Vaccines, Principles, Applications, Actualities, Monographies

http://www.sciencesetavenir.fr/sante/le-marche-mondial-des-vaccins-proche-des-80-milliards-de-dollars-en-2025_30124

Microbial and Pharmaceutical Applications of Microbial Biodiversity

Master 2 Microbiologie Appliquée et Génie Biologique

Jan 30th. 2025

Pr. Christophe Sola

Vaccine : Definition

- ***« A vaccine is a biological product that can be used to safely induce an immune response that confers protection against infection and/or disease on subsequent exposure to a pathogen »***.

Pollard and Bijker 2021 Nature Rev Immunology

Vaccination : definition

- ***« Injection of a weakened or inactivated pathogen or harmless product for immune protection »***

A more extended Definition of Vaccination

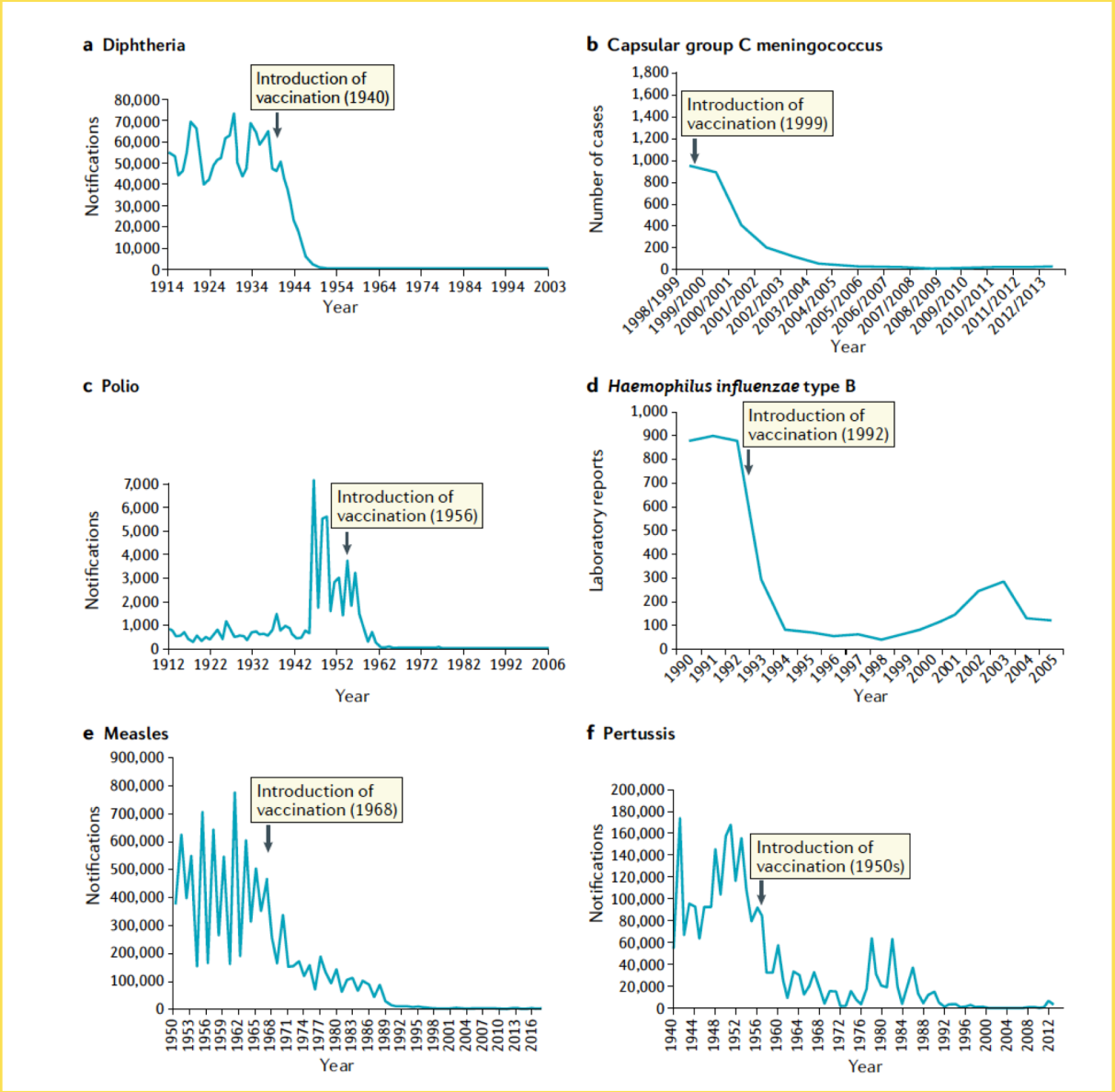
- ***Vaccination is a process of introducing an external agent (the vaccine) into a living organism to create a positive immune response against an infectious disease***

- The active ingredient in a vaccine must be a product that will stimulate the body's natural defenses (the immune system). The primary immune reaction allows in parallel a storage of the antigen presented so that in the future, during a true contamination, the acquired immunity can activate more quickly. There are five types of vaccines depending on their preparation

:

  - **Attenuated or Living agents : Yellow fever, chickenpox, rubella, mumps, measles, tuberculosis- (BCG), rotavirus**
  - **Inactivated infectious agents : Cholera, Plague, Hepatitis A, ...**
  - **infectious Agent Subunits : Hepatitis B, Papillomavirus, Whooping-cough, Flu, Hepatitis C)**
  - **Inactivated toxins : Tetanos, Diphteria**
  - **mRNA SARS-Cov2.**

Impact of Vaccines in Public Health in UK



The confidence in vaccines,

increases

But the global coverage of populations,

decreases

(trend 2025)

Pollard and Bijker 2021 Nature Rev Immunology

News item: The growing concern of Measles Vaccination status in UK

in 2016 the UK was declared measles-free

the majority of the 209 laboratory-confirmed cases of measles between 1 January 2023 and 30 November 2023 was in children under 10, reflecting the ***decline in vaccination rates***. 1,603 suspected cases in England and Wales in 2023, twice more than in 2022

Explainer

UK measles outbreaks: why are cases rising and vaccination rates falling?

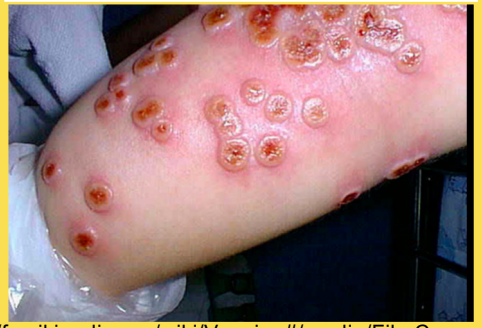
Covid confusion, debunked link to autism and lack of NHS funding all contributing to rise in this serious disease

https://www.theguardian.com/society/2024/jan/20/uk-measles-outbreaks-why-are-cases-rising-and-vaccination-rates-falling

History of vaccination-1 smallpox and cowpox

- **Lady Mary Wortley Montaigu** (**1689-1762**) **Edward Jenner** (**1749-1823**)
  Gloucestershire, Berkeley
  An inquiry into the causes and effects of the variolae vaccina 1798

Vaccination comes from Latin **vaccinia**, and **vacca**, vache (cow).



https://fr.wikipedia.org/wiki/Vaccine#/media/File:Cowpox_eruption.jpg

•**Smallpox** is a fearsome and immunizing eruptive infectious disease, caused by a **poxvirus**, known since the 4th century in China and imported early (7th century) in the Western world.

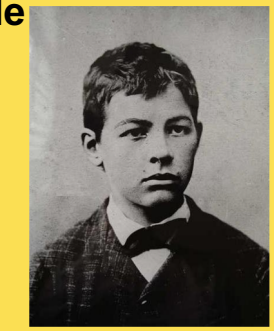
On October 29, 1979, WHO declared smallpox **eradicated** from the face of the earth

smallpox (variole), and cowpox (vaccine), monkeypox (2022 !)

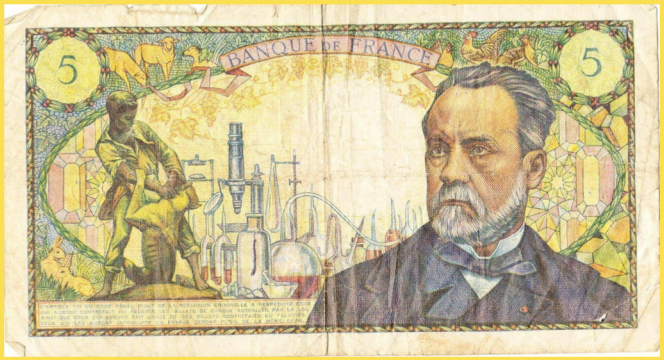
History of vaccination-2, rabies

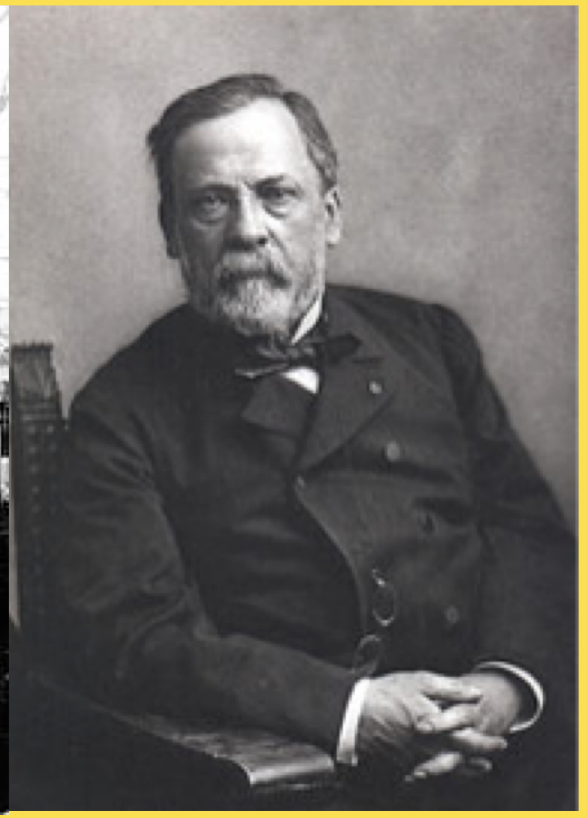
Louis Pasteur (1822-1895)

Jean-Baptiste Jupille
20-30 october 1985



Joseph Meister
6 jun 1885





Jean-Baptiste Jupille, chief doorkeeper of Pasteur in 1913

Completion of the rabies virus genome sequence determination: highly conserved domains among the L (polymerase) proteins of unsegmented negative-strand RNA viruses.
Tordo N, Poch O, Ermine A, Keith G, Rougeon F. Virology. 1988 Aug;165(2):565-76.

