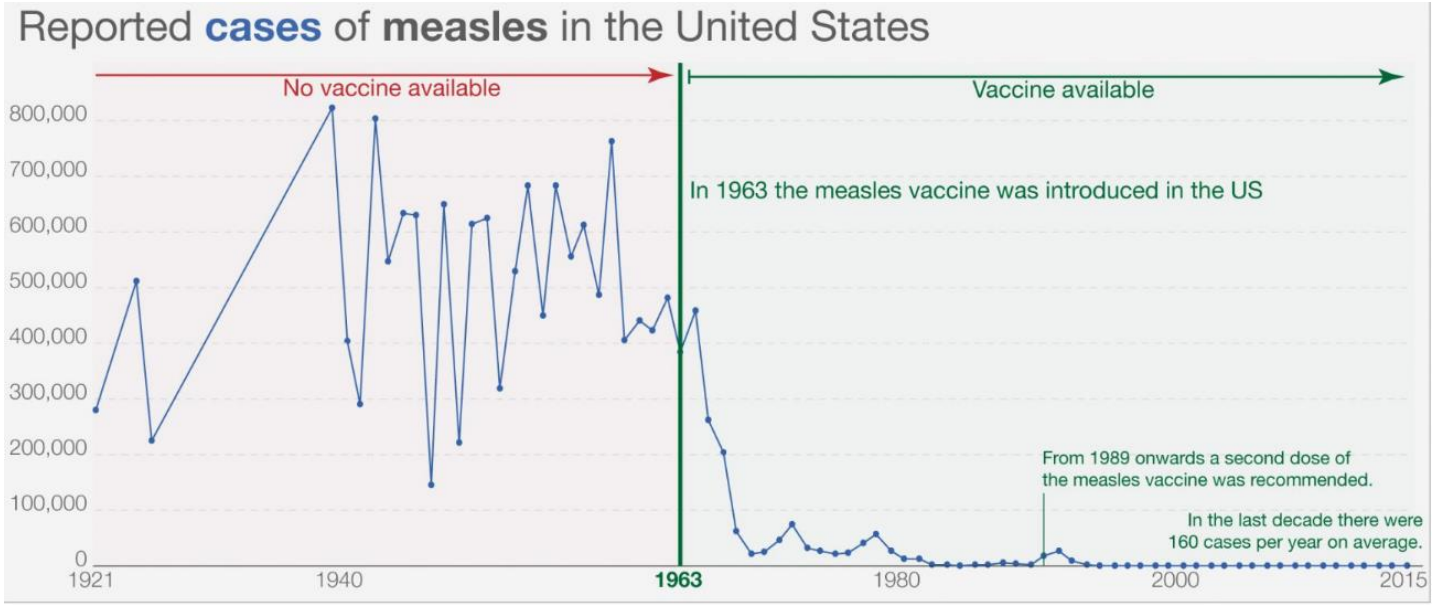
VACINAS

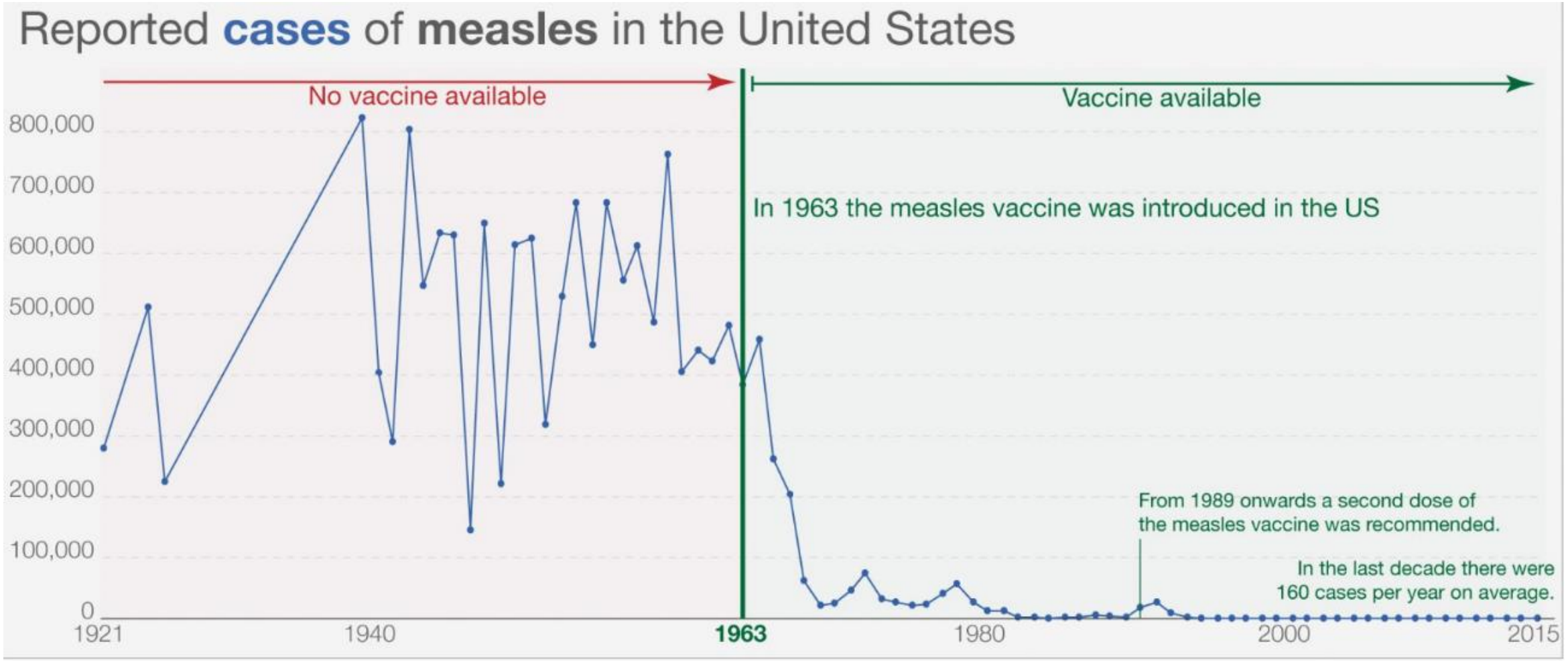
- Histórico
- Tipos
- Estratégias de P&D
- Falhas
- Nutrientes

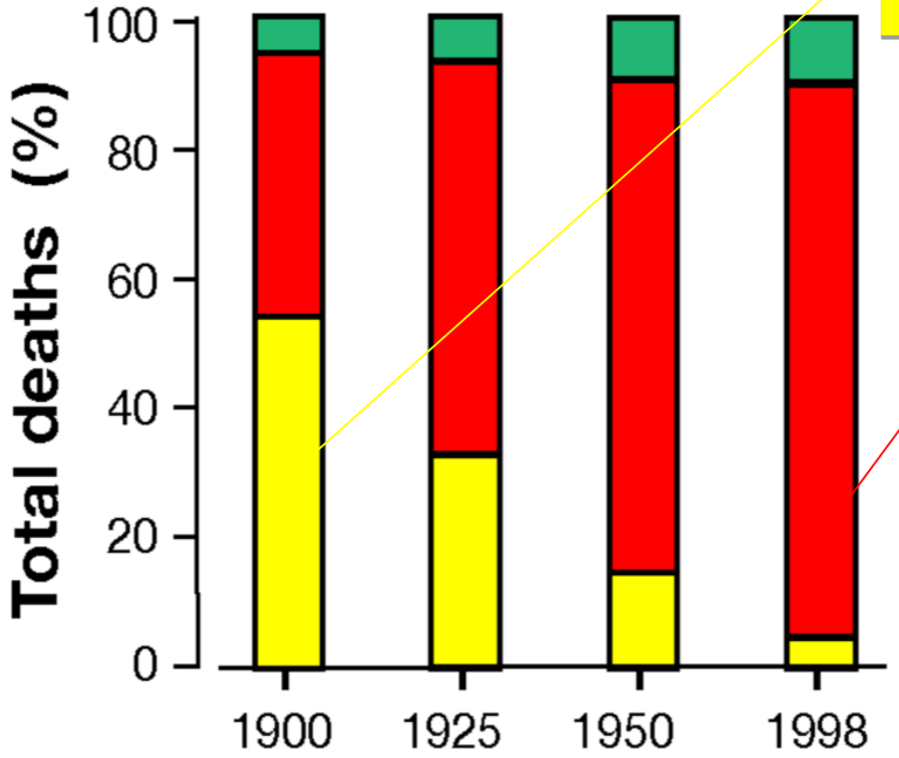


Isabel K F M Santos
r. 150192

VACCINE: a biological preparation that provides active acquired immunity to a particular infectious disease

Vaccination is the most effective means of controlling infectious diseases





Infectious Diseases

Diphtheria (40million prevented)
Measles (35 million prevented)
Smallpox ...

Non Communicable Diseases

Ischemic Heart Disese
Stroke
Cancer
Diabetes
Alzheimer
.....

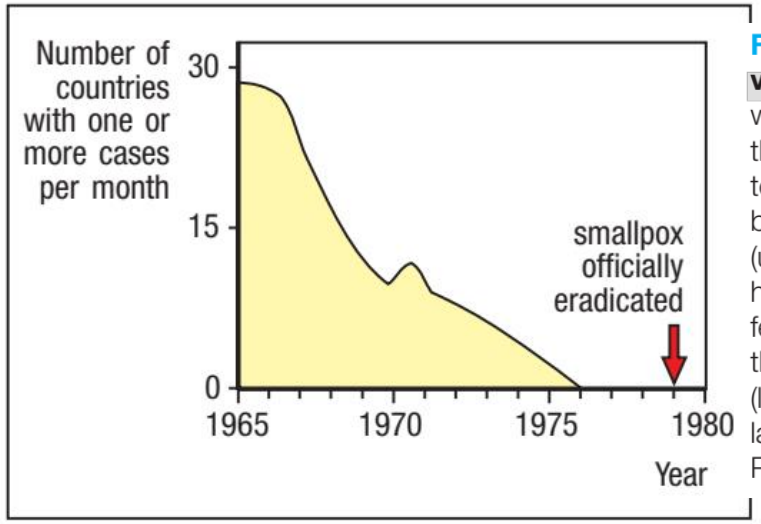
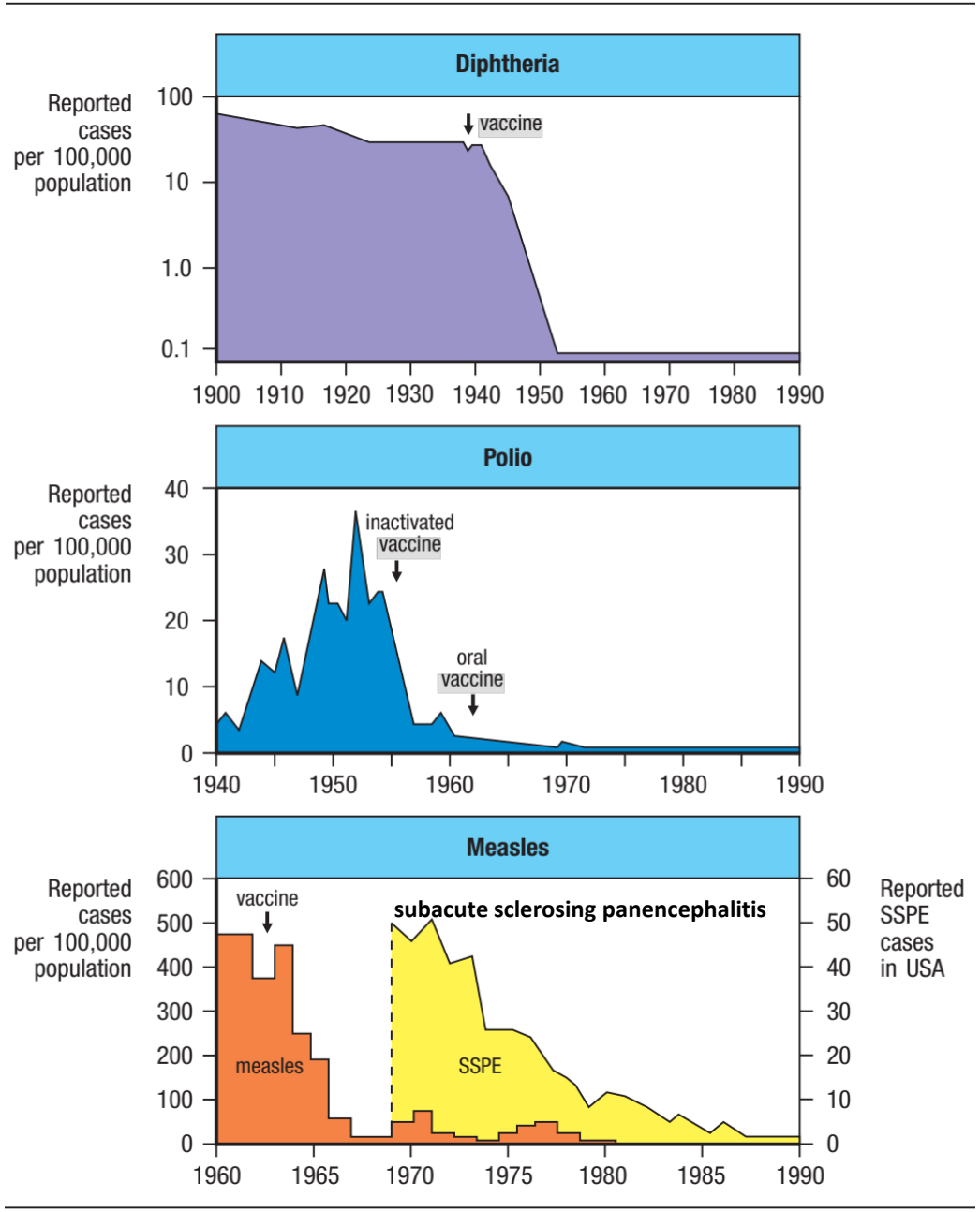


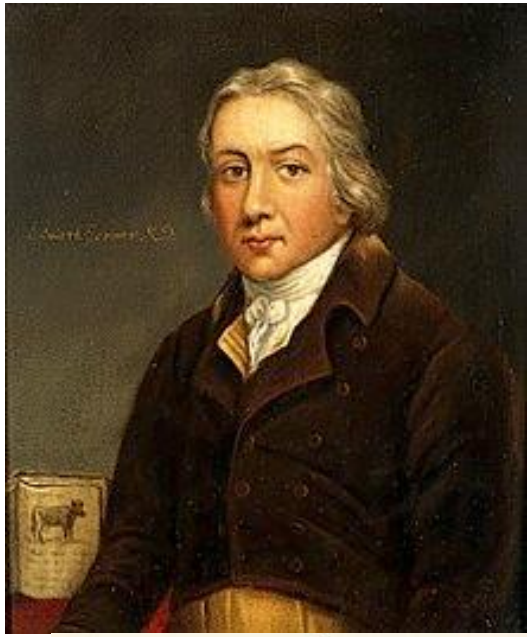
Fig. 1.2 The eradication of smallpox by vaccination. After a period of 3 years in which no cases of smallpox were recorded, the World Health Organization was able to announce in 1979 that smallpox had been eradicated, and vaccination stopped (upper panel). A few laboratory stocks have been retained, however, and some fear that these are a source from which the virus might reemerge. Ali Maow Maalin (lower panel) contracted and survived the last case of smallpox in Somalia in 1977. Photograph courtesy of Dr. Jason Weisfeld.

