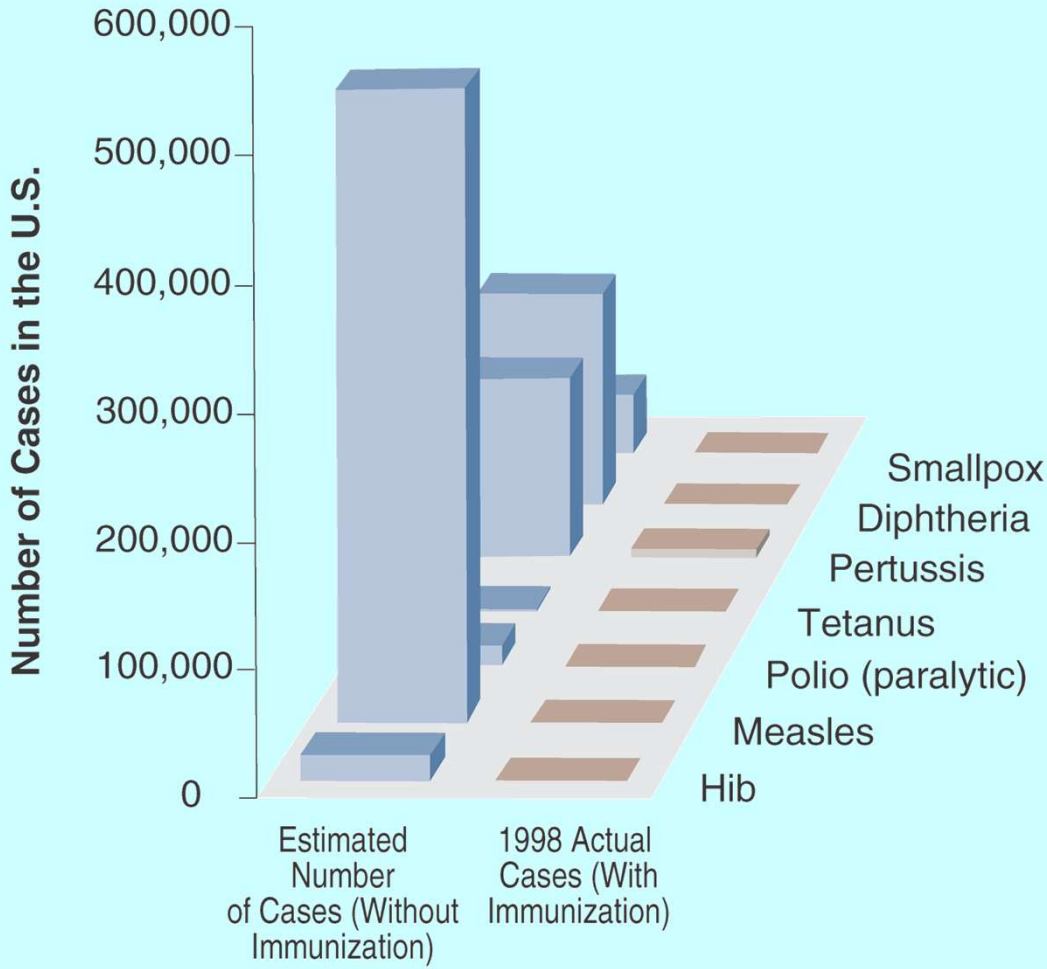
La maggior parte dei focolai di parotite si sono verificati nelle università e nei college, tra le cosiddette **"coorti di Wakefield"**, ovvero giovani adulti nati tra la fine degli anni '90 e l'inizio del 2000, anni in cui, a causa della **nota pubblicazione fraudolenta di Andrew Wakefield** e di tutta la disinformazione conseguente, le coperture per il vaccino MPR (morbillo, parotite, rosolia) in Inghilterra erano scese sotto l'80%.