History of vaccination-3, Tuberculosis

Albert Calmette (1863-1933)

Camille Guérin (1872-1961)

BCG: was compulsory between 1950 and 2007 for children entering to school.
1908-1921, 13 years of culture
18 juillet 1921: nursery of the charity hospital, Paris
The requirement for BCG vaccination in children and adolescents was officially suspended in the summer of 2007 (décret n° 2007-1111 du 17 juillet 2007), in favor of a recommendation for vaccination of a more targeted population

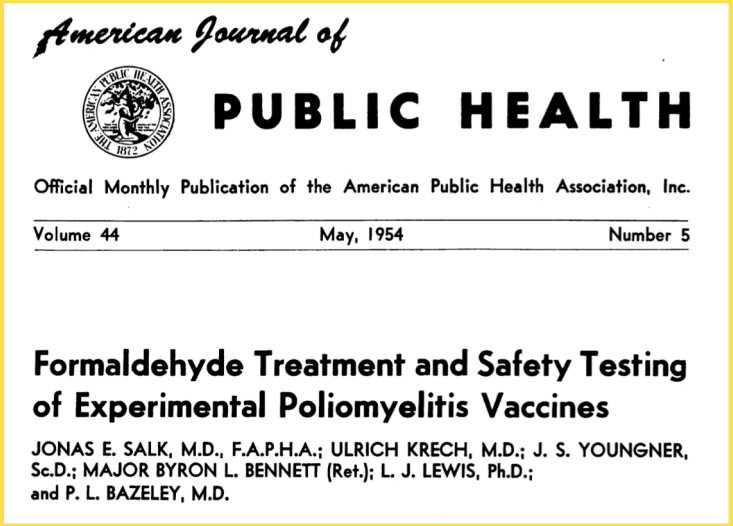
History of vaccination-4, Polyomyelitis

Jonas Salk (1914-1995)

April 12, 1955

Killed virus vaccine, Injectable

virus inactivated by formaldehyde



American Journal of

PUBLIC HEALTH

Official Monthly Publication of the American Public Health Association, Inc.

Volume 44 May, 1954 Number 5

Formaldehyde Treatment and Safety Testing of Experimental Poliomyelitis Vaccines

JONAS E. SALK, M.D., F.A.P.H.A.; ULRICH KRECH, M.D.; J. S. YOUNGNER, Sc.D.; MAJOR BYRON L. BENNETT (Ret.); L. J. LEWIS, Ph.D.; and P. L. BAZELEY, M.D.

Albert Sabin (1906-1993)

1960

Attenuated Vaccine, Oral Form

ARTICLE | August 6, 1960

LIVE, ORALLY GIVEN POLIOVIRUS VACCINE

EFFECTS OF RAPID MASS IMMUNIZATION ON POPULATION UNDER CONDITIONS OF MASSIVE ENTERIC INFECTION WIT OTHER VIRUSES

Albert B. Sabin, M.D.; Manuel Ramos-Alvarez, M.D.; José Alvarez-Amezquita, M.D.; William Pelon, Ph.D.; Ric H. Michaels, M.D.; Ilya Spigland, M.D.; Meinrad A. Koch, M.D.; Joan M. Barnes, Ph.D.; Johng S. Rhim, M.D.

'wild' poliovirus (WPV) type 2 is eradicated since 2015, so-called circulating vaccine-derived poliovirus (cVDPV) remains. as of 2020, Afghanistan and Pakistan remains the two single endemic countries

importance of enterovirus surveillance in a post-polio world

History of vaccination-5, Hepatitis B virus

Philippe Maupas (1939-1981)

Immunisation against hepatitis B in man.
Maupas P et al. Lancet. 1976 Jun 26;1(7974):1367-70.

Pierre Tiollais (1938-)

Nucleotide sequence of the hepatitis B virus genome (subtype ayw) cloned in E. coli
F. Galibert *et al.* Nature, 1979 Oct 25;281(5733):646-50

Biosynthesis of hepatitis B virus surface antigen in Escherichia coli.Charnay *et al*. Nature. 1980 Aug 28;286(5776):893-5

Structure and expression of the hepatitis B virus genome S. Wain-Hobson et al. 1981, Dev Biol Stand.50:293-300

History of vaccination-6, Covid19

Özlem Türeci (1967-)

Uğur Şahin (1965-)

Immunologists and entrepreneur couple Heidelberg Klinikum University

mRNA-based therapeutics--developing a new class of drugs.Sahin U, Karikó K, Türeci Ö**.** Nat Rev Drug Discov. 2014 Oct;13(10):759-80

Drew Weissman (1959-) **Katakin Karikó(1955-)**

Naturally occurring nucleoside modifications suppress the immunostimulatory activity of RNA: implication for therapeutic RNA development.Karikó K, Weissman D. Curr Opin Drug Discov Devel. 2007 Sep;10(5):523-32

Nobel Price 2023 Medicine

first RNA-based vaccine to get approval for Covid-19

TABLEAU I

Dates of development of different vaccines development

Année	Vaccin développé	
XVIII^e siècle		
1798	Variole	/Smallpox. cowpox
XIX^e siècle		
1885	Rage	Inactivated virus (human) or attenuated (dogs,…
1896	Typhoïde, choléra	Killed cells
XX^e siècle		
1923	Anatoxine diphtérique	Modified exotoxin, toxoid
1926	Anatoxine tétanique	Modified exotoxin, toxoid
1927	BCG	Attenuated bacterial strain
1936	Fièvre jaune	Attenuated virus
1945	Grippe	Flu Inactivated virus
1955	Poliomyélite	Attenuated (Sabin) or Inactivated virus (Salk)
1963	Rougeole	Attenuated virus
1967	Oreillons	Attenuated virus
1969	Rubéole	Attenuated virus
1980	*Haemophilus influenzae* b conjugué	Conjugated vaccine (polysacch+P)
1981	Hépatite B	Recombinant DNA vaccine or inactivated virus
1992	Encéphalite japonaise	
1995	Varicelle, hépatite A	Attenuated virus (V), Recombinant DNA (H)
1998	Rotavirus	Attenuated virus (V)
XXI^e siècle 2020	Covid19	mRNA-based vaccine
2006-2007	Papillomavirus	Recombinant DNA vaccine
2013	Dengue	Recombinant Live Attenuated DNA vaccine

The new Global Health Issues on communicable diseases Brings us back to a compartmentalized world

- in **2009** first launch of ***Public Health Emergency of International Concern*** by WHO
- in **2010**, infectious diseases caused 18.5% of all human deaths and 23% of disability-adjusted-life years (DALY)
- in **2019-2021 the world-wide pandemia of Covid-19 evoked a massive threat, premature deaths, and economical losses**
- **Viral and Bacterial diseases are intimately linked**
- Change of paradigm : preparedness for next pandemia***, implemention of Non Pharmaceutical Prevention Measures, going back to hygien, quarantine, lockdowns and restriction of travel***

Annelies Wilder-Smith and Sarah Osman; Public health emergencies of international concern: a historic overview Journal of Travel Medicine, 2020, 1–13

Lozano, R.*et al*.Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380,2095–2128 (2012).

Murray, C. J.*et al*. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010.Lancet 380,2197–2223 (2012)

Types of Vaccines, Classification

https://www.pharmacorama.com/pharmacologie/hormones-cytokinesantigenes-anticorps/antigenes/vaccins-classification

Classification
According to preparation mode

-Live attenuated vaccines,

bacterial such as BCG, viral such as measles, rubella, poliomyelitis (oral)

-killed inactivated vaccines, bacterial such as pertussis, viral such as poliomyelitis (injectable)

-purified antigenic fractions, bacterial against pneumococcus, typhoid and pertussis, viral against influenza and hepatitis B

-mRNA-based vaccines

Classification
According to type of targeted micro organisms

On a practical level, we can distinguish

-antiviral vaccines,

-antibacterial vaccines,

-combined vaccines, most often antibacterial and antiviral

-vaccines used in the prevention of respiratory tract infections.

The industrial evolution of vaccines

Viral vaccines = recombinant virus-like particles or live, live-attenuated or whole inactivated viruses or subunit vaccines

Bacterial vaccines= bacterial surface proteins, detoxified toxins or polysaccharides with or without conjugation to a carrier protein, subunits vaccines.