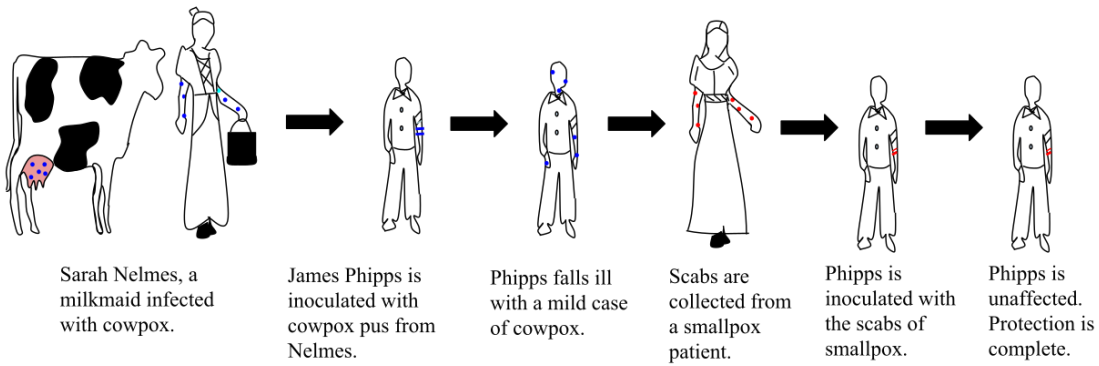


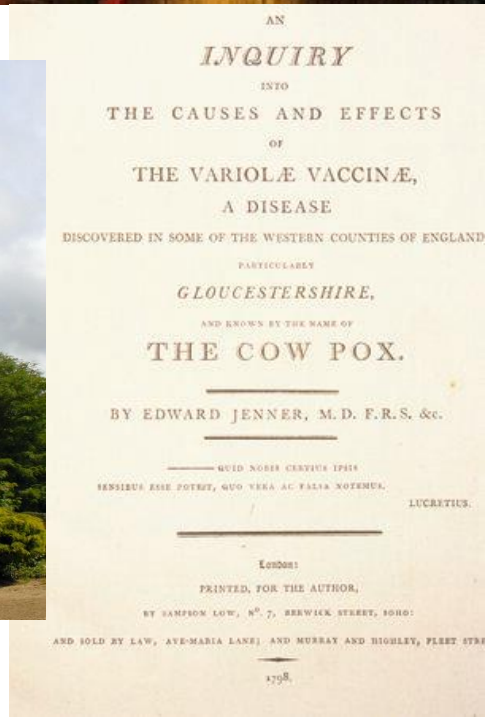
The World Health Organization reports that licensed vaccines are currently available for twenty-five different preventable infections

The terms *vaccine* and *vaccination* are derived from *Variolae vaccinae* (smallpox of the cow)

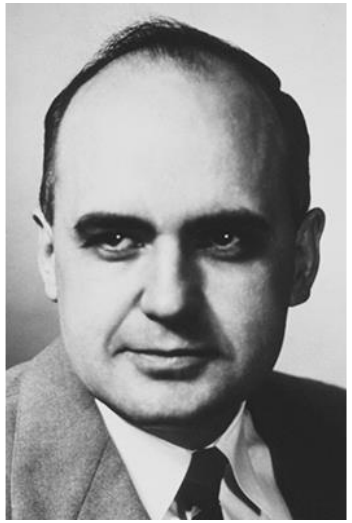
The Father of Immunology: the term "vaccine" devised by **Edward Jenner** to denote **cowpox**
Jenner both developed the concept of vaccines and created the first vaccine






AN
INQUIRY
INTO
THE CAUSES AND EFFECTS
OF
THE VARIOLÆ VACCINÆ,
A DISEASE
DISCOVERED IN SOME OF THE WESTERN COUNTIES OF ENGLAND
PARTICULARLY
GLOUCESTERSHIRE,
AND KNOWN BY THE NAME OF
THE COW POX.
BY EDWARD JENNER, M.D. F.R.S. &c.
QUID NOBIS CERTIUS IPSIS
SENSIBUS ESSE POTEST, QUO VERA AC FALSA NOTEMUS.
LUCRETIUS.
LONDON:
PRINTED, FOR THE AUTHOR,
BY SAMPSON LOW, N°. 7, BERWICK STREET, SOHO:
AND SOLD BY LAW, AVE-MARIA LANE; AND MURRAY AND HIGHLEY, FLEET STR
1798.

Maurice Hilleman, o ~~médico~~ microbiologista que criou a vacina mais rápida da história por causa da filha de 5 anos



E que desenvolveu mais vacinas que qualquer outro vacinologista (40...)

https://www.bbc.com/portuguese/internacional-53547623

https://www.youtube.com/watch?v=pLP51xC5mQw

Yellow fever and Max Theiler: the only Nobel Prize for a virus vaccine

https://doi.org/10.1084/jem.20072290

Table 1
Vaccinology — in the beginning

Capricious gods and devils cause disease.
Fear of disease — powerful tool for rulers, shamans and politicians.
Early observations. Transmissibility of disease, sanitation, resistance to repeat infection, codified religious taboos promoting health.
Early knowledge diminished by fall of Rome and Dark Ages.
Superstition prevails.
Reawakening in the late 1700s.
  Jenner investigates phenomenon of absence of smallpox occurrence in milkmaids infected with cowpox.
  Jennerian prophylaxis.
    Beginning science of vaccines and immunology.
Eclipse (period of maturation, smallpox vaccine improvement) of vaccinology to 1875 awaiting Pasteur's seminal findings.
  Spontaneous generation of life does not occur.
  Fermentation by microbes.
  Establishment of germ theory of disease.

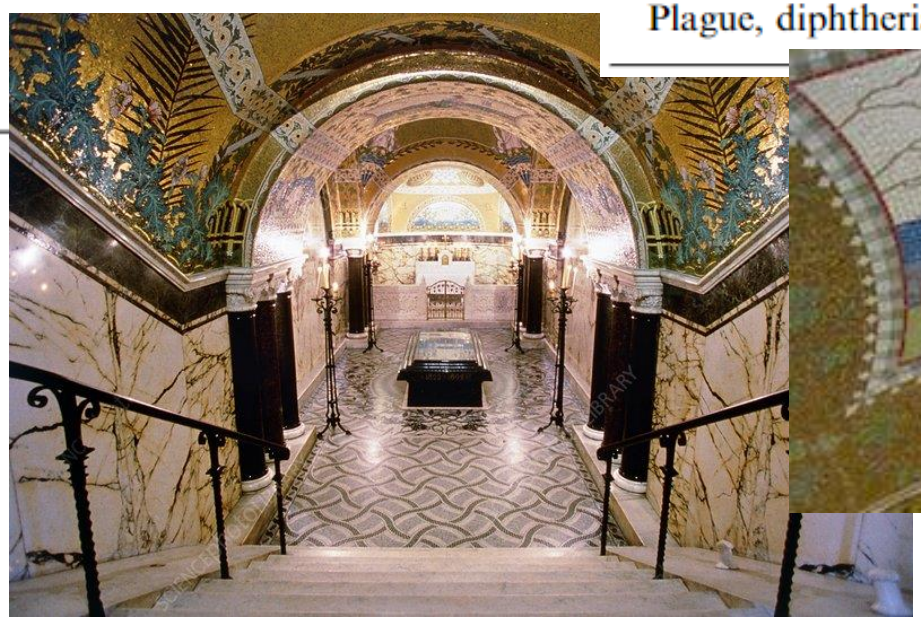
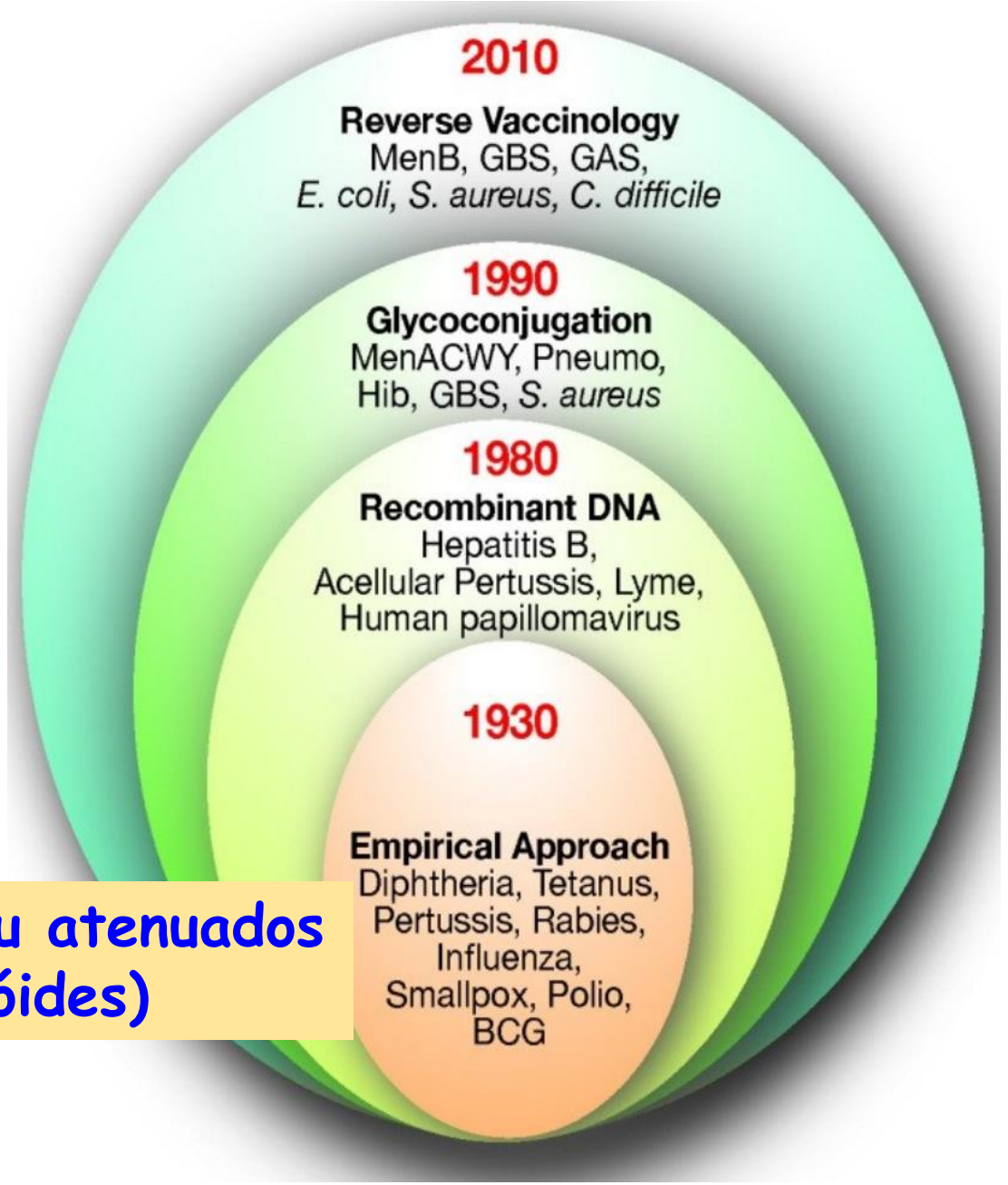


Table 2
Vaccinology — 1875 through World War I and 1930

Great awakening 1875 — discovery and rational empiricism. Focus on bacteria and antibodies (rabies virus exception).
Giants were
  Louis Pasteur — immunoprophylaxis, attenuation.
  Robert Koch — methodology, etiology, hypersensitivity, postulates.
  Emil von Behring — antibodies and immunotherapy.
  Paul Ehrlich — specific receptor—ligand binding, specific chemotherapy, antibody quantificaton.
By 1929:
  Humoral immunologic phenomena described
  Immunotherapy dominates the field
  Credible and useful vaccines
    Smallpox and rabies
    Killed and/or attenuated typhoid, shigella, cholera
    Plague, diphtheria, tetanus, pertussis, and tuberculosis

Linha do Tempo no Desenvolvimento de Vacinas



Organismos inteiros mortos ou atenuados
Subunidades purificadas (toxóides)

Organismos inteiros mortos ou atenuados
Subunidades purificadas (toxóides)

Table 3
Vaccinology — transition 1930–1948, including early studies on influenza and adenovirus agents and vaccines at Walter Reed 1948–1957

1931	*Goodpasture* — virus propagation on membranes of embryonated hens' eggs.
1935	*Theiler* — safe and effective yellow fever vaccine attenuated by passage in minced chick embryo cultures.
Squibb Virus Laboratories	
Early 1940s	*Cox*'s formalin-inactivated embryonated hen's egg (yolk sac) typhus vaccine for European invasion.
1944	Formalin inactivated mouse brain Japanese B encephalitis vaccine for Far East invasion, based on earlier Japanese and Russian studies and a Sabin report.
1945	*Wendell Stanley's* sharpless-purified chick embryo allantoic fluid-derived influenza virus vaccine. A paradigm for purified virus vaccines.
	Process and manufacturing developments at E.R. Squibb & Sons Labs. Military and civilian.
Walter Reed Army Institute of Research (WRAIR)	
1948–58	Discovery of progressive antigenic change (drift) and major change (shift) in influenza viruses by prospective and retrospective viral and seroepidemiologic studies.
	Detection of 1957 Pandemic; Vaccine development, 1957.
1953–57	Discovery of Adenoviruses (Epidemic — WRAIR; Latent — NIH) — 1953.
	Killed virus vaccine developed and proved effective(98%) — 1956. Commercial — 1958.

Vaccines contain attenuated, inactivated or dead organisms or purified products derived from them
Types of vaccines to develop and use depend of physiopathology of the disease

Attenuated Vaccines

Active pathogens that have been cultivated under conditions that disable their virulent properties

Viral diseases: polio, yellow fever, measles, mumps, and rubella;

Bacterial disease: typhoid

❖ Typically provoke more durable immunological responses

✓ May be unsafe for immunocompromised individuals, and on rare occasions mutate to virulent form and cause disease

Inactivated Vaccine (killed vaccine)

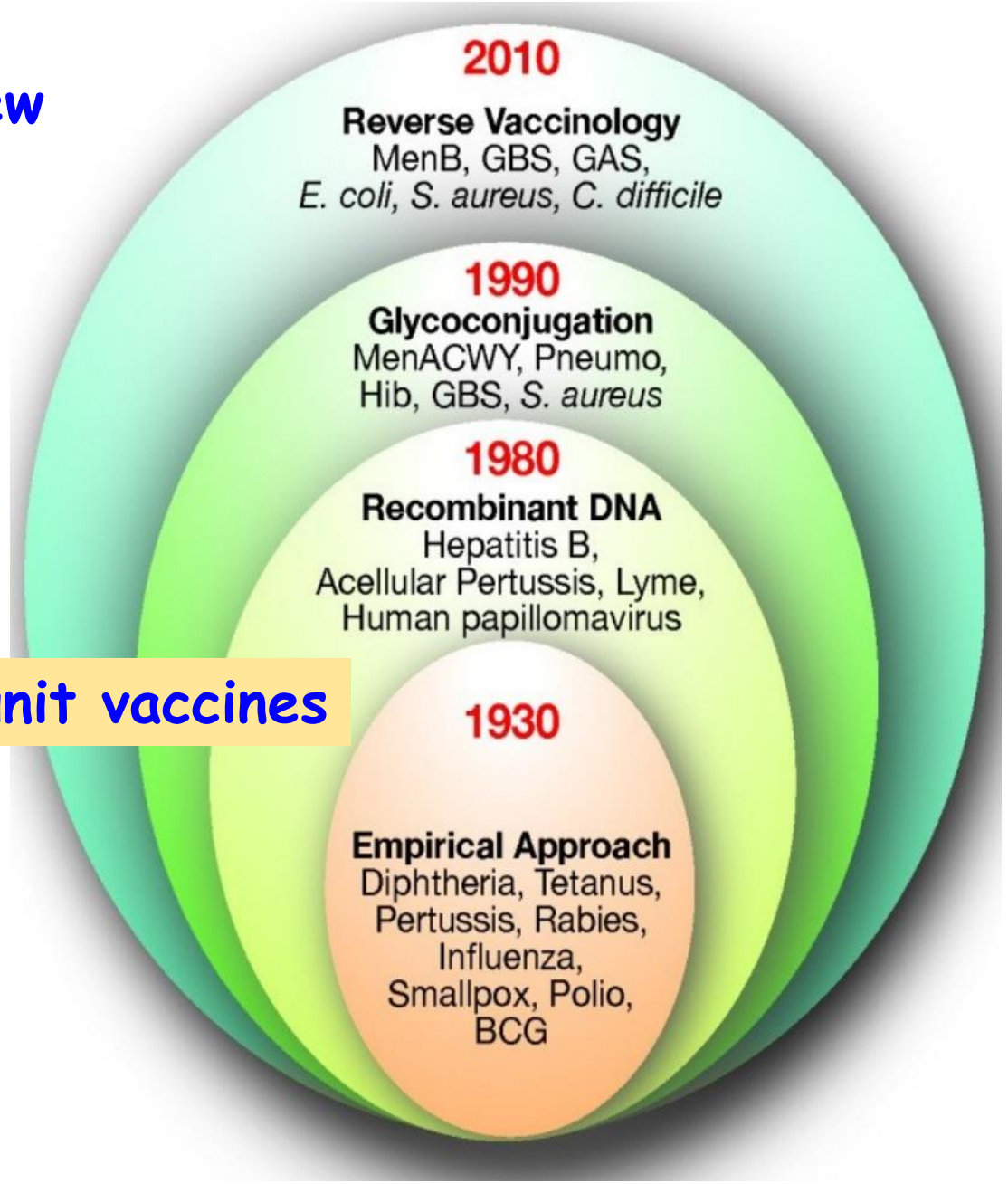
Virus particles, bacteria, or other pathogens grown in culture and then killed to destroy disease-producing capacity

Viral diseases: Injected polio vaccine Salk vaccine; Hepatitis A vaccine; Rabies vaccine; Most influenza vaccines; Tick-borne encephalitis vaccine; Some COVID-19 vaccines: CoronaVac, Covaxin, Sinopharm;

Bacterial diseases: injected typhoid vaccine; Cholera vaccine; Plague vaccine; Pertussis vaccine

- More stable than live pathogens. Increased stability facilitates storage and transport
- Unlike live attenuated vaccines, inactivated vaccines:
  - ❖ Cannot revert to a virulent form. Example of polio vaccines: OPV X IPV and polio transmission.
  - ❖ Do not replicate and are not contraindicated for immunocompromised individuals
  - ✓ Reduced ability to produce a robust immune response for long-lasting immunity when compared to live attenuated vaccines; adjuvants and boosters are often required to produce and maintain protective immunity
  - ✓ Pathogens must be cultured and inactivated for the creation of vaccines, slowing down vaccine production
  - ✓ Disease-enhancing antibodies in some cases

During the last 40 years, several new technologies made possible vaccines that were previously impossible



Subunit vaccines

Subunit Vaccines

Toxoids

Made from inactivated toxic compounds that cause illness rather than the micro-organism

Bacterial diseases: tetanus; diphtheria; require adjuvant (soluble proteins are not immunogenic)

- ❖ Highly efficacious
- ❖ MANY helper T cell epitopes in these antigens (> 100) = good coverage of MHC

Recombinant protein

Selected protein(s) of a pathogen.