Sulla questione è intervenuto il Segretario di Stato per la salute e gli affari sociali del Regno Unito, Matt Hancock; le sue parole sono state pubblicate pochi giorni fa dal British Medical Journal (BMJ): *"L'aumento dei casi di parotite è allarmante ed è l'ennesimo esempio dei danni a lungo termine causato dalla disinformazione sulle vaccinazioni. La scienza dimostra che i vaccini sono la migliore forma di difesa contro una serie di malattie potenzialmente mortali e sono più sicuri ed efficaci che mai. Chi sostiene il contrario, mette a rischio la vita delle persone".*

Sempre secondo il BMJ, il Governo Inglese presto renderà note le prossime strategie vaccinali, che comprenderanno piani per aumentare le coperture vaccinali, per limitare la diffusione di disinformazione in ambito vaccinale e per garantire che ogni bambino riceva due dosi del vaccino MPR.

RISKS OF NOT VACCINATING

Cases of Vaccine-Preventable Diseases With and Without Immunization, United States



Adapted from MMWR, April 2, 1999, Vol. 48, No. 12.

CDC Immunization

Immunization coverage

15 July 2024

Key facts

- **Globally in 2023, there were 14.5 million children missing out on any vaccination – so-called zero-dose children.**
- **Coverage of a third dose of vaccine protecting against diphtheria, tetanus, and pertussis (DTP3) was 84% in 2023.**
- **The proportion of children receiving a first dose of measles vaccine was 83% in 2023, well below the 2019 level of 86%.**
- **Global coverage for the first dose of HPV vaccine in girls grew from 20% in 2022 to 27% in 2023.**
- **Coverage of yellow fever vaccine in the countries at risk of it is 50%, well below the recommended 80%.**

While immunization is one of the most successful public health interventions, coverage plateaued in the decade prior to COVID-19. The COVID-19 pandemic, associated disruptions, and vaccination efforts strained health systems in 2020 and 2021, resulting in dramatic setbacks. Data from 2023 show that performance has not yet returned to 2019 levels.

Some infections for which effective vaccines are not yet available

Disease	Estimated annual mortality
Malaria	618,248
Schistosomiasis	21,797
Intestinal worm infestation	3304
Tuberculosis	934,879
Diarrheal disease	1,497,724
Respiratory infections	3,060,837
HIV/AIDS	1,533,760
Measles*	130,461

Figure 16.22 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Safety and efficacy of malaria vaccine candidate R21/Matrix-M in African children: a multicentre, double-blind, randomised, phase 3 trial

Mehreen S Datoo, Alassane Dicko, Halidou Tinto*, Jean-Bosco Ouédraogo, Mainga Hamaluba†, Ally Olotu†, Emma Beaumont, Fernando Ramos Lopez, Hamtandi Magloire Natama, Sophie Weston, Mwajuma Chemba, Yves Daniel Compaore, Djibrilla Issiaka, Diallo Salou, Athanase M Some, Sharon Omenda, Alison Lawrie, Philip Bejon, Harish Rao, Daniel Chandramohan, Rachel Roberts, Sandesh Bharati, Lisa Stockdale, Sunil Gairola, Brian M Greenwood, Katie J Ewer‡, John Bradley, Prasad S Kulkarni, Umesh Shaligram, Adrian V S Hill, theR21/Matrix-M Phase 3 Trial Group§*

Open Access • Published: February 01, 2024 • DOI: https://doi.org/10.1016/S0140-6736(23)02511-4 •

World Health Organization

Shipment of newest malaria vaccine, R21, to Central African Republic marks latest milestone for child survival