Monovalent vaccines are almost no longer available in France, with some exceptions

The number of valences is increasing and vaccines are therefore more and more complex

The safety of certain excipients has been strongly questioned

The definition of terms for vaccine targets has had to evolve

***Newborn* : from 0 to 28 days, *Infant* : from 29 days to 23 months**

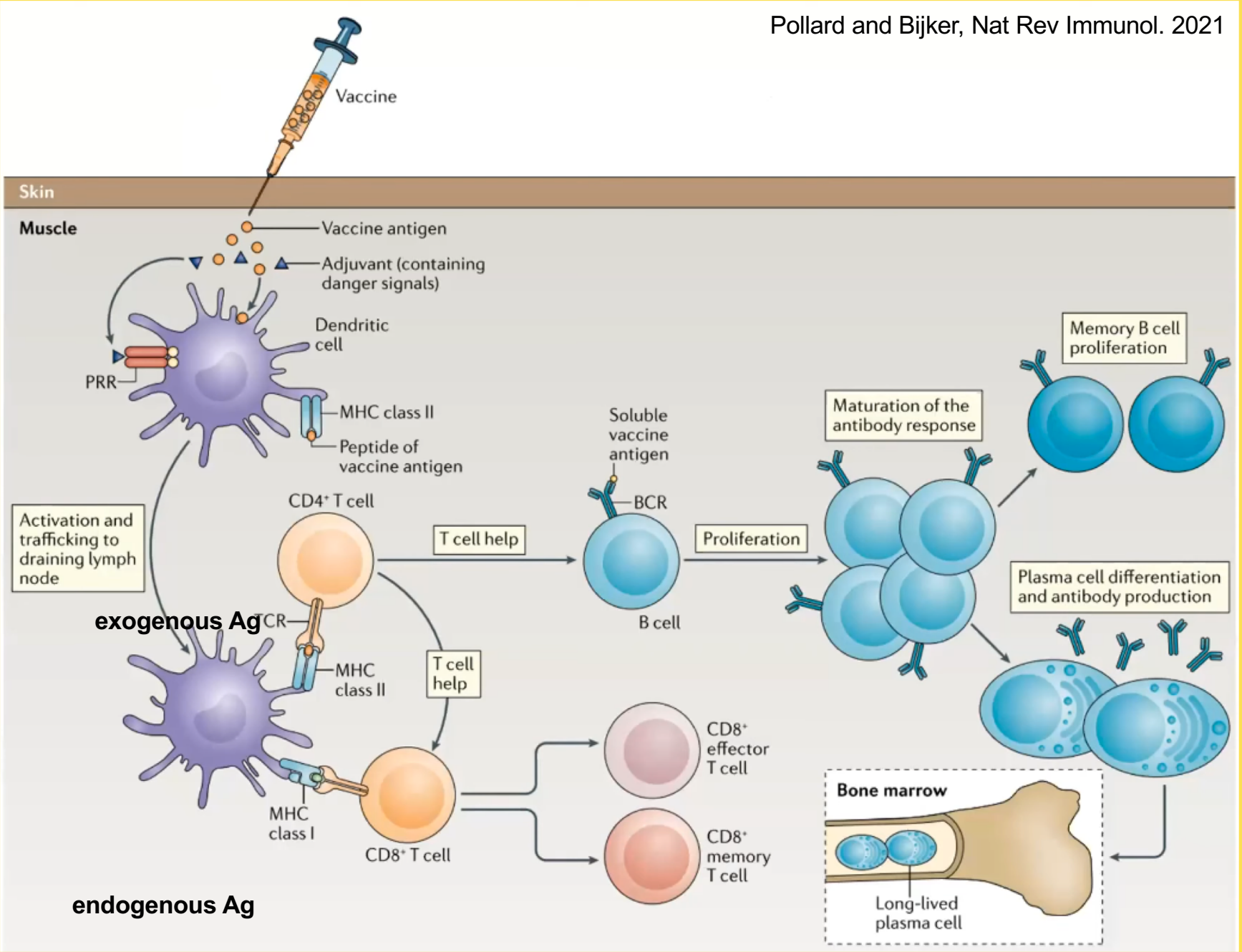
***Child* : from 2 to 18 years , *Adult* : more than 18 years old**

Vaccination against Invasive meningococcal infections of serogroup C, pneumococcus, and MMR (measles-mumps-rubella) is compulsory in children from January 1, 2018. (11 vaccines: mandatory)

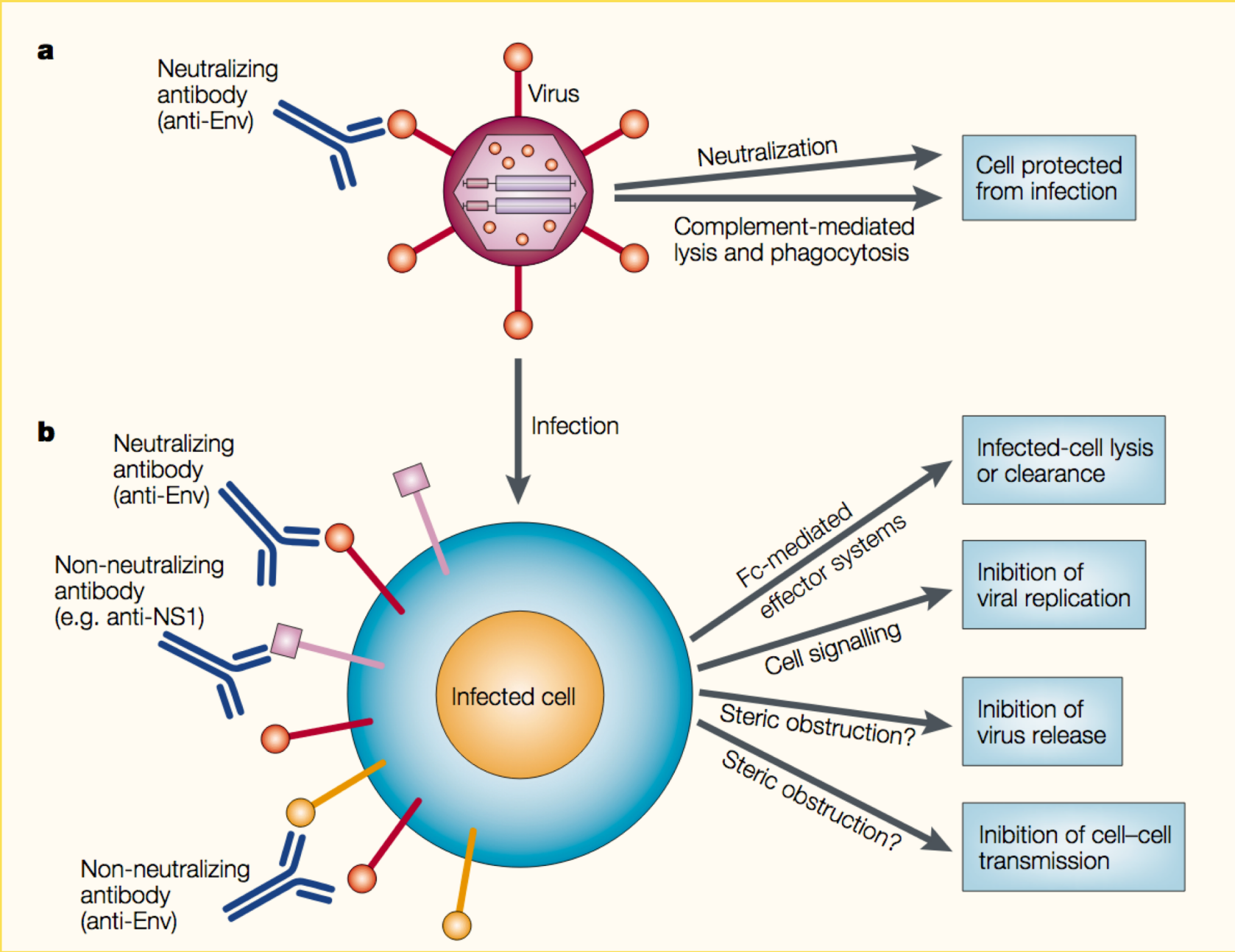
2020: first massive launch of an mRNA-based vaccines by Pfizer-BioNtech

How does vaccination work ?

Pollard and Bijker, Nat Rev Immunol. 2021



The antiviral activities of antibodies



Burton DR 2002;, Antibodies, Virus Vaccines , Nature Immunol Sept. 2002, 2, 706

4.1 Tableau des vaccinations chez les enfants et les adolescents - 2018

Pour toute personne ayant déjà reçu un ou des vaccins avant la mise en place du calendrier vaccinal en 2013, se référer aux chapitres correspondants et/ou tableaux 4.7

	Vaccins contre :	Naissance	2 mois	4 mois	5 mois	11 mois	12 mois	16-18 mois	6 ans	11 - 13 ans	15 ans	16-18 ans
Recommandations générales	Diphtérie (D), Tétanos (T), coqueluche acellulaire (Ca), Poliomyélite (P)		DTCaP	DTCaP		DTCaP			DTCaP			
	Haemophilus influenzae b (Hib)		Hib	Hib		Hib						
	Hépatite B (Hep B)		Hep B	Hep B		Hep B						
	Pneumocoque (PnC)[1]		PnC	PnC		PnC						
	Méningocoque C (vaccin conjugué MnC)				MnC		MnC					
	Rougeole (R), Oreillons (O), Rubéole (R)						ROR 1	ROR 2				
	diphtérie (d), Tétanos (T), coqueluche acellulaire (ca), Poliomyélite (P)[2]									dTcaP		
	Papillomavirus humains (HPV) chez jeunes filles									2 doses (0, 6 mois) : vaccin quadrivalent ou vaccin bivalent ou vaccin neufvalent (11/14 ans)		
Rattrapage	Hépatite B							3 doses selon le schéma 0, 1, 6 mois ou, de 11 à 15 ans révolus, 2 doses selon le schéma 0, 6 mois[3]				
	Méningocoque C (vaccin conjugué)							1 dose jusqu'à 24 ans[4]				
	Papillomavirus humains (HPV) chez jeunes filles										3 doses selon le schéma 0, 1, 6 mois ou 0, 2, 6 mois (jeunes filles de 14 ou 15 à 19 ans révolus) selon le vaccin utilisé	
	Rougeole (R), Oreillons (O), Rubéole (R)								2 doses à au moins 1 mois d'intervalle si pas de vaccin antérieur ; 1 dose si une seule dose vaccinale antérieure			

BACTERIA=6
Corynebacterium diphteriae
Clostridium tetanicum
Bordetella pertussis
Hemophilus influenzae
Streptococcus pneumoniae
Neisseria meningitidis
VIRUS=5
Polyomyelitis virus
Measles virus
Mumps virus
Rubela virus
Hepatitis B virus

Nota bene : les vaccins indiqués sur fond bleu sont obligatoires pour les enfants à partir du 1er janvier 2018. Encadrés verts : co-administration possible.