So far only for viral diseases: Hepatitis B; two Nobel prizes; human papillomavirus (HPV), for each strain, a single viral protein is isolated. When these proteins are expressed, virus-like particles (VLPs) are created

- ✓ Candidate antigens are not always chosen accurately, must understand biology of pathogen and disease
- ✓ Poor coverage of MHC in case of HB vaccine

Virus-like particles (VLPs) are molecules that closely resemble viruses, but are non-infectious because they contain no viral genetic material

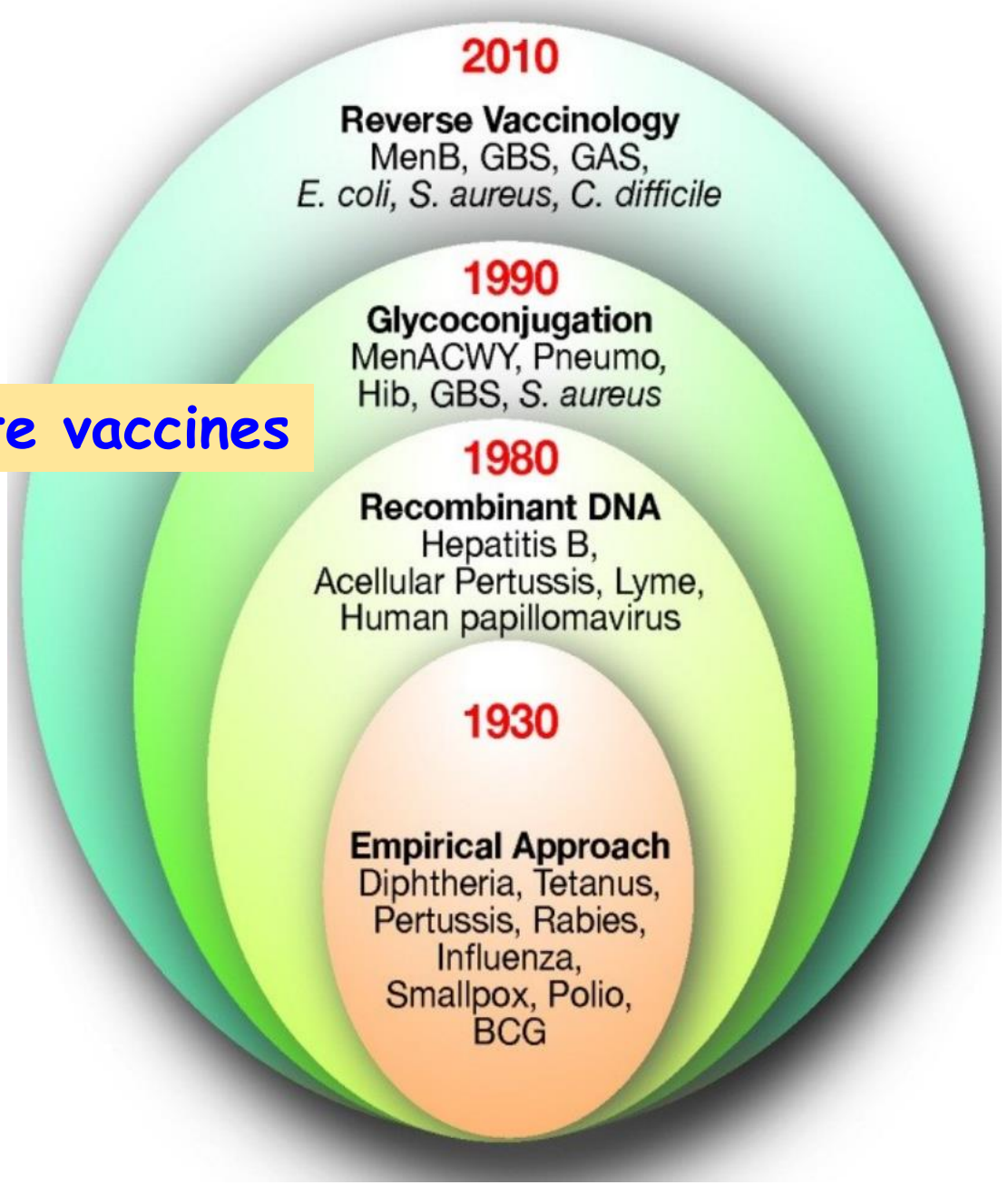
Polyssacharide Bacterial diseases: Haemophilus, Pneumococcal, typhoid

Pure: adults and older children (>6 years of age)

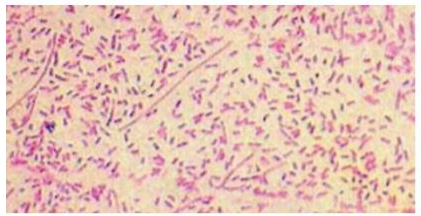
Conjugated to protein: for children younger than 6, who lack marginal zone B cells…

Genetic: Viral diseases mRNA Pfizer-BionTech; Moderna (COVID-19); DNA ZyCoV-D (COVID-19)

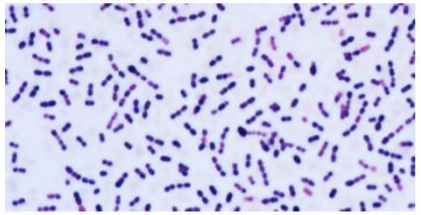
Conjugate vaccines



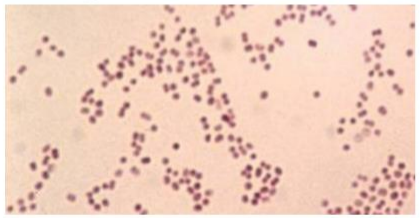
Haemophilus influenzae type B (Hib)



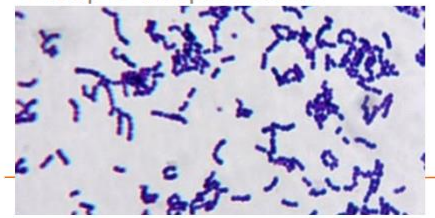
Pneumococcus



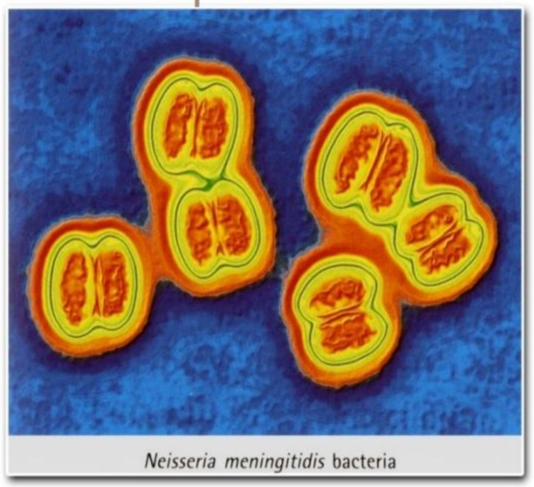
Meningococcus



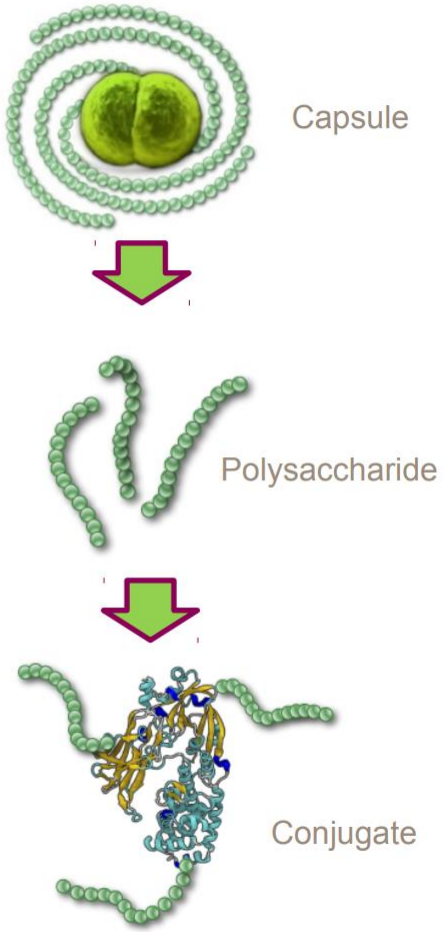
Group B streptococcus



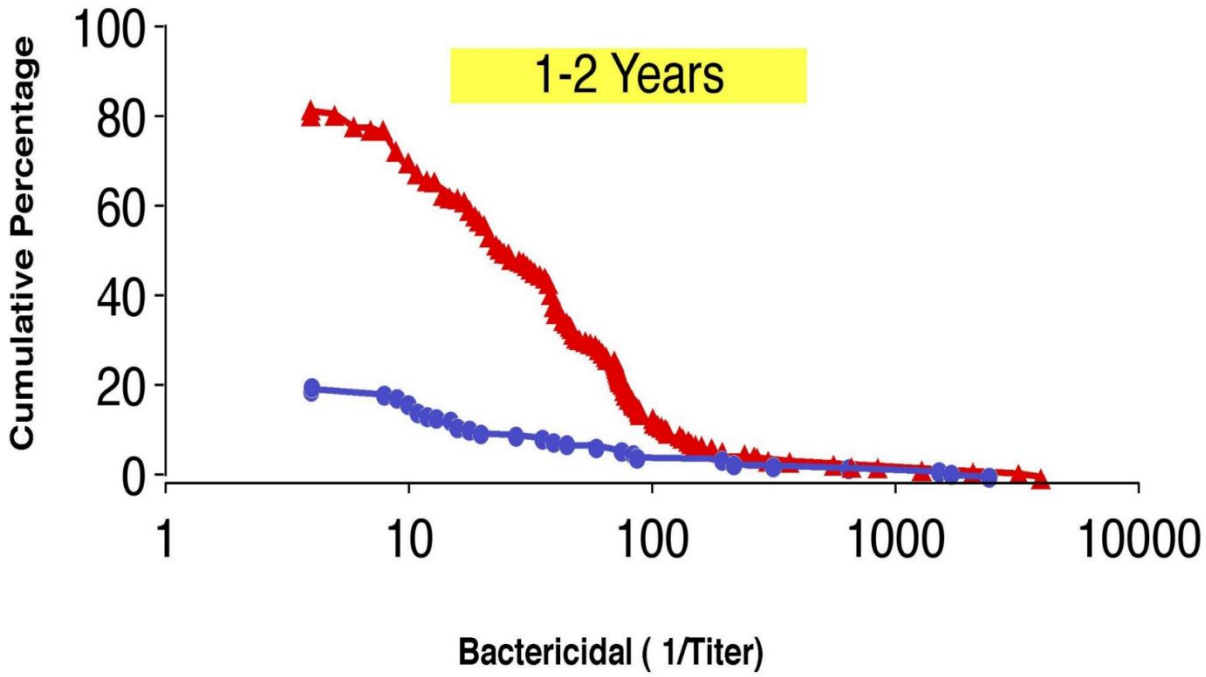
Capsule

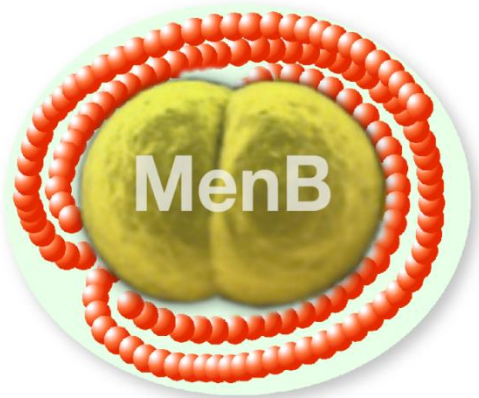


Neisseria meningitidis bacteria

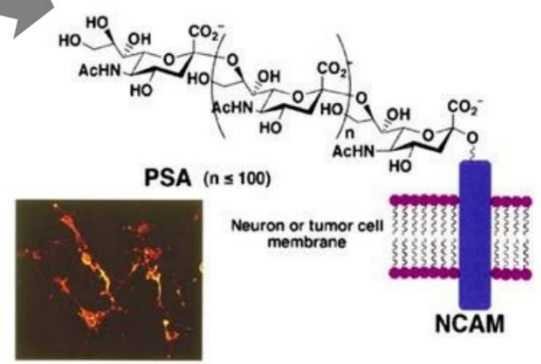


MenC Conjugate Vaccine (red) Induced high level of Bactericidal Antibodies in Infants. **Plain Polysaccharide** (blue) was a poor Immunogen





