Corso di Immunologia - III anno
Prof. Paolini

Lezione 28/11/2025

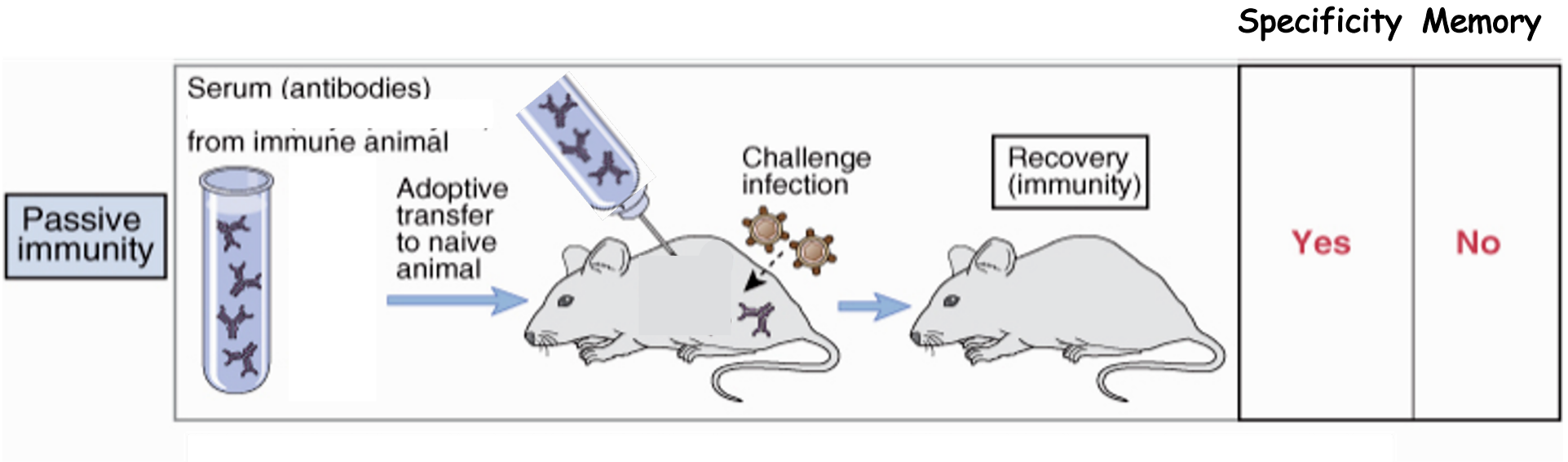
"I vaccini"

Passive Immunity and Immunization

- **Passive immunity** occurs when antibodies are transferred from one individual to another (artificial passive immunity).

  Passive immunity:

  - provides temporary protection.
  - does not activate the patient's own B cell and T cells.
  - is also known as serum therapy.
  - is highly beneficial against bacterial produced toxins.



- **Passive immunization** can also occur naturally as maternal IgG passes through a mother's placental barrier to the developing fetus.
  - IgA antibodies in breast milk can also provide passive immunity.

Examples of antisera or antibodies used for passive immunization

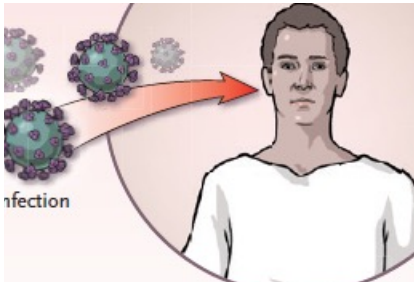
Disease	Agent
Black widow spider bite	Horse antivenin
Botulism	Horse antitoxin
Cytomegalovirus	Human polyclonal Ab
Diphtheria	Horse antitoxin
Hepatitis A and B	Pooled human immunoglobulin
Measles	Pooled human immunoglobulin
Rabies	Human or horse polyclonal Ab
Respiratory disease	Monoclonal anti-RSV*
Snake bite	Horse antivenin
Tetanus	Pooled human immunoglobulin or horse antitoxin
Varicella zoster virus	Human polyclonal Ab

*Respiratory syncytial virus

SOURCE: *Adapted from A. Casadevall, 1999, *Clinical Immunology* **93**:5.

Active Immunity and Immunization

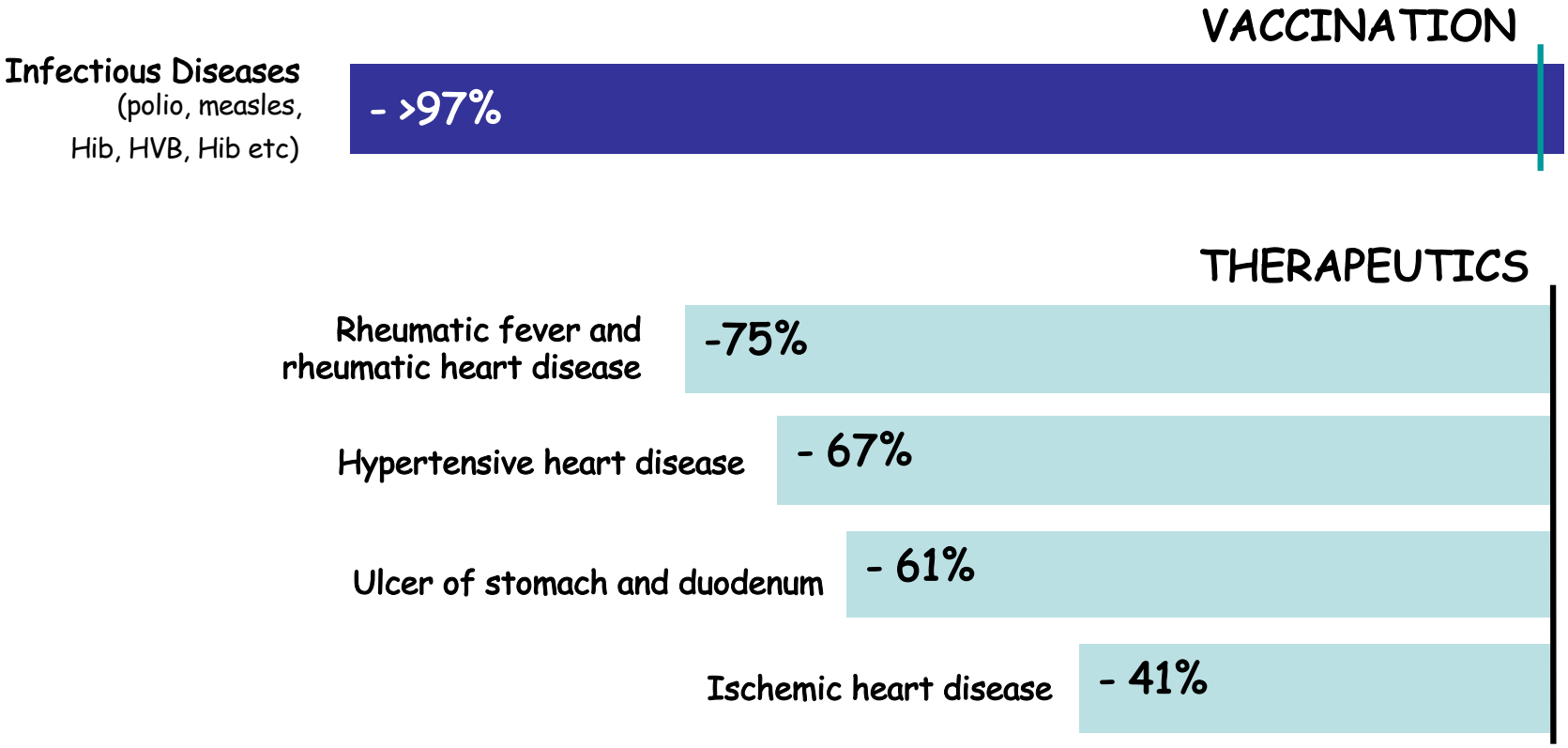
- **Active immunization** triggers the adaptive immune response to elicit protective immunity.



  - Long-lived immunological memory cells are generated.
  - Memory cells respond during secondary exposure to help eliminate the infectious agent and prevent disease.

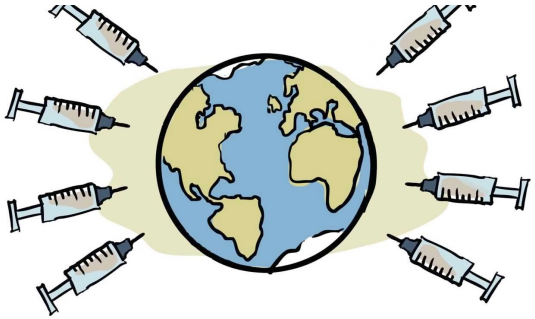
- Active immunization can be acquired artificially via vaccination or naturally via exposure to an infectious agent.

Vaccination has been instrumental in reducing infectious diseases and remains the most effective of the successful medical interventions



EFPIA 1999 – 2002

World Health Organization (WHO) has estimated that *vaccines* have *saved more than 500 million lives in the past 50 years.*

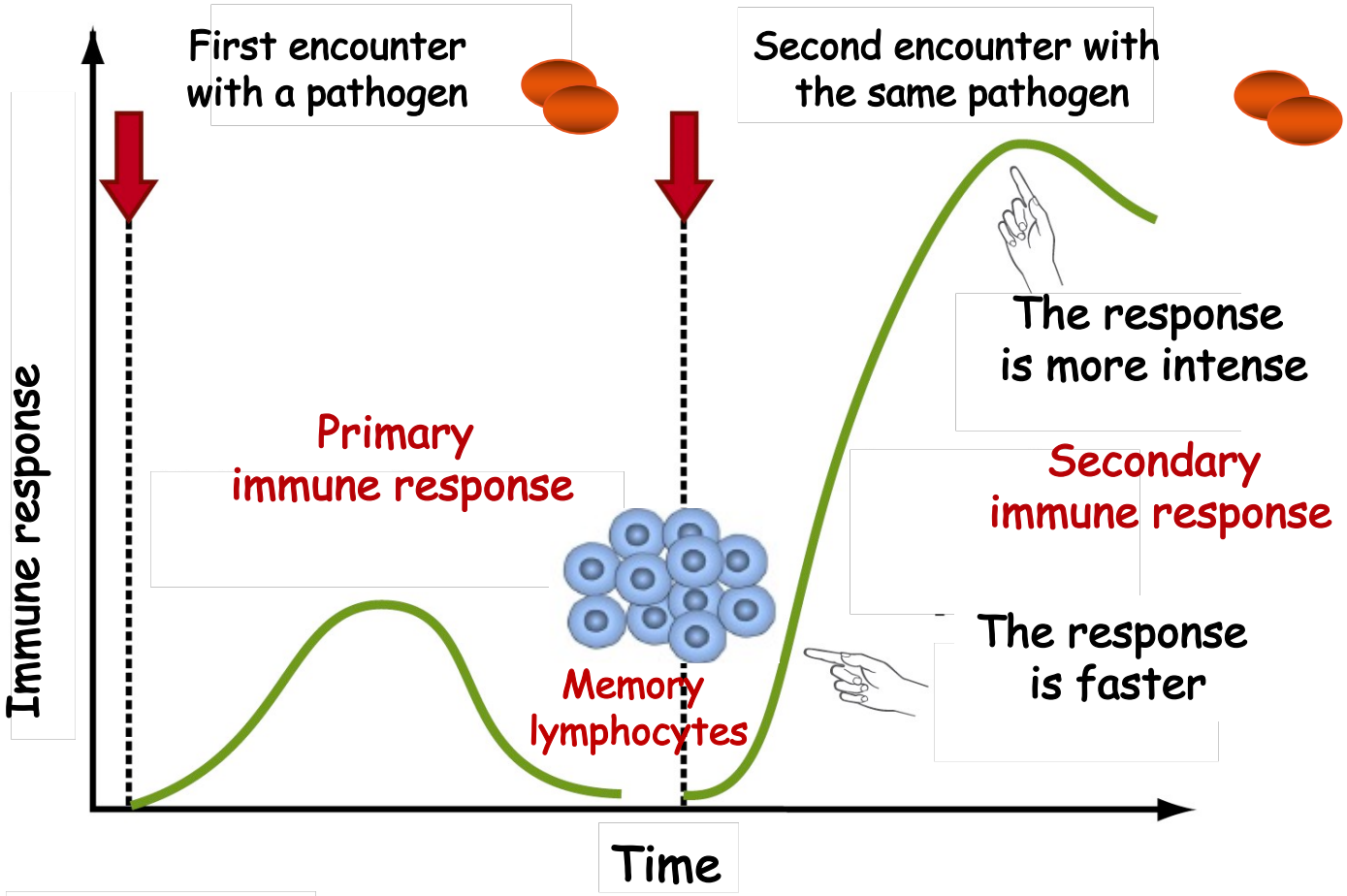


Vaccines currently *save an estimated 2.5 million lives annually*, meaning…..

- 7000/day
- 300/hour
- 5/min

But how do vaccines work……..?

A matter of memory!

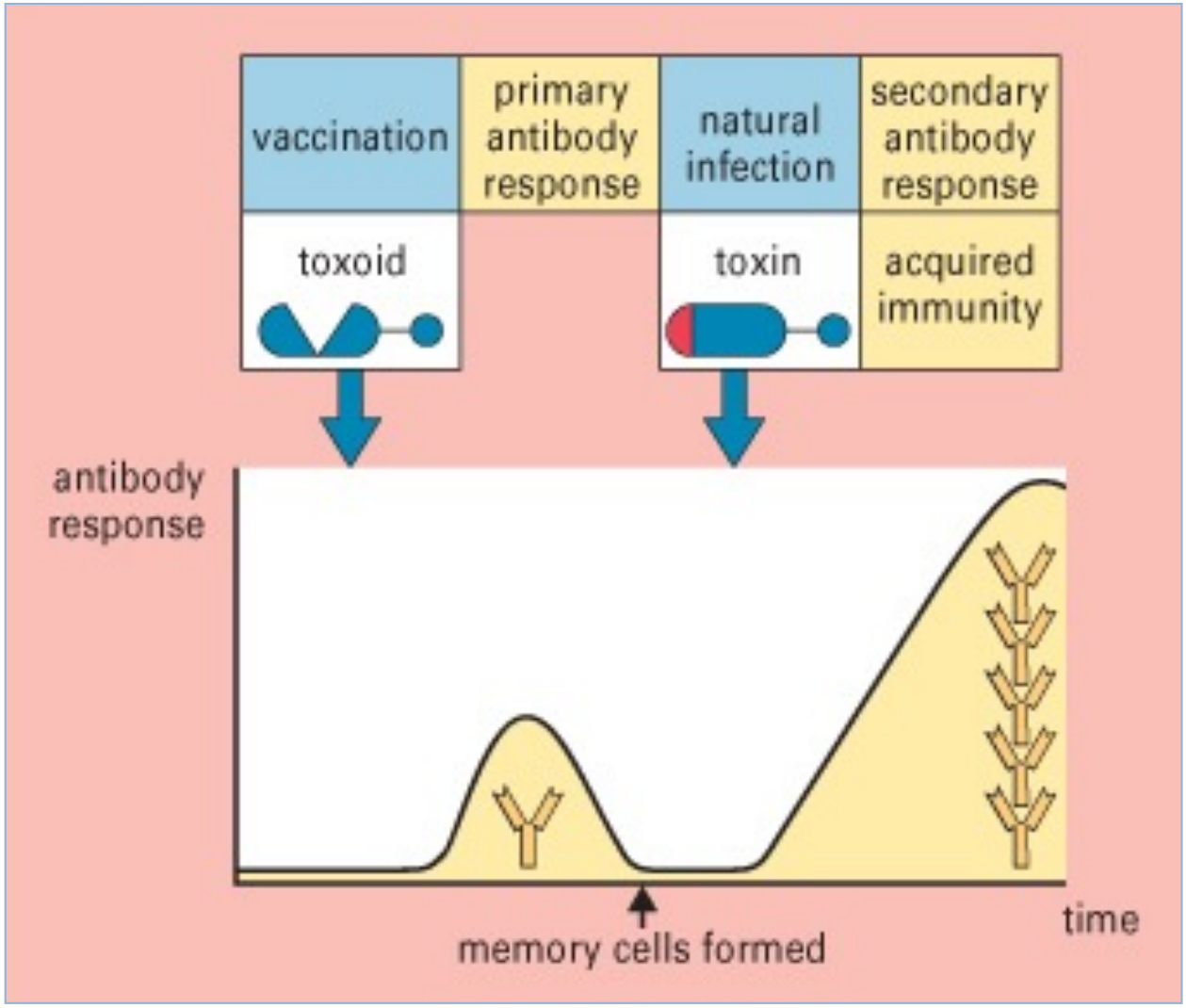


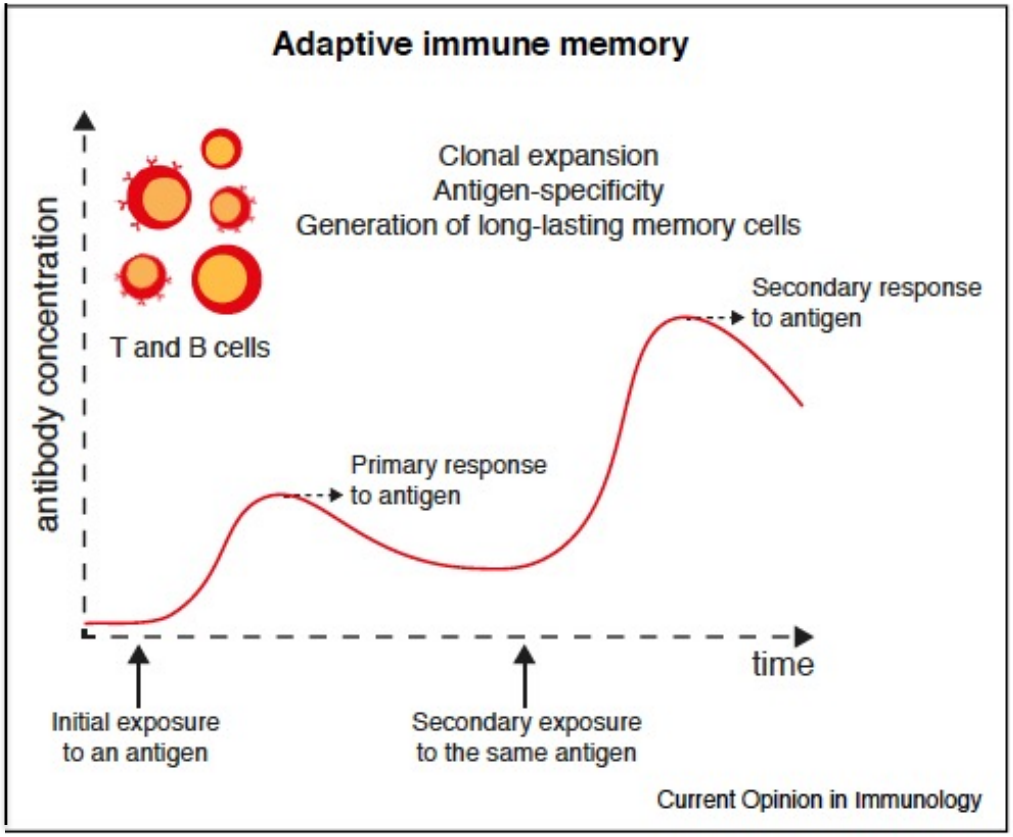
Primary - long latency period; IgM predominates followed by a gradual isotype switch; low affinity.