Lorsqu'un retard est intervenu dans la réalisation du calendrier de vaccinations indiqué, il n'est pas nécessaire de recommencer tout le programme vaccinal ce qui imposerait des injections répétées. Il suf de reprendre ce programme au stade où il a été interrompu et de compléter la vaccination en tenant compte du nombre de doses manquantes et de l'âge de la personne.

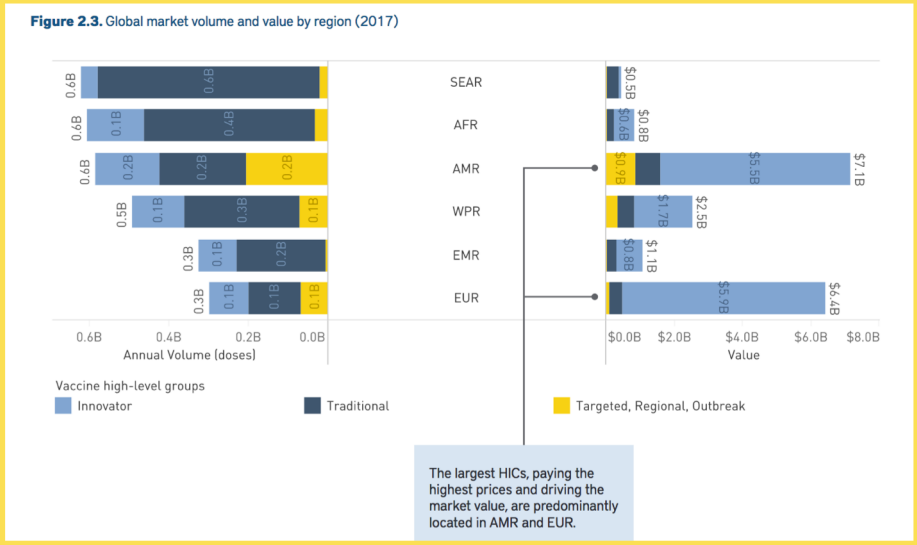
44

Mandatory vaccinations in France 2021: B =6, V =5

Vaccines markets were already on the rise before Covid19 crisis

Le marché mondial des vaccins a enregistré une progression de 24% entre 2011 et 2014 et cette croissance *"devrait se maintenir voire s'intensifier"*, prévoit le cabinet Alcimed, qui table sur un chiffre d'affaires multiplié par 2,5 d'ici 2025. Les ventes mondiales de vaccins sont passées de 26 milliards de dollars en 2011 à 32,3 milliards de dollars en 2014 et devraient avoisiner les 80 milliards de dollars en 2025, selon cette étude.

http://www.sciencesetavenir.fr/sante/le-marche-mondial-des-vaccins-proche-des-80-milliards-de-dollars-en-2025_30124



https://apps.who.int/iris/bitstream/handle/10665/311278/WHO-IVB-19.03-eng.pdf?sequence=1&isAllowed=y

La place de l'Europe et de la France

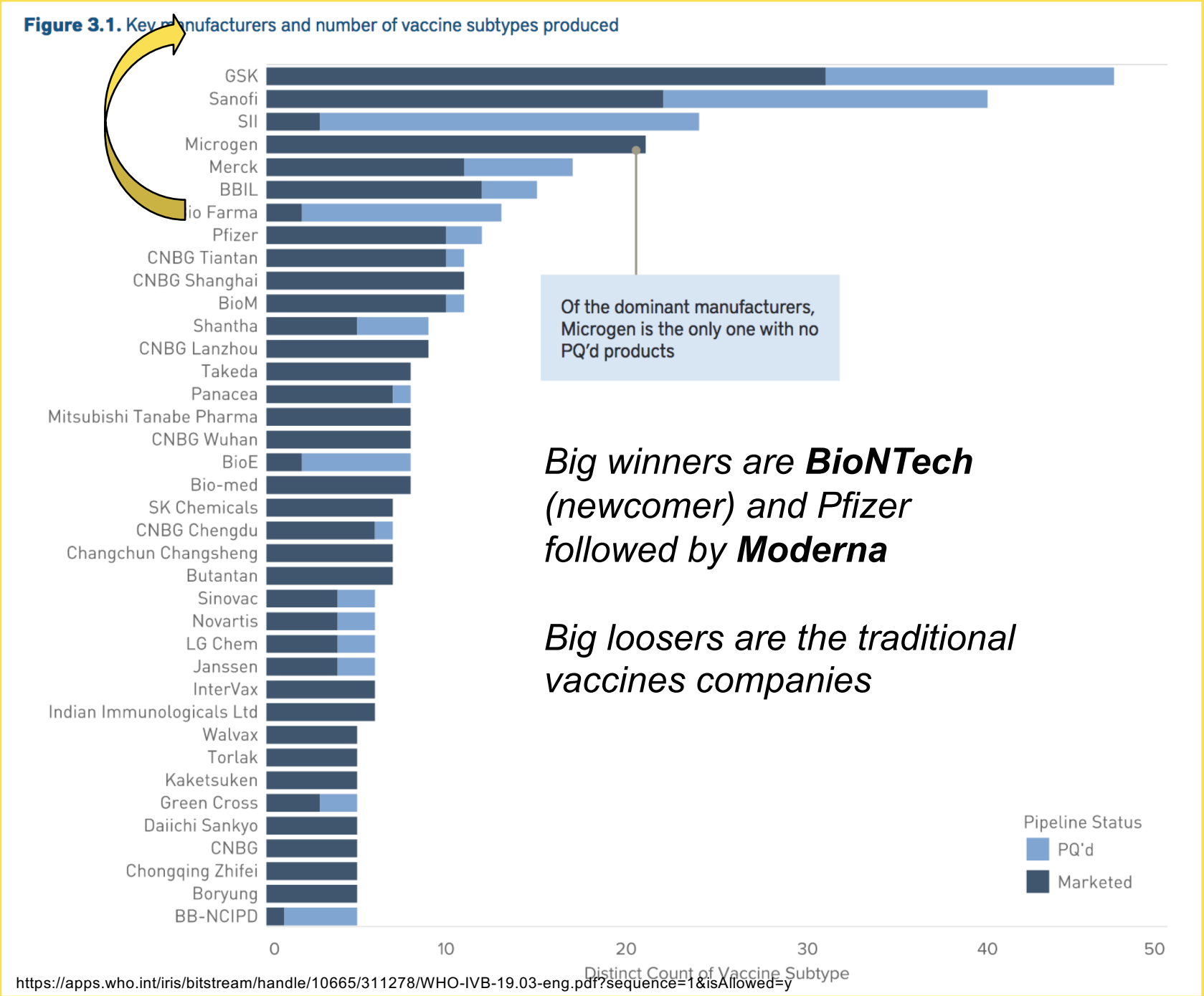
Les industriels européens produisent 90 %[3] des vaccins utilisés dans le monde. Ils exportent 84 % de leur production, soit 3,5 milliards de doses par an. L'Europe attire 65 % des projets d'investissement en recherche.

Parmi les 32[4] principaux sites de production mondiaux, plus de 60 % sont en Europe. Treize pays européens accueillent ces sites de production qui emploient plus de 20 000 personnes. Dans le reste du monde, seuls cinq pays sont dotés de tels sites, la plupart en Amérique du Nord.

La France, à égalité avec l'Allemagne, abrite trois centres de R&D et deux centres de production, ainsi qu'un pôle de compétitivité consacré à l'infectiologie basé à Lyon.

http://www.leem.org/sites/default/files/100questions_Leem_Fiche-77.pdf

The winners and the loosers after Covid19...