Meningococcus B capsule is a self antigen and cannot be used for vaccination



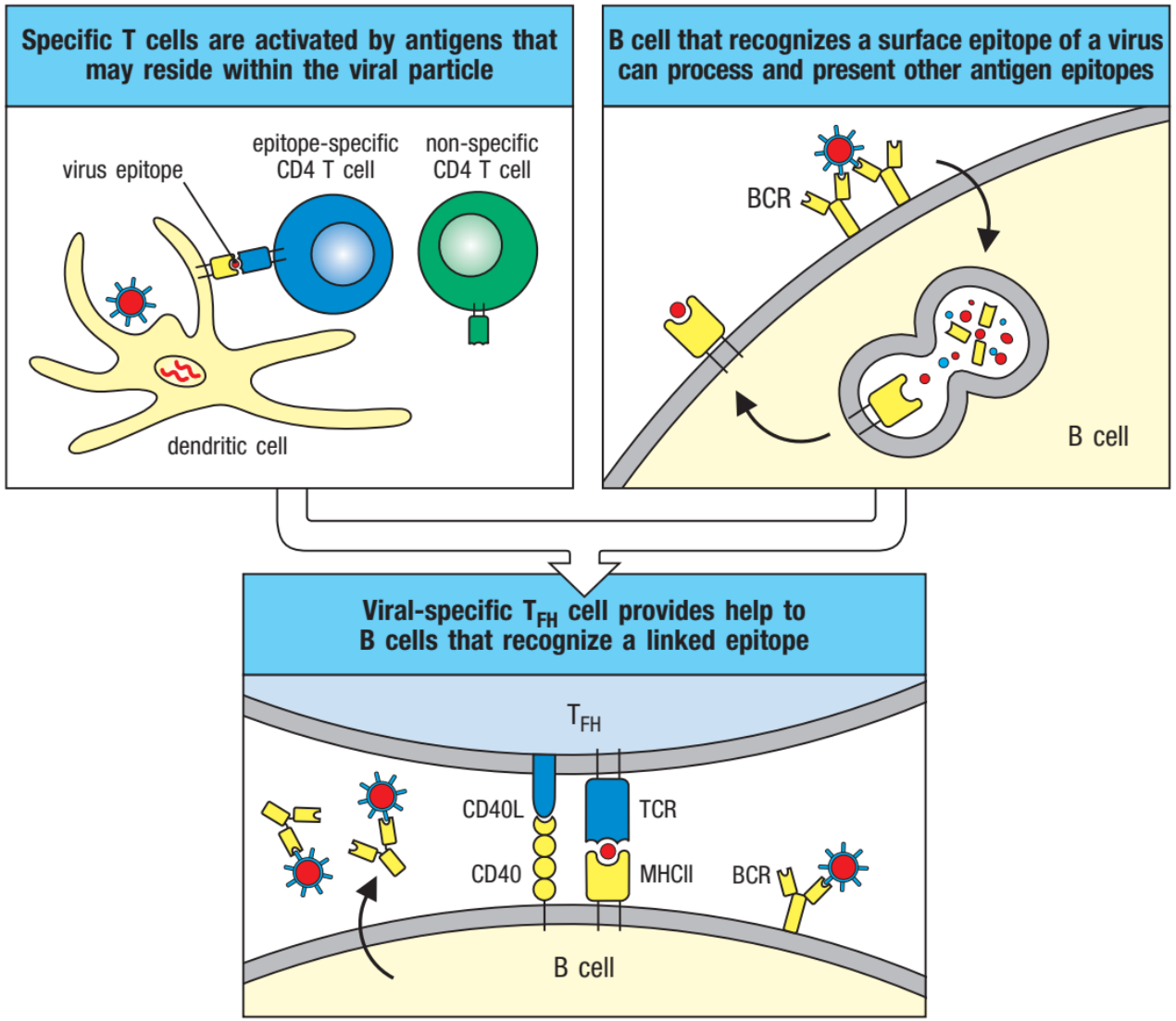
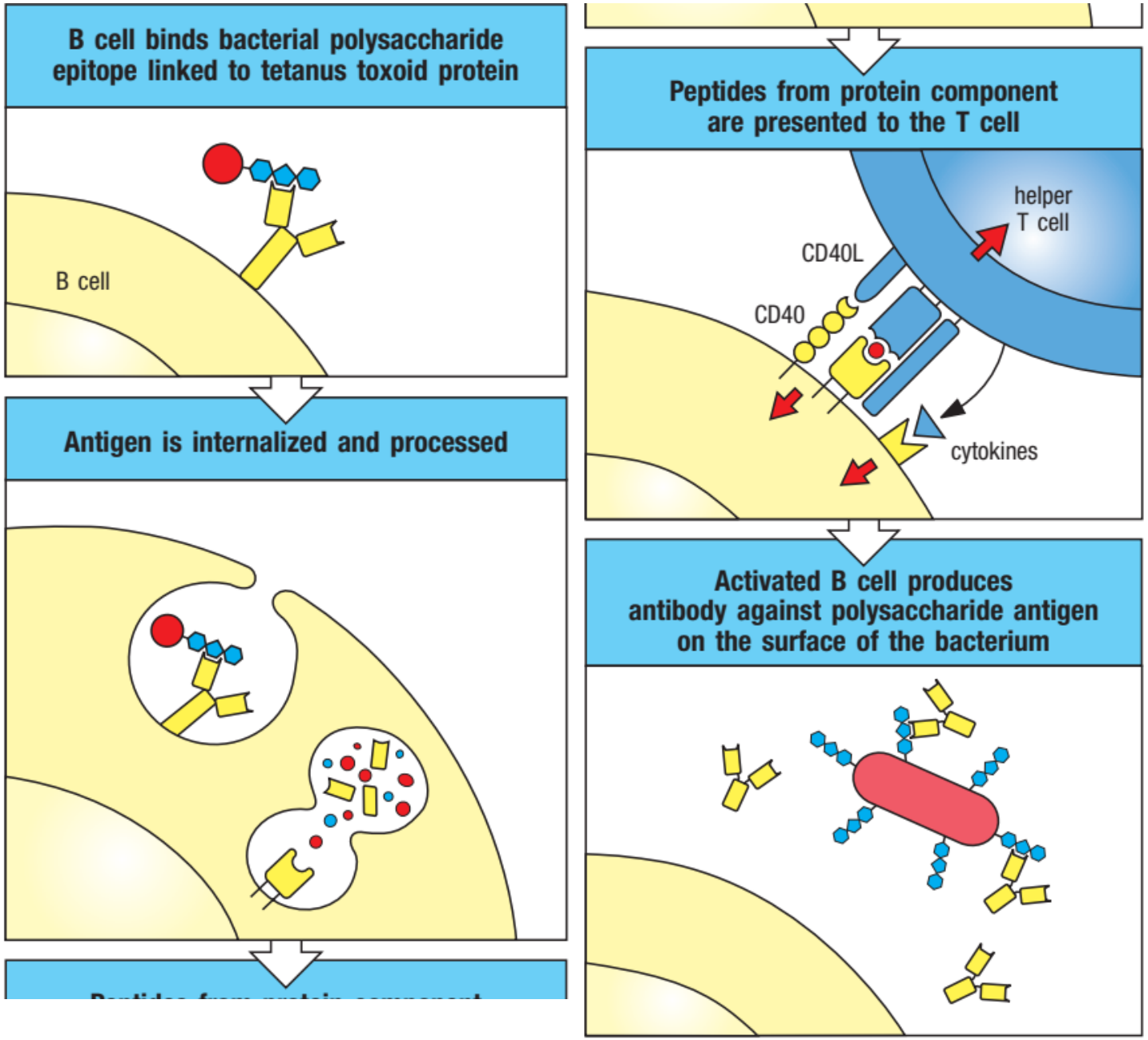


Fig. 10.4 T cells and B cells must recognize antigens contained within the same molecular complex in order to interact. In this example, an internal viral protein harbors a peptide epitope (shown as red) that is presented by MHC class II molecules and is recognized by a CD4 T cell. The virus also harbors a native epitope on an external viral coat protein (shown as blue) that is recognized by the surface immunoglobulin on a B cell. If the virus is captured and presented by a dendritic cell, a peptide-specific CD4 T cell (blue) becomes activated (top left panel), whereas nonspecific T cells (green) remain inactive. If the virus is recognized by a specific B cell (top right panel), peptides derived from internal viral protein are processed and presented by MHC class II molecules. When the activated T cell recognizes its peptide on this B cell (bottom panel), the T cell will deliver various accessory signals to the B cell that promote antibody production against the coat protein. This process is known as linked recognition.

Linked recognition works to preserve self-tolerance, since autoreactive antibodies will arise only if self-reactive TFH and self-reactive B cells are present at the same time.

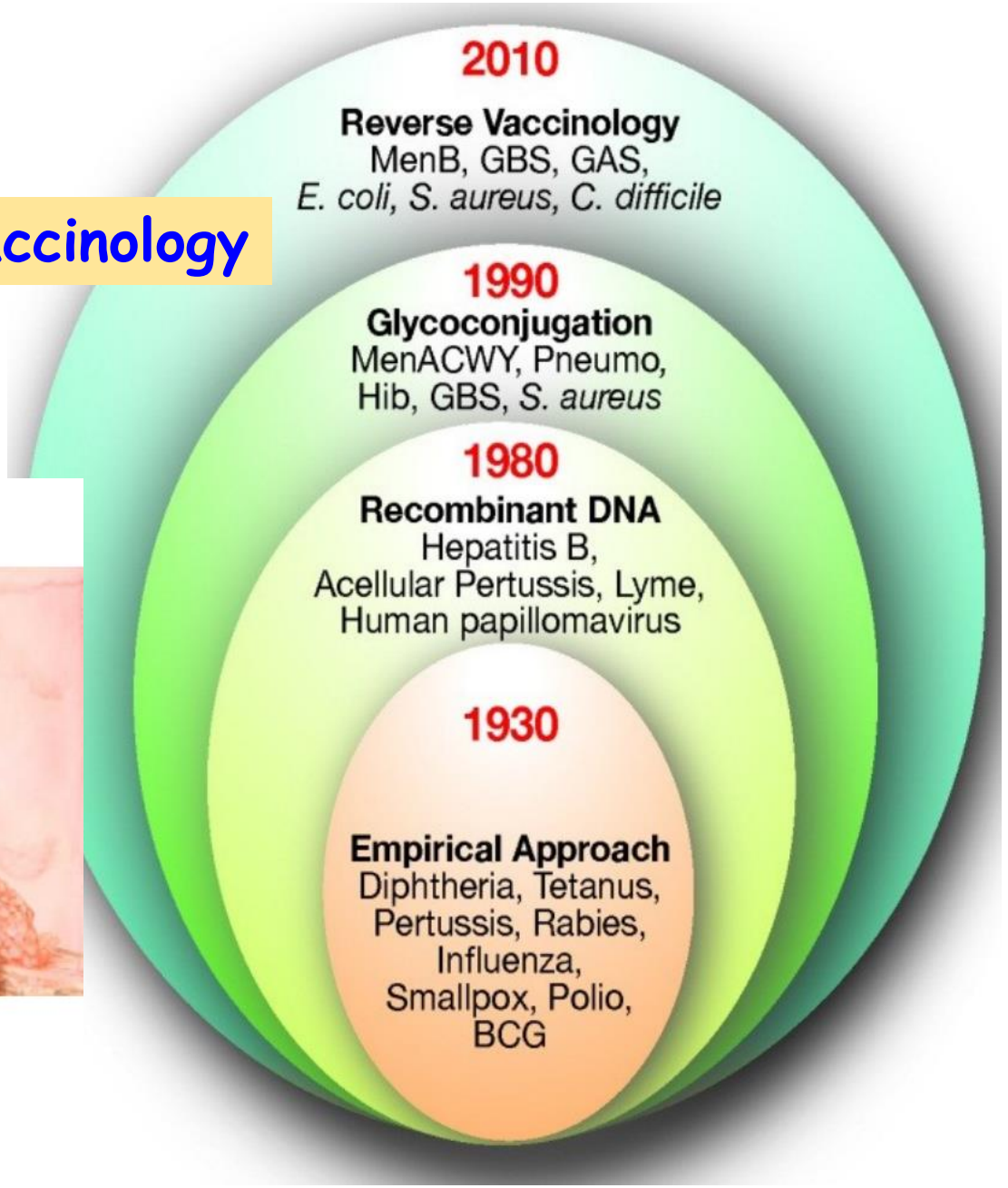


Conjugate vaccines take advantage of linked recognition to boost B-cell responses against polysaccharide antigens.

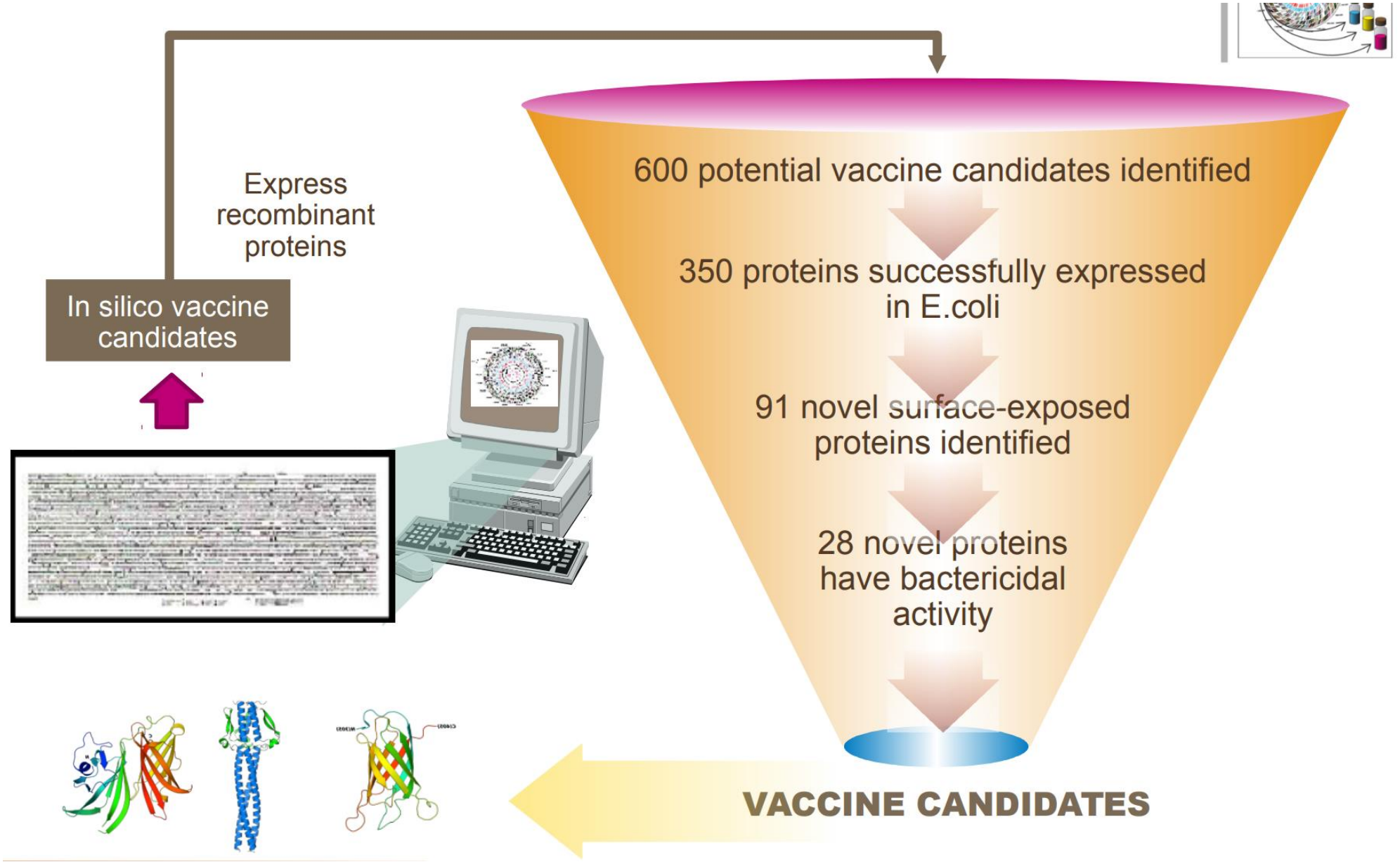
- The Hib vaccine against Haemophilus influenzae type b is a conjugate of bacterial polysaccharide and the tetanus toxoid protein.
- The B cell recognizes and binds the polysaccharide, internalizes and degrades the whole conjugate, and then displays toxoid-derived peptides on surface MHC class II molecules.
- Helper T cells generated in response to earlier vaccination against the toxoid recognize the complex on the B-cell surface and activate the B cell to produce anti-polysaccharide antibody.
- This antibody can then protect against infection with H. influenzae type b.