Secondary - short latency period; more intense response; IgG prevails over IgM; high affinity.

Immunological memory ensures a faster and more intense secondary response!

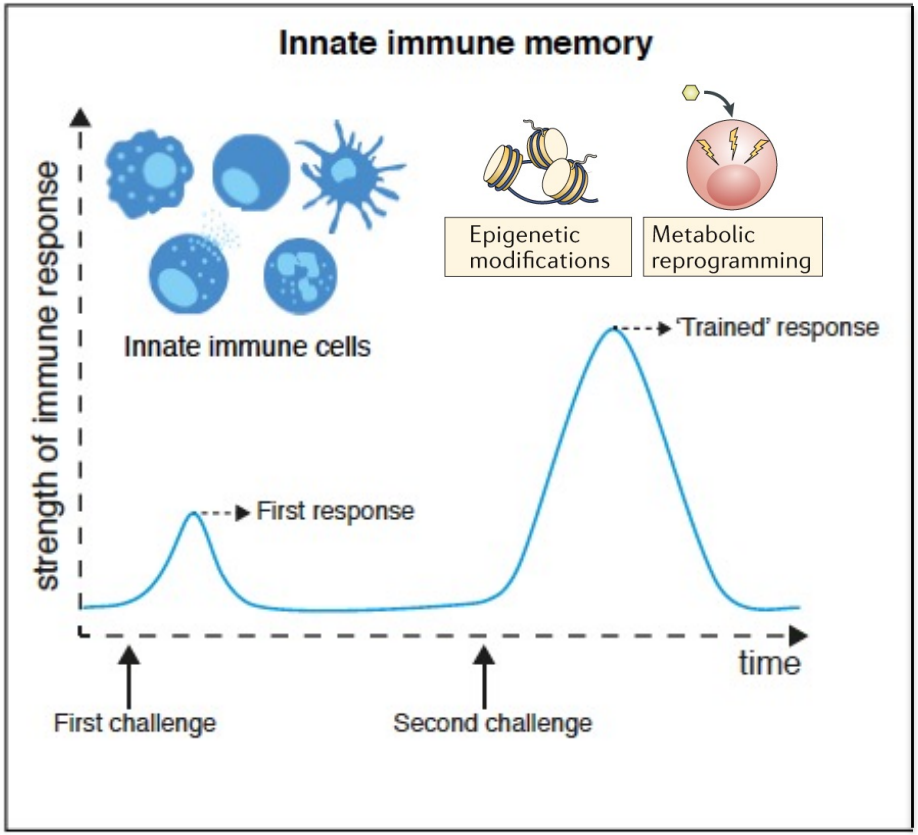
Vaccines also generate immunological memory!





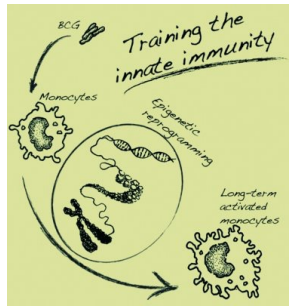
Immunological memory is not exclusive of T and B lymphocytes !

The term «trained immunity» was introduced in 2011 by ***Mihai Netea***



The Two-Step Model for the evolution of immunological memory:

Innate immunological memory, or "trained immunity," is a primitive form of adaptation in host defense, resulting from metabolic and epigenetic reprogramming, which provides an increased but non-specific response to re-infection.



Adaptive immunological memory is more advanced (described until now only in vertebrates) and results in increased magnitude of response involving the development of specific memory T and B cells selected from a large repertoir obtained through gene recombination and clonal expansion.

Key concept:

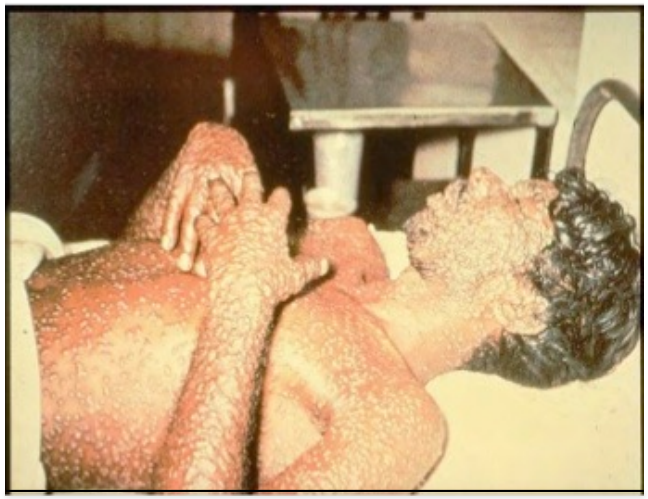
The principle behind vaccination is that exposure to safe forms of an infectious agent can result in future acquired protection or immunity to the real and more dangerous agent.

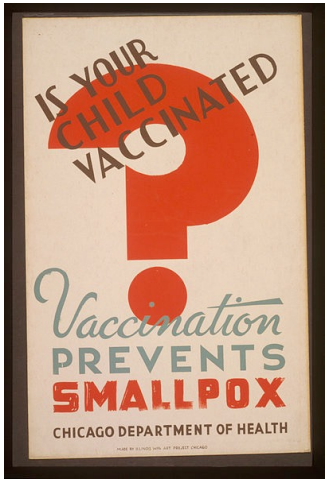
Smallpox: An ancient and mortal disease

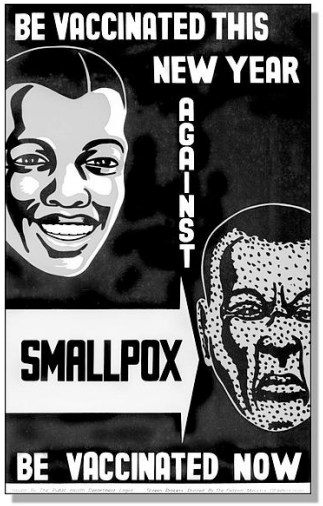
At the end of 18th century 600.000 people died because smallpox in Europe every year

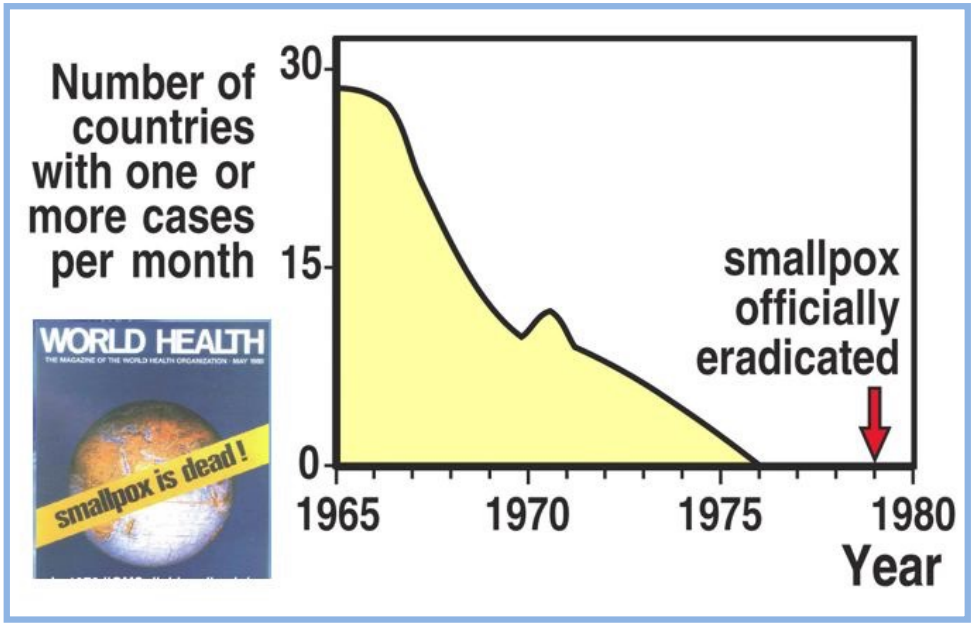
The European people around 80 Million

1person/140 died because smallpox every year









Impact of vaccination on many other infectious diseases

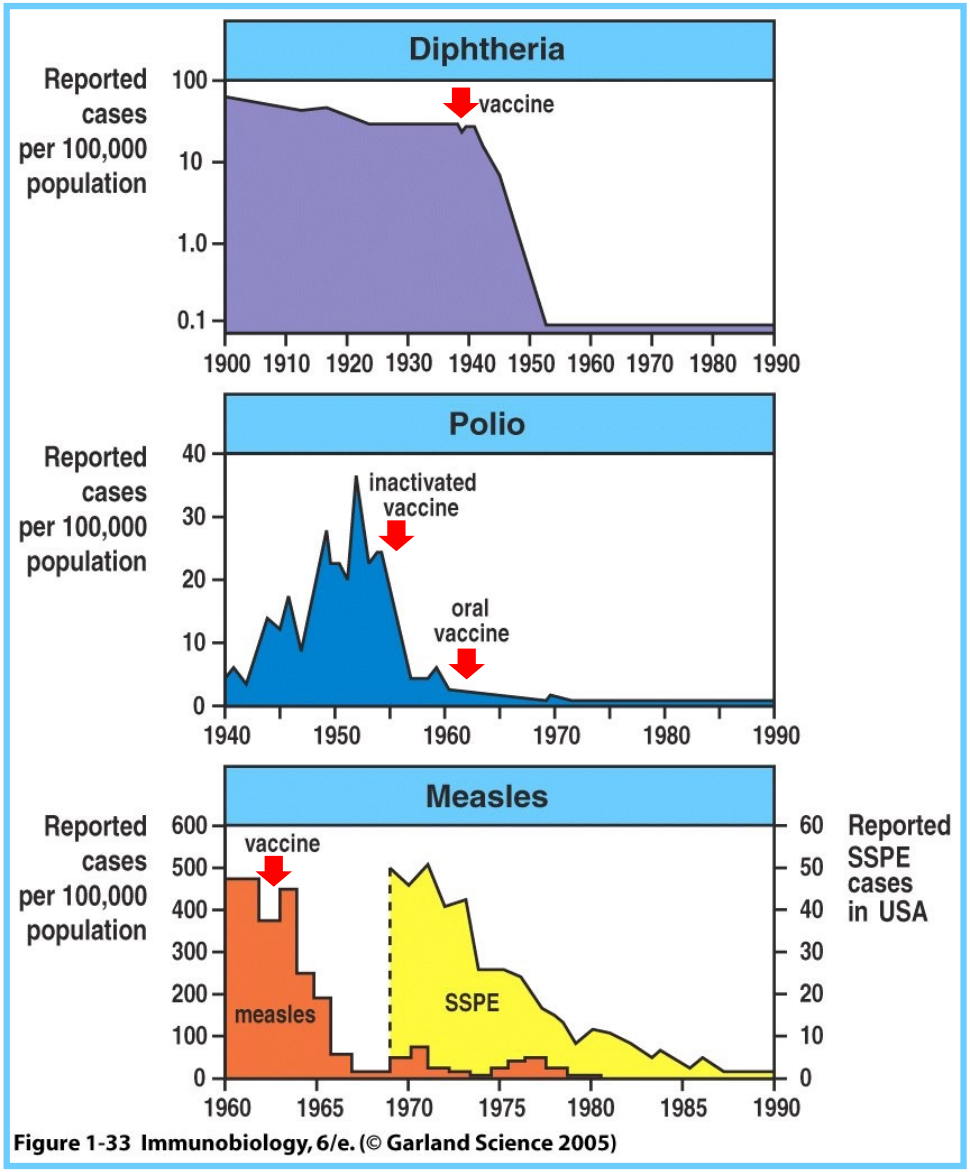


Figure 1-33 Immunobiology, 6/e. (© Garland Science 2005)

Disease	Maximum number of cases (year)	Number of cases in 2004	Percent change
Diphtheria	206,939 (1921)	0	-99.99
Measles	894,134 (1941)	37	-99.99
Mumps	152,209 (1968)	236	-99.90
Pertussis	265,269 (1934)	18,957	-96.84
Polio (paralytic)	21,269 (1952)	0	-100.0
Rubella	57,686 (1969)	12	-99.98
Tetanus	1,560 (1923)	26	-98.33
Haemophilus influenzae type B	~20,000 (1984)	16	-99.92
Hepatitis B	26,611 (1985)	6,632	-75.08

SSPE: Subacute sclerosing panencephalitis

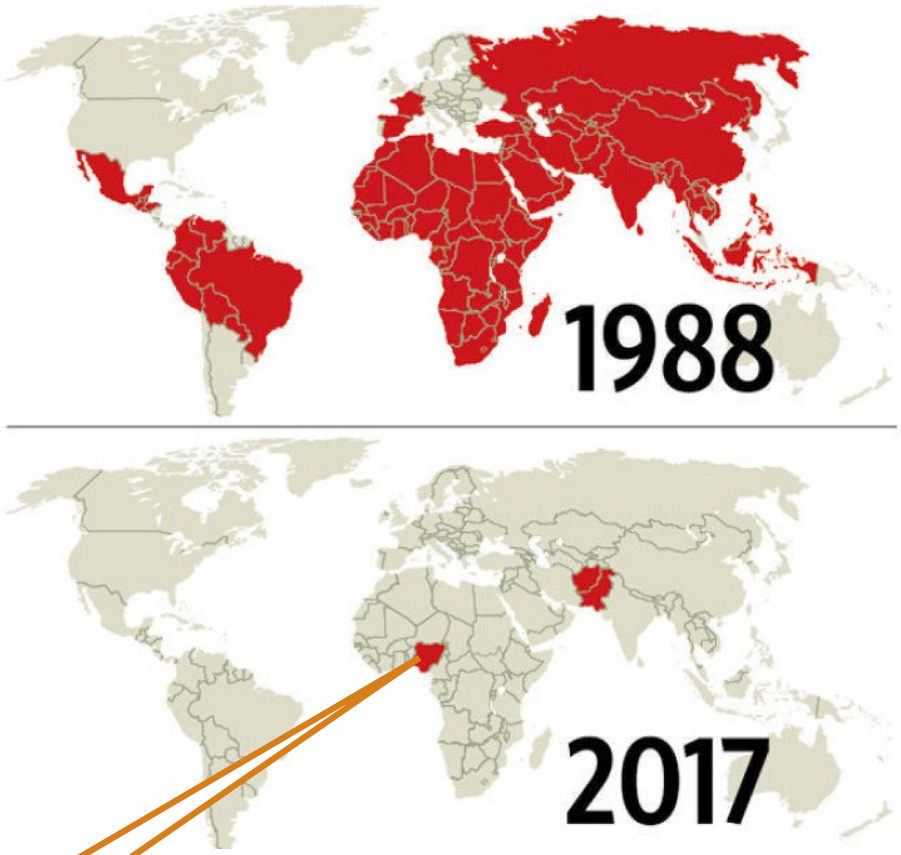
Eradication of poliovirus: next goal of WHO

The polio endgame

Since 1988, when the WHO resolved to eradicate polio, its footprint has shrunk dramatically. It is only considered endemic in Afghanistan, Pakistan and Nigeria (which hasn't seen a case since 2016). Last year there were only 22 new cases reported.