*Big winners are **BioNTech** (newcomer) and Pfizer followed by **Moderna***

Big loosers are the traditional vaccines companies

https://apps.who.int/iris/bitstream/handle/10665/311278/WHO-IVB-19.03-eng.pdf?sequence=1&isAllowed=y

composition of a mRNA-based vaccine Comirnaty® Pfizer

mRNA

nanolipids & other excipients

various specialties forms

Composition du médicament COMIRNATY

	p dose	p dose
Tozinaméran (ARN messager codant pour la protéine Spike du SARS-CoV-2)	10 µg	30 µg

Substance active : Tozinaméran

Excipients communs : ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldécanoate), 1,2-distéaroyl-sn-glycéro-3-phosphocholine, 2-[(polyéthylène glycol)-2000]-N, N-ditétradécylacétamide, Cholestérol, Eau ppi, Saccharose
Autres excipients (spécifiques à certaines formes) : Acide chlorhydrique, Phosphate disodique dihydrate, Phosphate monopotassique, Potassium chlorure, Sodium chlorure, Sodium hydroxyde, Trométamol, Trométamol chlorhydrate

Adults (>12 years)

Children (5-11 years old)

Présentations du médicament COMIRNATY

COMIRNATY 10 µg/dose : dispersion à diluer pour dispersion injectable IM ; boîte de 10 flacons de 10 doses
Sur ordonnance (Liste I) - Non remboursé - Prix libre

COMIRNATY 30 µg/dose : dispersion à diluer pour dispersion injectable IM ; boîte de 195 flacons de 6 doses
Sur ordonnance (Liste I) - Non remboursé - Prix libre

COMIRNATY 30 µg/dose : dispersion injectable IM ; boîte de 1 flacon de 6 doses
Sur ordonnance (Liste I) - Non remboursé - Prix libre

COMIRNATY 30 µg/dose : dispersion injectable IM ; boîte de 10 flacons de 6 doses
Sur ordonnance (Liste I) - Non remboursé - Prix libre

Main actors of vaccines markets (80 Milliards US$ in 2025 before Covid 19)

the position varied a lot...first data were from 2014

le chiffre

5[1]

laboratoires se partagent 80 % du marché mondial.

Sanofi (+ 50% Sanofi P

SANOFI

2012 Vaccine revenue: $5.54 billion

2022 Vaccine revenues: $7,8 billion

PENT Act-HIB, a DTPq, Hib and polio vaccine, and Fluzone/Vaxigrip, a seasonal flu shot
VidPrevtyn Beta= Covid 19

Sanofi Pasteur Vaccins, Toronto ONT, Marcy L'Etoile F, val de Reuil F, Swiftwater, PA, FR (4)

Cervarix GlaxoSmithKline

GlaxoSmithKline

2012 Vaccine revenue: $5.26 billion

2022 Vaccine revenues: $12,7 billion

GSK UK (2) vaccine plant : Tuas, SGP

Pfizer

2012 Vaccine revenue: $4.11 billion

Prevnar 13: top vaccine
Comirnaty, $18,9 billion

2022 Vaccine revenue: $37,8 billion

Pfizer USA (1)

Gardasil

MERCK

Be well

2012 Vaccine revenue: $5.27 billion

2022 Vaccine revenues: $11,7 billion

Merck GER 3 (22%)

NOVARTIS

Novartis International AG (Bâle) CH n° 5

Solvay Biologicals : Weesp, NLD

Protein Sciences CORPORATION

Protein Sciences Corporation

(Meriden, Connecticut) vaccin antigrippe

SOLVAY

MedImmune

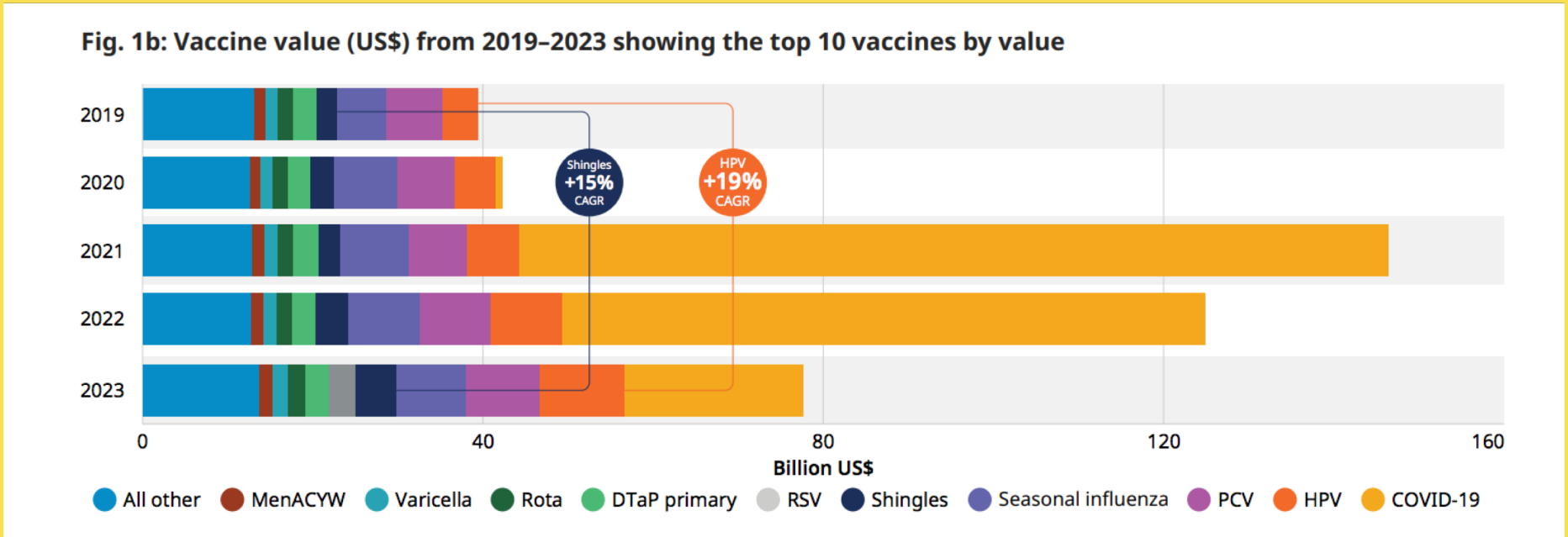
MedImmune, LLC
Astra-Zeneca
FluMist, vaccine in spray nasal

Gaithersburg, MD, Mountain View, CA, Santa Clara, CA, Hayward, CA, Cambridge, UK

http://www.fiercepharma.com/special-report/top-5-vaccine-companies-by-revenue-2012
https://www.sciencesetavenir.fr/sante/le-marche-mondial-des-vaccins-proche-des-80-milliards-de-dollars-en-2025_30124

Christophe Sola, MPAMB 2025

Vaccine Market Shares 2024



World Health Organization

Global vaccine market report 2024

Vaccine Market Evolution 2025-2029

PR Newswire
Thu, January 30, 2025 at 6:08 AM GMT+1 • 10 min read

NEW YORK, Jan. 30, 2025 /PRNewswire/ -- Report with the AI impact on market trends - The global vaccines market size is estimated to grow by USD 193.7 billion from 2025-2029, according to Technavio. The market is estimated to grow at a CAGR of almost 23% during the forecast period. Increased funding for vaccine development and new vaccine launches is driving market growth, with a trend towards development of nanoparticle vaccines. However, high cost of vaccine research, development, and manufacturing poses a challenge. Key market players include Astellas Pharma Inc., AstraZeneca Plc, Bavarian Nordic AS, Bharat Biotech Ltd., BrightPath Biotherapeutics Co., Ltd., CSL Ltd., Daiichi Sankyo Co. Ltd., Emergent BioSolutions Inc., GSK Plc, Gradalis Inc., Inovio Pharmaceuticals Inc., Johnson and Johnson Inc., Merck KGaA, Mitsubishi Chemical Group Corp., Novavax Inc., Pfizer Inc., Sanofi SA, Serum Institute of India Pvt. Ltd., Takeda Pharmaceutical Co. Ltd., and Valneva SE.

Veterinay vaccines, regional vaccines

Merial (now part of **Boehringer-Ingelheim**) : a world leading animal-health company
http://merial.com/en/about-us

23 milliards of USdollars in 2013,
41 to 43 milliards forecasted 2019
100% filiale Sanofi before 2017, now Boehringer-Ingelheim

8,1 milliards US$ en 2022

Les Etats-Unis exigent des cessions pour l'opération Boehringer-Sanofi

https://www.usinenouvelle.com/article/les-etats-unis-exigent-des-cessions-pour-l-operation-boehringer-sanofi.N481614

Vivalis (Nantes) + **Intercell** (Autriche)= **Valneva**

— IXIARO®
VACCIN CONTRE L'ENCÉPHALITE JAPONAISE (PURIFIÉ, INACTIVÉ)

— DUKORAL®
VACCIN ORAL INACTIVÉ CONTRE LE CHOLÉRA / (ETEC)

Markets

US$ 10 billion in 2007 , **83%** Human, **17%** Veterinary
USA= 50% of the market
+50% in the next five years : 30 billion US$ 2012, 80 in 2015

New players: Emerging countries

Some producers from emerging countries are needed ", adds the study * which mentions Indian, Brazilian and Chinese groups »

India : Serum Institute of India, https:/www.seruminstitute.com/
India : Biological E, http://www.biologicale.com/
Brazil: Institut Butantan *www.butantan.gov.br/*
Brazil: FIOCRUZ Bio-Manguinhos https://www.bio.fiocruz.br/
China: CNBG http://www.dcvmn.org/_**China-National-Biotec-Group-Company-Limited**_

*https://www.sciencesetavenir.fr/sante/le-marche-mondial-des-vaccins-proche-des-80-milliards-de-dollars-en-2025_30124

China, Sinavac

Classical vaccine

Covid 19 Vaccines

Inactivated Virus

Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial

Yanjun Zhang, Gang Zeng*, Hongxing Pan*, Changgui Li*, Yaling Hu, Kai Chu, Weixiao Han, Zhen Chen, Rong Tang, Weidong Yin, Xin Chen, Yuansheng Hu, Xiaoyong Liu, Congbing Jiang, Jingxin Li, Minnan Yang, Yan Song, Xiangxi Wang, Qiang Gao†, Fengcai Zhu†*

Lancet Infect Dis 2021

https://en.wikipedia.org/wiki/CoronaVac

Covid 19 Vaccines

Sputnik V, adenoviral-based vaccine

Currently there are over 200 different COVID-19 vaccines under development around the world.

