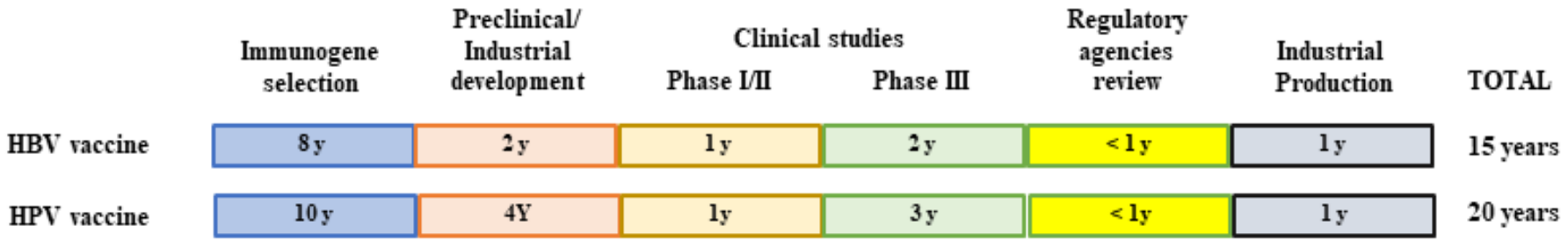
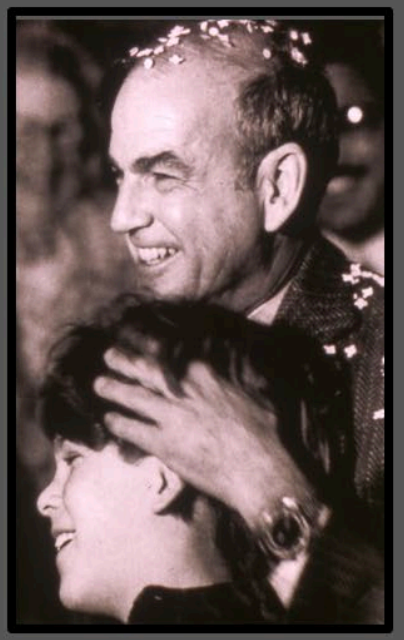
Development and implementation of HBV and HPV vaccines



Developement of the HBV vaccine

1967-70 :	Australia Ag was linked to Hepatitis B.
1970 :	Australia Ag is identified as the surface Ag of the Dane particle (HBV).
1975 :	Anti-HBs antibodies are protectives (passive immunization).
1975 :	Immunization with HBsAg particles confer protection in chimpanzee.
1976 :	First experimental HBV vaccine in humans.
1982 :	First commercially available HBV vaccine (Pasteur et MSD)



B.S. Blumberg
Nobel price 1976

Philippe Maupas

Difficulties in producing Hepatitis B vaccine

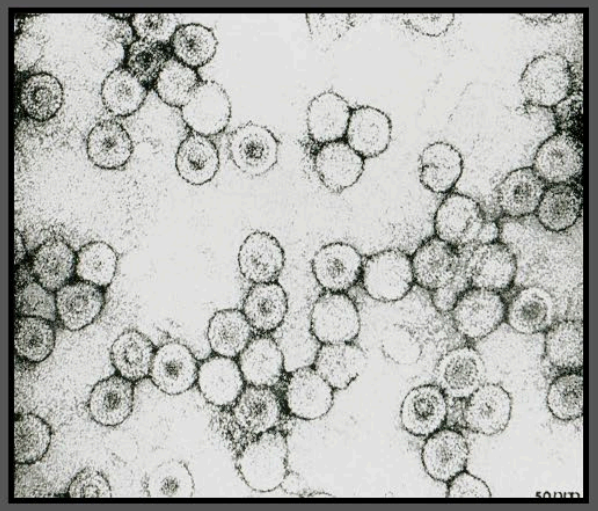
- Absence of replication of HBV in cell cultures