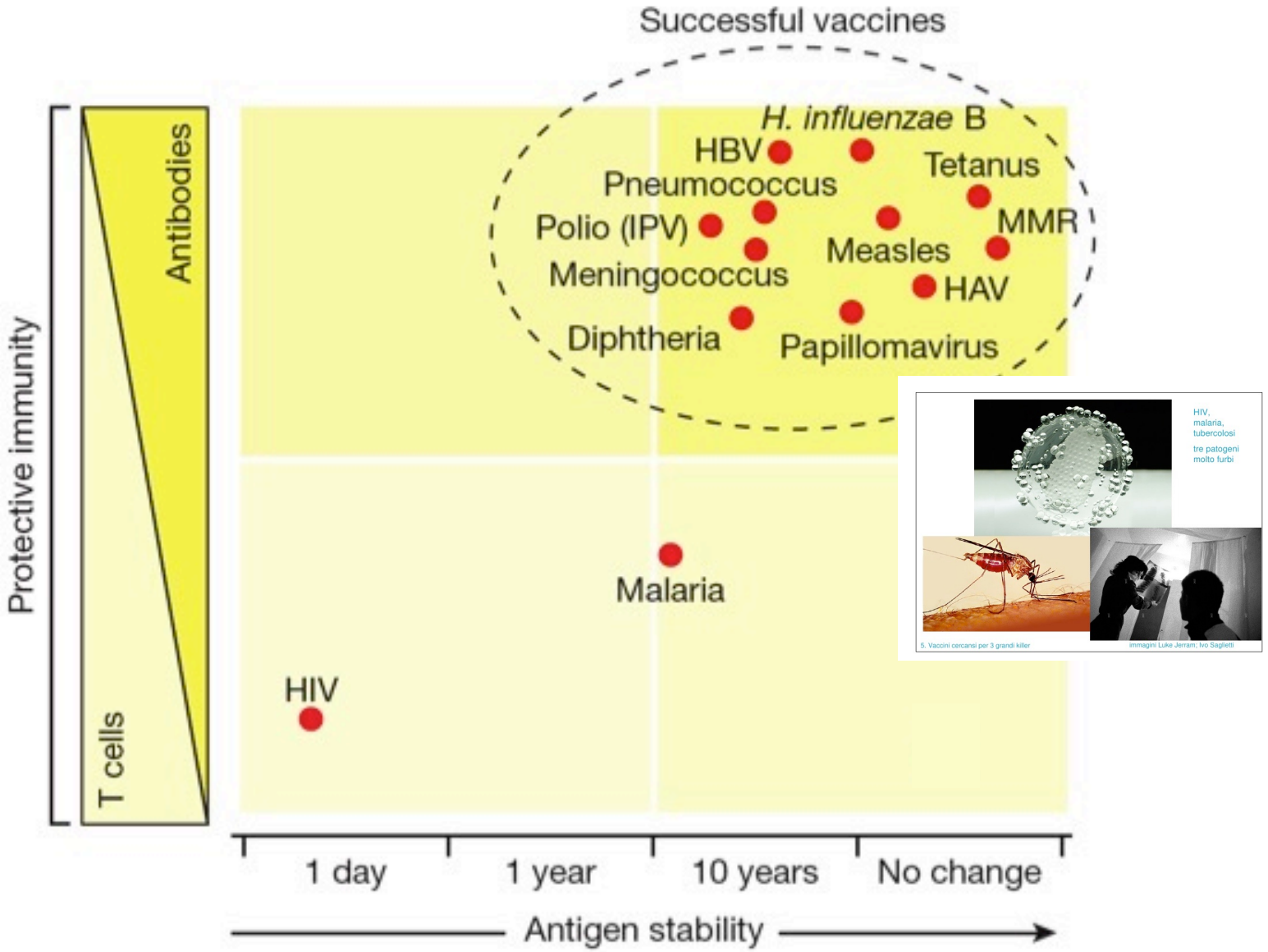
	1988	2017
Endemic countries	125	3

SOURCE: World Health Organization
TORONTO STAR GRAPHIC



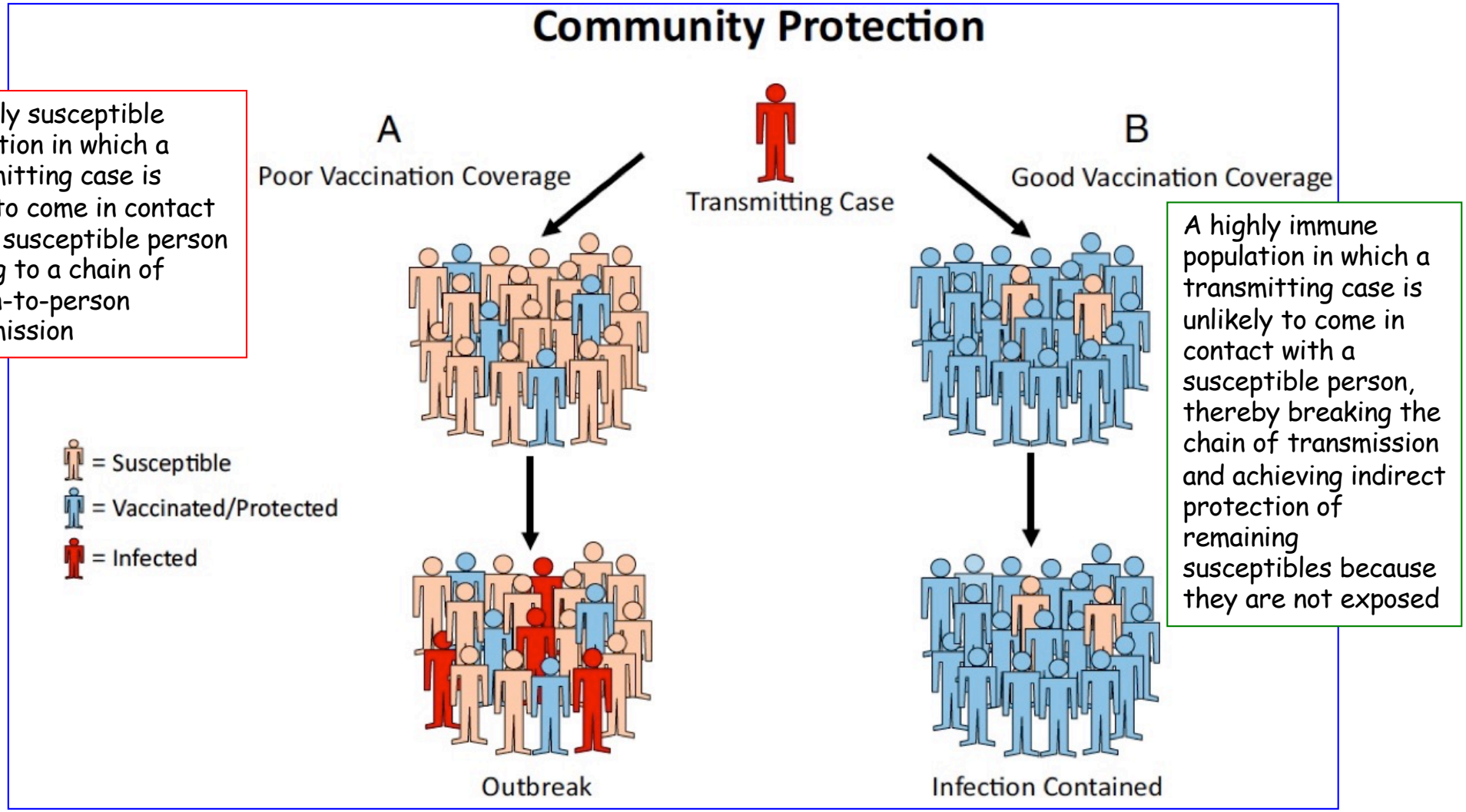
On August 25, 2020, WHO announced that the African continent is also polio-free!!

Successful vaccines have been developed against those pathogens that can be treated by antibodies and have a stable antigen repertoire



The «herd» immunity

A highly susceptible population in which a transmitting case is likely to come in contact with a susceptible person leading to a chain of person-to-person transmission

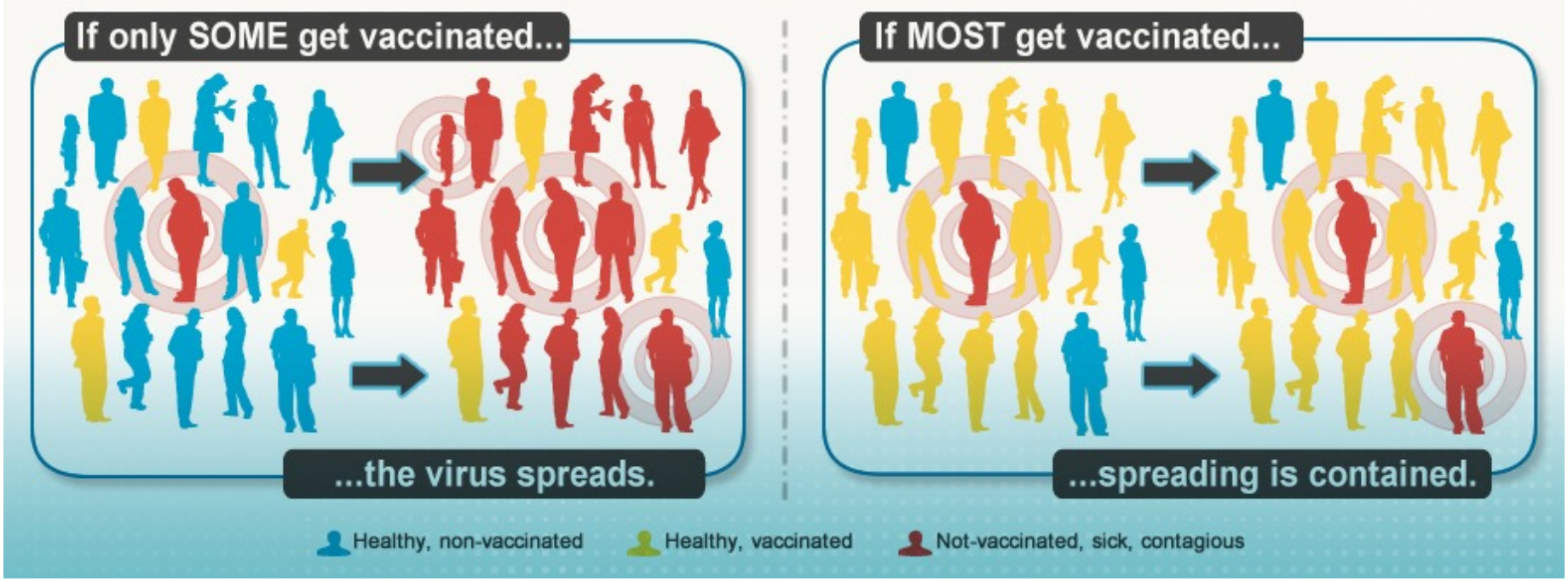


A highly immune population in which a transmitting case is unlikely to come in contact with a susceptible person, thereby breaking the chain of transmission and achieving indirect protection of remaining susceptibles because they are not exposed

The social value of the vaccine: altruistic consideration

⇩

The reduced diffusion of the pathogen allows even the weakest subjects to be protected



Despite the achievements and successes.....

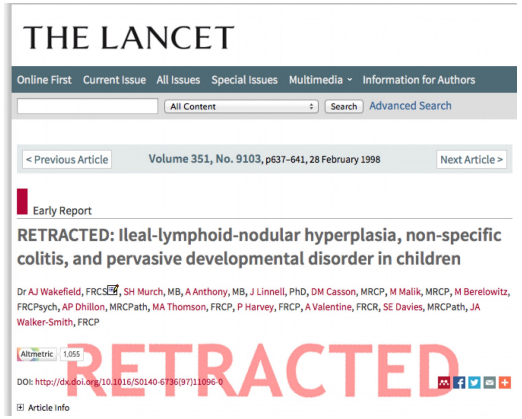
Vaccines encounter a major crisis

Victims of their own success!

Poor memory and awareness of the potential severity of infectious diseases and their side effects

In 1998, a study hypothesized a link between the measles vaccine and autism

- The results were not reproducible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Early Report

RETRACTED: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

Dr AJ Wakefield, FRCS, SH Murch, MB, A Anthony, MB, J Linnell, PhD, DM Casson, MRCP, M Malik, MRCP, M Berelowitz, FRCPsych, AP Dhillon, MRCPath, MA Thomson, FRCP, P Harvey, FRCP, A Valentine, FRCR, SE Davies, MRCPath, JA Walker-Smith, FRCP

Altmetric 1,055

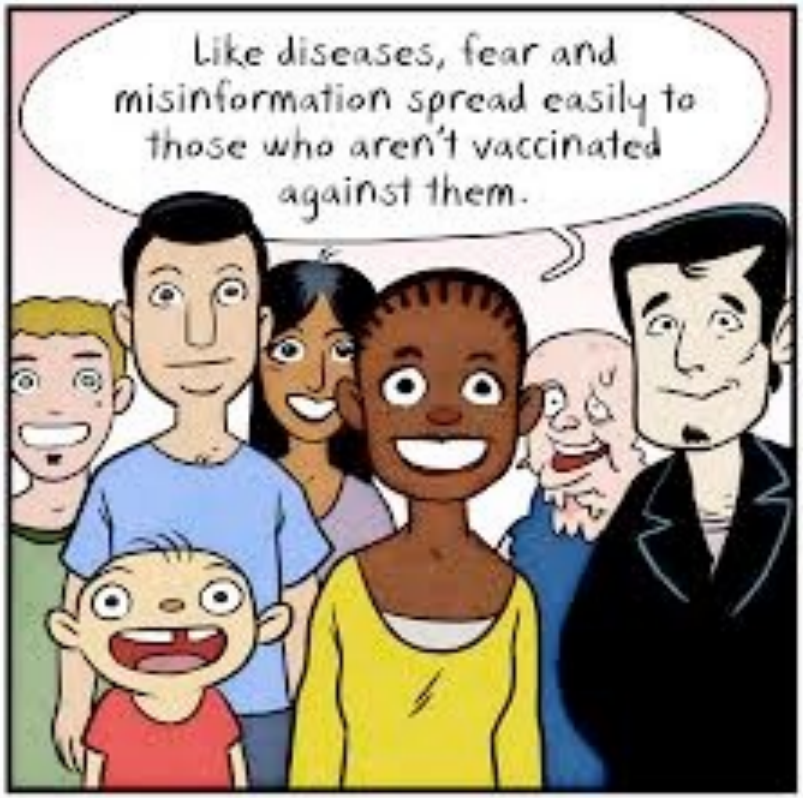
RETRACTED

DOI: http://dx.doi.org/10.1016/S0140-6736(97)11096-0

Article Info

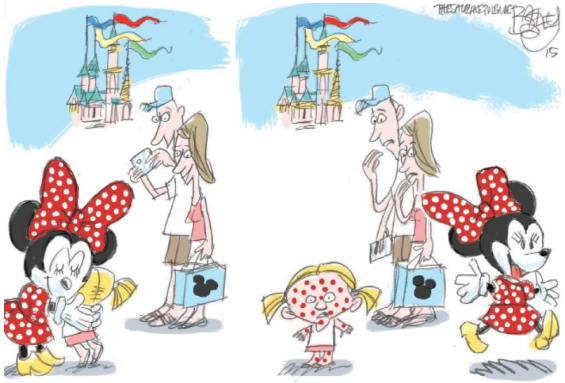
An incredible fake news!

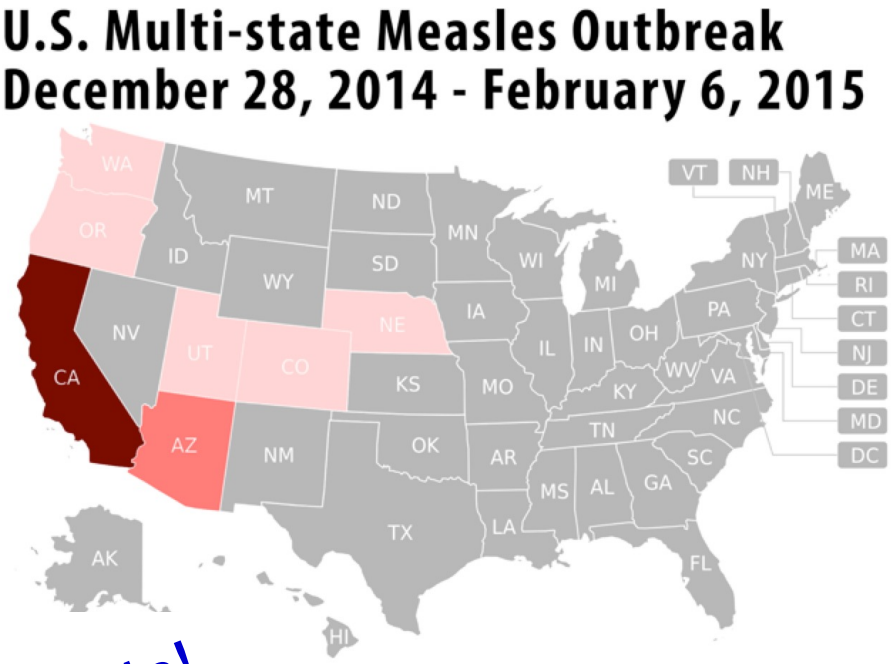
- The author, Andrew Wakefield, was banned from practicing medicine

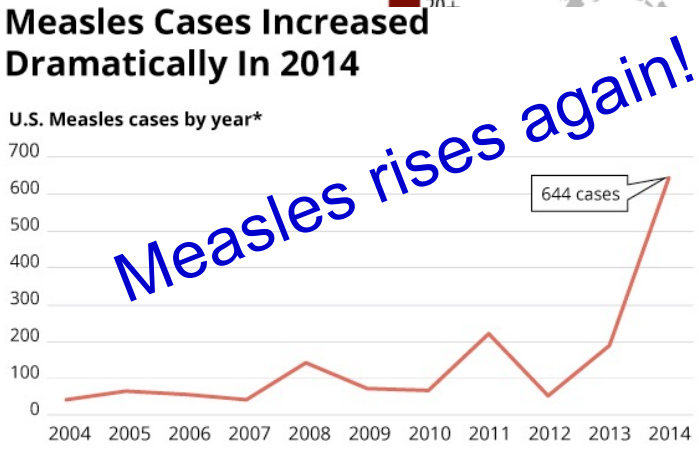


.....but which were the consequences?

The Disneyland Measles outbreak





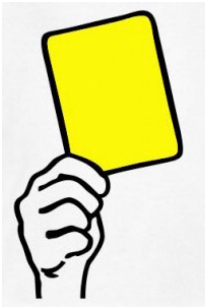


Measles rises again!

February 6, 2015, 114 people from 7 states [AZ (7), CA (99), CO (3), WA (2)] were reported to have measles and are considered ongoing outbreak linked to an amusement park in California*.

al Center for Immunization and Respiratory Diseases

CDC

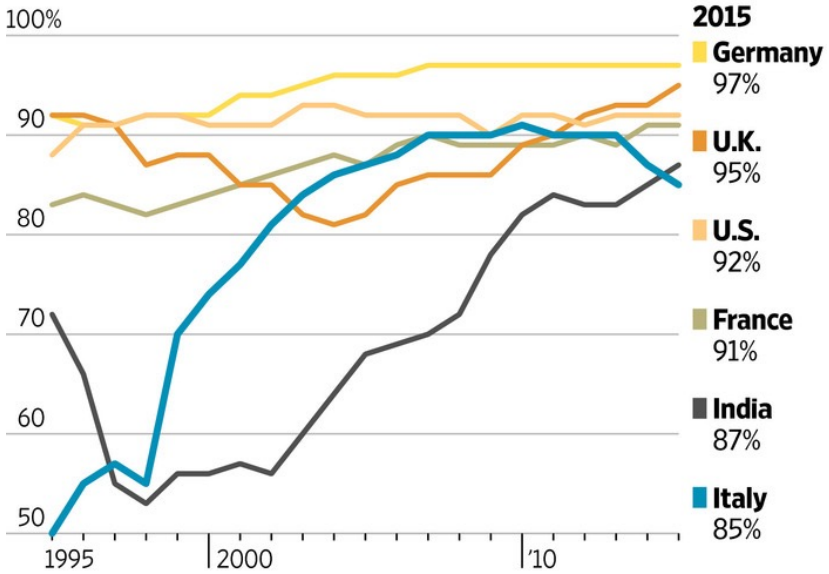


WHO Warning to Italy

Drop-off

Italy's vaccination rate has seen an especially steep fall in recent years in the face of antivaccine sentiment.

Percentage of 1-year-olds with measles immunization coverage



Source: World Health Organization

THE WALL STREET JOURNAL.

Italy's Vaccination Rates Raise Government's Concern

Measles inoculations have dipped below level of India amid stubborn antivaccine sentiment

Italian Health Minister Beatrice Lorenzin has been fighting to counter the decline in Italy's childhood vaccination rates.

The occurrence of a large measles outbreak in January 2017, triggered the establishment of a new law…..