Sputnik V is the world's first registered vaccine based on a well-studied human adenoviral vector-based platform. It currently ranks among top-10 candidate vaccines approaching the end of clinical trials and the start of mass production on the World Health Organization's (WHO) list.

The ongoing Sputnik V post-registration clinical trial in Russia involves 40,000 volunteers.
Clinical trials of Sputnik V have been announced in the UAE, India, Venezuela and Belarus.
This website has been created to provide accurate and up-to-date information about Sputnik V.

https://sputnikvaccine.com/about-vaccine/

Pfizer and BioNTech
Preclinical results, Sept 9th 2020

RNA vaccine

Covid 19 Vaccines

BNT162b2 mRNA-based vaccine program

Immunization of non-human primates (rhesus macaques) with BNT162b2, a nucleoside-modified messenger RNA (modRNA) candidate that expresses the SARS-CoV-2 spike glycoprotein, resulted in strong anti-viral effects against an infectious SARS-CoV-2 challenge

BNT162b2 immunization prevented lung infection in 100% of the SARS-CoV-2 challenged rhesus macaques, with no viral RNA detected in the lower respiratory tract of immunized and challenged animals. The BNT162b2 vaccination also cleared the nose of detectable viral RNA in 100% of the SARS-CoV-2 challenged rhesus macaques within 3 days after the infection

The BNT162b2 vaccine candidate induced SARS-CoV-2 neutralizing antibodies in rhesus macaques, pseudovirus neutralizing antibodies in mice, and strong, antigen-specific CD4+ and CD8+ T cells in mice and macaques

https://www.businesswire.com/news/home/20200909005570/en/

Pfizer and BioNTech
clinical III results, Nov 9th 2020

Covid 19 Vaccines

BNT162b2 mRNA-based vaccine program

Vaccine candidate was found to be more than 90% effective in preventing COVID-19 in participants without evidence of prior SARS-CoV-2 infection in the first interim efficacy analysis

Analysis evaluated 94 confirmed cases of COVID-19 in trial participants

Study enrolled 43,538 participants, with 42% having diverse backgrounds, and no serious safety concerns have been observed;

Safety and additional efficacy data continue to be collected

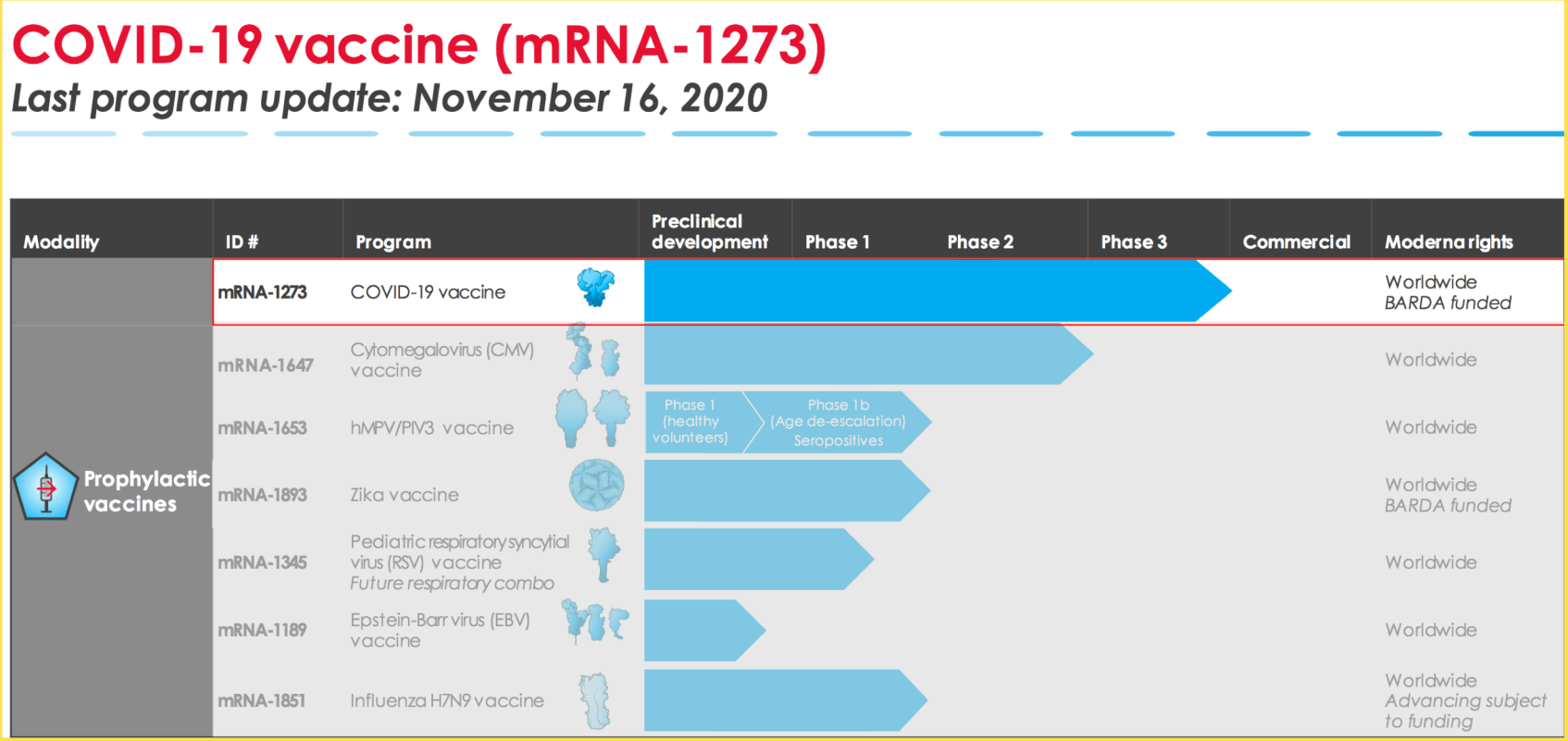
Submission for Emergency Use Authorization (EUA) to the U.S. Food and Drug Administration (FDA) planned for soon after the required safety milestone is achieved, which is currently expected to occur in the third week of November

Clinical trial to continue through to final analysis at 164 confirmed cases in order to collect further data and characterize the vaccine candidate's performance against other study endpoint

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against

Covid 19 Vaccines

mRNA-1273, our vaccine candidate against the novel coronavirus.



Astra Zeneca-Oxford

Classical vaccine

Covid 19 Vaccines

replication-deficient chimpanzee viral vector based on a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees and contains the genetic material of the SARS-CoV-2 virus spike protein

Positive high-level results of clinical trials of AZD1222 in the UK and Brazil showed the vaccine was highly effective in preventing COVID-19, the primary endpoint, and no hospitalisations or severe cases of the disease were reported in participants receiving the vaccine. One dosing regimen (n=2,741) showed vaccine efficacy of 90% when AZD1222 was given as a half dose, followed by a full dose at least one month apart, and another dosing regimen (n=8,895) showed 62% efficacy when given as two full doses at least one month apart. The combined analysis from both dosing regimens (n=11,636) resulted in an average efficacy of 70%. All results were statistically significant (p<=0.0001). More data will continue to accumulate and additional analysis will be conducted, refining the efficacy reading and establishing the duration of protection. An independent Data Safety Monitoring Board determined that the analysis met its primary endpoint showing protection from COVID-19 occurring 14 days or more after receiving two doses of the vaccine. No serious safety events related to the vaccine have been confirmed. AZD1222 was well tolerated across both dosing regimens.

AstraZeneca will now immediately prepare regulatory submission of the data to authorities around the world that have a framework in place for conditional or early approval. The Company will seek an Emergency Use Listing from the World Health Organization for an accelerated pathway to vaccine availability in low-income countries. In parallel, the full analysis of the interim results is being submitted for publication in a peer-reviewed journal. Professor Andrew Pollard, Chief Investigator of the Oxford Vaccine Trial at Oxford, said: “These findings show that we have an effective vaccine that will save many lives. Excitingly, we’ve found that one of our dosing regimens may be around 90% effective and if this dosing regime is used, more people could be vaccinated with planned vaccine supply. Today’s announcement is only possible thanks to the many volunteers in our trial, and the hard working and talented team of researchers based around the world.”

Pascal Soriot, Chief Executive Officer, said: “Today marks an important milestone in our fight against the pandemic. This vaccine’s efficacy and safety confirm that it will be highly effective against COVID-19 and will have an immediate impact on this public health emergency. Furthermore, the vaccine’s simple supply chain and our no-profit pledge and commitment to broad, equitable and timely access means it will be affordable and globally available, supplying hundreds of millions of doses on approval.”