- Absence of animal models

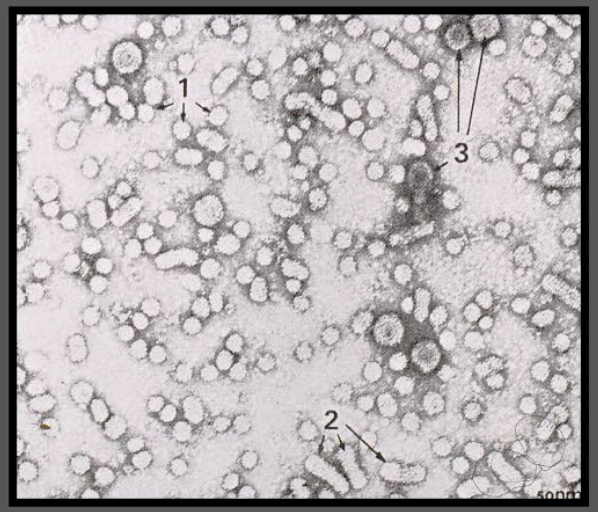
- Transmission to animal species limited to chimpanzee
(high cost and limited availability)

First generation of hepatitis vaccine (Pasteur Production and MSD)

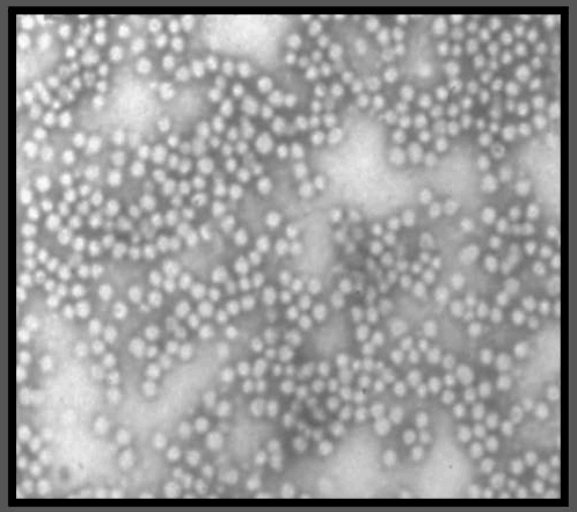
Plasma vaccines are obtained by purification and inactivation of HBV 22 nm particles present in the plasma of HBsAg positive individuals



Dane particle (HBV)



viral particles detected in human sera of HBV chronic carriers



HBV vaccine
22 nm particles

Second generation of HB Vaccines in 1986

A necessity due to

- A shortage in HBsAg positive plasma
- The theorical risk of transmission of HIV
- The possibility to produce recombinant HBsAg

Recombinant HBsAg vaccines were the first recombinant vaccines:

- Recombinant Yeast
- Recombinant CHO cell

° Burell et al., 1979; Charney et al., 1980; Valenzuella et al., 1982; Michel et al., 1984.