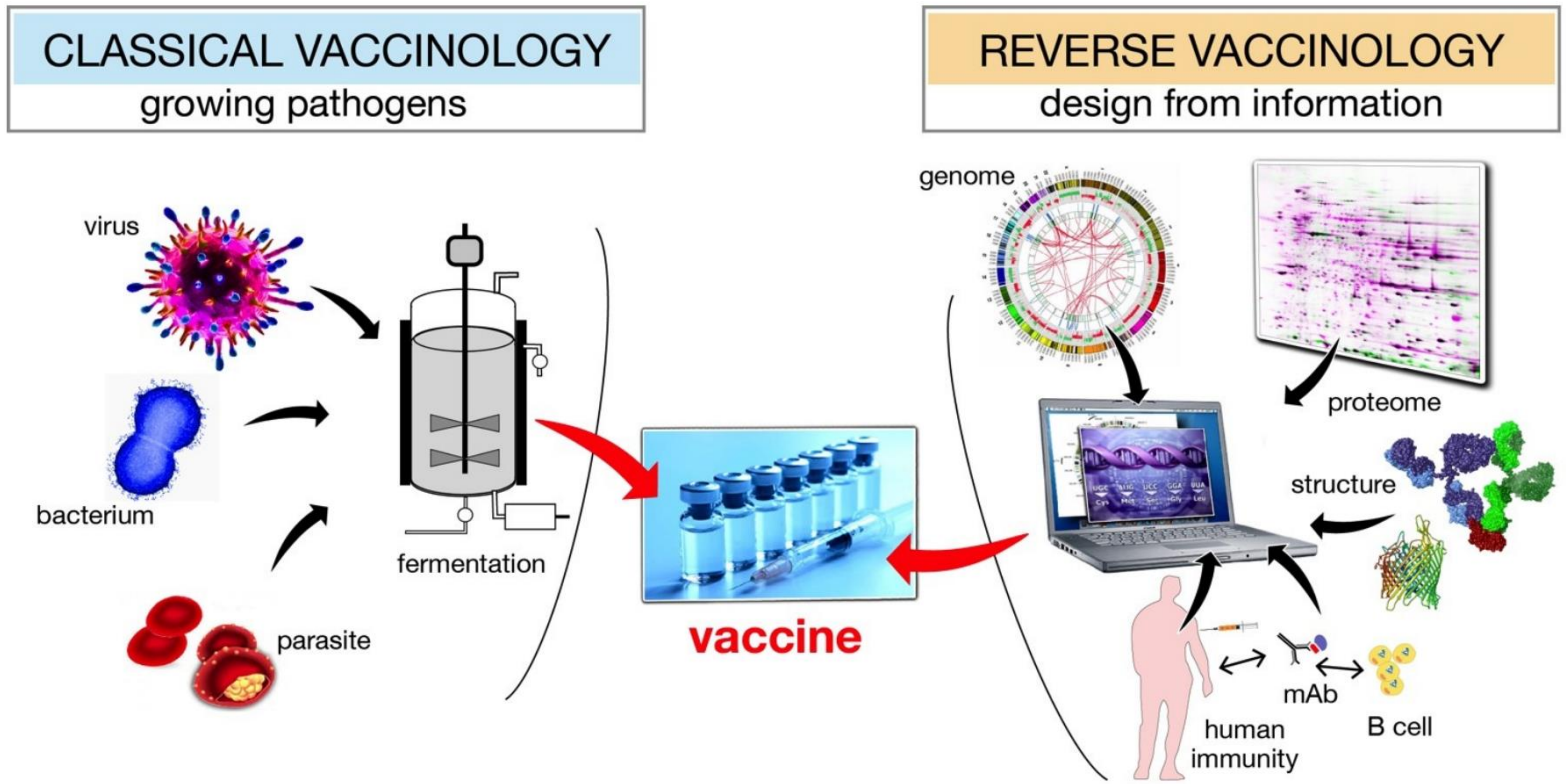
Reverse vaccinology

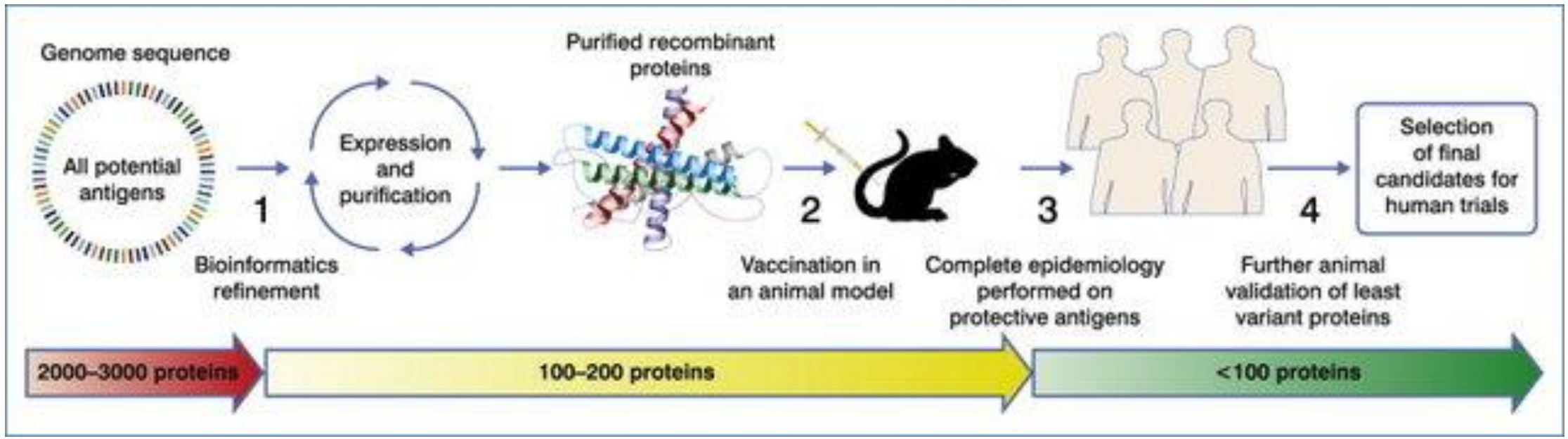
Reverse Vaccinology and a vaccine for Meninigococcus B



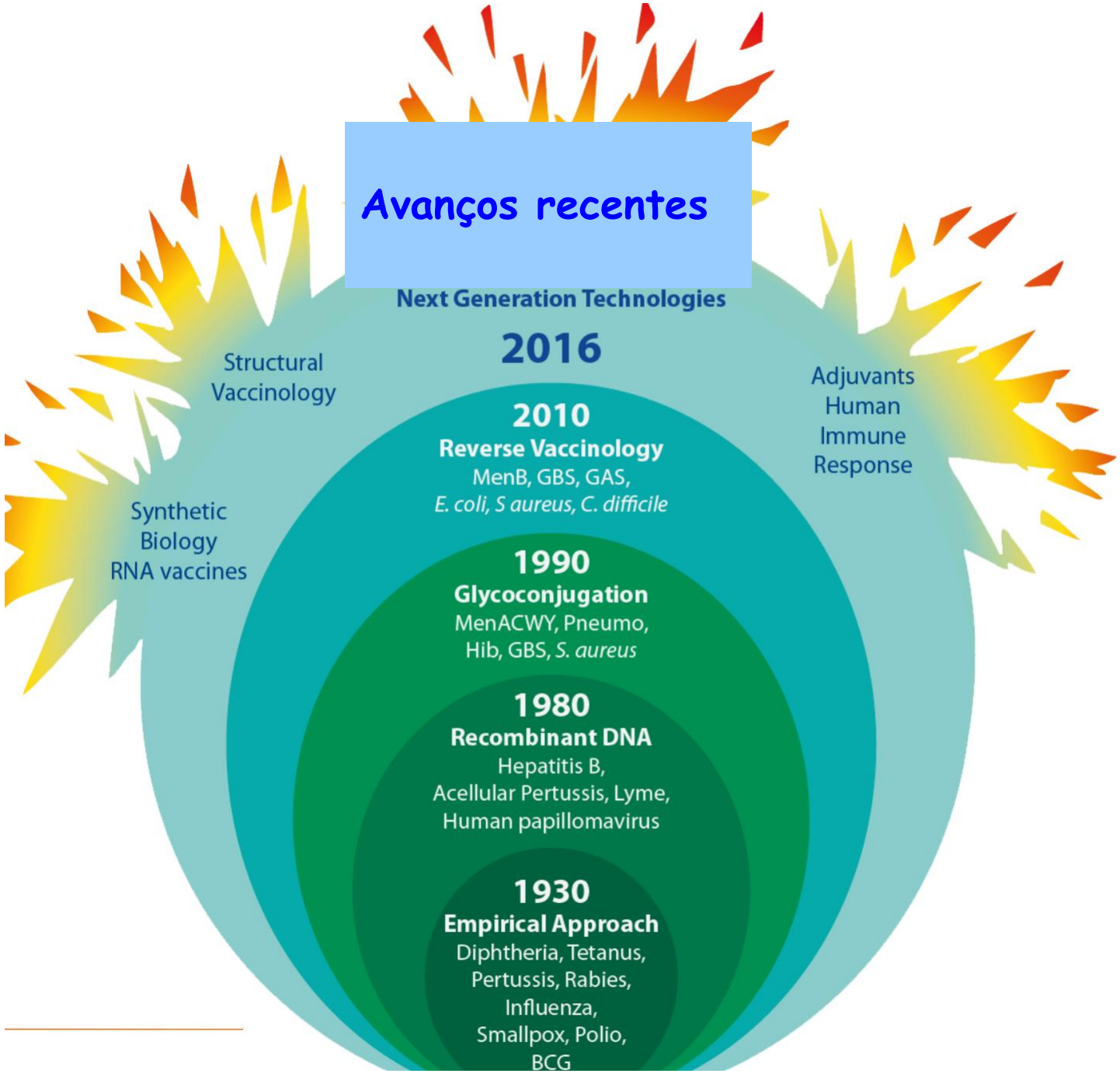
Reverse Vaccinology A genomic approach for a Meningococcus B vaccine



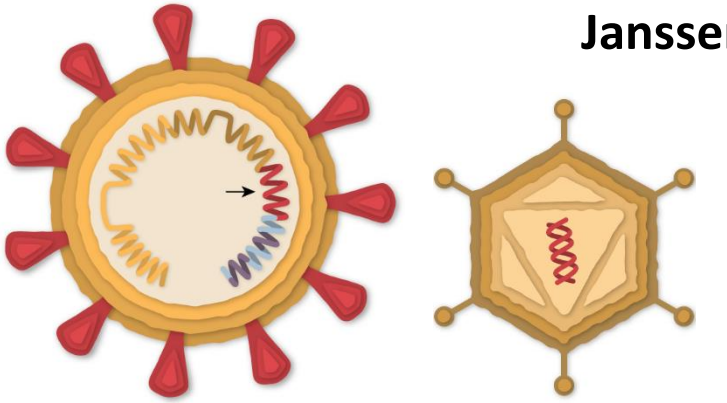

CLASSICAL VACCINOLOGY
growing pathogens
REVERSE VACCINOLOGY
design from information
virus
bacterium
parasite
fermentation
vaccine
genome
proteome
structure
mAb
B cell
human immunity

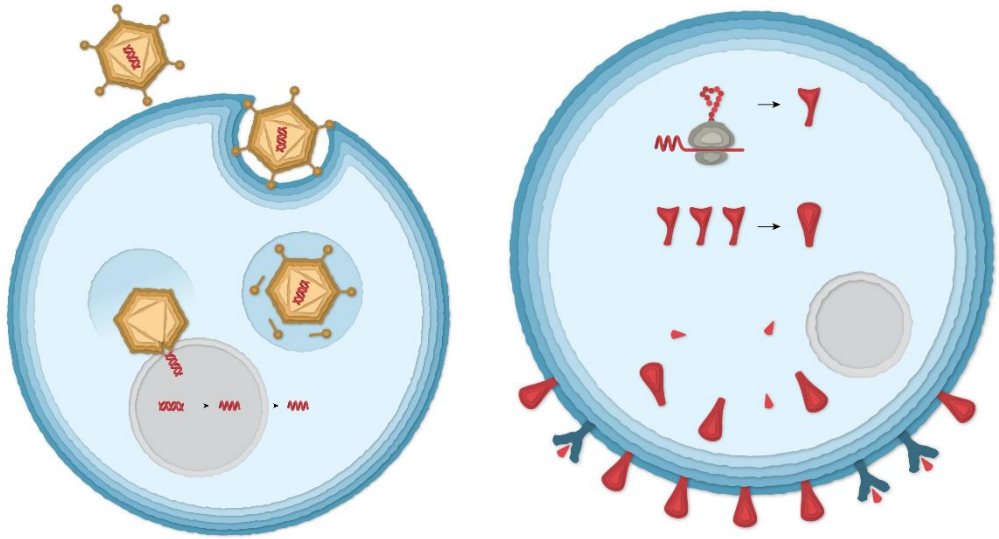

Genome sequence
All potential antigens
1
Bioinformatics refinement
Expression and purification
Purified recombinant proteins
2
Vaccination in an animal model
3
Complete epidemiology performed on protective antigens
4
Further animal validation of least variant proteins
Selection of final candidates for human trials
2000–3000 proteins
100–200 proteins
<100 proteins

Avanços recentes

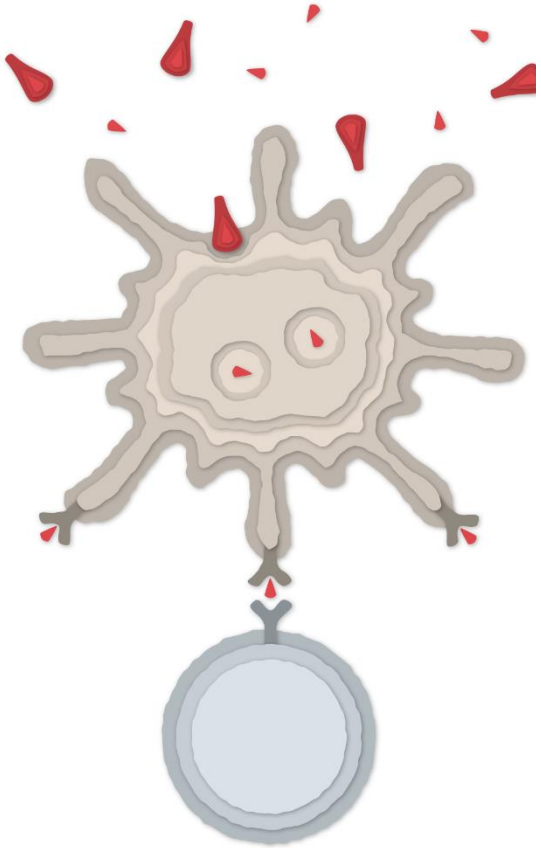


Janssen vaccine with adenovirus vector



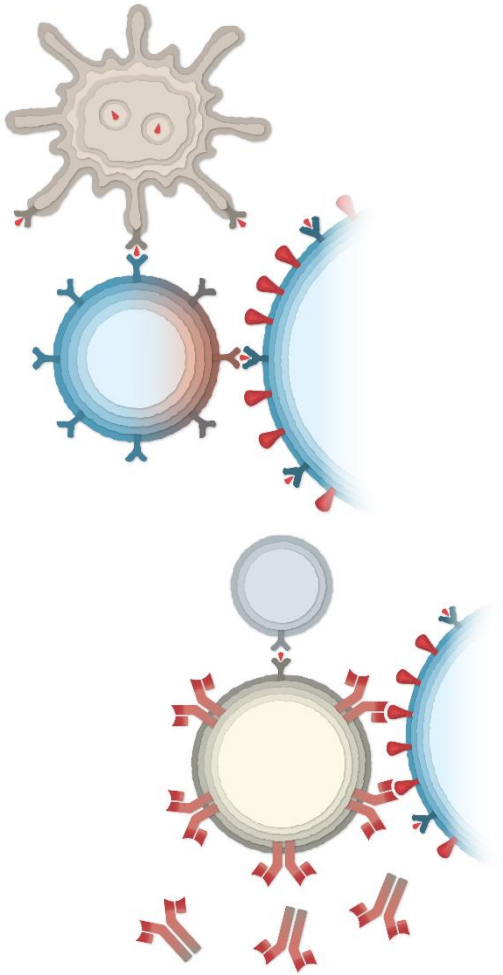


The adenovirus pushes its DNA into the nucleus. The adenovirus is engineered so it can't make copies of itself, but the gene for the coronavirus spike protein can be read by the cell and copied into a molecule called messenger RNA, or mRNA.