THE NEW LAW ON VACCINE (L. 119/2017)

Italy introduced a national law extending the number of mandatory vaccines from 4 to 10 in July 2017:

Mandatory vaccines

- Tetanus
- Diptheria
- Hepatitis B
- Polio

- Pertussis
- *Haemophilus influenzae* type B
- Measles
- Mumbs
- Rubella
- Varicella

MMR

The obligation also exists for boosters, although it will be re-evaluated every three years based on epidemiological data

Vaccines for every age

Pre-birth
- Cytomegalovirus
- Group B streptococcus
- Hepatitis B virus
- Influenza virus
- Meningococcus serogroups A, B, C, Y and W135
- Pertussis
- Respiratory syncytial virus
- Tetanus

Infants and children
- Diphtheria
- Group A streptococcus
- *H. influenzae* type b
- *Helicobacter pylori*
- Hepatitis A virus
- Hepatitis B virus
- Inactivated poliovirus vaccine
- Influenza virus
- Measles
- Meningococcus serogroups A, B, C, Y and W135
- Mumps
- Pertussis
- Pneumococcus
- Respiratory syncytial virus
- Rotavirus
- Rubella
- Tetanus
- Varicella zoster virus

Adolescents
- Cytomegalovirus
- Diphtheria, tetanus acellular pertussis
- Epstein–Barr virus
- Herpes simplex virus
- Human papilloma virus
- Influenza virus
- Meningococcus serogroups A, B, C, Y and W135
- Parvovirus B19

Adults
- Diphtheria
- Hepatitis B virus
- Influenza virus
- Meningococcus serogroups A, B, C, Y and W135
- Pertussis
- Respiratory syncytial virus
- Tetanus

Elderly

Recurrent infections:
- Group B streptococcus
- Influenza virus
- Meningococcus serogroups A, B, C, Y and W135
- Pneumococcus
- Respiratory syncytial virus
- Varicella zoster virus

Antibiotic resistance:
- *Acinetobacter baumannii*
- *C. difficile*
- *Candida* spp.
- Enterotoxigenic *E. coli*
- *Klebsiella pneumoniae*
- *P. aeruginosa*
- *S. aureus*

Cancer:
- Breast cancer
- Colorectal cancer
- Prostate cancer

"Calendario delle vaccinazioni 2017-2019"

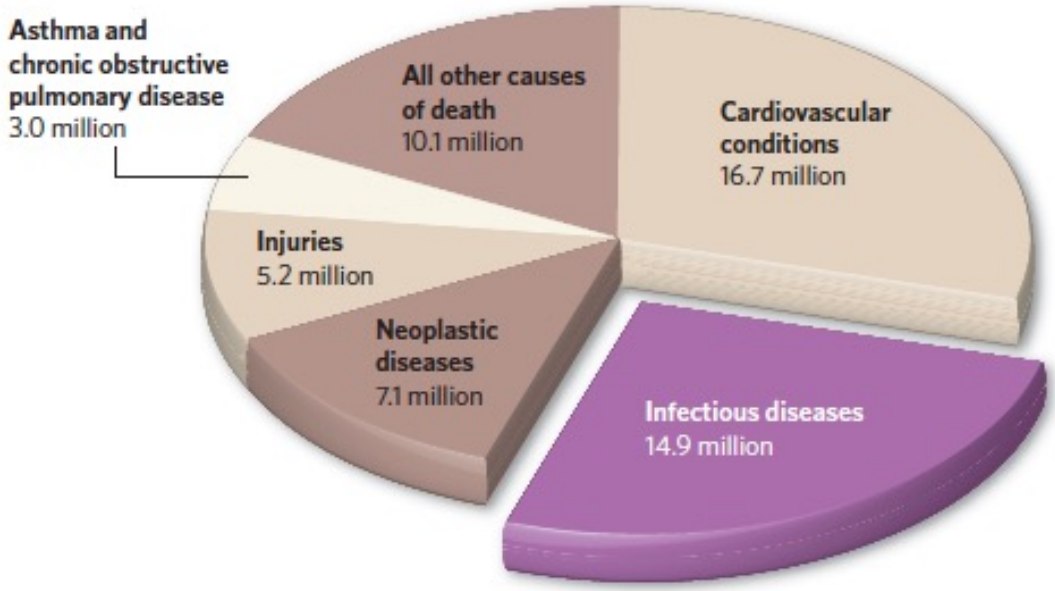
Vaccino	0gg-30gg	3° mese	4° mese	5° mese	6° mese	7° mese	11° mese	13° mese	15° mese	⇨	6° anno	12°-18° anno	19-49 anni	50-64 anni	> 64 anni
DTPa** difterite-tetano-pertosse		DTPa		DTPa			DTPa				DTPa***	dTpaIPV	1 dose dTpa**** ogni 10 anni		
IPV poliomielite		IPV		IPV			IPV				IPV				
Epatite B		Ep B		Ep B			Ep B								
Hib *Haemophilus influenzae b*		Hib		Hib			Hib								
Pneumococco		PCV		PCV			PCV								PCV+PPSV
MPRV								MPRV			MPRV				
MPR								*oppure* MPR + V			*oppure* MPR + V				
Varicella															
Meningococco C								Men C§				Men ACWY coniugato			
Meningococco B*^		Men B	Men B		Men B			Men B							
HPV papilloma virus												HPV°: 2-3 dosi (in funzione di età e vaccino)			
Influenza															1 dose all'anno
Herpes Zoster															1 dose#
Rotavirus		Rotavirus## (due o tre dosi a seconda del tipo di vaccino)													
Epatite A															

IPV = vaccino antipolio inattivato
Ep B = vaccino contro il virus dell'epatite B
Hib = Vaccino contro le infezioni invasive da Haemophilus influenzae tipo b
DTPa = vaccino antidifterite-tetano-pertosse acellulare
dTpa = vaccino antidifterite-tetano-pertosse acellulare, formulazione per adulti
dTpa-IPV = vaccino antidifterite-tetano-pertosse acellulare e polio inattivato, formulazione per adulti
MPRV = Vaccino tetravalente per morbillo, parotite, rosolia e varicella
MPR = Vaccino trivalente per morbillo, parotite, rosolia
V = Vaccino contro la varicella

PCV = Vaccino pneumococcico coniugato
PPSV = Vaccino pneumococcico polisaccaridico
MenC = Vaccino contro il meningococco C coniugato
MenB = Vaccino contro il meningococco B
HPV = Vaccino contro i papillomavirus
Influenza = Vaccino contro l'influenza stagionale
Rotavirus = Vaccino contro i rotavirus
Ep A = vaccino contro il virus dell'epatite A

Cosomministrare nella stessa seduta
Somministrare in seduta separata

Infectious diseases are still a leading cause of death



Some diseases for which effective vaccines are not yet available

Disease	Estimated annual mortality	Estimated annual incidence
Malaria*	1,124,000	300–500 million
Schistosomiasis	15,000	no numbers available
Worm infestation	12,000	no numbers available
Tuberculosis	1,644,000	~8 million
Diarrheal disease	2,001,000	~4,100 million
Respiratory disease	3,947,000	~362 million
HIV/AIDS	2,866,000	~2 million

About 15 millions (>25%) of annual deaths worldwide are caused by infectious diseases

Morens DM et al Nature 2004

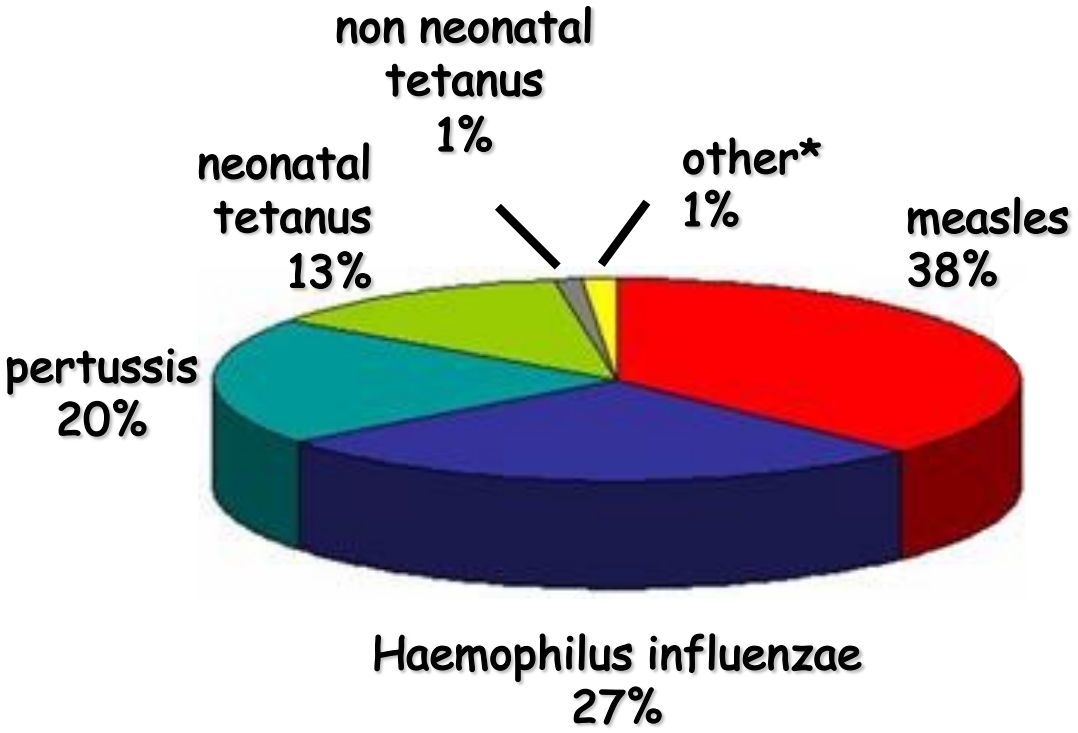
Childhood diseases are still the leading cause of death in developing countries

Estimated annual deaths worldwide of children under 5 years of age, by pathogen	
Pathogen	**Deaths (thousands)**
Pneumococcus*	841
Measles	530
Haemophilus (strains a–f)†	945
Rotavirus†	800
Malaria	700
HIV	500
RSV	500
Pertussis	285
Tetanus	201
Tuberculosis	100

*Bold signifies pathogens for which an effective vaccine exists.

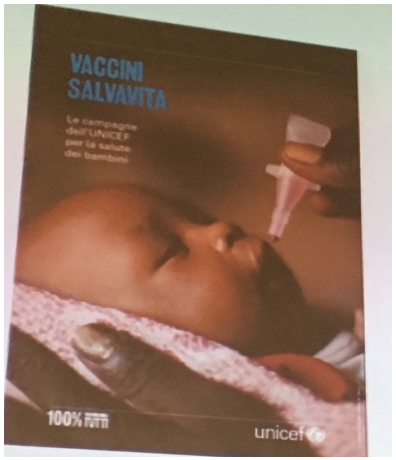
†A licensed vaccine is being tested for possible side effects.

SOURCE: Data derived from WHO publications.



*other= polio, diphtheria, yellow fever

In 2000, WHO estimated that 1.5 million of deaths among children under 5 years were due to diseases that could have been prevented by routine vaccination.



Despite increased uptake by developing countries

19 MILLION CHILDREN

ARE NOT FULLY IMMUNISED
WITH BASIC VACCINES

that is

TWICE

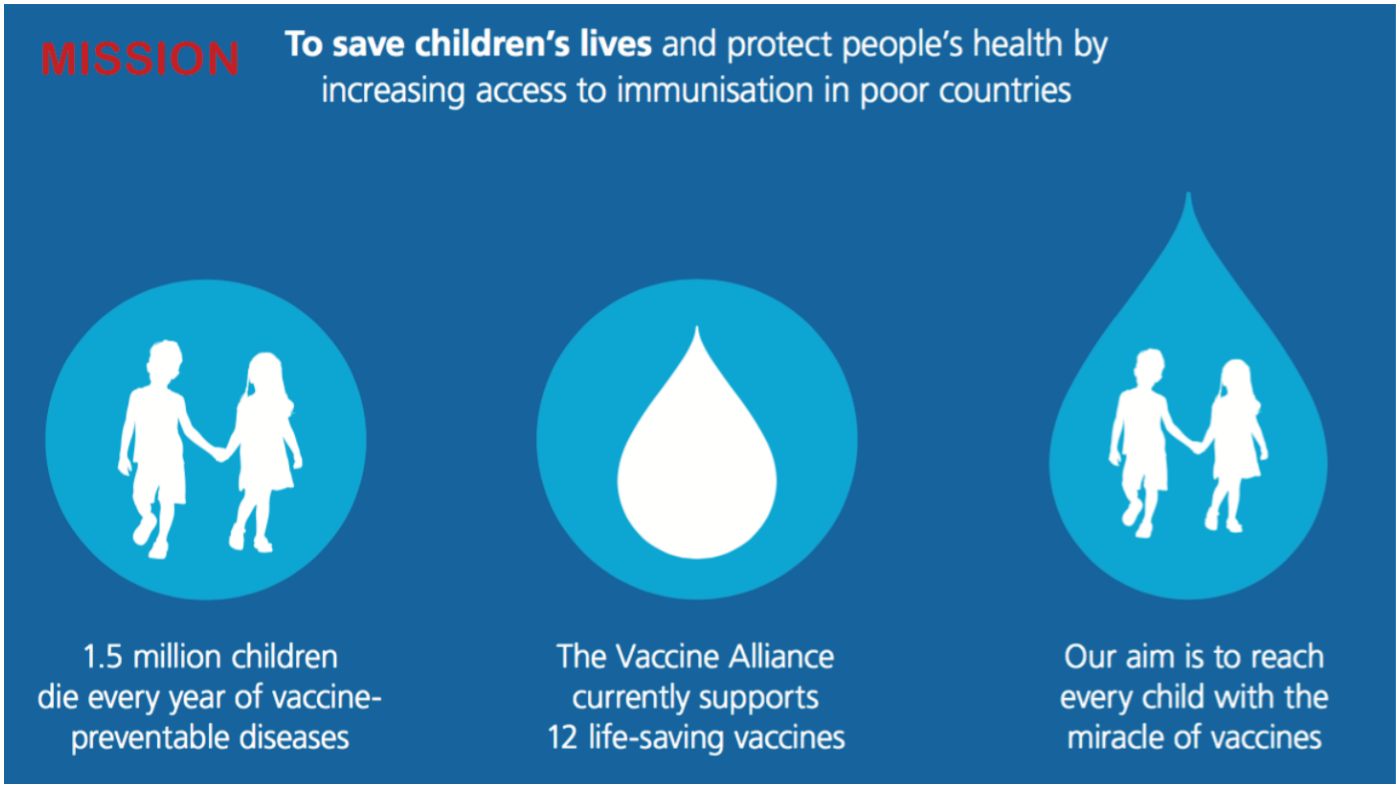
AS MANY CHILDREN AS ARE
BORN EACH YEAR IN THE USA
AND THE EUROPEAN UNION
COMBINED

GAVI ALLIANCE

An innovative public-private partnership

"To save children's lives and protect people's health through the widespread use of vaccines"

GAVI was created in 2000, operates in 73 developing countries and has distributed almost 10 billion euro, so far.



GAVI has helped immunize about 300 million children against deadly diseases such as diphtheria, tetanus, whooping cough, and hepatitis B.

Need to design vaccines for emerging infectious diseases

Emerging infections

- AIDS
- Anthrax
- Avian influenza
- Cholera
- Dengue
- Diphtheria
- Ebola virus disease
- EV71
- Malaria
- Meningococcus serogroup X
- Plague
- SARS
- Smallpox
- Swine influenza
- Tuberculosis
- West Nile

Table 2 | **Examples of newly emerging and re-emerging infectious diseases***

Disease	Affected demographic	Current vaccine or vaccines
Newly emerging		
Anthrax	Individuals affected by bioterrorism	Anthrax vaccine is licensed and in use in the US for military and laboratory personnel who are at risk
Cryptosporidiosis	Europe, North America	None
Cyclosporiasis	North America	None
Ebola virus disease	Africa	No vaccine approved for humans; vaccines under evaluation in animal models
Enterovirus 71	Asia	None
Escherichia coli 0157:H7	Asia, Europe, North America	None
H1N1 2009 pandemic influenza A	Global	Adjuvanted and unadjuvanted inactivated vaccines, live-attenuated vaccine
H5N1 influenza A	Asia	Adjuvanted and unadjuvanted inactivated vaccines
Hantavirus pneumonia	North and South America	None
Lassa fever	Africa	No vaccine approved for humans; vaccines under evaluation in animal models
Marburg haemorrhagic fever	Africa	No vaccine approved for humans; vaccines under evaluation in animal models
SARS	Global	No vaccine approved for humans; vaccines under evaluation in animal models
Re-emerging		
Cholera	Asia, South America	Multiple vaccines in use globally
Dengue	Asia, North and South America	No vaccine approved for humans; vaccines under evaluation in clinical trials in humans
Human monkeypox	Africa	None
Malaria, multidrug resistant	Africa, Asia	No vaccine approved for humans; vaccines under evaluation in clinical trials in humans, with RTS,S being the furthest along in clinical trials
Plague	Africa	Vaccines approved for human use, with others in development
Staphylococcus aureus, multidrug resistant	Asia, Europe, North and South America	No vaccine approved for humans; vaccines under evaluation in clinical trials in humans, with one glycoconjugate vaccine having failed to show efficacy in a Phase III trial
Tuberculosis, multidrug resistant	Global	BCG in routine use, with other vaccines in development
Yellow fever	Africa, Asia, South America	Live-attenuated vaccines in use globally, with others in development

BCG, bacille Calmette–Guérin; SARS, severe acute respiratory syndrome. *Information in this table is taken from REFS 16,17.

What are the main features of effective vaccines?

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

Figure 14-23 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Features of effective vaccines	
Induces neutralizing antibody	Some pathogens (such as poliovirus) infect cells that cannot be replaced (eg, 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 14-23 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

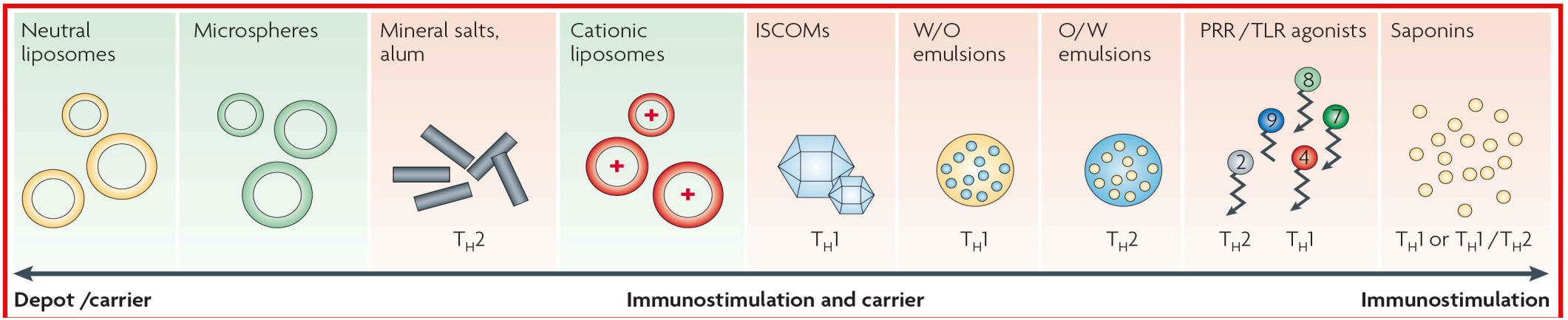
Factors that influence the immunogenicity of proteins

Parameter	Increased immunogenicity	Decreased immunogenicity
Size	Large	Small (MW<2500)
Dose	Intermediate	High or low
Route	Subcutaneous > intraperitoneal > intravenous or intragastric	
Composition	Complex	Simple
Form	Particulate	Soluble
	Denatured	Native
Similarity to self protein	Multiple differences	Few differences
Adjuvants	Slow release	Rapid release
	Bacteria	No bacteria
Interaction with host MHC	Effective	Ineffective