HB Vaccines in 1998

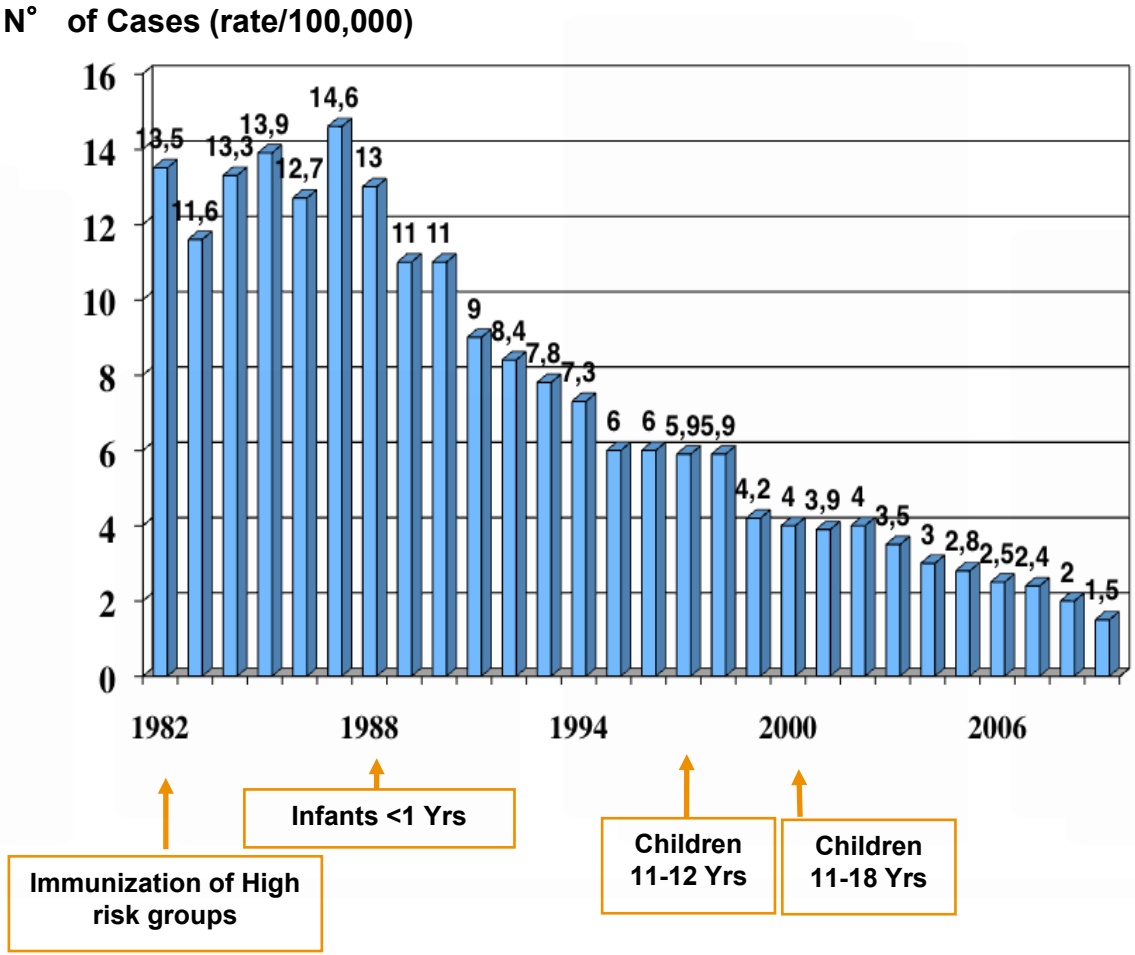
Producers	Vaccine type	Dose (ug)	Country
Cheil-Sugar	Plasma	1.5-3	Korea
Daïchi Pharm.	Plasma	20	Japan
Korean Green Cross	Plasma	5	Korea
Lan Zhou	Plasma	10	China
Lifeguard	Plasma	5	Taiwan
Fujisawa Pharm.	Recombinant Yeast	20	Japan
Pasteur vaccins	Recombinant CHO cell	20	France
Pasteur Merieux MSD	Recombinant Yeast	5-40	USA
GlaxoSmithKline	Recombinant Yeast	10-40	Belgium
Biotechnologia	Recombinant Yeast	20	Cuba

HB immunization strategies in France

- **1982 : Immunization of High risk groups :**
  - **Medical personnel,**
  - **Polytransfuse patients,**
  - **Injectable drug user,**
  - **Homosexuals.**