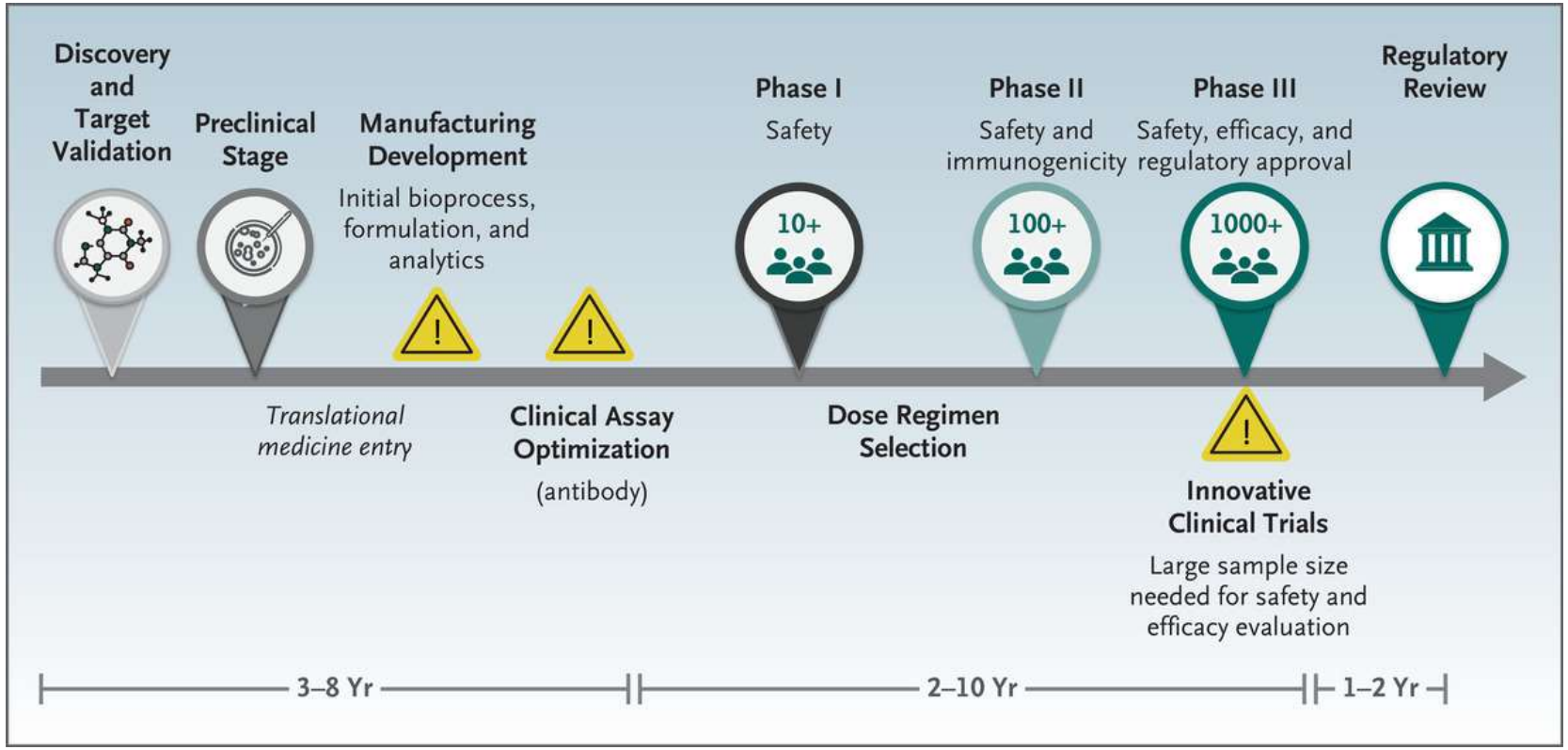
24 May 2024 | Joint News Release | Geneva/Copenhagen/New York
|Reading time: 4 min (1045 words)