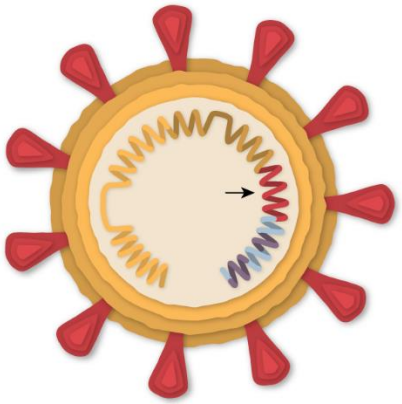
APC and helper T cell

APC and NK T cell

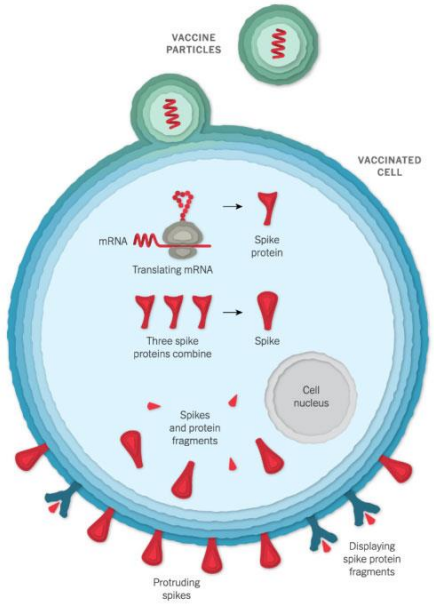


T cell helps B cell to make neutralizing antibodies and ADCC

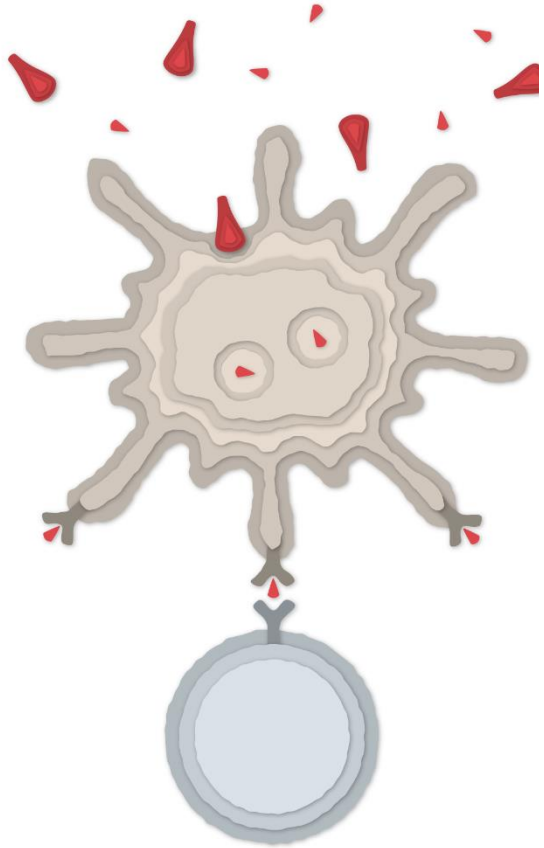
Pfizer and Moderna RNA-based vaccines



Lipid nanoparticles surrounding mRNA

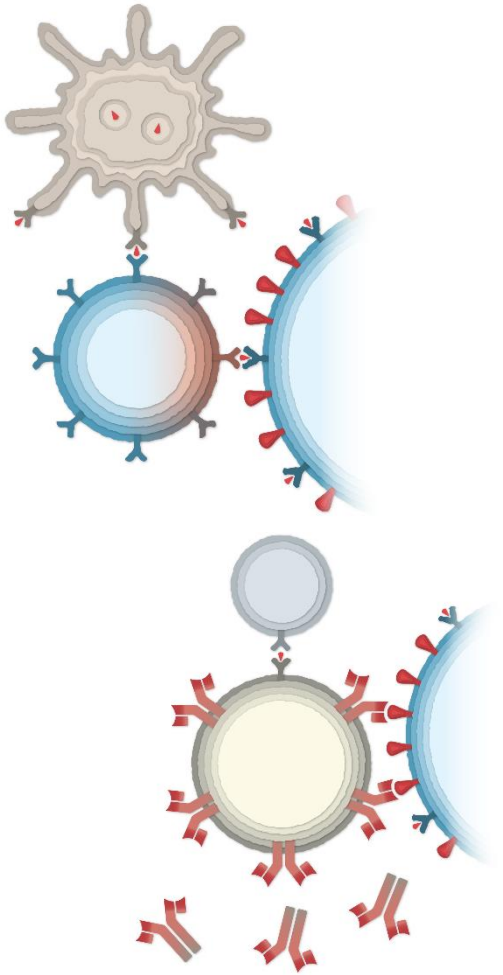


etc



APC and helper T cell

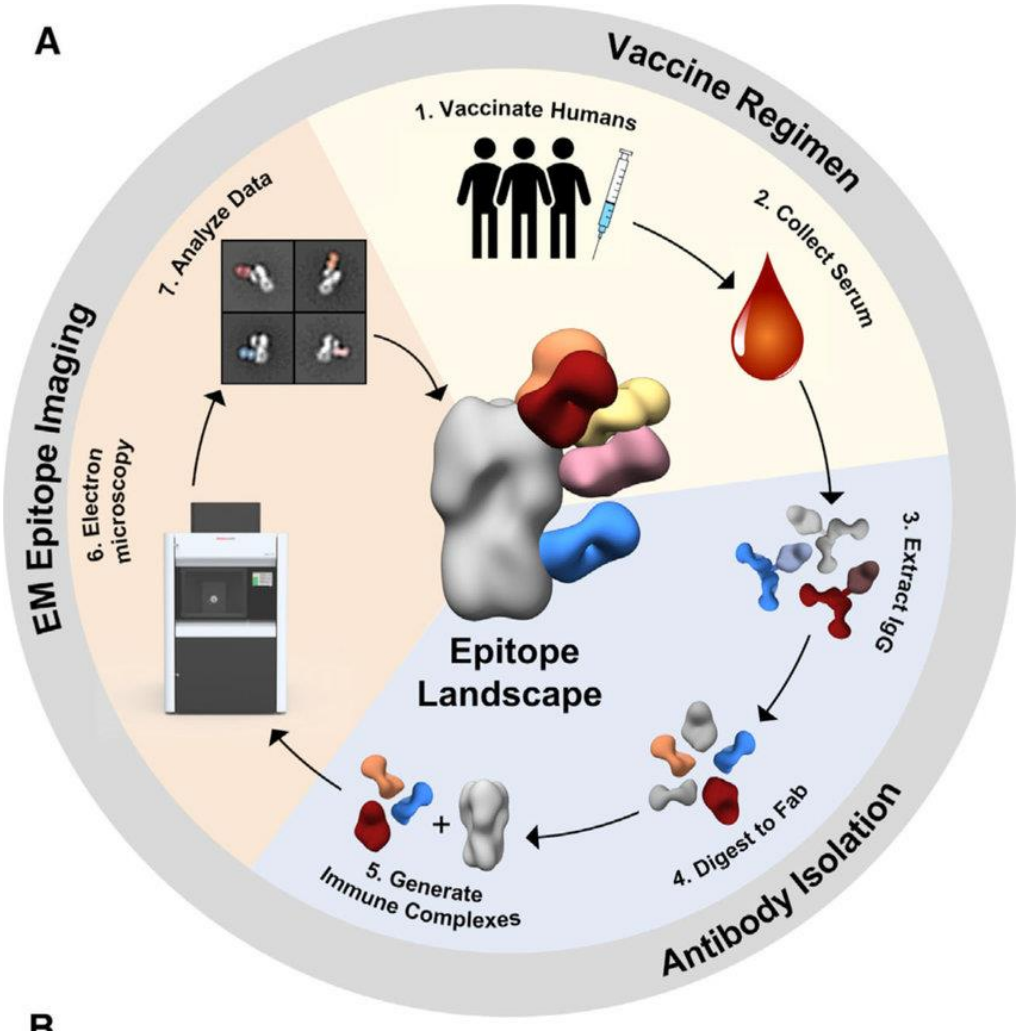
APC and NK T cell

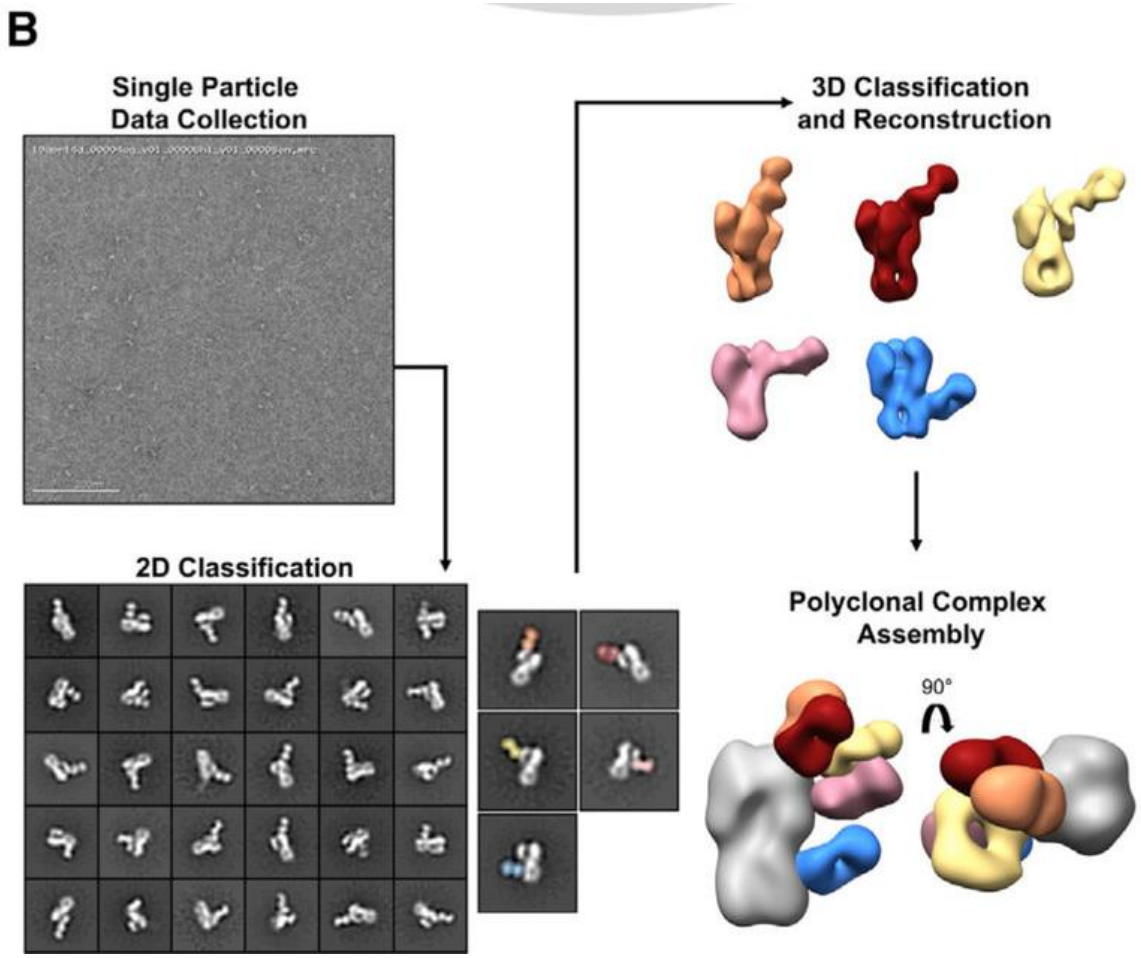


T cell helps B cell to make neutralizing antibodies and ADCC

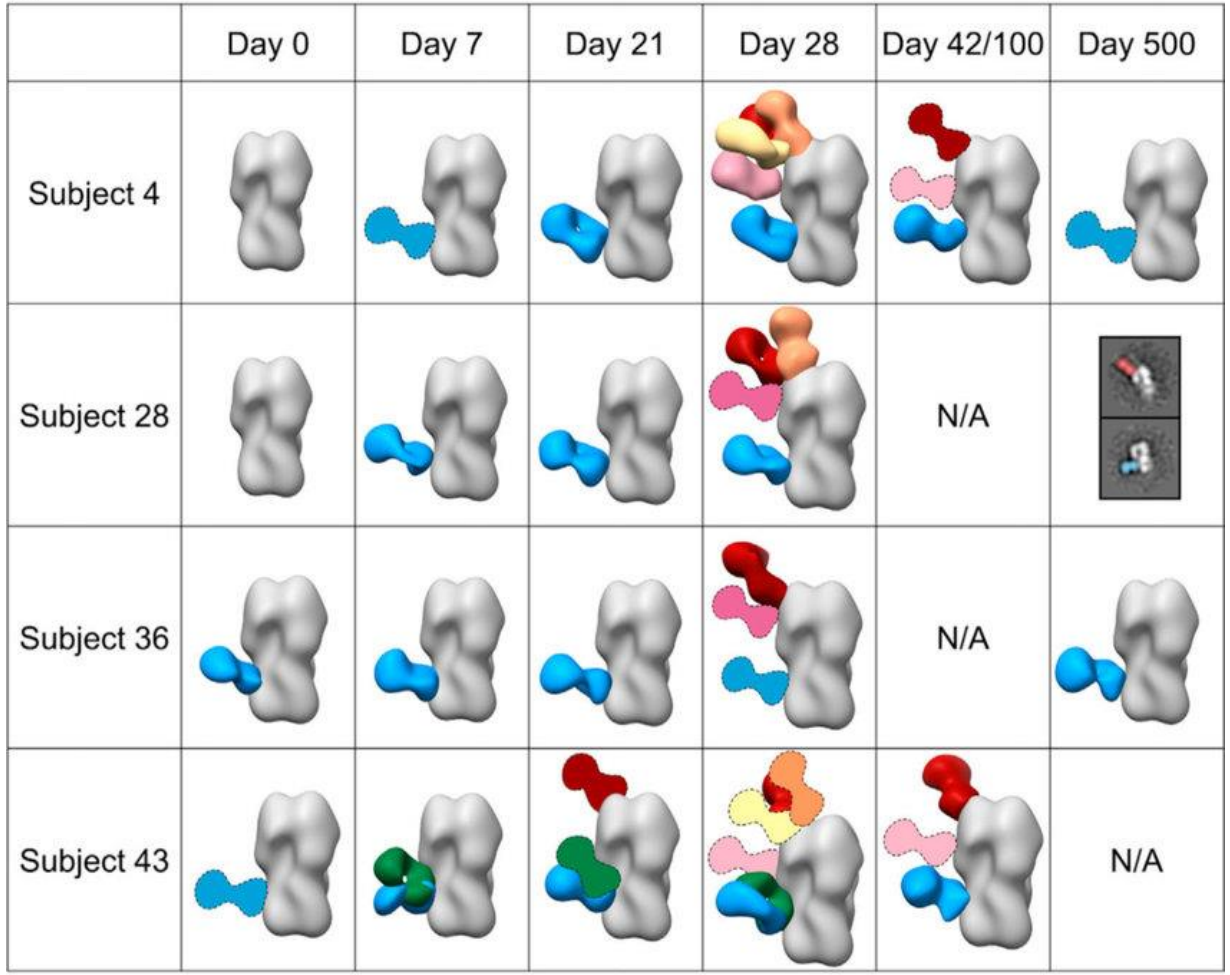
Structural Vaccinology

Analyze individual imune complexes to locate epitopes

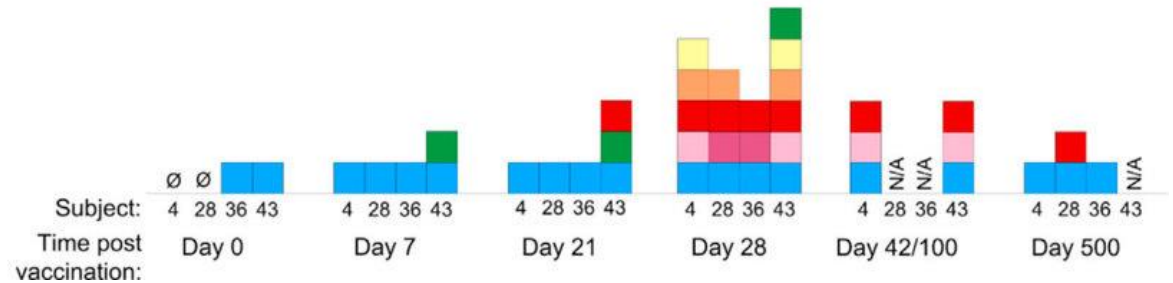




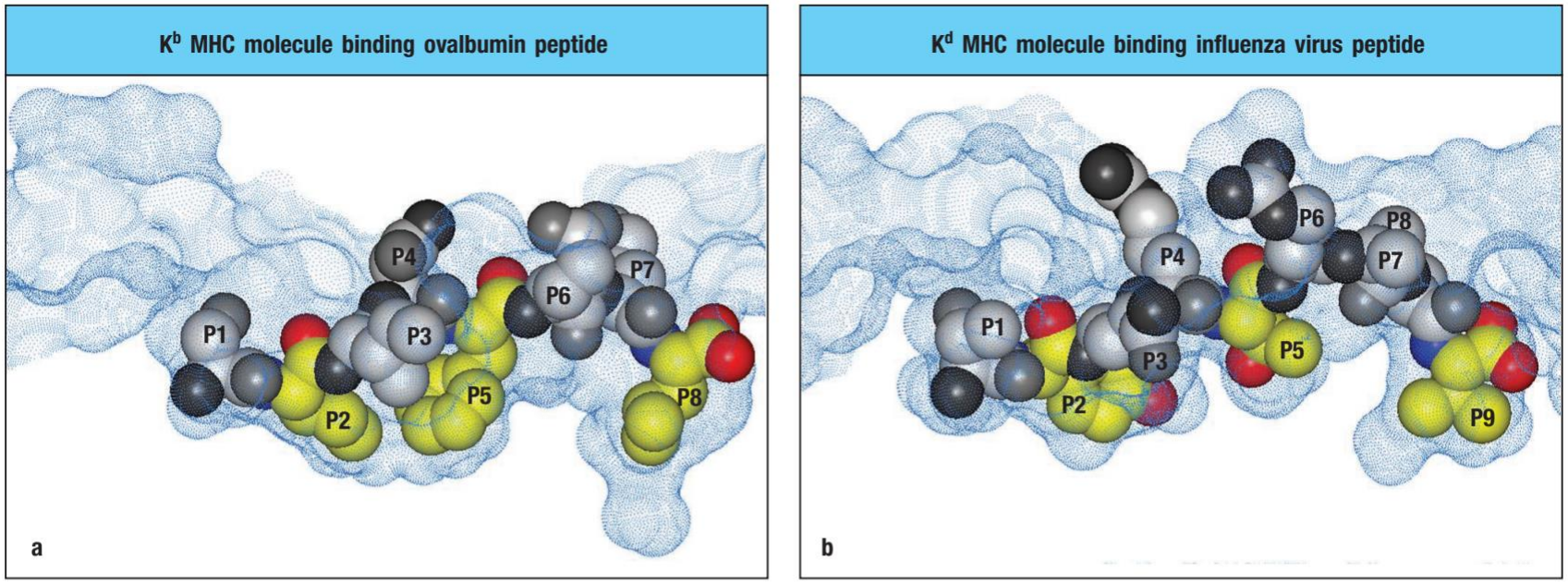
A


Day 0
Day 7
Day 21
Day 28
Day 42/100
Day 500
Subject 4
Subject 28
Subject 36
Subject 43
N/A
N/A
N/A
N/A

B


Ø Ø
N/A
N/A
N/A
Subject:
4 28 36 43
Time post vaccination:
Day 0
Day 7
Day 21
Day 28
Day 42/100
Day 500

Vacinas baseadas em peptídeos



	P1	P2	P3	P4	—	P5	P6	P7	P8
Ovalbumin (257–264)	S	I	I	N		F	E	K	L
HBV surface antigen (208–215)	I	L	S	P		F	L	P	L
Influenza NS2 (114–121)	R	T	F	S		F	Q	L	I
LCMV NP (205–212)	Y	T	V	K		Y	P	N	L
VSV NP (52–59)	R	G	Y	V		Y	Q	G	L
Sendai virus NP (324–332)	F	A	P	G	N	Y	P	A	L

	P1	P2	P3	P4	P5	P6	P7	P8	P9
Influenza NP (147–155)	T	Y	Q	R	T	R	A	L	V
ERK4 (136–144)	Q	Y	I	H	S	A	N	V	L
P198 (14–22)	K	Y	Q	A	V	T	T	T	L
P. yoelii CSP (280–288)	S	Y	V	P	S	A	E	Q	I
P. berghei CSP (25)	G	Y	I	P	S	A	E	K	I
JAK1 (367–375)	S	Y	F	P	E	I	T	H	I