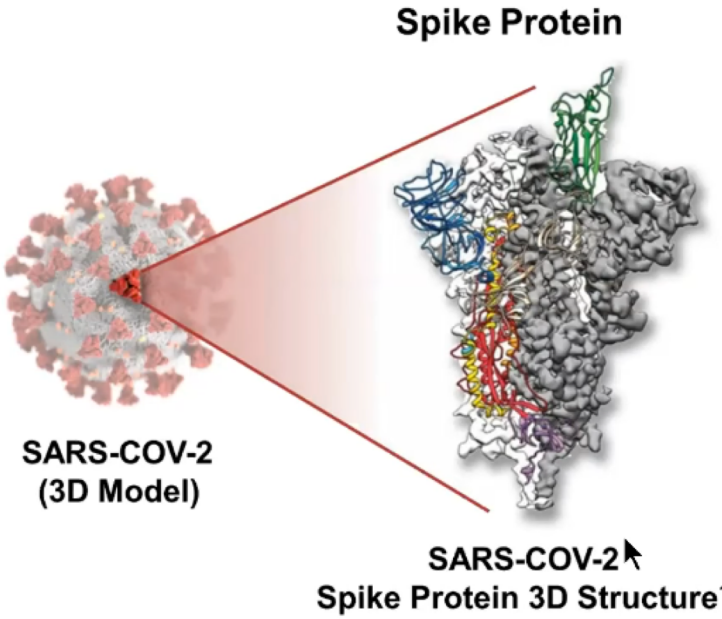
The pooled analysis included data from the COV002 Phase II/III trial in the UK and COV003 Phase III trial in Brazil. Over 23,000 participants are being assessed following two doses of either a half-dose/full-dose regimen or a regimen of two full doses of AZD1222 or a comparator, meningococcal conjugate vaccine called MenACWY or saline. The global trials are evaluating participants aged 18 years or over from diverse racial and geographic groups who are healthy or have stable underlying medical conditions.

Clinical trials are also being conducted in the US, Japan, Russia, South Africa, Kenya and Latin America with planned trials in other European and Asian countries. In total, the Company expects to enrol up to 60,000 participants globally. The Company is making rapid progress in manufacturing with a capacity of up to 3 billion doses of the vaccine in 2021 on a rolling basis, pending regulatory approval. The vaccine can be stored, transported and handled at normal refrigerated conditions (2-8 degrees Celsius/ 36-46 degrees Fahrenheit) for at least six months and administered within existing healthcare settings. AstraZeneca continues to engage with governments, multilateral organisations and collaborators around the world to ensure broad and equitable access to the vaccine at no profit for the duration of the pandemic.

https://www.astrazeneca.com/media-centre/press-releases/2020/azd1222hlr.html

Optimization of Genetic Sequence

Selection of Pfizer/BioNTech COVID-19 Vaccine BNT162b2



Initially Four Vaccine Candidates

	Variant	Target	RNA Construct	Regimen
1	162a1	RBD subunit	uRNA	Prime/boost
2	162b1	RBD subunit	modRNA	Prime/boost
3	162b2	P2-mutated full spike protein	modRNA	Prime/boost
4	162c2	P2-mutated full spike protein	saRNA	Single injection

RNA: unmodified mRNA
odRNA: nucleoside modified mRNA saRNA: self-amplifying mRNA
. Wrapp et al., 2020, *Science*.

CC-

Covid-19: new vaccine

Sanofi–GSK COVID-19 vaccine

VidPrevtyn Beta
approved nov 12th, 2022

Spike of SARS-CoV-2 (strain B.1.351) *obtained by DNA recombinant technology using a* ***baculovirus*** *expression system in an insect cell line Sf9 from the automn caterpillar* ***Spodoptera frugiperda***

1. Antigène

Il s'agit de deux flacons multidoses (flacon d'antigène et flacon d'adjuvant) qui doivent être mélangés avant utilisation. Après reconstitution, le flacon de vaccin contient 10 doses de 0,5 mL.

Une dose (0,5 mL) contient 5 microgrammes de protéine Spike du SARS-CoV-2 (souche B.1.351) produite par la technologie de l'ADN recombinant utilisant un système d'expression de baculovirus dans une lignée cellulaire d'insectes issue de cellules Sf9 de la chenille légionnaire d'automne, Spodoptera frugiperda.

L'adjuvant AS03 est composé de squalène (10,69milligrammes), de DL-alpha-tocophérol (11,86 milligrammes) et de polysorbate 80 (4,86 milligrammes).

VidPrevtyn Beta peut contenir des traces d'éthoxylate d'octylphénol.

https://www.mesvaccins.net/web/vaccines/685-vidprevtyn-beta

Human infectious diseases and Related Vaccines

Maladies bactériennes	vaccin
Anthrax	Anatoxine
Diphtérie	Anatoxine
Tetanos	Anatoxine
Coqueluche	Bact. Tuées ou Prot
Fièvre typhoide	Bact. Tuées
Fièvre paratyphoide	Bact. Tuées
Choléra	Bact. Tuées ou extrait cel.(Dukoral)
Peste	Bact. Tuées ou extrait cel.
Tuberculose	Bact vivant
Méningite	Polysaccharides purifiés
Pneumonie bactérienne	Polysaccharides purifiés
Typhus	Bactéries tuées

Maladies virales	vaccin
Fièvre jaune	Virus atténué
Oreillons	Virus atténué
Rougeole	Virus atténué
Rubéole	Virus atténué
Polyomyélite	Virus atténué (Sabin ou Salk)
Grippe	Virus inactivé
Rage	Virus inactivé (homme) ou atténué (Chien)
Variole	Relation croisée avec vaccine
Hepatite A	ADN recombinant
Hepatite B	ADN recombinant ou virus inactivé
Varicelle	Virus atténué
Coronavirus	mRNA

The Infectious process, the Vaccine objectives

- *Vaccines are designed as prophylactic measures, which induce a lasting immune response in such a way that despite further exposure to a specific infectious agent, the extent of the infection is reduced and the disease no longer occurs*.

- *Today we can also consider therapeutic vaccines and not only prophylactics*

Types of infectious processes

- **1.1. Intracellular Versus Extracellular pathogens**

  It is easy to see that, depending on whether a pathogen has intracellular phases of its life or not, the type of infection and its mode of control will differ significantly

- **1.2. Acute Versus Chronic (Persisting) pathogens**
  - In the case of an acute infection, exposing a naïve individual to a sublethal dose of the infectious agent can cause the disease, but the immune response generated will clear the infection in a few days or weeks
  - Death occurs if the infecting dose is so high that the immune response is qualitatively or quantitatively insufficient to prevent the continuous replication of the infectious agent to the point that the host is wiped out.
  - In contrast, many infections persist for months or even years if the agent's infection process triggers the escape or subversion of what would normally have been an effective immune control reaction

Immunization

- **Vaccine administration triggers active immunity.**

  but: some risks and side effects

  – Inactivating agents: heat, phenol, formaldehyde (Salk)
  – Exotoxins: chemical treatment (toxoid)
  – “Attenuated” (viable) strains: not usable in people with immune deficiency

- **Antibody administration provides passive Immunity**

  – non involvement of immune system, direct action.

Comparaison :	**Active Immunity**	**Passive Immunity**
	-presentation of Ag	*-no presentation of Ag*
	-Immunity obtained by injection of Ag	***-Immunity obtained by injection of Ab***
	-specific response is due to the fact that and individual will develop an immunity	*-specific response is obtained by a secondary host*
	immune system towards Ag is actived	*-no activation of immune system.*
	- activated immunological memory	*- no immunological memory*
	-immune response may be maintained by stimulation of memory cells	*immune response cannot be maintained and et rapidly decrease*
	- immune status develop in ***many weeks***	*-immune status is* ***immediate***

AB production and immune memory

- Ag reach secondary lymphoid organs , lymphoid tissues associated to mucosa (**MALT**)
  - if IV -> spleen,
  - if SC, ID, IP -> progression towards the closest Lymphatic Ganglia
  - if muq -> MALT

- B cells are x nd differenciate into plasmocytes (productors of AB) and in memory cells. Plasmocytes live one week : IgM+++. primary response, latency

- Memory B cells live +++ years. If meet known Ag, they transform rapidly in Plasmocyte and produce IgG (Titer= 10x to 100x). secondary response

- slow decrease : reminder injection (ex : antirabies vaccine in pet animals). long-lasting protection

MALT=Mucosa Associated Lymphoid Tissue

Advisory Committee on Immunization Practices (CDC)

https://www.cdc.gov/vaccines/acip/index.html

Preparetedness history in France : Creation of EPRUS in France : March 2007 (former and current website page), merged to SPF later

The **Alert and Crisis Department** comprises three main areas of activity, translated into three units. These units are:

-the **pharmaceutical establishment**;

- the **health reserve unit**;

-the **coordination, alert and crisis unit**, which is also the focal point for the establishment's alerts

Vaccination of Specific populations

- **Pregnant women Vaccination**
- **Allergic people Vaccination**
- **Immunodepressed people Vaccination**
  - Congenital immunodeficiencies
  - Secondary immunodeficiencies
  - Corticosteroid treatments
  - People infected with HIV
  - Vaccination of adults infected with HIV
  - Vaccination of children infected with HIV or born to mothers infected with HIV
  - Children with clinical signs of AIDS
  - HIV-infected and asymptomatic children
- **Travelers Vaccination**
- **Premature children Vaccination**
- **Armed forces Vaccinations**

Development of Vaccines Today Versus Yesterday

From a « trials and errors » Industry, to the Development of a scientific-based rational of pathogen risk control

- *Many inert vaccines are developed using no longer the infectious agent itself, but only one or more of their antigens. The first step is to identify proteins or the genes (**Reverse Vaccinology**) that are safe, but capable of triggering a sufficient immune response. These antigens are then isolated and purified. As an example, the influenza vaccine is thus made up of proteins from the envelope of the virus, while the vaccines against tetanus and diphtheria are made from proteins secreted by these bacteria, toxoids, which are purified and then treated by a chemical process for their lose their toxicity*.