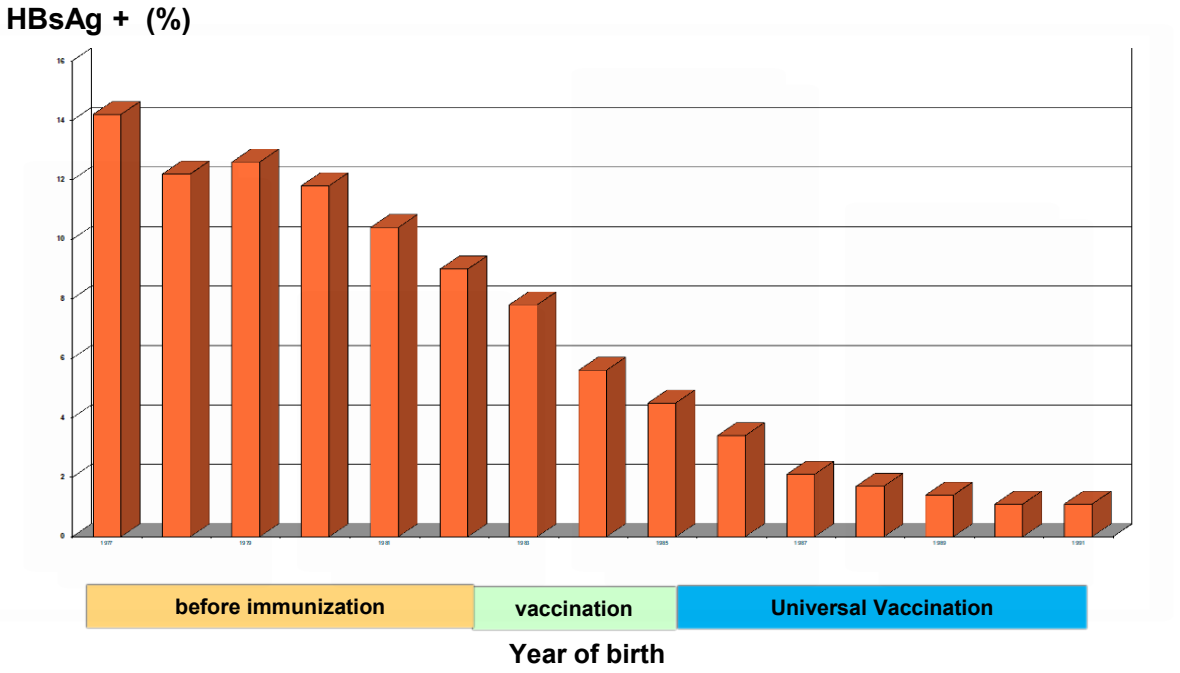
Changes in the hepatitis B virus epidemiology in USA (1980-2009)

Acute Hepatitis B

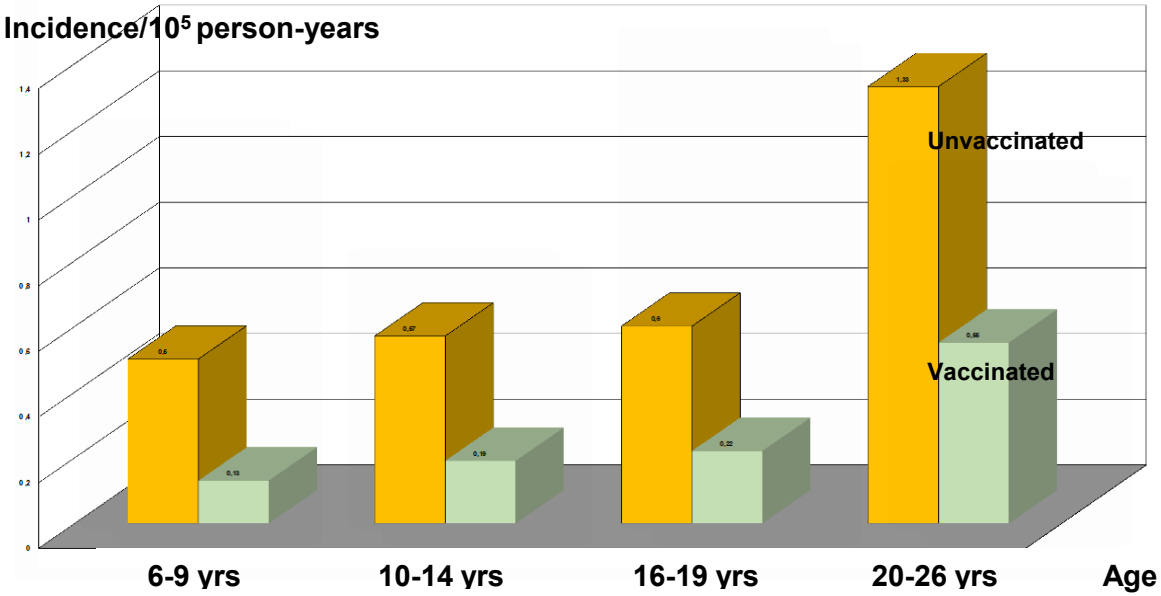


HB Vaccine efficacy in Taiwan

HBsAg carrier state in 18 years old subjects (university)