Thinking of vaccines in a different way in the time of COVID-19

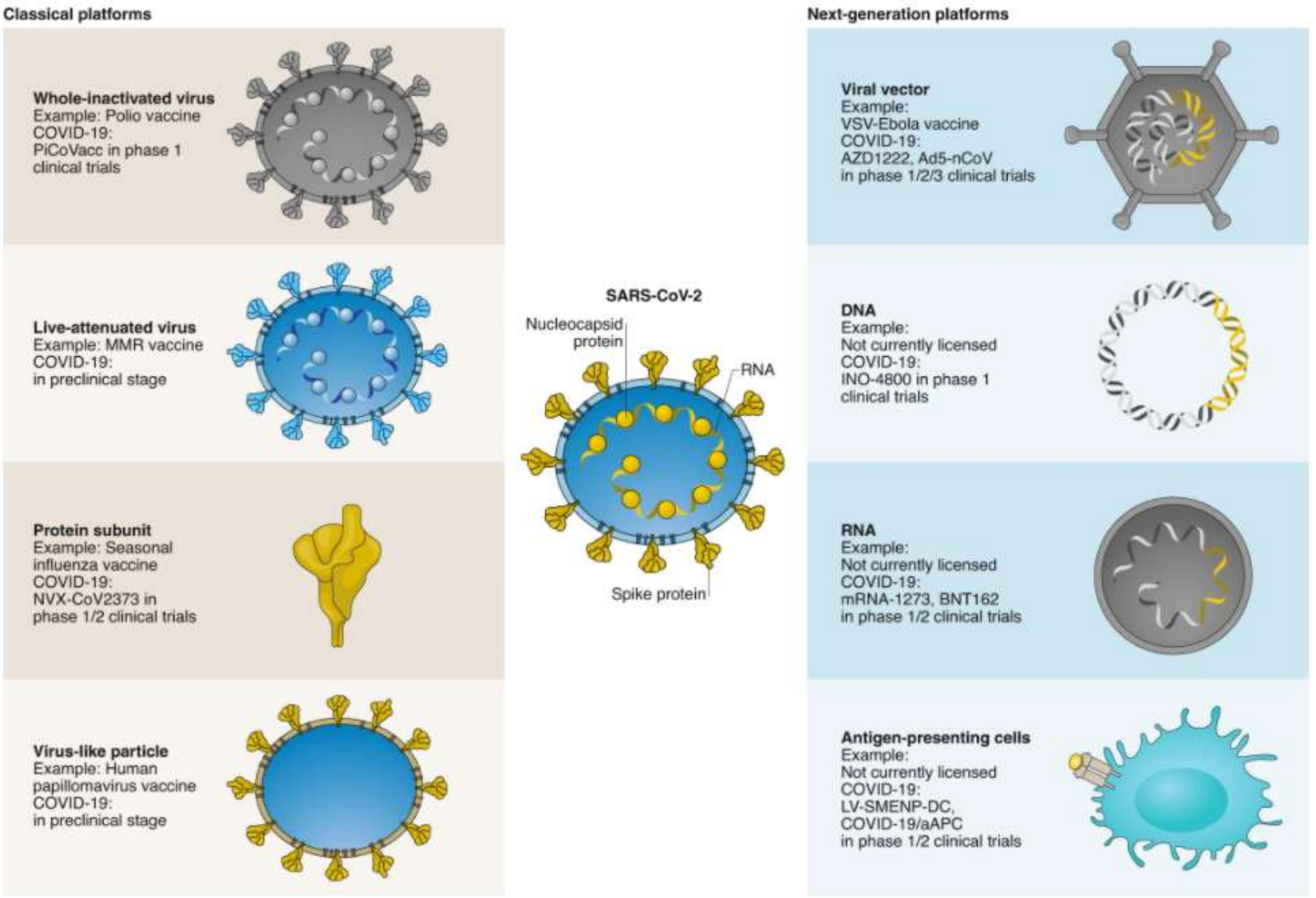
HEALTH

SCIENTIFIC ADVANCES

Traditional Vaccine Development Pathway.



An overview of the different vaccine platforms in development against COVID-19



Nature Materials, 2020

How an immigrant scientist paved the way for covid-19 vaccine

Katalin Karikó saw her early research rejected but she persisted and is now tipped for a Nobel Prize together with her colleague Dr Drew Weissman. Their breakthrough invention is now the key to the Moderna and Pfizer vaccines, and could open the door to new medical cures. (Leer en español)