- *The mRNA-based **SARS-CoV-2 vaccine** is a new vaccine type, a mix of in vitro synthesized mRNA embedded in nanolipidic particles*

Living Vaccines Fabrication

Germ banks

- The manufacture of these vaccines begins with the constitution of a germ bank, obtained by the cultivation of an infectious agent, with very strict asepsis rules and under strictly constant conditions (temperature, culture medium, etc.) , so as to obtain a large quantity of germs which are identical in every respect

- The choice of strain grown depends on the type of vaccine.
- Live vaccines can be obtained from spontaneously harmless organisms. This is the case with the smallpox vaccine which contains the vaccinia virus, which is not pathogenic for humans, but close enough to the smallpox virus to cause an effective immune response. But for most live vaccines, the strains are attenuated, either by passing through successive cultures, either by using different chemical techniques to limit their infectious power. Among the bacterial vaccines commonly used, only BCG is made from living attenuated bacteria.

Synthesis of a Vaccine

- Antigens are now obtained by genetic engineering. The **Hepatitis B vaccine** is thus composed of an antigen synthesized by **yeast cells** (or others,**CHO**), transformed into a synthesis factory by the introduction of the gene controlling the production of this antigen. The vaccine is produced **inside the cell** and must be recovered and purified.

- After this first stage of development of the vaccine product, comes the stage of **manufacturing** the final pharmaceutical product. It consists of possibly mixing antigenic preparations to obtain combined vaccines, and adding different products (adjuvants, stabilizers, diluents) necessary for the efficacy and conservation of the vaccine.

Yeast or CHO= (eucaryotic expression systems) CHO= Chinese Hamster Ovary

sf9= insect cell system, baculovirus expression system

.../...

Géneralities vaccines- 1

- **Live attenuated vaccines**
  - **Capable of replicating in the host**
  - Attenuated pathogenicity
  - Benefits: can trigger broader immunological responses
  - May require lower doses
  - Have longer lasting protection
  - Prepared by heat, by a chemical process which removes their infectious power without suppressing their ability to trigger an immune response.
  - Agents capable of multiplying but without danger

Generalities vaccines-2

- **Subunit, killed or inactivated vaccines**
  - **Unable to replicate**
  - Benefits cannot multiply and return to a pathogenic revertant
  - Generally less reactogenic
  - Not transferable to another person
  - Generally easier to manufacture.

Generalities vaccines-3

- **Genetic vaccines (based on DNA or now RNA)**
  - -Stimulate the synthesis of antigens only in cells
  - -Benefits: Trigger cellular immune responses
  - -Standardized production methods

Attenuation concept

- **Definition**：***Transplanting strains under laboratory conditions and not on animals causes the virulence to be lost, partially or entirely***
  - Reinjection of attenuated strains into the animal can recover virulence, but in many cases the loss of virulence is permanent
  - Attenuated strains are often used for vaccine production
  - exemple : BCG obtained with loss of « RD1 » starting from an *M. bovis* isolate that underwent a unique deletion event of genetic material

Attenuation in cell culture

- *In vitro* passage on one or more cell types

Attenuation has been demonstrated for **polioviruses** by passage through primate cells

This empirical approach has been successful both for the preparation of **oral** (polio) and **injectable** (measles, mumps, rubella) virus vaccines

The reactogenicity of these vaccines has been low enough for some of them (polio, measles) to be widely accepted worldwide for pediatric use

Obtention of Temperature-sensitive mutants

- ***Temperature sensitive mutants can be selected based on their growth properties at different temperatures***. These viruses are generally referred to as (**ts** temperature sensitive) or (**ca**, cold adapted)
- The goal is that these viruses will replicate less vigorously in vivo than wild viruses, and therefore will be phenotypically attenuated and therefore less virulent
- Mutations can occur: ex: IRES (internal ribosome entry site)

Cold-adapted influenza viruses as a promising platform for viral-vector vaccines

Irina Isakova-Sivak, Tatiana Tretiak & Larisa Rudenko

Expert Review of Vaccines, 15:10, 1241-1243, DOI: 10.1080/14760584.2016.1208088

González-Aseguinolaza G, Nakaya Y, Molano A, et al. Induction of protective immunity against malaria by priming-boosting immunization with recombinant cold-adapted influenza and modified vaccinia Ankara viruses expressing a CD8+-T-cell epitope derived from the circumsporozoite protein of Plasmodium yoelii. J Virol. 2003;77 (21):11859–11866.

This is the only published study reporting the use of cold-adapted influenza virus as a viral vector.

Variant viruses of other species

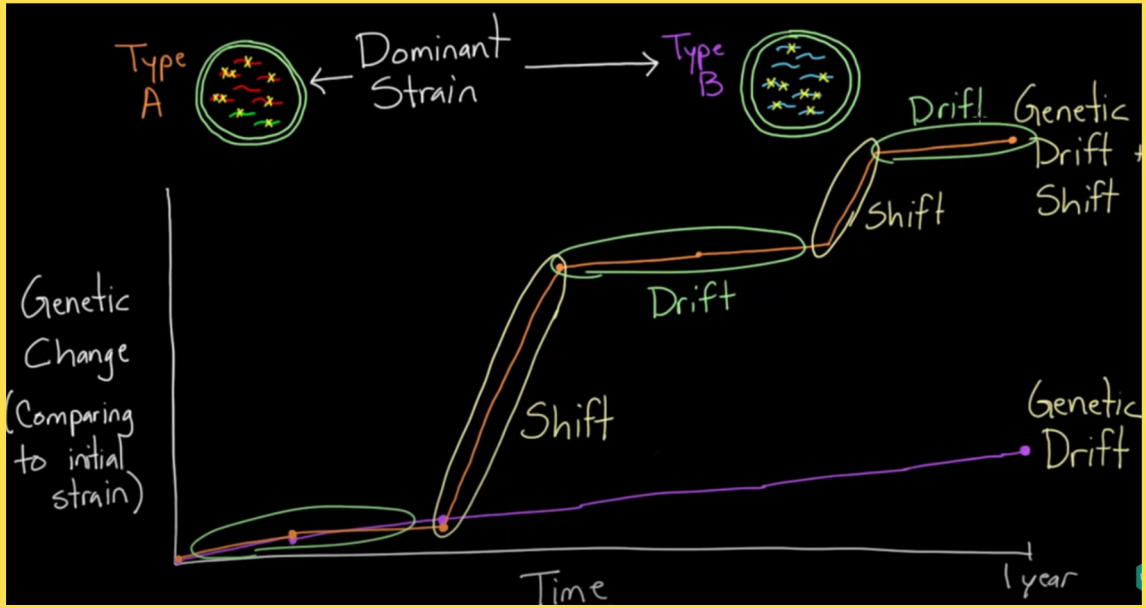
- **Objective**: to cultivate a similar animal variant virus, which causes a disease similar to human disease, with the objective that the animal virus will become attenuated for humans, while remaining sufficiently immunologically linked to the natural human virus to trigger protective immunity for humans

Reassortment of viruses

Definition = Virus reassortment, or simply reassortment, is a process of genetic recombination that is exclusive to segmented RNA viruses in which co-infection of a host cell with multiple viruses may result in the shuffling of gene segments to generate progeny viruses with novel genome combinations

1957 Asian flu
1968 Hong Kong flu ,
2009 Swine flu

3 pandemia created by reassorment



Shift and **Drift** of influenza viruses

https://www.youtube.com/watch?v=tjGGxA7AF9E

Recombinant virus

- *These are viruses in which **certain genes have been deleted**, for example to be certain that they cannot regain their virulent character, or the expression of viral antigens in heterologous systems allowing the triggering of immunity*
- **Adenovirus**
- ***Recombinant West Nile virus envelope protein E and domain III expressed in insect larvae protects mice against West Nile disease.*** Alonso-Padilla J, de Oya NJ, Blázquez AB, Escribano-Romero E, Escribano JM, Saiz JC, Vaccine. 2011 Jan 3

DNA of RNA vaccines

- In 1960, *Y. Ito shows that* ***injection of naked papillomavirus DNA could induce tumors in rabbits*****.**

Ito Y. A tumor-producing factor extracted by phenol from papillomatous tissue (Shope) of cottontail rabbits. Virology 1960;12:596–601

In relation to various TLR (Toll-like receptors), which are part of the Innate Immune System, DNA or RNA is able to trigger immunity

Engineering may allow to boost or to hide these immune reactions by the innate immune system

RNA vaccines production

Chapter 2

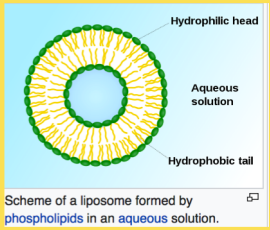
In Vitro Transcription of Long RNA Containing Modified Nucleosides

Norbert Pardi, Hiromi Muramatsu, Drew Weissman, and Katalin Karikó

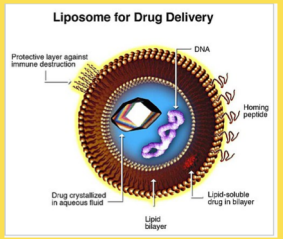
Peter M. Rabinovich (ed.), Synthetic Messenger RNA and Cell Metabolism Modulation: Methods and Protocols, Methods in Molecular Biology, vol. 969, DOI 10.1007/978-1-62703-260-5_2, © Springer Science+Business Media New York 2013

Nano lipo particles (Liposomes)

multilamellar vesicle	MLV
small unilamellar vesicle	SUV
large unilamellar vesicle	LUV
gian unilamellar vesicle	GUV



Scheme of a liposome formed by phospholipids in an aqueous solution.



RNA vaccines production also depends on Nano Lipo Particles (NLPs)