Fig. 6.22 Different allelic variants of an MHC class I molecule bind different peptides. Shown are cutaway views

P5 and P8; the C pocket binds the P5 side chain of the peptide [a tyrosine (Y) or a phenylalanine (F)], and the F pocket binds the P8

Fatores que interferem na resposta a vacinas

- Reforços (“boosts”)
- Fibrose de linfonodos
- Infecções concomitantes
- Vacinação concomitante com dois virus atenuados
- Uso de antibióticos e disbiose intestinal
- Doença Enteropática Ambiental
- Desnutrição

	Source of B cells	
	Unimmunized donor Primary response	**Immunized donor Secondary response**
Frequency of antigen-specific B cells	$1:10^4 - 1:10^5$	$1:10^2 - 1:10^3$
Isotype of antibody produced	IgM > IgG	IgG, IgA
Affinity of antibody	Low	High
Somatic hypermutation	Low	High

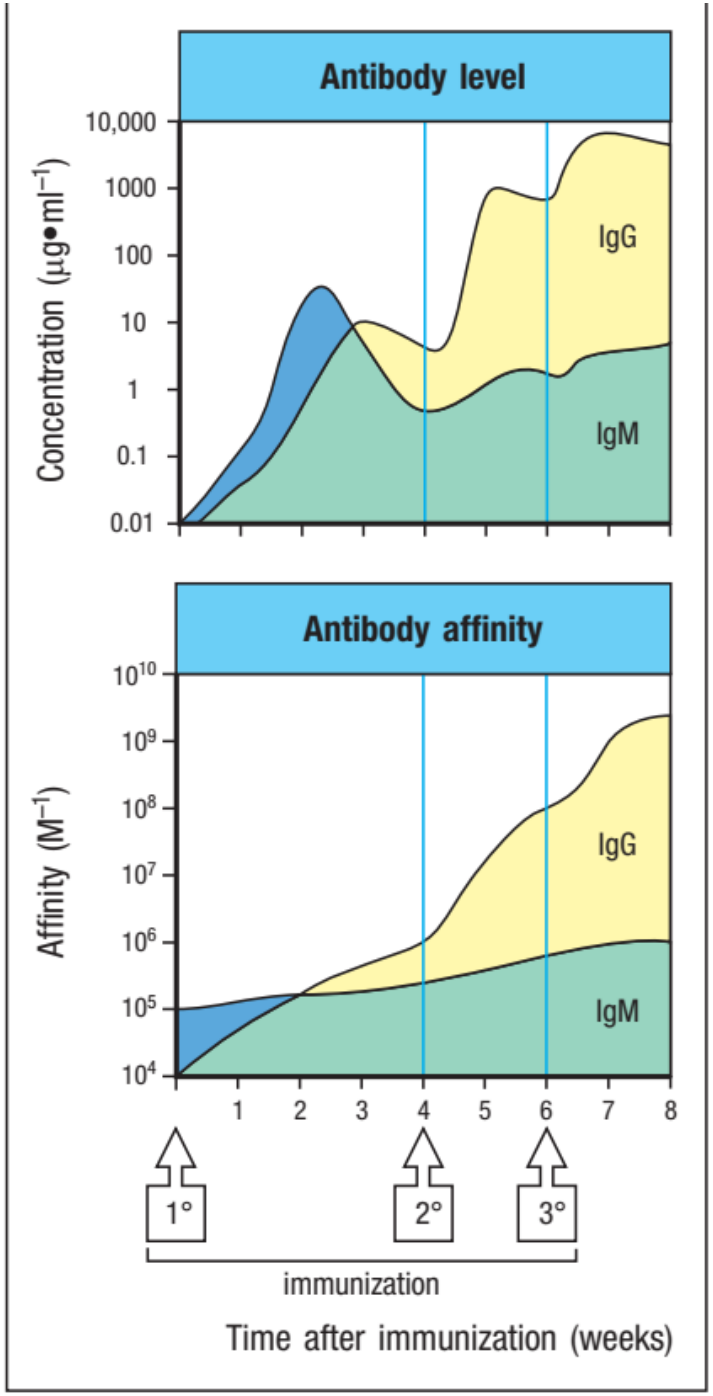


Fig. 11.24 The generation of secondary antibody responses from memory B cells is distinct from the generation of the primary antibody response. These responses

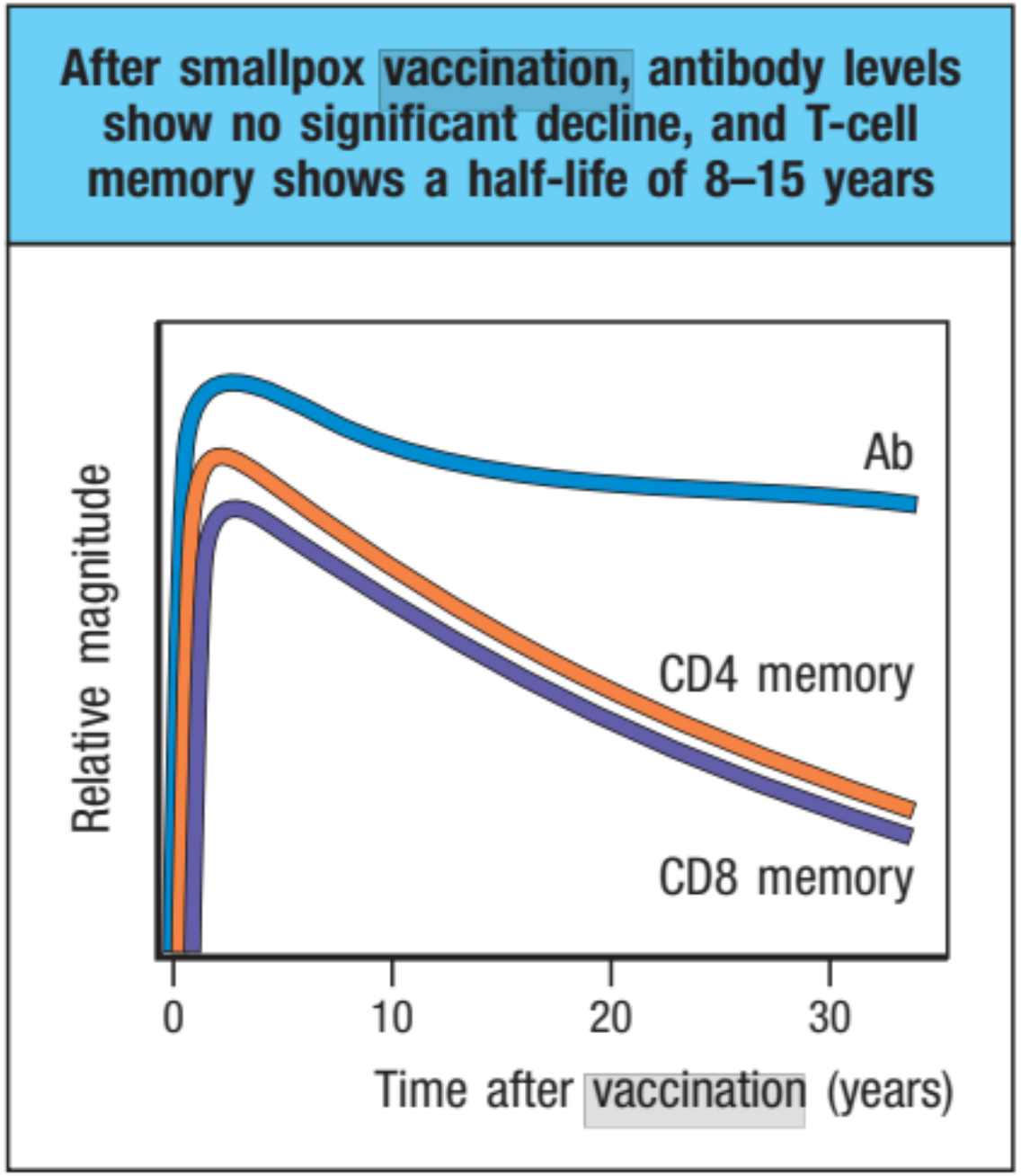


Fig. 11.23 Antiviral immunity after smallpox vaccination is long lived. Because smallpox has been eradicated, recall responses measured in people who were vaccinated for smallpox can be taken to represent true memory in the absence of reinfection. After smallpox vaccination, antibody levels show an early peak with a period of rapid decay, which is followed by long-term maintenance that shows no significant decay. CD4 and CD8 T-cell memory is long lived but gradually decays, with a half-life in the range of 8–15 years.

The Journal of Clinical Investigation

RESEARCH ARTICLE

Lymphoid tissue fibrosis is associated with impaired vaccine responses

Cissy Kityo,[1] Krystelle Nganou Makamdop,[2] Meghan Rothenberger,[3] Jeffrey G. Chipman,[3] Torfi Hoskuldsson,[3] Gregory J. Beilman,[3] Bartosz Grzywacz,[3] Peter Mugyenyi,[1] Francis Ssali,[1] Rama S. Akondy,[4] Jodi Anderson,[3] Thomas E. Schmidt,[3] Thomas Reimann,[3] Samuel P. Callisto,[3] Jordan Schoephoerster,[3] Jared Schuster,[3] Proscovia Muloma,[1] Patrick Ssengendo,[1] Eirini Moysi,[2] Constantinos Petrovas,[2] Ray Lanciotti,[5] Lin Zhang,[3] Maria T. Arévalo,[6] Benigno Rodriguez,[7] Ted M. Ross,[6] Lydie Trautmann,[8,9] Rafick-Pierre Sekaly,[7] Michael M. Lederman,[7] Richard A. Koup,[10] Rafi Ahmed,[4] Cavan Reilly,[3] Daniel C. Douek,[2] and Timothy W. Schacker[3]

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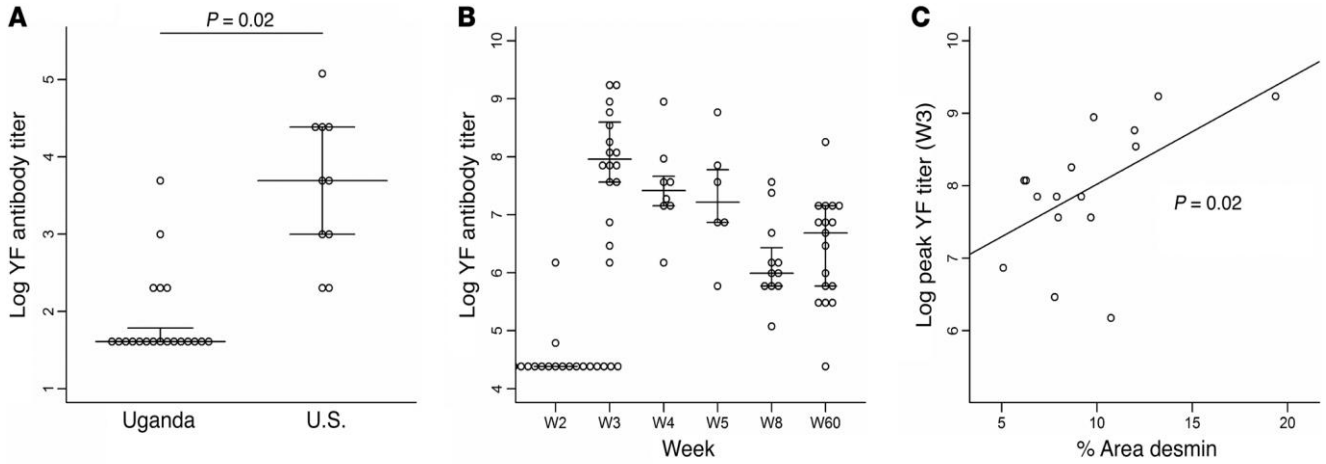
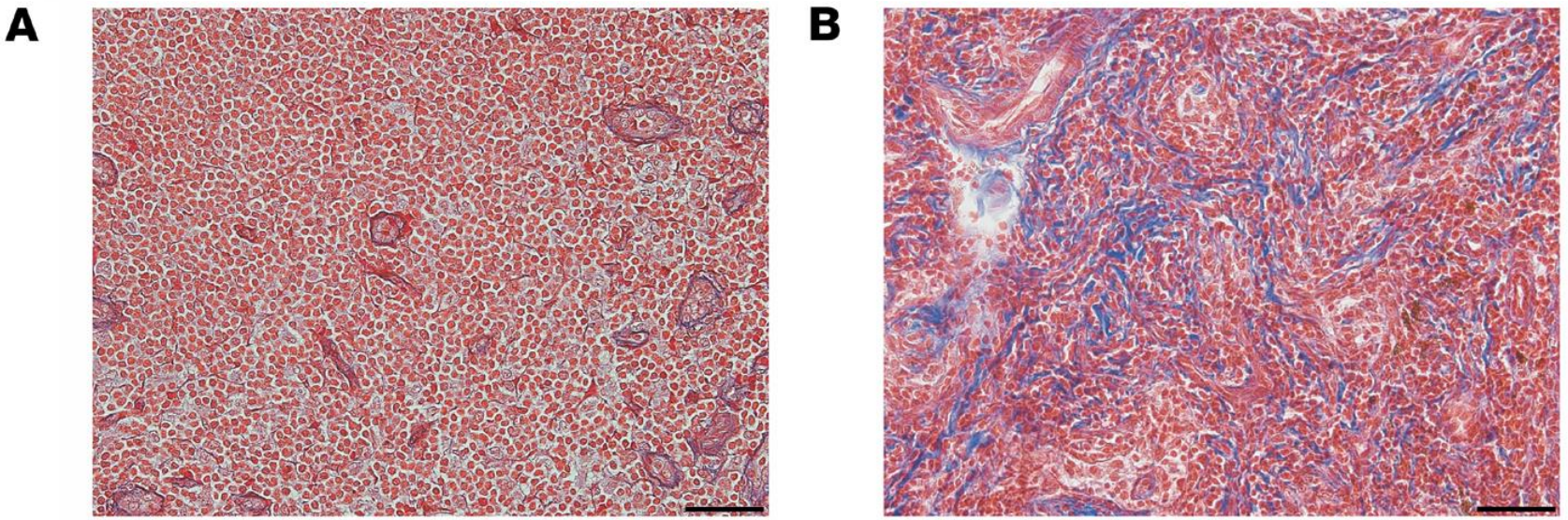
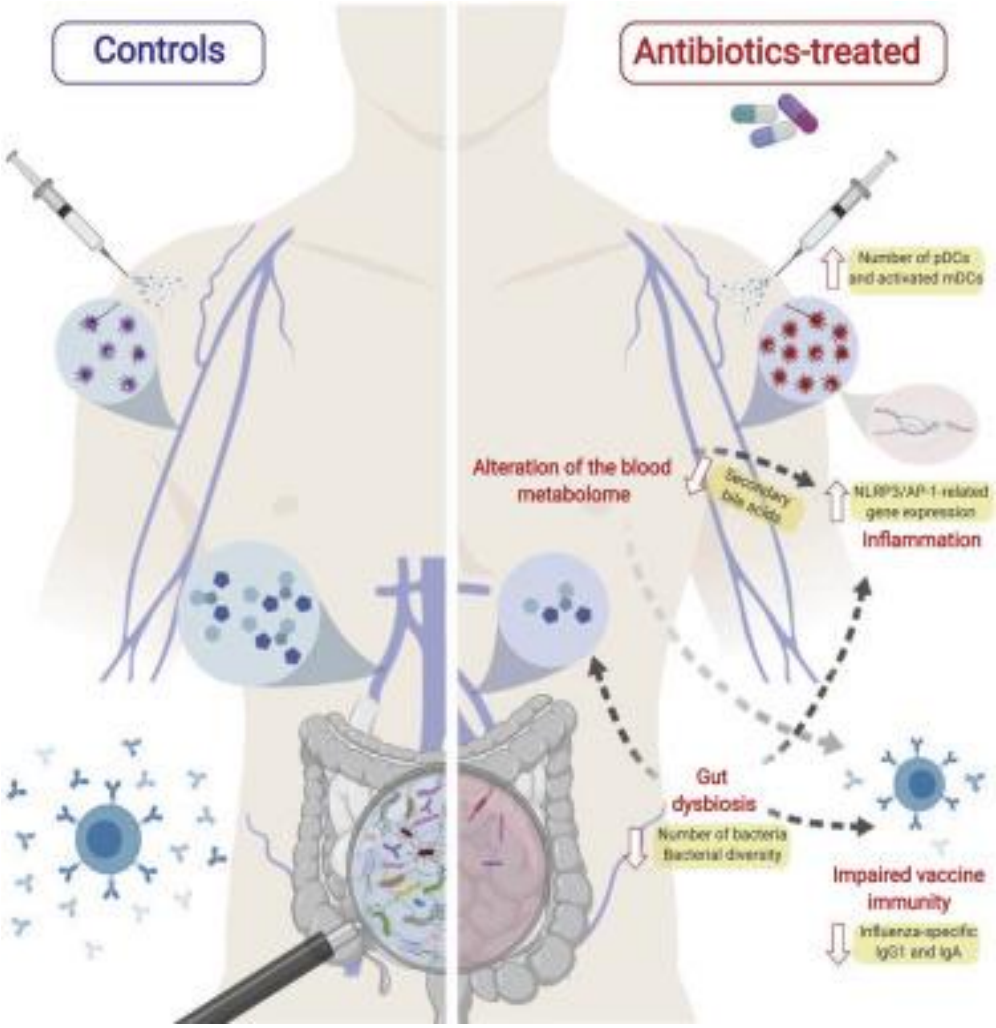
Lymph node fibrosis and dermatopathic lymphadenopathy affects responses of humans to vaccines