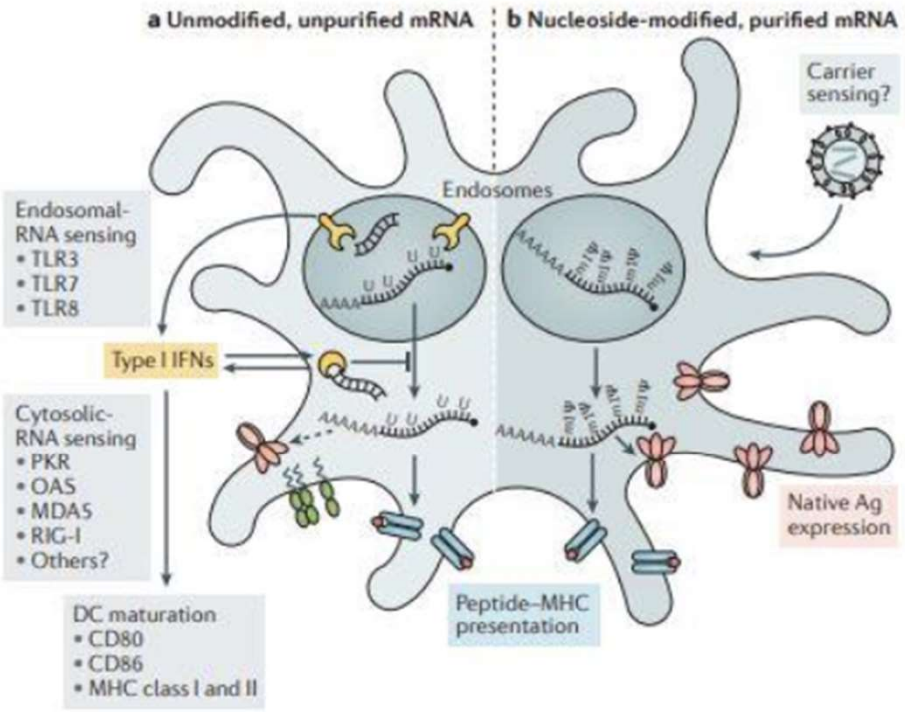
POR: DAVID C ADAMS Follow
20 DIC 2020 – 11:10 AM EST

COMPARTE

Scientists Katalin Kariko and Drew Weissman invented the RNA messenger technology for the covid-19 vaccine prodiced by Pfizer and Moderna.
Crédito: David Maris

When biochemist Katalin Karikó came to the United States in 1985 as a young immigrant from communist Hungary, she had to sell her car on the black market to afford the trip.

mRNA vaccines initially did not work… until they were improved



Key advances in the development of mRNA therapeutics

1961
- Discovery of mRNA[215]

1976
- First in vivo nucleic acid delivery by polymeric particles[5]

1978
- Delivery of mRNA to human and mouse cells by liposomes[78]

1995
- First mRNA-based cancer vaccine evaluated in mice[216]

2005
- Kariko, Weissman and colleagues[11] reported for the first time that nucleoside modifications substantially reduced TLR signaling in response to mRNAs

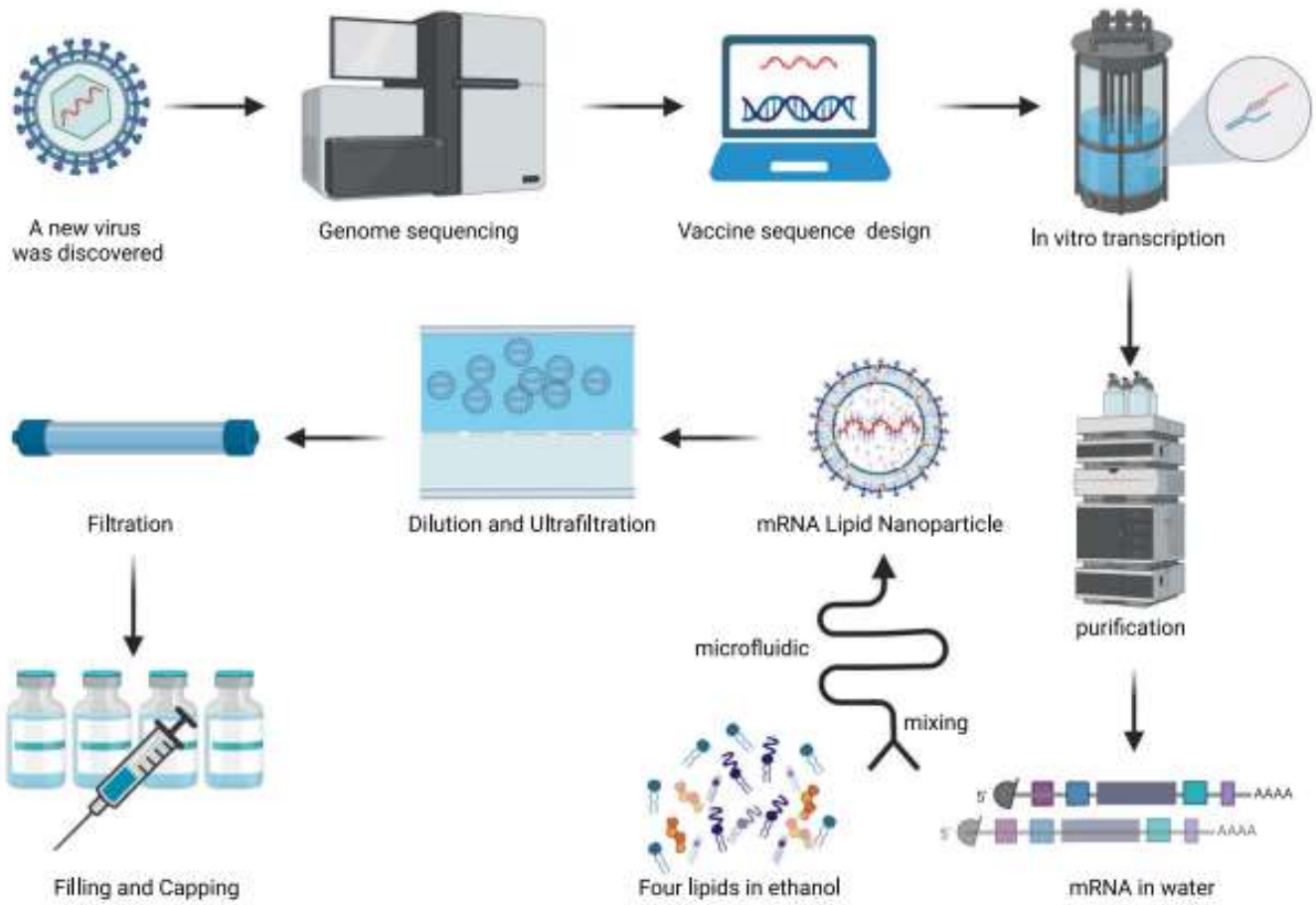
2008–2012
- Kariko, Weissman and colleagues further demonstrated that nucleoside modifications could limit PKR[38] and 2′-5′-oligoadenylate synthetase activation, promote resistance to cleavage by RNase L[51] and eventually enhance the translational capacity and stability of mRNA[49,50].