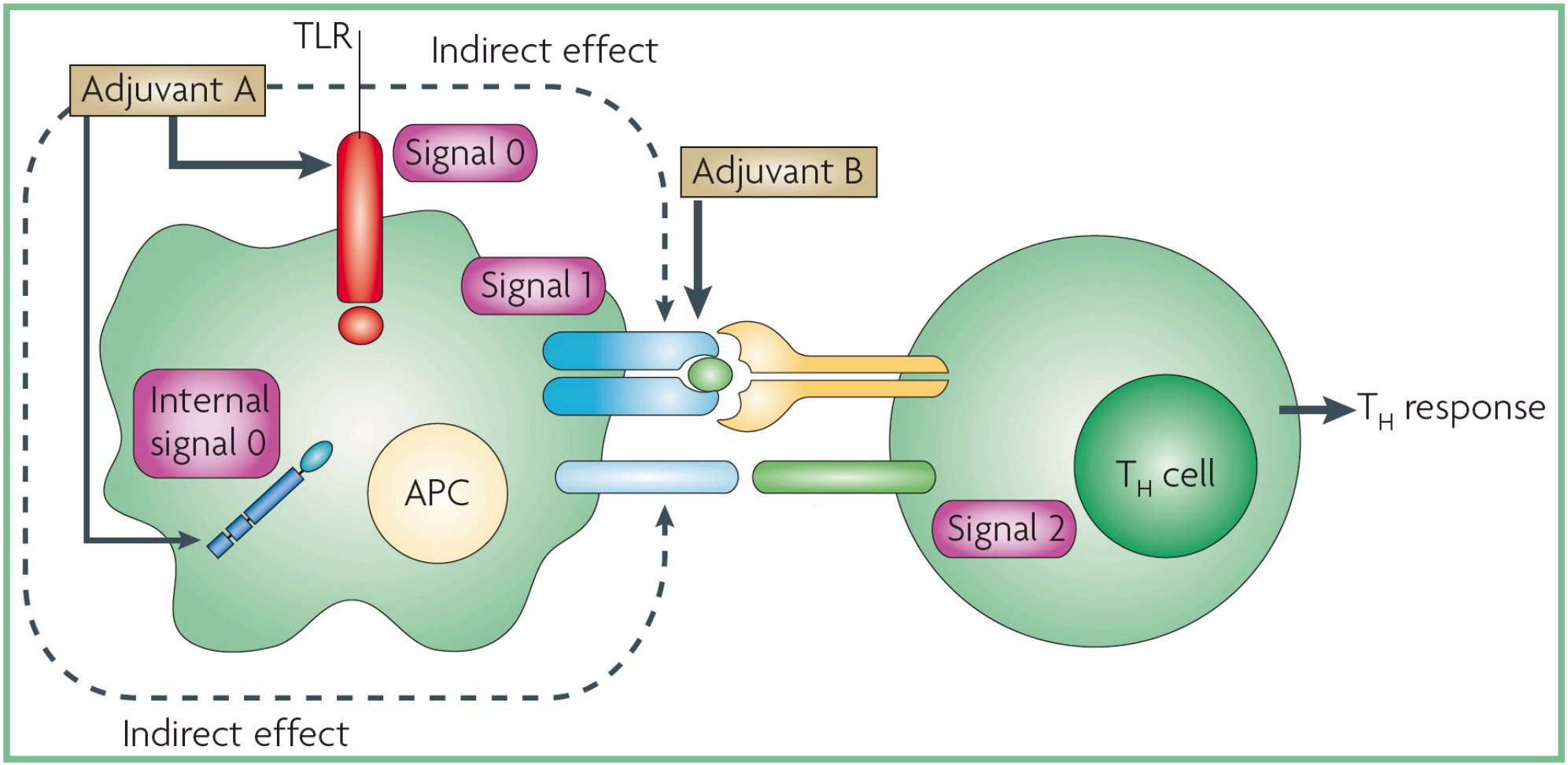
Figure A-2 Immunobiology, 6/e. (© Garland Science 2005)

Mechanisms of Adjuvant Effects

- Adjuvants enhance immunity by promoting key innate response mechanisms.
- Five mechanisms are proposed:
  - slow the release of antigen to produce a depot effect
  - recruit leukocytes to induce proinflammatory cytokines and chemokines
  - promote local APC phagocytosis by aggregating antigens
  - promote antigen presentation by increasing MHC class II and costimulatory molecules
  - encourage pAPC activation and migration to lymph nodes
- Some adjuvants also serve as packaging systems (VLPs, virosomes, etc.).



Adjuvant actions on APC



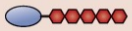
Type A adjuvants (TLR agonists): APC activation
Type B adjuvants (liposomes, mineral salts and emulsions): favor antigen capture and presentation

Designing Vaccines for Active Immunization

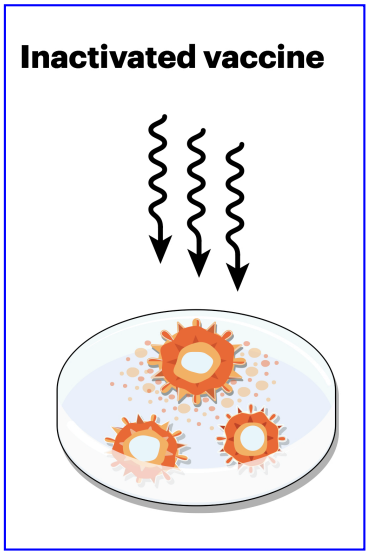
- Many common vaccines use
  - **inactivated** (killed), but still antigenic or
  - live/altered – **attenuated** microorganisms.
    - Caused to loose pathogenicity (cultured in abnormal conditions)
  - substance (e.g., protein, polysaccharide) from pathogen, capable of producing an immune response
- **DNA vaccines** currently being tested for human use

Different types of vaccines

- There are different vaccine types:
  - whole pathogen vaccines containing killed or live microbes
  - subunit vaccines
  - nucleic acid
- Each vaccine type includes multiple subtypes.

Vaccine type	Vaccine subtype		Licensed vaccines currently using this technology	First introduced
Whole pathogen	Live, attenuated		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
	Killed, inactivated		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)
Subunit	Protein		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	1970 (anthrax)
	Polysaccharide		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid	1987 (*H. influenzae* type b)
	Toxoid		Diphtheria, tetanus	1923 (diphtheria)
	Virus-like particle		Human papillomavirus	1986 (hepatitis B)
Nucleic acid	DNA		Experimental	
	mRNA		SARS-CoV-2	2020 (SARS-CoV-2)

Characteristics of inactivated (killed) vaccines



The pathogen is treated with heat or chemical to lose its ability to replicate.
The inactivated pathogen retain the ability to be recognized by the immune system, triggering a humoral response.
Examples: polio, hepatitis A, rabies

Pros:

- Stable and easy to store and transport
- Safe and well-tolerated (no reversion to pathogenic form)
- Low risk of causing infection

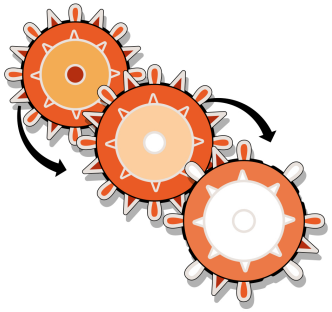
Cons:

- Do not replicate in host or induce cell-mediated immunity (humoral only)
- Often require repeated booster doses and the incorporation of an adjuvant
- Potentially dangerous if not all pathogen is killed/inactivated

Modified form Nature | Vol 575 | 28 November 2019

Characteristics of attenuated (live) vaccines

Live, attenuated vaccine



Attenuated viruses are generated upon serial passage in cell cultures or unconventional hosts: they accumulates genetic mutations and/or loses virulence genes and therefore the ability to cause disease in the original host.

Examples: measles, mumps, rubella, varicella,

Pros:

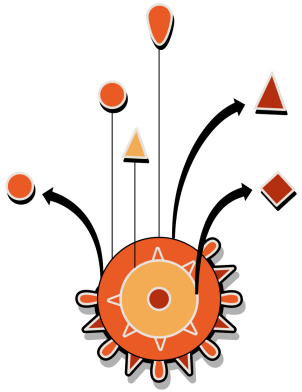
- retain their ability to replicate, promoting both humoral and cell-mediated responses
- often do not need boosters

Cons:

- may mutate back (revert) to pathogenic form
- may have more side effects and complications
- may require a “cold chain” for stability during transport

Subunit Vaccines

Subunit vaccine



One or more parts of the pathogen, such as a protein, are isolated and used to evoke an immune response.

- Low risk of adverse reaction.
- Can be used in people with weakened immune systems.
- Can be difficult to manufacture.
- May require boosters.

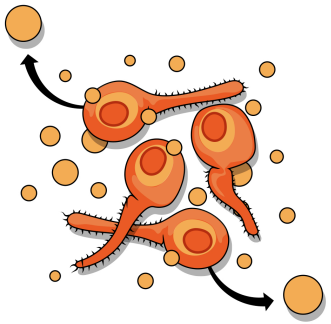
Examples: hepatitis B, influenza, pertussis

Three general forms of such vaccines are in current use:

- **inactivated exotoxins,**
- capsular polysaccharides,
- synthetic peptide vaccines

Modification of toxin into toxoid

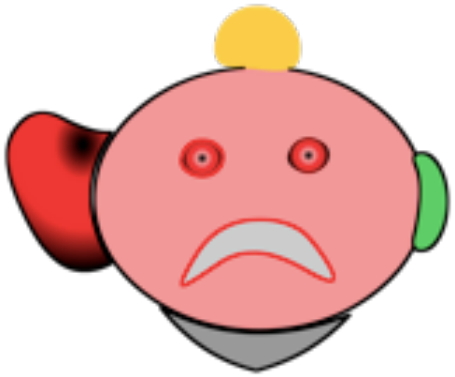
Toxoid vaccine



A toxin produced by the pathogen, instead of the pathogen itself, is deactivated and used to produce the immune response.

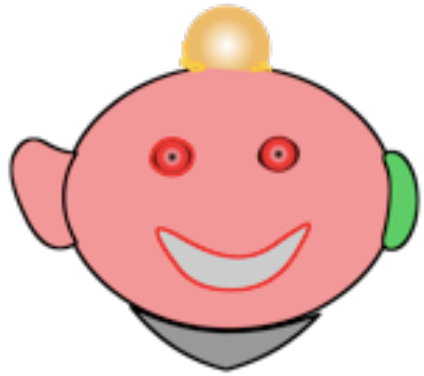
- Unable to cause disease or to spread.
- Stable, so easy to distribute.
- May require boosters to maintain immunity.

Toxin



chemical modification

Toxoid



toxic compounds

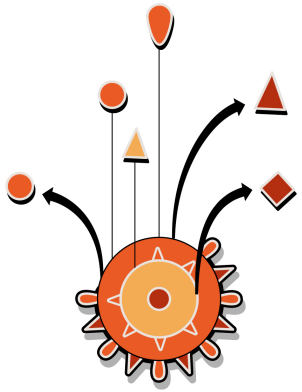
Immunogenic determinants

Examples: tetanus, diphteria

(often administered in the hexavalent DTaP5-IPV-Hib-HepB vaccine)

Subunit Vaccines

Subunit vaccine



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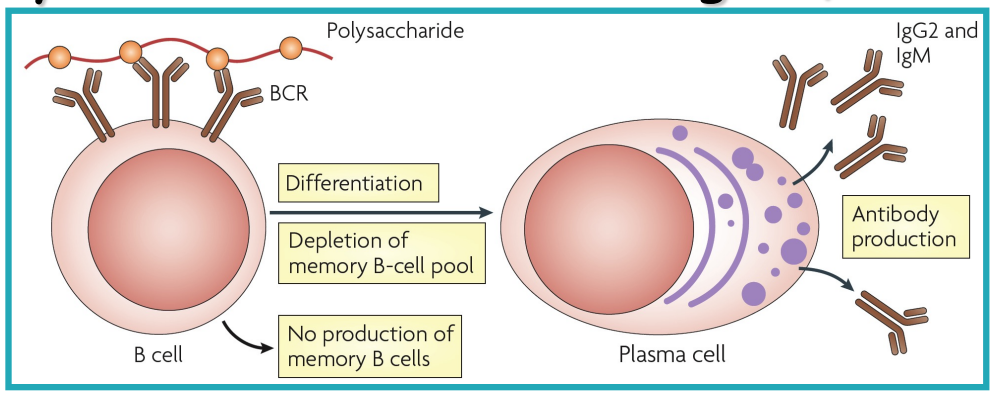
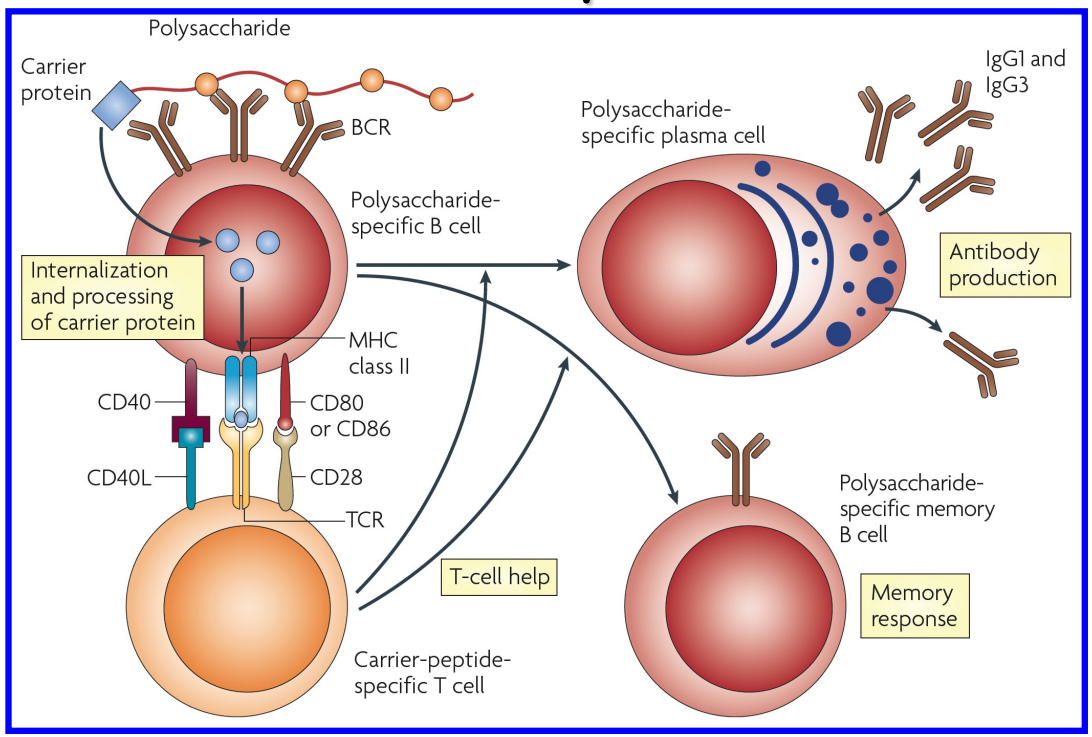
- synthetic peptide vaccines

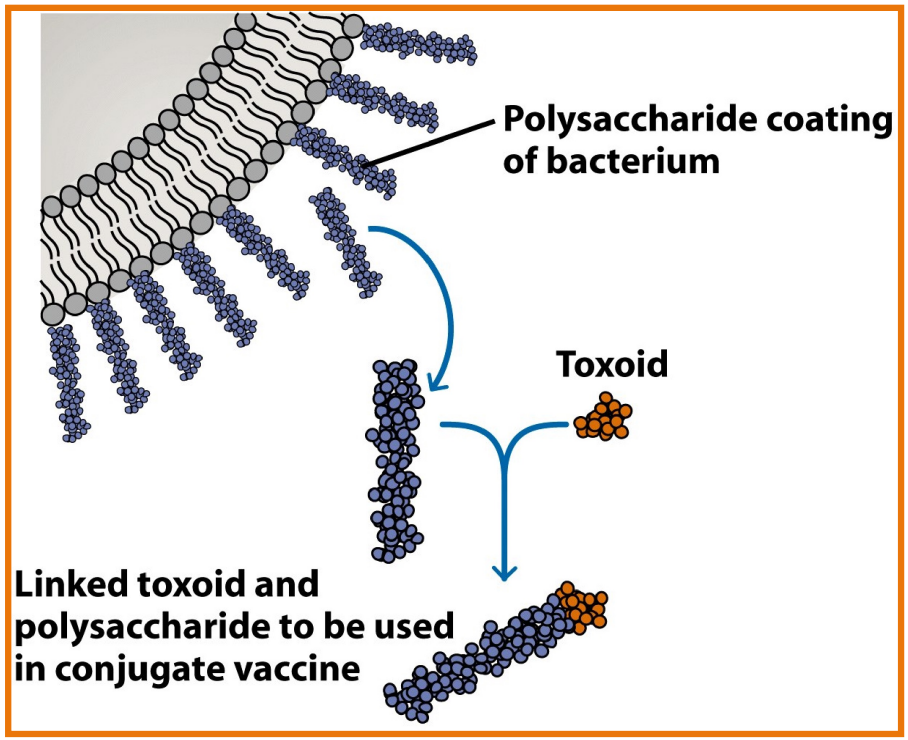
Subunit vaccines: polysaccharide-protein conjugate vaccine

Polysaccharides are T-I antigens, but…



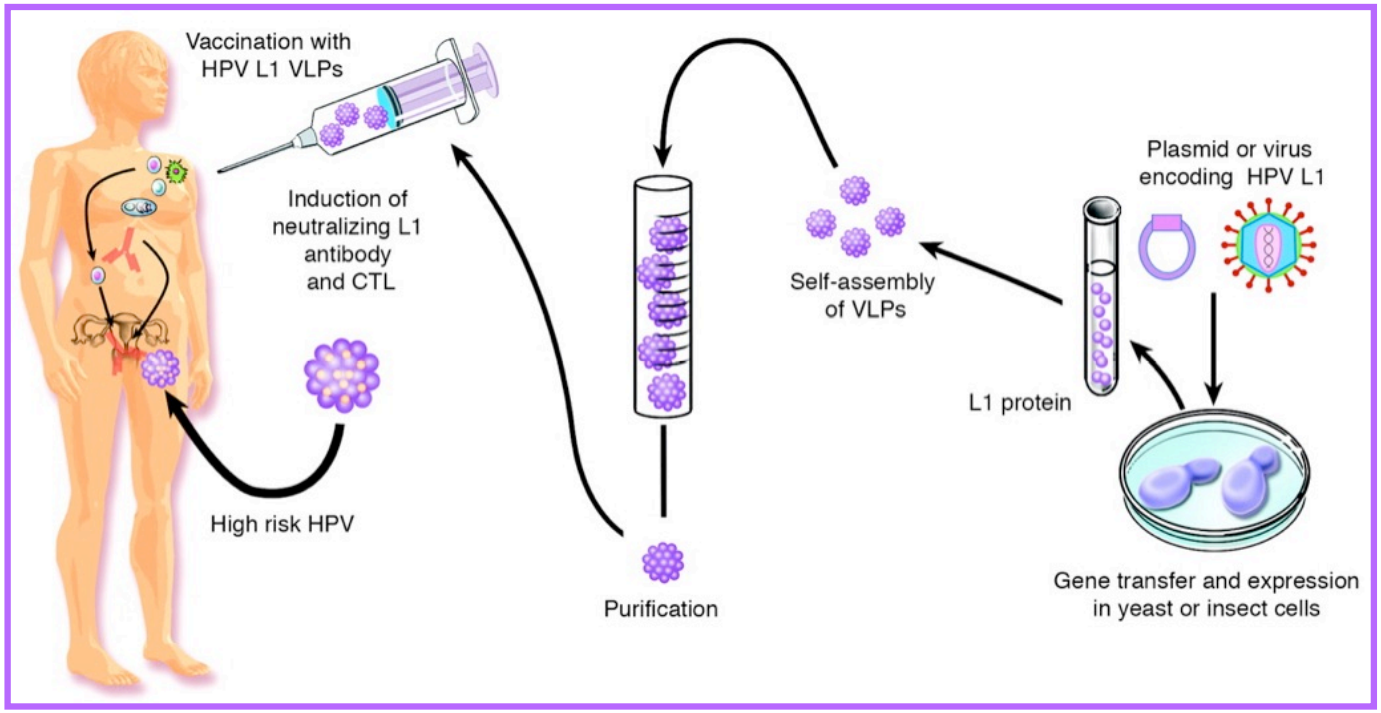
…the association with a protein moiety can recruit T cell help!