Development of Hepatocellular carcinoma



	6-9 yrs	10-14 yrs	16-19 yrs	20-26 yrs
Vaccine efficacy	74%	66%	63%	58%

Chen et al., J Clin Virol 2011 ; Chang et al., Gastroenterology 2016

HB immunization strategies in France

• **1994 - 1998 : Massive Immunization of infants <1 yr, adolescents at school, and High risk adults**

In 1996 : 249 cases of central demyelinating disorders were identified among the 20 millions adolescent and young adults immunized.

Due to the absence of data concerning the incidence of MS in France, the Minister of Health decided to stop HBV vaccination.

This was interpreted by the population as the recognition by health authorities that the vaccine is dangerous.

HB immunization strategies in France

2003 : Universal immunization of children (<1 yr)

2017 : HB Vaccination mandatory

Observed-to-expected analysis of incidence of Multiple sclerosis (per 100,000) in vaccinated people in France

Study period	Estimated Nb of vaccinated people	Expected number of MS cases	Number of episodes of MS	Observed to expected ratio
1984 - 2000	26.4 millions	1,200	422	35.2%
2007 - 2010	11.0 millions	222	11	4.9%
Total	37.4 millions	1,422	433	30,5%

(Incidence of MS in france varies from 4 to 8 case a year for 100,000 inhabitants)

(Adapted AFSAPP, 2012 and Mouchet & Bégard 2019)

Side effects reported among 1.4 million of infants (0-24 month old) immunized in 2019 with Hexavalent vaccines

(DT-Polio, Pertussis, Hib, HepB).

127 side effects reported :

79 local reactions and 48 serious (mainly fever).

1 hyper sensibility reaction,

1 thrombocytopenic purpura,

11 apnea (observed in premature infants)

1 death (unrelated to vaccine)