2017
- First clinical trial of personalized mRNA-based cancer vaccine[217]

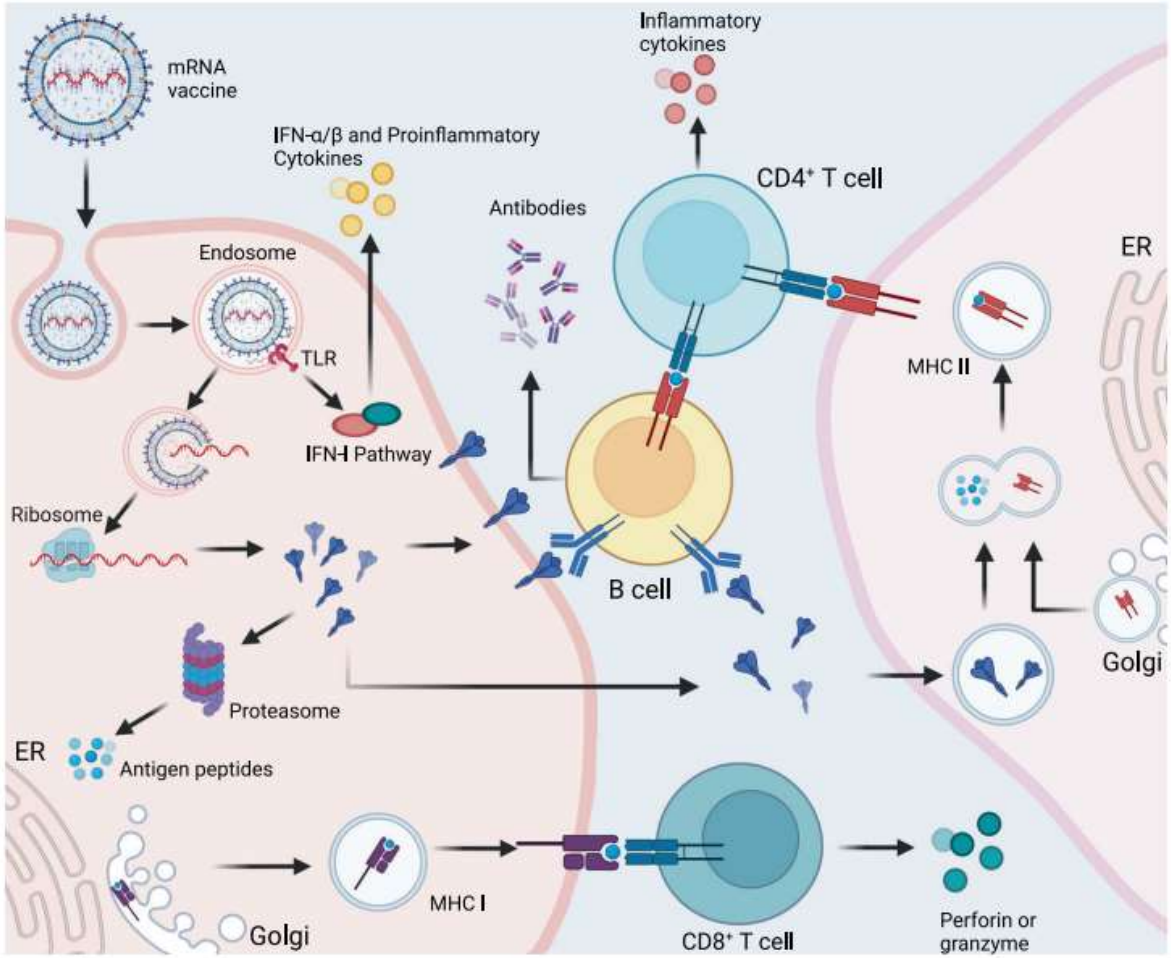
2020
- Two COVID-19 mRNA vaccines (mRNA-1273 and BNT162b2) received emergency use authorization in the United States