This technology has allowed the development and licensure of vaccines against *Haemophilus influenza* type B; meningococcus C; and pneumococcus.

Subunit vaccines: HPV vaccine consisting of L1 (capsid protein) Virus-Like Particles (VLP)



Recombinant L1 capsid protein (HPV-16 or HPV-18) made in yeast or insect cells self-assembles to form VLPs that are very potent at inducing neutralizing antibodies but are not infectious because they lack any viral nucleic acid.

VLP technology has been used to produce other experimental vaccines including respiratory syncytial virus (RSV) and influenza vaccines

First- and second-generation vaccines

Key points

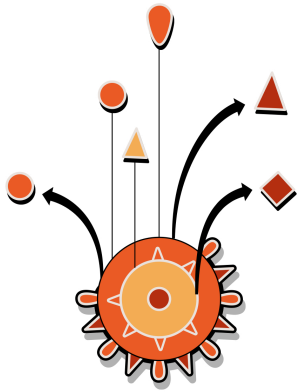
- Live vaccines provide the most robust and longest-lived immune response.
  - They generally do not require boosters or adjuvants.
- Subunit-based vaccines tend to provide a poorer immune response with a shorter protection time.
  - Adjuvants and boosters are generally required with these vaccines.

Adjuvants for general use in humans

Name	Components	Innate triggers	Adaptive response	Examples
Alum	Aluminum salts	NLRP3, inflammasome	T_H2 cells, B cells	Many, including Daptacel (DTaP), Havrux (HepA), Recombivax (HepB), PedvaxHIB (HIB)
MF59	Squalene, polysorbate, Span 85	DAMP release (ATP)	T_H1 cells, CTLs, B cells	Fluad (influenza virus)
AS04	Alum, MPLA	TLR4	T_H1 cells, CTLs, B cells	Cervarix (HPV), Fedrix (HepB)
AS03	Squalene, polysorbate, α-tocopherol	UPR pathway (ER stress response)	T_{FH} cells, B cells	Prepandrix, Pandemrix, Arepanrix (influenza virus)
AS01	MPLA, QS-21 saponin	TLR4	T_H1 cells, CTLs, B cells	Shingrix (herpes-zoster), RTS,S (malaria)
CpG 1018	22-mer, unmethylated, ssDNA	TLR9	T_H1 cells, B cells	Heplisav-B (HepB)
Poly-ICLC	Polyinosinic:polycytidylic acid (dsRNA)	TLR3	T_H1 cells, CTLs, B cells	(In clinical trials)
Imiquimod	Imidazoquinolines (mimic ssRNA)	TLR7/8	T_H1 cells, CTLs, B cells	(In clinical trials)

Subunit Vaccines

Subunit vaccine



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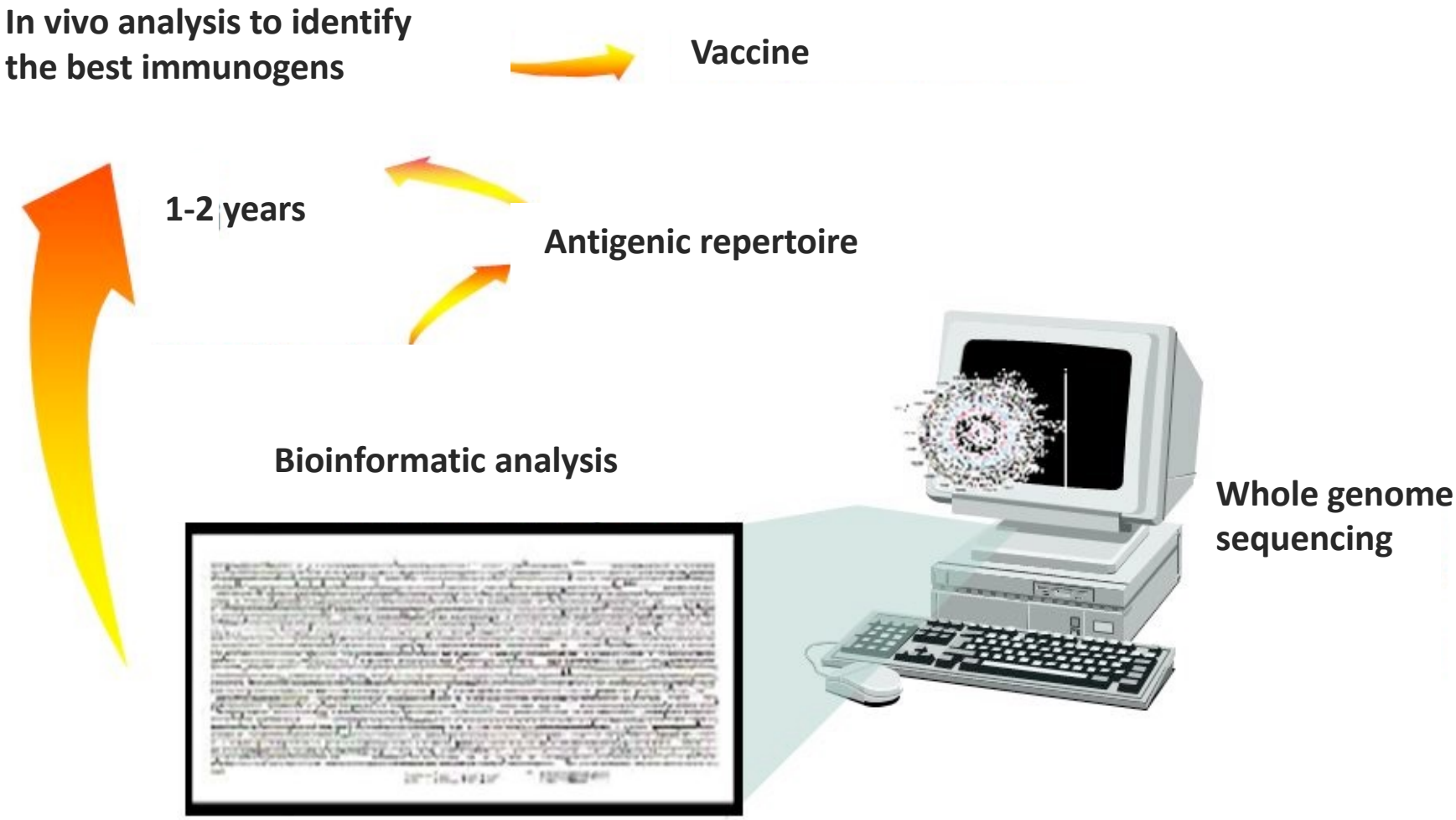
- Can be difficult to manufacture.
- May require boosters.

Examples: hepatitis B, influenza, pertussis

Three general forms of such vaccines are in current use:

- inactivated exotoxins,
- capsular polysaccharides,
- **synthetic peptide vaccines**

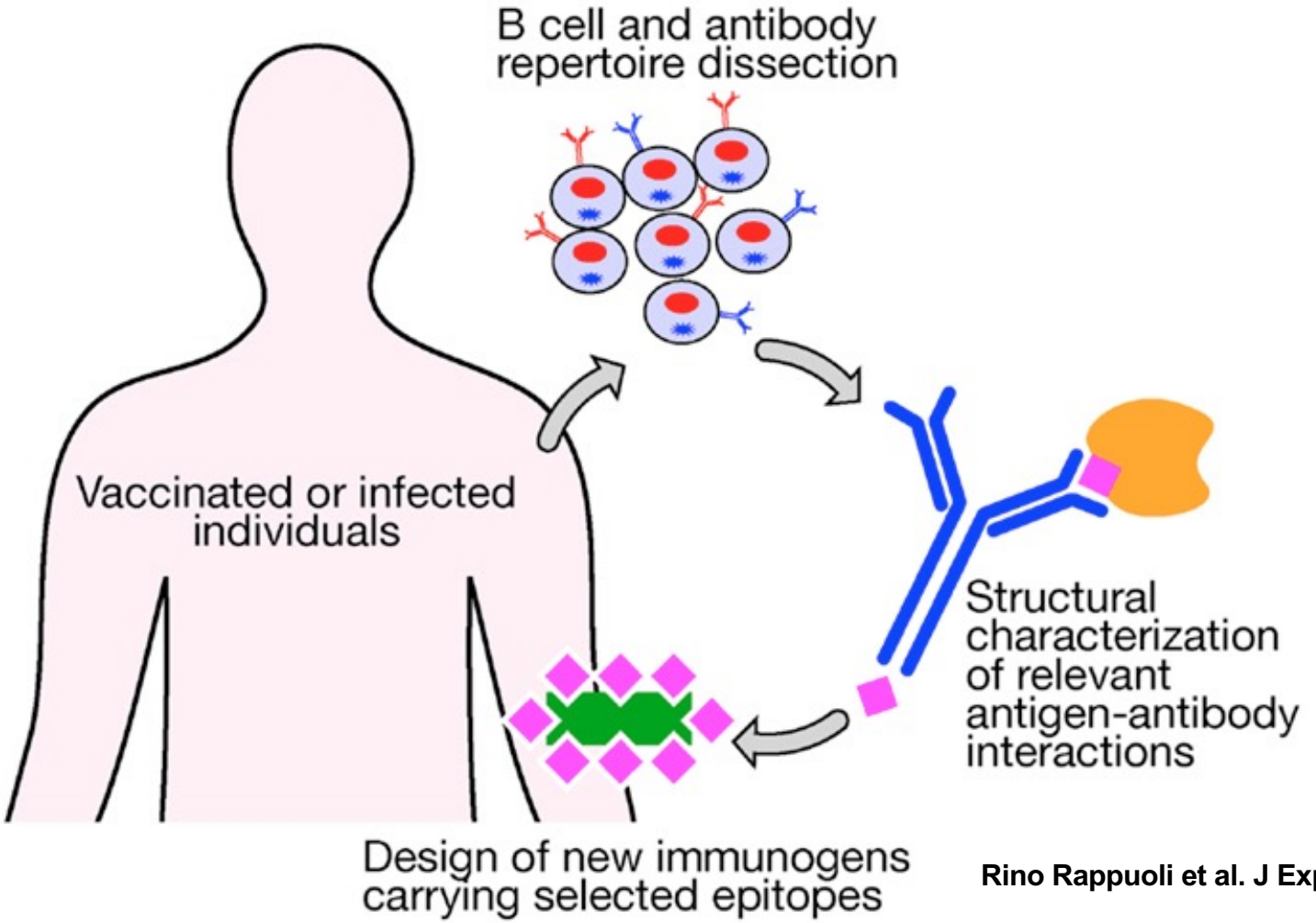
The advent of reverse vaccinology (RV)



Tettelin H, et al. *Science*. 2000;287:1809–1815.
Rappuoli R. *Vaccine*. 2001;19:2688–2691.
Pizza M, et al. *Science*. 2000;287:1816–1820.

This technology allowed the development of the vaccine against meningococcus B and advanced preclinical and clinical vaccine studies against several bacteria, including those resistant to antibiotics such as *Staphylococcus aureus* and *E. coli*

Second generation reverse vaccinology



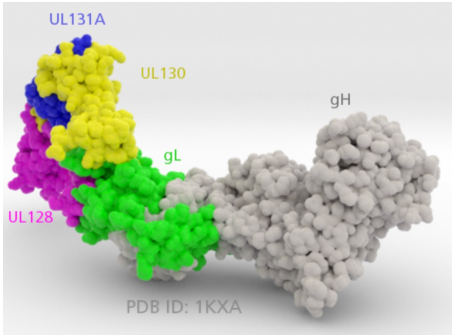
Rino Rappuoli et al. J Exp Med 2016;213:469-481

- A method for constructing synthetic peptide vaccines that contain immunodominant for both
  - B-cell and T-cell epitopes.

This methodology is currently used as a strategy for the preparation of new vaccines against malaria

Antibody-guided vaccine design

- Potent neutralizing antibodies identify the HCMV pentamer as a critical target for vaccine development (*J Virol* 2009)



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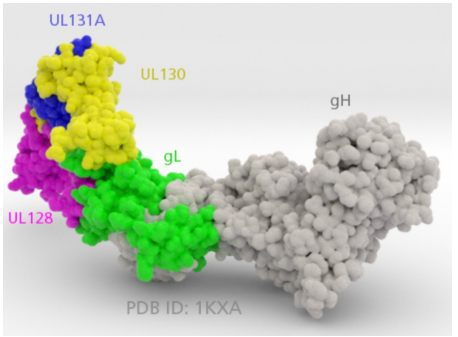

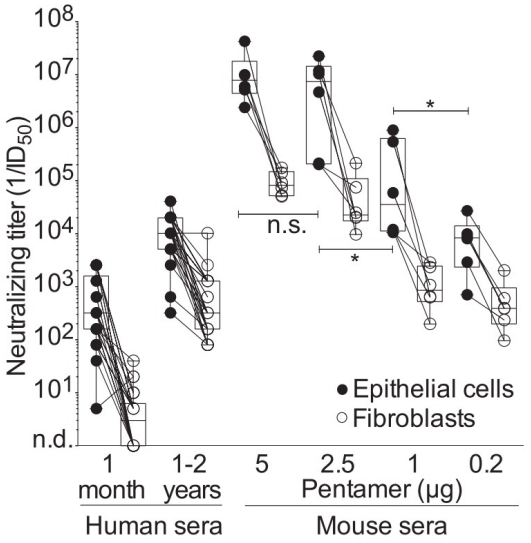

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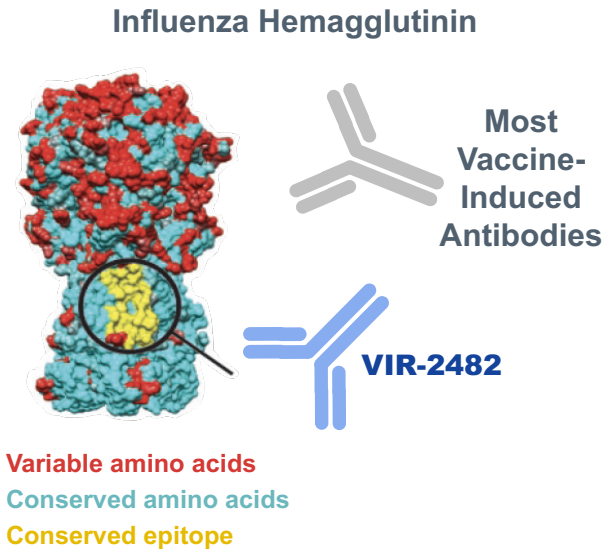

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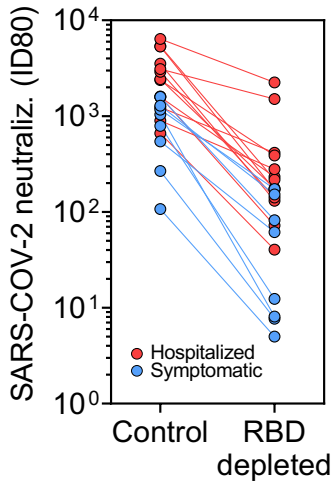
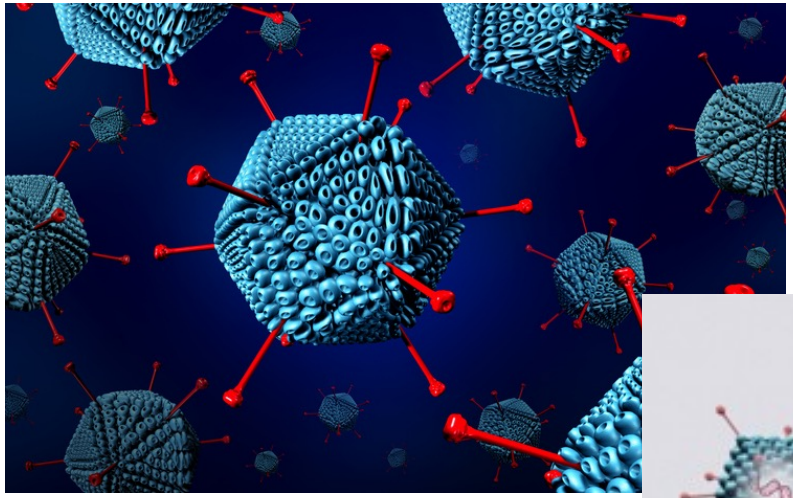
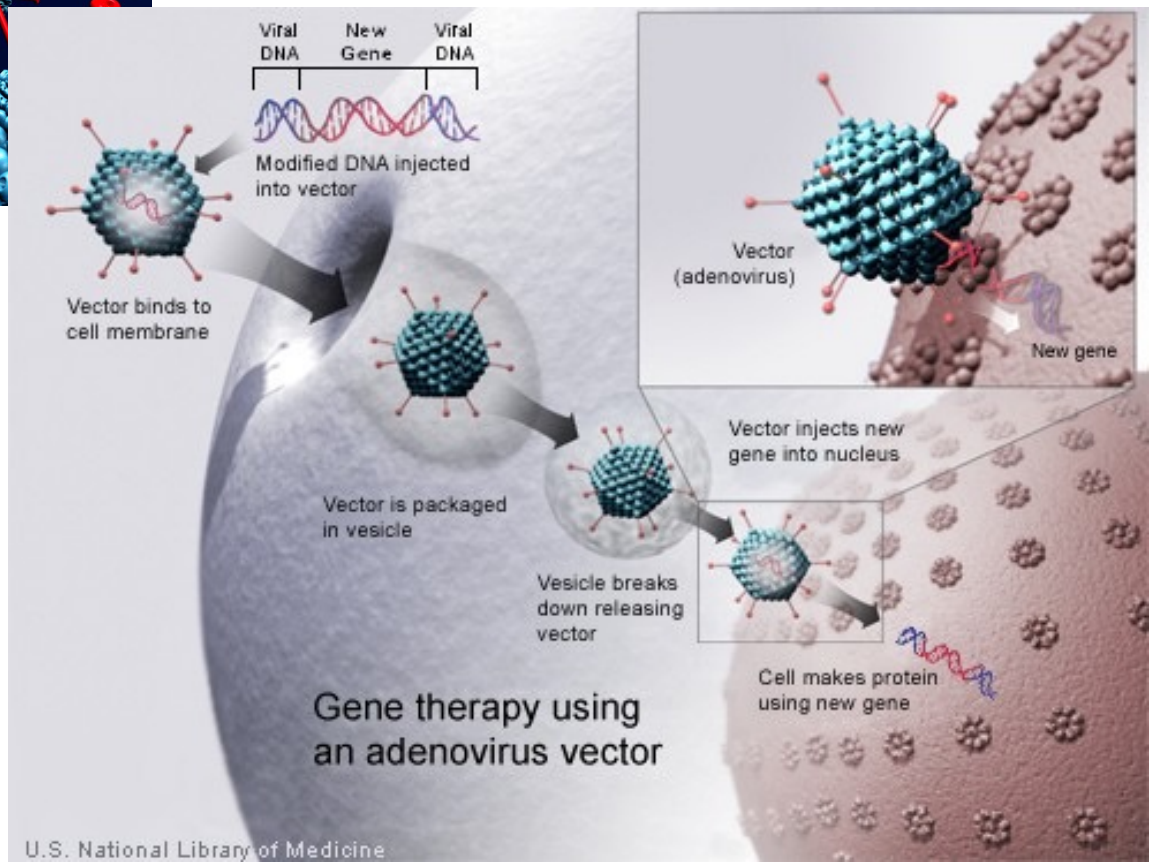
- Broadly neutralizing antibodies identify a conserved region in the stem of influenza hemagglutinin relevant for a universal influenza vaccine (*JCI* 2010, *Science* 2011, *Cell* 2016)
- The finding that most neutralizing antibodies recognize the RBD of SARS-CoV2 provides a rationale for developing an RBD-based vaccine (*Cell 2020*)