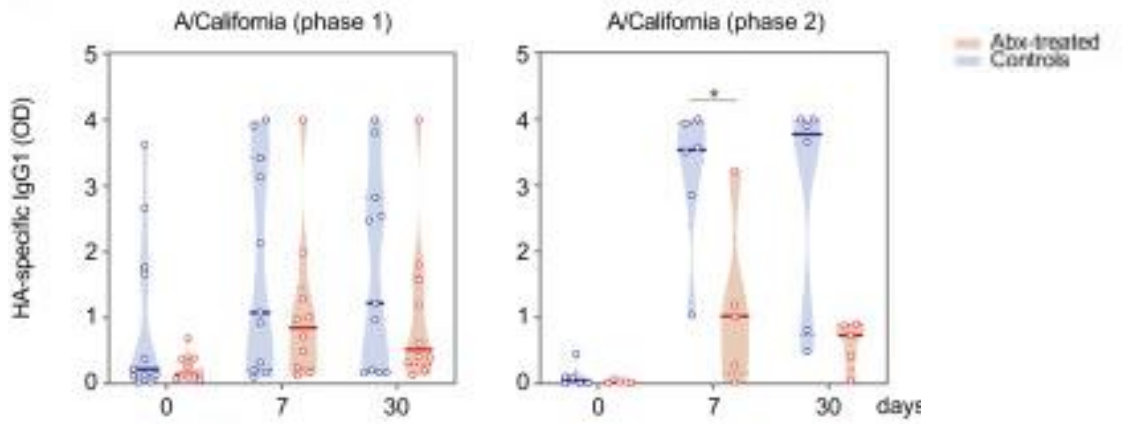




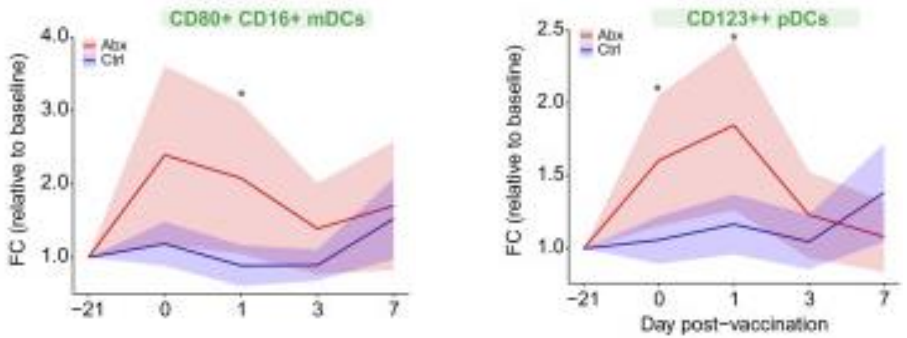
Antibiotics-Driven Gut Microbiome Perturbation Alters Immunity to Vaccines in Humans

Cell, 2019. Hagan *et al.*





Antibiotics Use Induces Pro-inflammatory Transcriptional and Cellular Responses in Blood



Antibiotics-driven depletion of the gut microbiome:

- Drives inflammatory signaling in innate immune cells
  - in a manner consistent with age-associated changes in immune responses
- Decreases in B cell and cell-cycle-related expression
- Bile-derived microbial metabolites activate the inflammasome

Table 1. Microbiota composition and response to vaccination.

Author	Setting	Number of Subjects	Type of Vaccine	Outcome Measure	Reference
Huda et al., 2019	Infants	291	Bacillus Calmette-Guérin, oral polio virus, tetanus toxoid, hepatitis B virus	*Bifidobacterium* richness is associated with the efficacy of vaccines.	[110]
Eloe-Fadrosh et al., 2013	Infants	17	Oral live-attenuated typhoid vaccine Ty21a	Cell-mediated immune response was associated with more diverse and complex gut microbiota populations.	[111]
Kim et al., 2022	Infants	122	Oral Rotavirus Vaccine	Association of Streptococcus and Enterobacteriaceae with seroconversion	[112]
Parker et al., 2021	Infants	486	Oral Rotavirus Vaccine	Negative correlation between microbiota diversity and vaccine immunogenicity	[113]
Harris et al., 2018	Infants	30	Oral Rotavirus Vaccine	Association between vaccine response and higher abundance of Gammaproteobacteria (*Serratia* and *E. coli*)	[114]
Robertson et al., 2021	Infants	158	Oral Rotavirus Vaccine	No association observed with the microbiota composition	[115]

Clinical Infectious Diseases

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doi: 10.1093/cid/ciu611

PMCID: PMC4204607
PMID: 25305297

Evaluating Associations Between Vaccine Response and Malnutrition, Gut Function, and Enteric Infections in the MAL-ED Cohort Study: Methods and Challenges

Christel Hoest,[1] Jessica C. Seidman,[1] William Pan,[2] Ramya Ambikapathi,[1] Gagandeep Kang,[3] Margaret Kosek,[4] Stacey Knobler,[1] Carl J. Mason,[5] and Mark Miller[1], The MAL-ED Network Investigators[a]

Clin Infect Dis

X

Grant et al. Malaria Journal (2022) 21:59
https://doi.org/10.1186/s12936-022-04077-x

Malaria Journal

RESEARCH Open Access

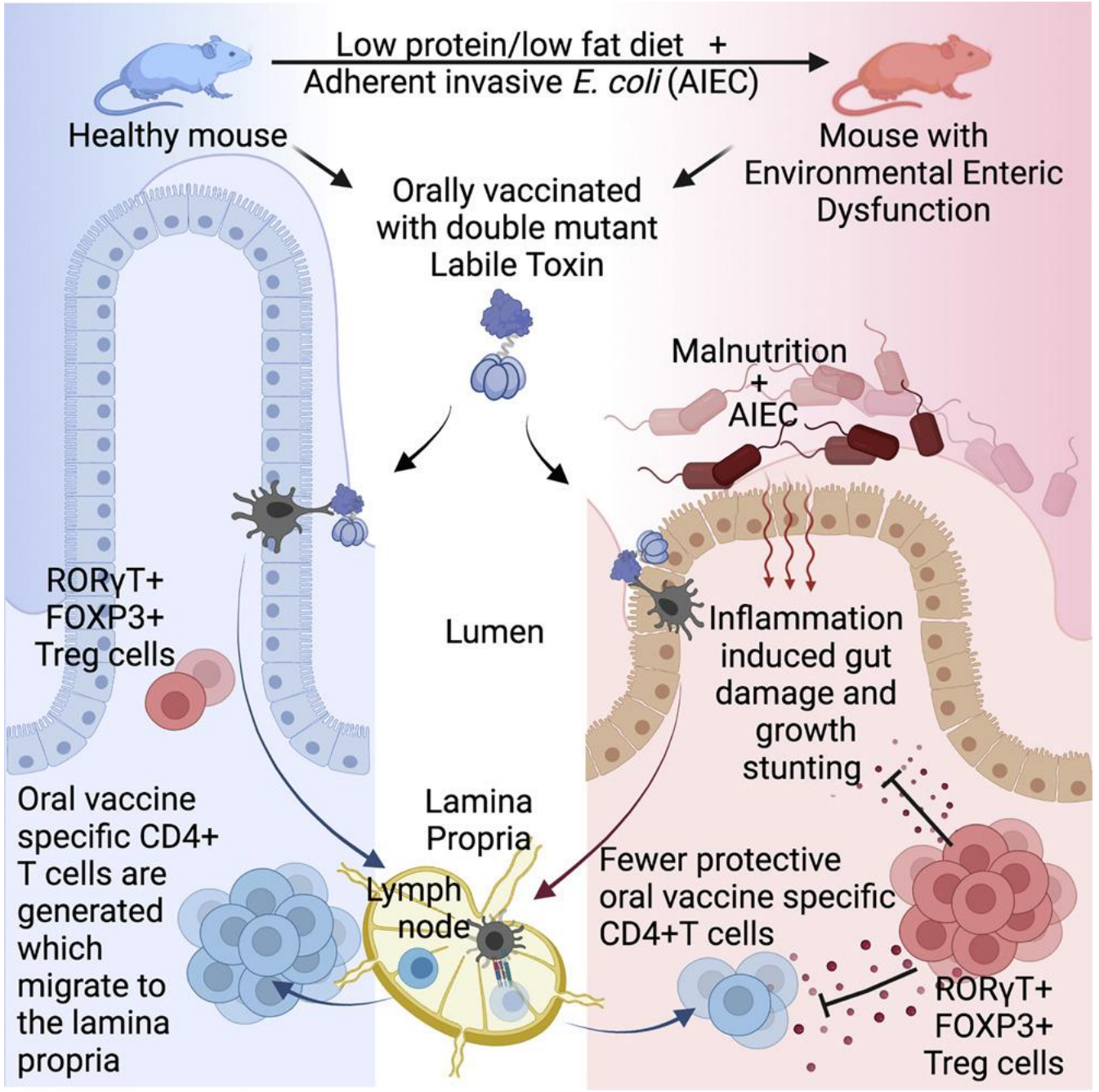
Impact of seasonal RTS,S/AS01$_E$ vaccination plus seasonal malaria chemoprevention on the nutritional status of children in Burkina Faso and Mali

Jane Grant[1*], Issaka Sagara[2], Issaka Zongo[3], Matthew Cairns[1], Rakiswendé Serge Yerbanga[3], Modibo Diarra[2], Charles Zoungrana[3], Djibrilla Issiaka[2], Frédéric Nikièma[3], Frédéric Sompougdou[3], Amadou Tapily[2], Mahamadou Kaya[2], Alassane Haro[3], Koualy Sanogo[2], Abdoul Aziz Sienou[3], Seydou Traore[2], Ismaila Thera[2], Hama Yalcouye[2], Irene Kuepfer[1], Paul Snell[1], Paul Milligan[1], Christian Ockenhouse[4], Opokua Ofori-Anyinam[5], Halidou Tinto[3], Abdoulaye Djimde[2], Daniel Chandramohan[1], Brian Greenwood[1], Alassane Dicko[2] and Jean-Bosco Ouédraogo[3]

Immunity 2021 doi: 10.1016/j.immuni.2021.07.005.

Environmental enteric dysfunction induces regulatory T cells that inhibit local CD4+ T cell responses and impair oral vaccine efficacy

Amrita Bhattacharjee et al.



scientific reports 2022

OPEN

The impact of glucose tolerance state on seropositivity rate after hepatitis B vaccination

Maria Mercedes Chang Villacreses[1,2], Rudruidee Karnchanasorn[3], Horng-Yih Ou[4], Raynald Samoa[1,2], Lee-Ming Chuang[5,6] & Ken C. Chiu[2,7]

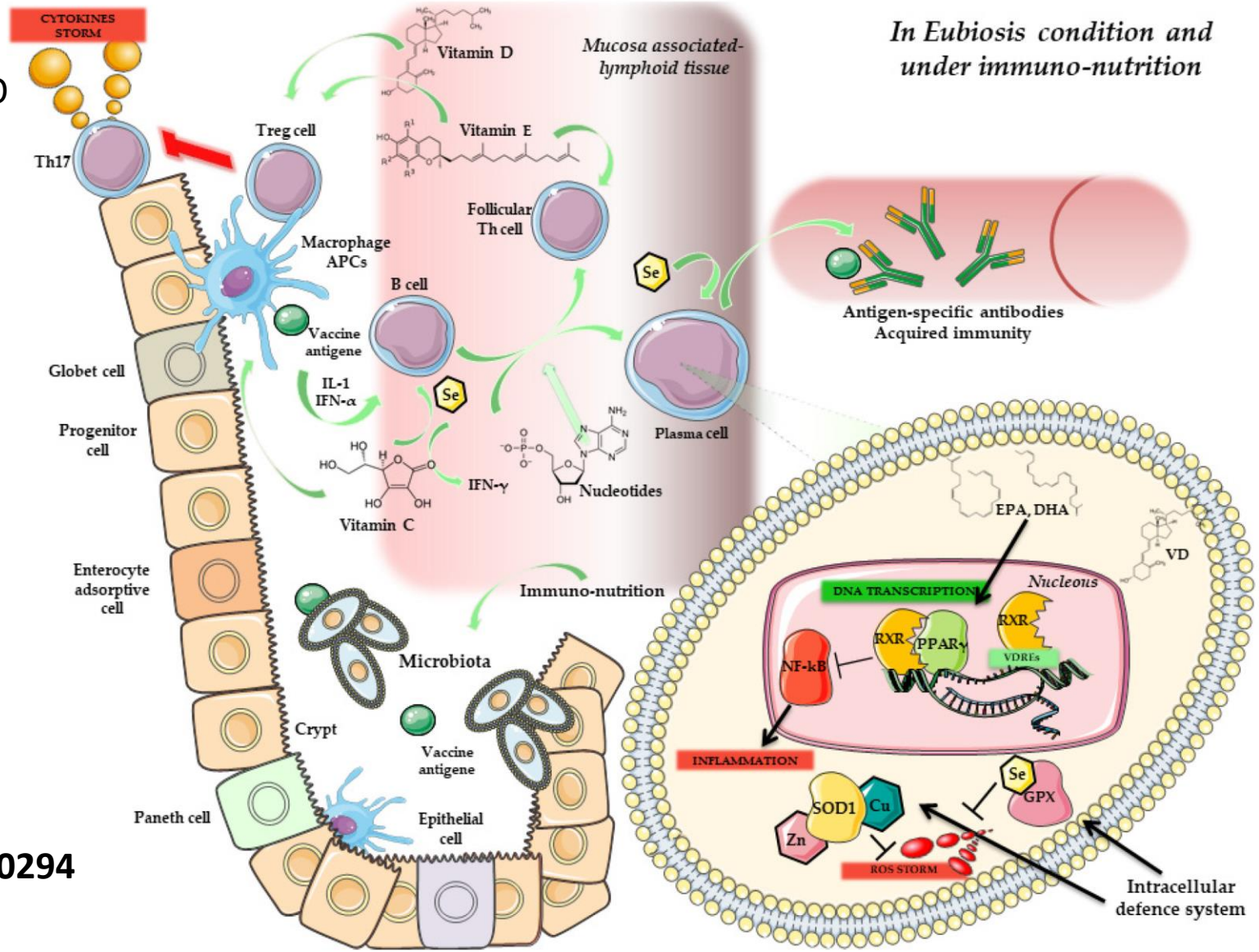
	Total	Unweighted	Weighted[a]
	n	n, (%)	%, (95%CI)
Normal glucose tolerance (NGT)	4639	2340	53.64%
		(50.44%)	(53.63–53.66)
Abnormal glucose tolerance (AGT)	1989	810	45.52%
		(40.72%)	(45.49–45.54)
Diabetes mellitus (DM)	1017	266	28.84%
		(26.16%)	(28.80–28.87)

Table 2. The impact of glucose tolerance on seropositivity rates (%, with 95% confidence intervals [CI]) after hepatitis B vaccination. [a]$P < 0.0001$ for weighted percent among three states of glucose tolerance.

Microbiota and Nutritional Status
- Gut Microbiota Composition
- Impact of Diet on Gut Microbiota
- Gut Microbiota and Inflammatory Status
  - SCFAs X trimethylamine N-oxide/TMAO

Immunonutrition: An Overview
- Nutritional Status in Human Health
- Nutrients and Immune System
- Immunonutrition: The Key Actors
  - Glutamine
  - Arginine
  - Omega-3
  - Alfa-Linolenic Acid
  - Vitamin D
  - Vitamin E
  - Vitamin C
  - Selenium
  - Zinc

Microbiota, Immunonutrition and Probiotics: Improving Vaccine Response



vaccine 2022 doi.org/10.3390/vaccines10020294

Review

Vaccines, Microbiota and Immunonutrition: Food for Thought

Laura Di Renzo [1], Laura Franza [2], Diego Monsignore [1], Ernesto Esposito [3], Pierluigi Rio [4], Antonio Gasbarrini [4], Giovanni Gambassi [4], Rossella Cianci [4,*,†] and Antonino De Lorenzo [1,†]