2021
- Adjuvant activity of LNPs in COVID-19 mRNA vaccines was identified[193]

Processo di produzione dei vaccini a mRNA



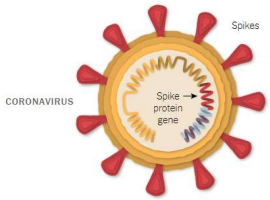
Cellular and humoral immune responses induced by mRNA vaccine



1) proteasoma, MHC classe I
   → Risposta CD8

2) Proteina solubile, captazione da APC
   → Risposta CD4 e anticorpale

3) Effetto adiuvante



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

mRNA Inside an Oily Shell

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

New Pfizer Results: Coronavirus Vaccine Is Safe and 95% Effective

The company said it planned to apply for emergency approval from the Food and Drug Administration "within days."

November 18, 2020

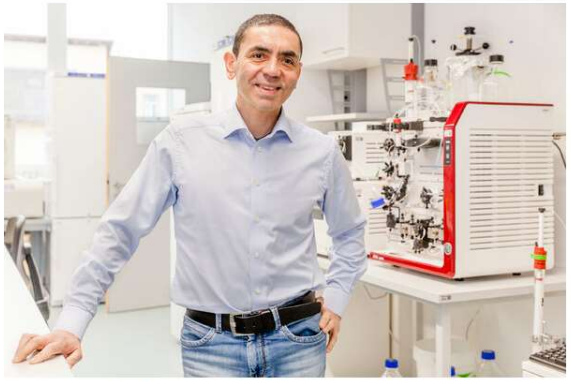
Early Data Show Moderna's Coronavirus Vaccine Is 94.5% Effective

Moderna is the second company to report preliminary results from a large trial testing a vaccine. But there are still months to go before it will be widely available to the public.

November 16, 2020

Vaccine Timeline

January, 2020 BioNTech begins work on a vaccine after Dr. Ugur Sahin, one of the company's founders, becomes convinced that the coronavirus will spread from China into a pandemic.



Dr. Ugur Sahin of BioNTech. BioNTech

Dec. 8 William Shakespeare, age 81, is among the first people to receive a shot of the vaccine in Britain, on the first day of vaccinations for at-risk health care workers and people over 80.

Dec. 11 The F.D.A. grants Pfizer-BioNTech vaccine the first emergency use authorization for a coronavirus vaccine in the United States. Mexico also approves the vaccine for emergency use.

Dec. 14 Vaccination begins in the United States.

Dec. 21 The European Union authorizes the vaccine.