Adsorption with RBD removes ≈90% of serum neutralizing activity



Vaccine delivery methods using viral vectors



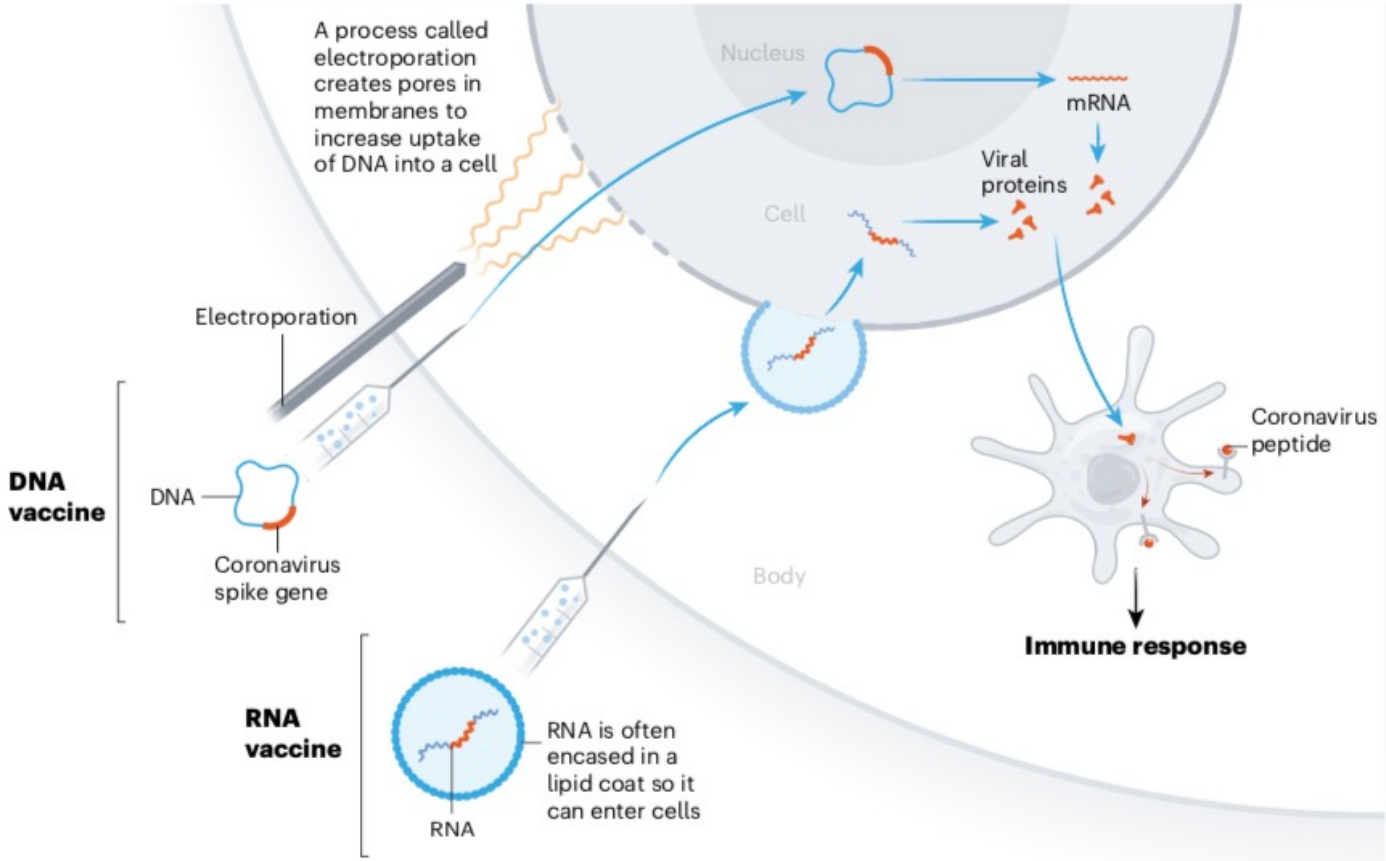


Nucleic-acid Vaccines

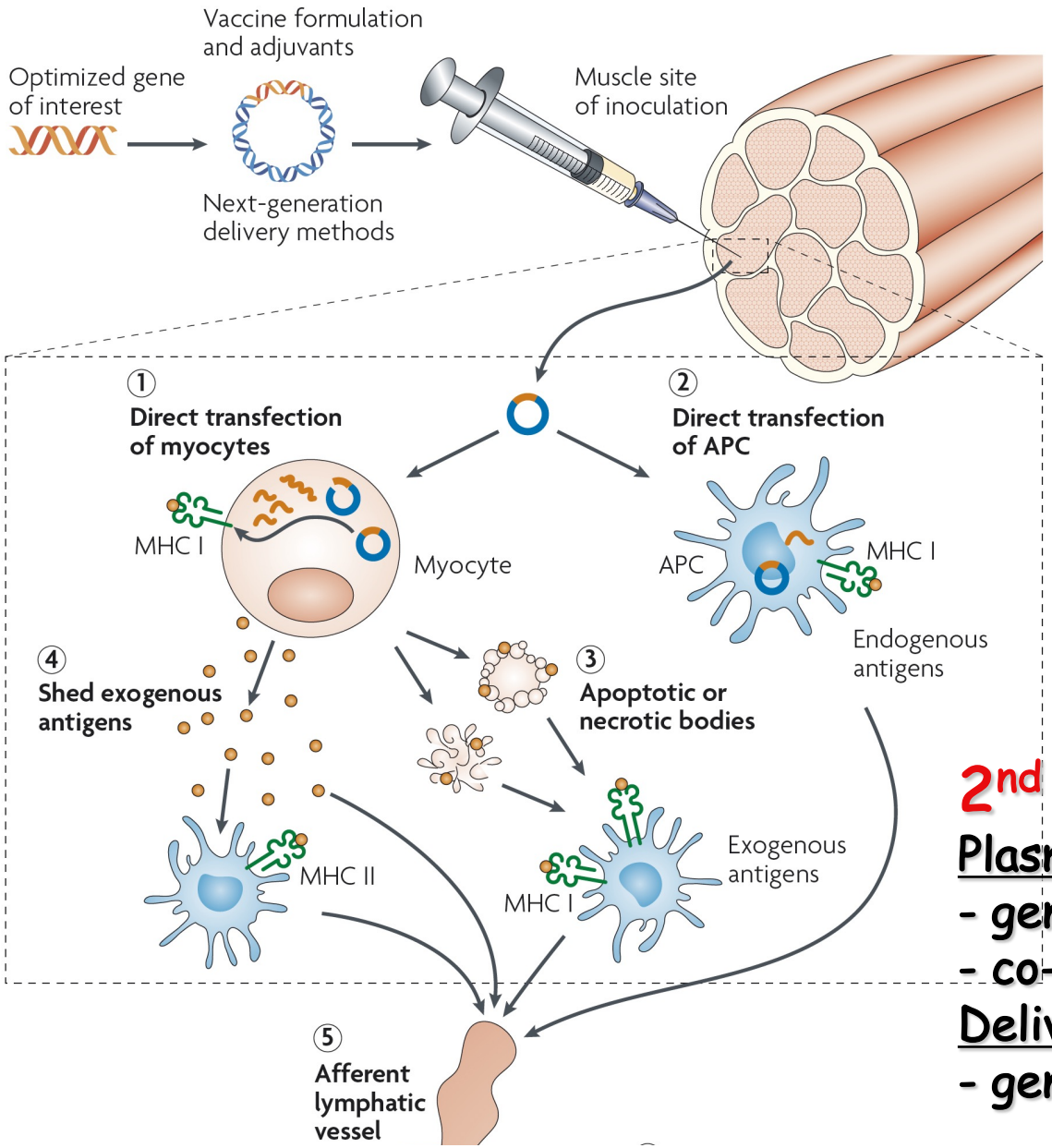
NUCLEIC-ACID VACCINES

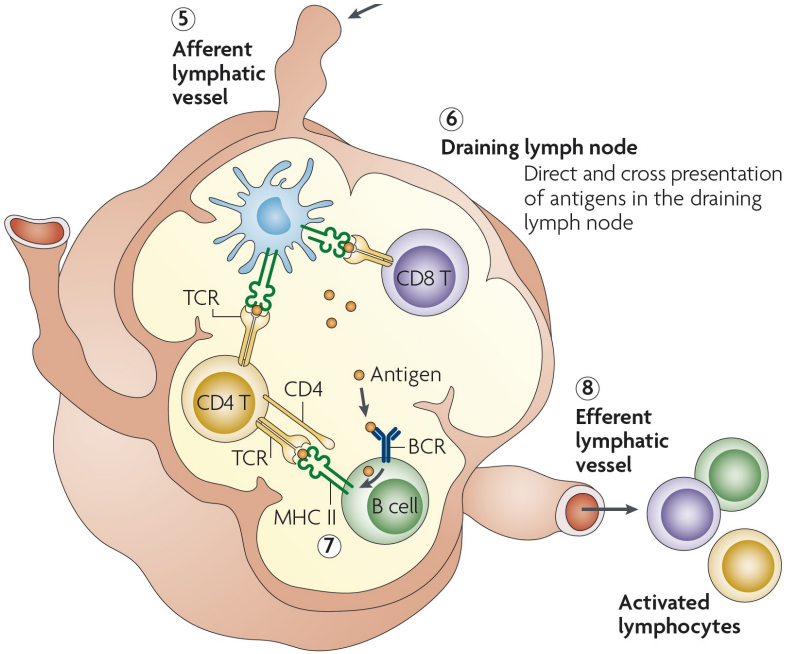
At least 20 teams are aiming to use genetic instructions (in the form of DNA or RNA) for a coronavirus protein that prompts an immune response. The nucleic acid is inserted into human cells, which then churn out copies of the virus protein; most of these vaccines encode the virus's spike protein.

RNA- and DNA-based vaccines are safe and easy to develop: to produce them involves making genetic material only, not the virus. But they are unproven: no licensed vaccines use this technology.



DNA vaccines can induce cell-mediated AND antibody-mediated responses





2nd generation DNA vaccines

Plasmid alterations:

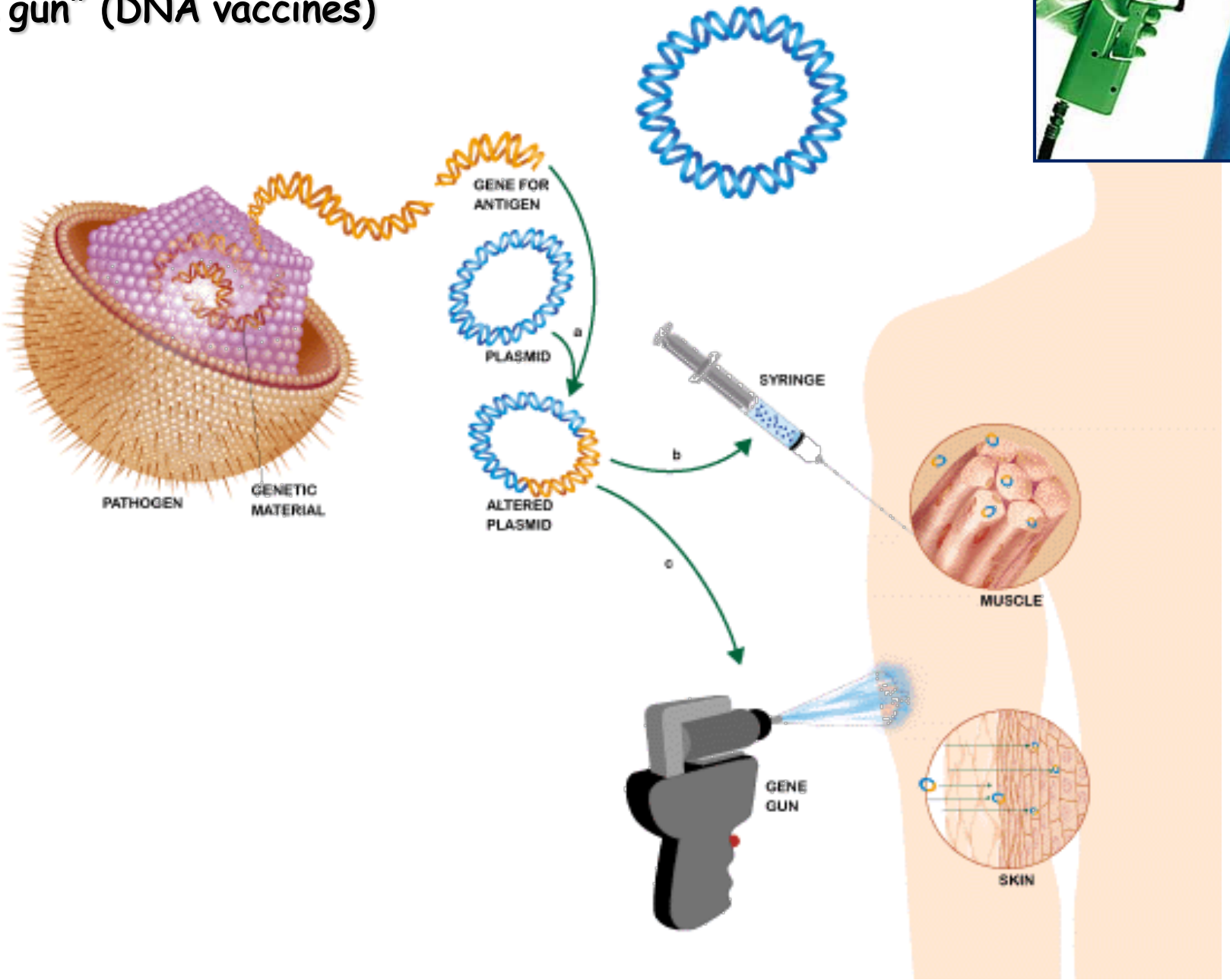
- gene expression regulation
- co-expression of immune modulators

Delivery devices:

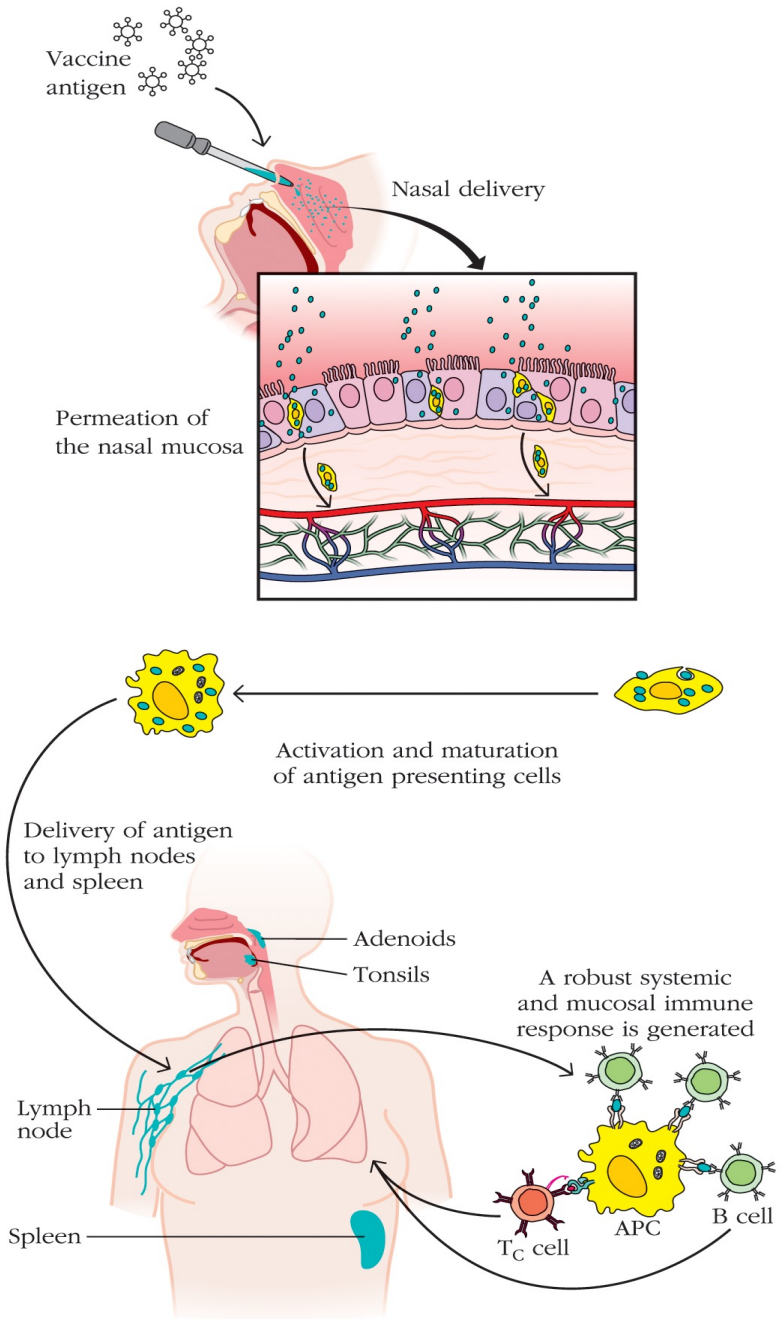
- gene gun; mucosal injectors; microneedle

Alternatives to vaccination with a needle

- "gene gun" (DNA vaccines)



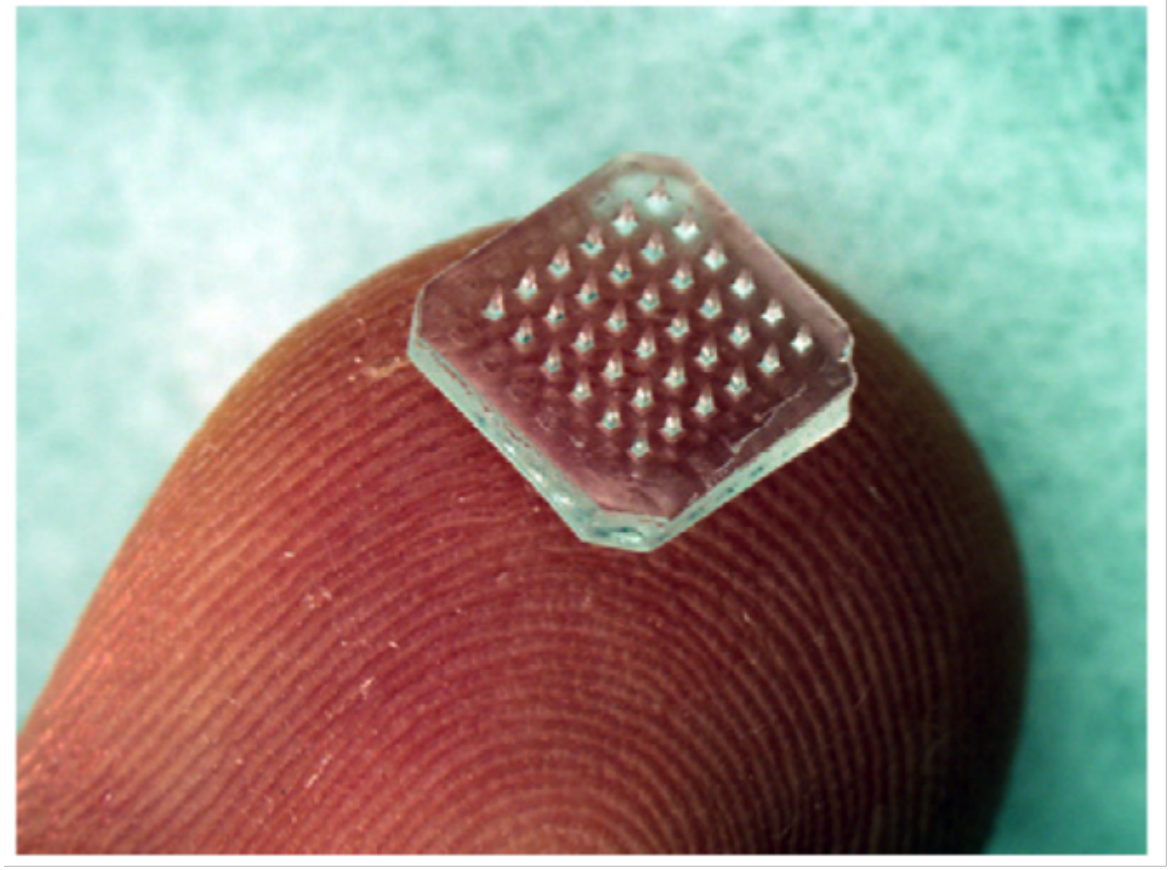
Mucosal administration of live, attenuated microbes



- Some live, attenuated vaccines have been used with mucosal administration.
- FluMist™
  - Attenuated vaccine which uses a cold-adapted strain that cannot replicate at human body temperature (37°C)
- Oral polio vaccine (OPV)
  - a trivalent formula
  - requires three administrations because a new strain predominates each time

An innovativy delivery method: microneedle patches

A patch containing 36 dissolving microneedles is shown on a fingertip

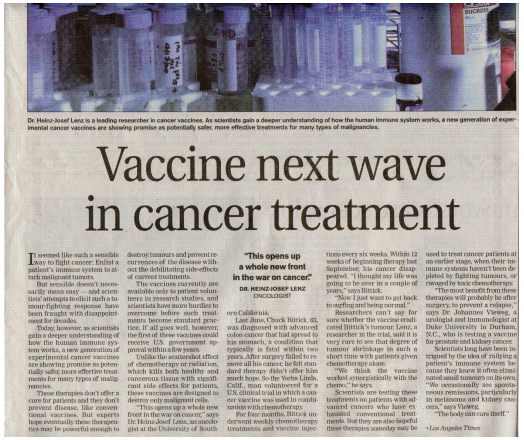


The microneedles dissolve within minutes
after insertion into skin to release encapsulated vaccine.
Each microneedle is 900-μm tall.

Key concepts:

- Vaccines are commonly **prophylactic** and designed to initiate an immune response before the onset of disease or an antigen encounter.

- New **therapeutic vaccines** may enhance the antitumor immune response.
  - They are intended to enhance or redirect immune response after disease has occurred



Dr. Heinz-Josef Lenz is a leading researcher in cancer vaccines. As scientists gain a deeper understanding of how the human immune system works, a new generation of experimental cancer vaccines are showing promise as potentially safer, more effective treatments for many types of malignancies.

Vaccine next wave in cancer treatment

It seemed like such a sensible way to fight cancer: Enlist a patient's immune system to attack malignant tumors.

But sensible doesn't necessarily mean easy — and scientists' attempts to elicit such a tumour-fighting response have been fraught with disappointment for decades.

Today, however, as scientists gain a deeper understanding of how the human immune system works, a new generation of experimental cancer vaccines are showing promise as potentially safer, more effective treatments for many types of malignancies.

These therapies don't offer a cure for patients and they don't prevent disease, like conventional vaccines. But experts hope eventually these therapeutics may be powerful enough to destroy tumours and prevent recurrences of the disease without the debilitating side-effects of current treatments.

The vaccines currently are available only to patient volunteers in research studies, and scientists have more hurdles to overcome before such treatments become standard practice. If all goes well, however, the first of these vaccines could receive U.S. government approval within a few years.

Unlike the unintended effect of chemotherapy or radiation, which kills both healthy and cancerous tissue with significant side effects for patients, these vaccines are designed to destroy only malignant cells.

"This opens up a whole new front in the war on cancer," says Dr. Heinz-Josef Lenz, an oncologist at the University of South-

"This opens up a whole new front in the war on cancer."

DR. HEINZ-JOSEF LENZ
ONCOLOGIST

ern California.

Last June, Chuck Bittick, 63, was diagnosed with advanced colon cancer that had spread to his stomach, a condition that typically is fatal within two years. After surgery failed to remove all his cancer, he felt standard therapy didn't offer him much hope. So the Yorba Linda, Calif., man volunteered for a U.S. clinical trial in which a cancer vaccine was used in combination with chemotherapy.

For four months, Bittick underwent weekly chemotherapy treatments and vaccine injections every six weeks. Within 12 weeks of beginning therapy last September, his cancer disappeared. "I thought my life was going to be over in a couple of years," says Bittick.

"Now I just want to get back to surfing and being normal."

Researchers can't say for sure whether the vaccine eradicated Bittick's tumour. Lenz, a researcher in the trial, said it is very rare to see that degree of tumour shrinkage in such a short time with patients given chemotherapy alone.

"We think the vaccine worked synergistically with the chemo," he says.

Scientists are testing these treatments on patients with advanced cancers who have exhausted conventional treatments. But they are also hopeful these therapies someday may be used to treat cancer patients at an earlier stage, when their immune systems haven't been depleted by fighting tumours, or ravaged by toxic chemotherapy.

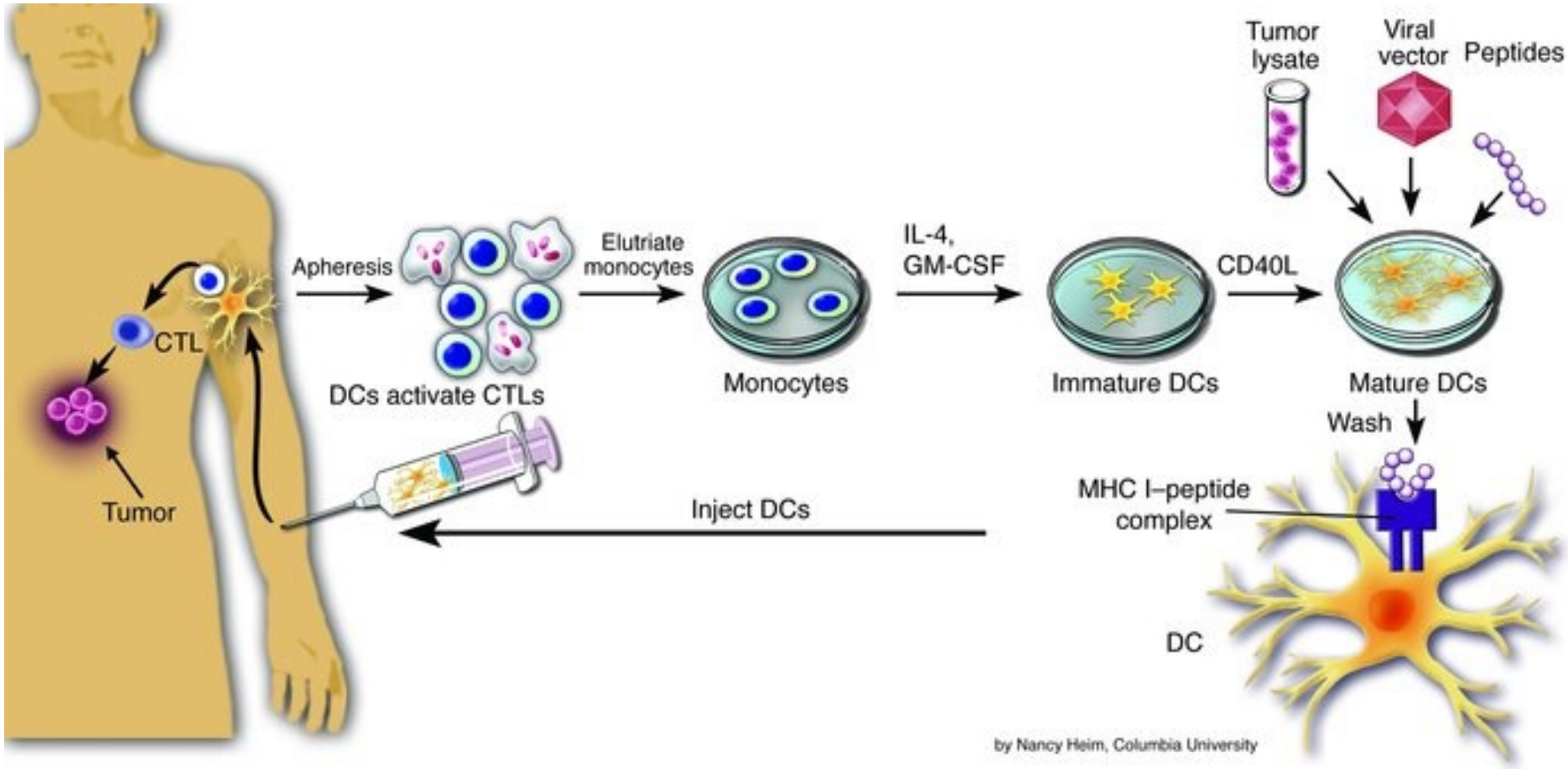
"The most benefit from these therapies will probably be after surgery, to prevent a relapse," says Dr. Johannes Vieweg, a urologist and immunologist at Duke University in Durham, N.C., who is testing a vaccine for prostate and kidney cancer.

Scientists long have been intrigued by the idea of rallying a patient's immune system because they know it often eliminated small tumours on its own. "We occasionally see spontaneous remissions, particularly in melanoma and kidney cancers," says Vieweg.

"The body can cure itself."

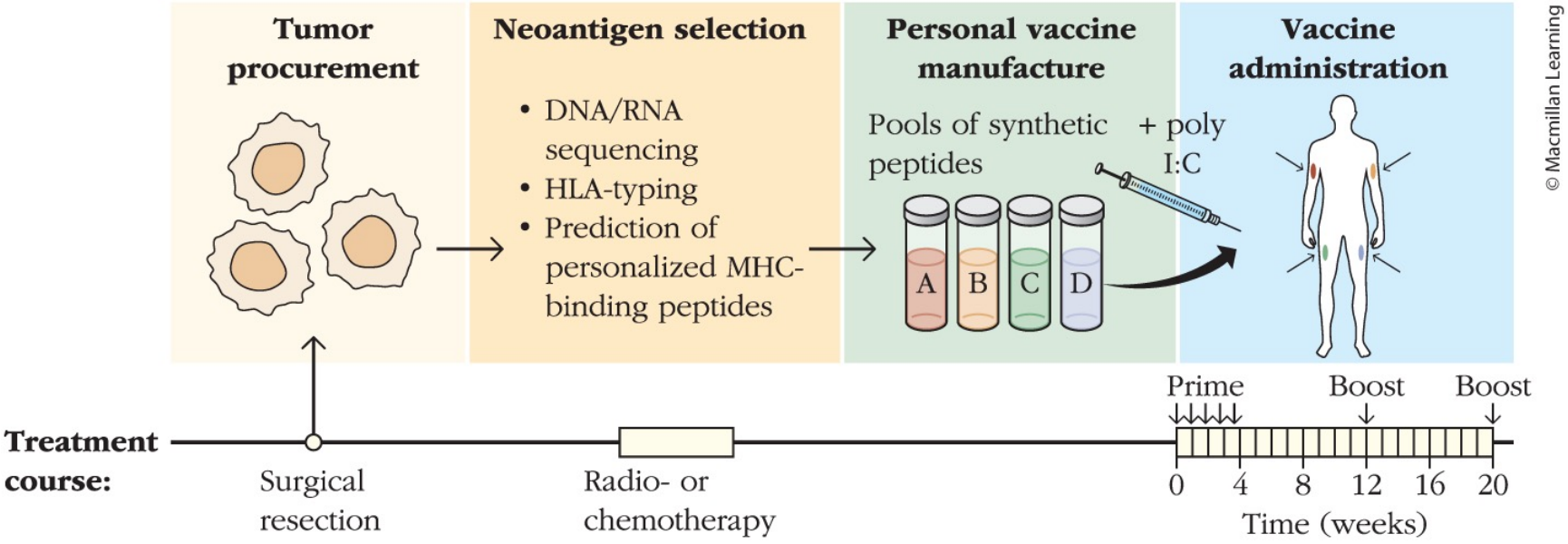
• Los Angeles Times

Cancer Vaccines

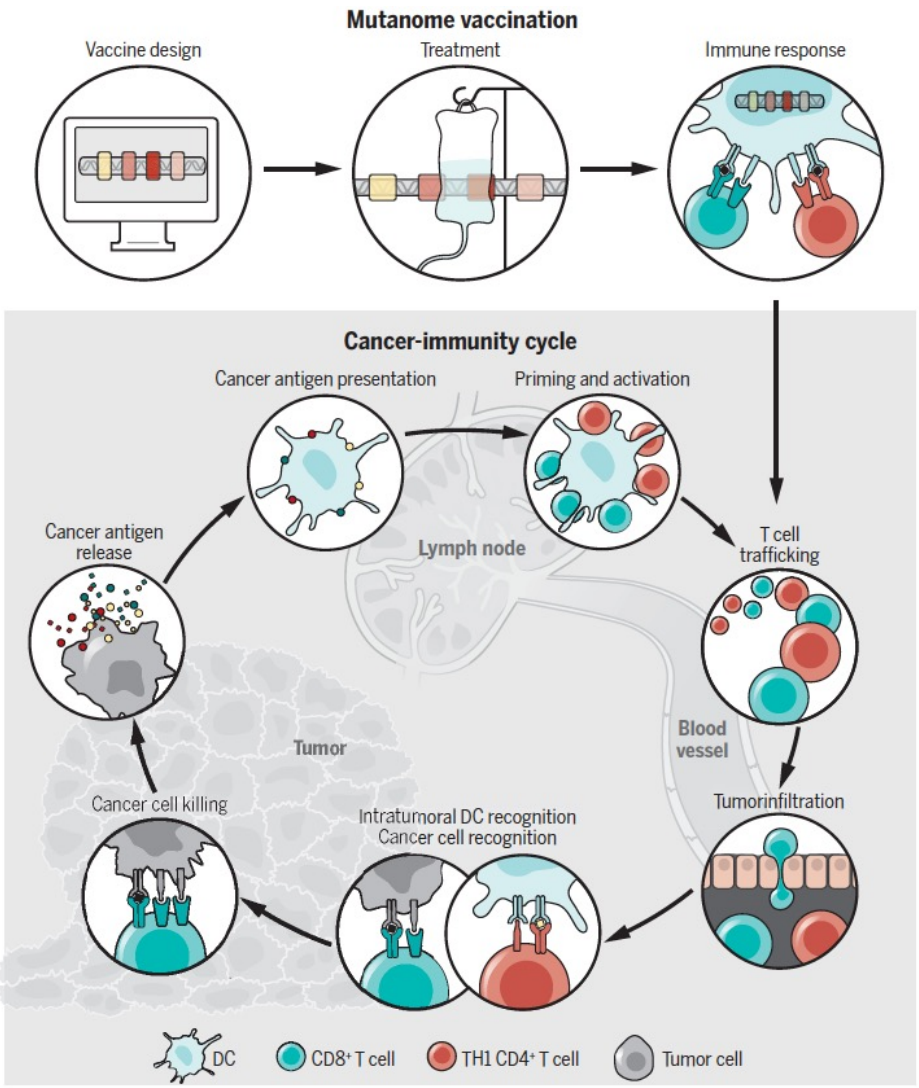


The NeoVax Cancer Vaccine Platform

- Scientists at Dana Farber Cancer Institute have been using the **NeoVax** system to produce personalized, neoantigen-based vaccines based on unique mutations from the patient's own cancer cells.

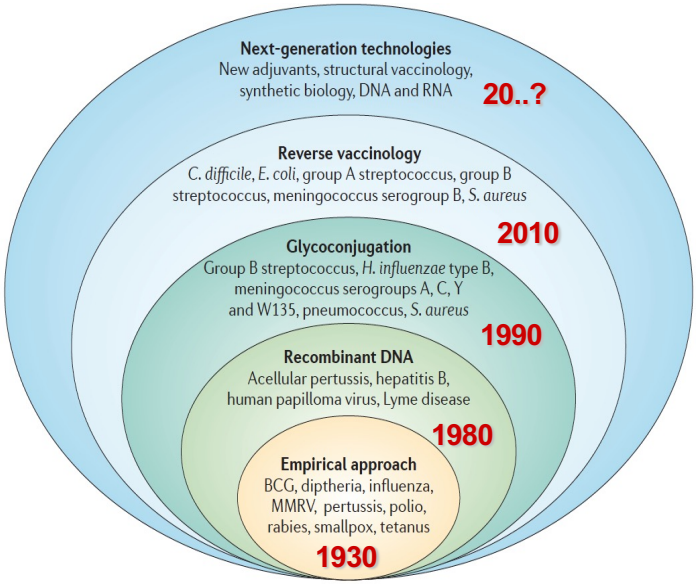


Personilized neoantigens-based vaccines



The personalized vaccine can act at various levels by promoting:

1. The activation of lymphocytes at the lymph node level
2. An inflammatory microenvironment
3. The activity of CD4 and CD8 T lymphocytes in the tumor



Challenges in the vaccination field

- To enhance antibody-mediated and cell-mediated responses
- To augment the quality of T cell responses
- To efficiently elicit mucosal immunity
- To design therapeutical vaccines, beside preventive ones