2 Thrombopenia,

6 convulsions

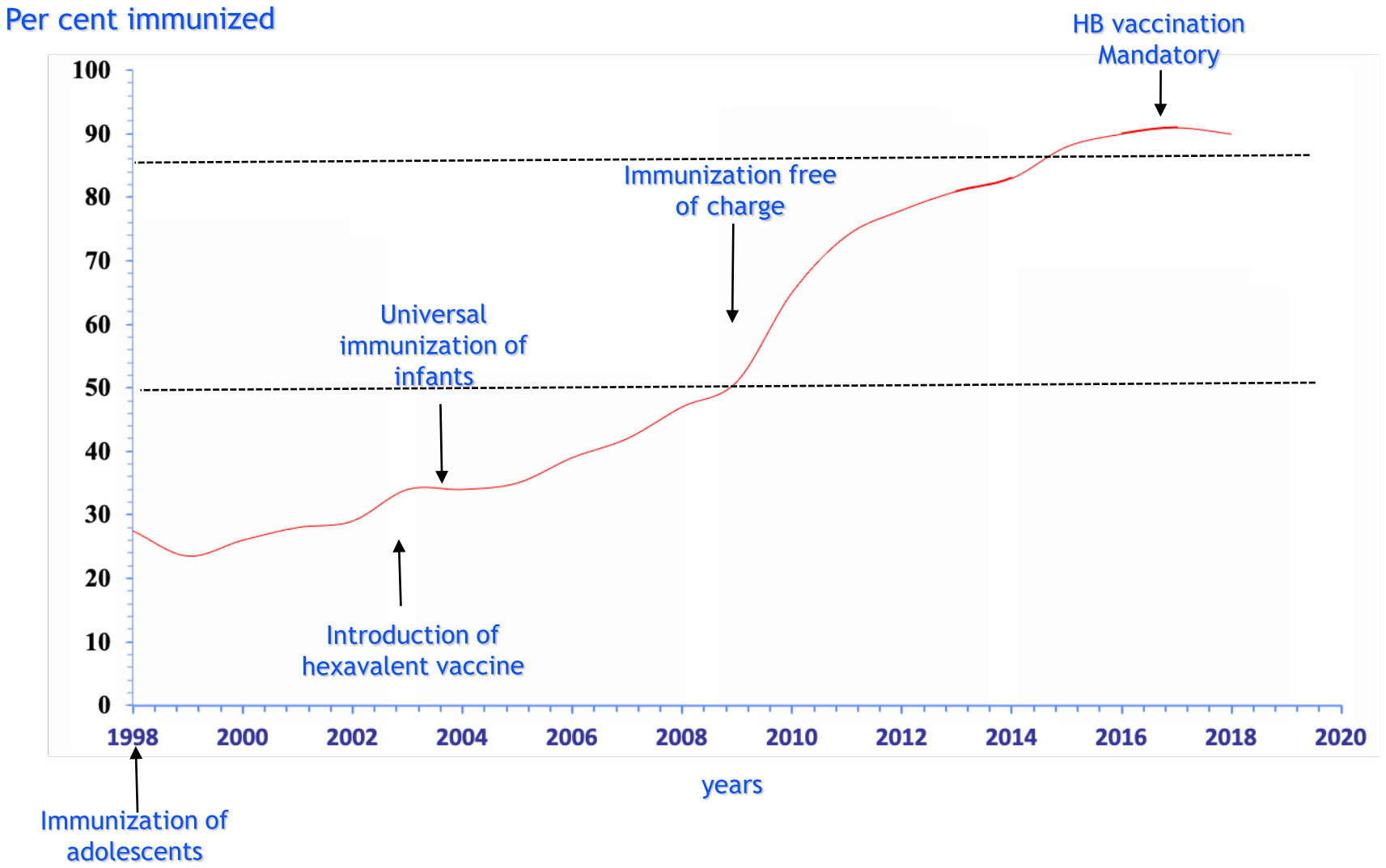
4 hypotonia/hyporeactive

No case of multiple sclerosis, no case of Kawasaki disease

(Adapted from Ansm report 2020)

HB Vaccine coverage in France

Percent of infants (< 24 month old) who received 3 doses of HB vaccine



(adapted from DREES, Santé Publique France)

Human Papillomavirus Vaccines

Development of the HPV vaccine

1983 : Some human papillomaviruses were linked to cervical neoplasia.

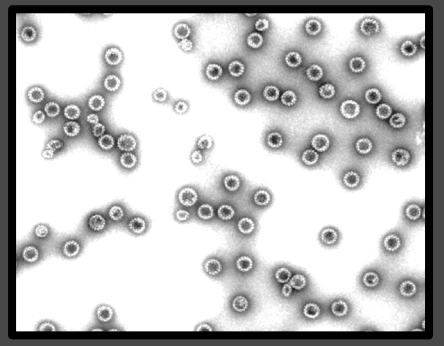
1992-99 : HPVs confirmed as the necessary cause of cervical cancer (N. Munoz, IARC)

1975 : Identification of the capsid antigens as the immunizing antigen using animal models

1976 : Obtention of recombinant virus-like particles (VLPs) for animal models, then for HPV11 and HPV16

2006 : First commercially available HPV vaccine (MSD and GSK)

A. Zur Haussen
Nobel price 2008



HPV VLPs

Development of HPV vaccines

(Muñoz N, Crawford L, Coursaget P. HPV vaccines for cervical neoplasia. Lancet. 1995)

Difficulties in producing HPV vaccine

Absence of replication of HPV viruses in cell cultures

Absence of transmission to animal species

Development of vaccines was possible due to the existence of animal models : **- Bovine Papillomavirus (BPV4)**

- Cottontail Rabbit Papillomavirus (CRPV)

- Canine Oral Papillomavirus (COPV)

Production of recombinant human papillomavirus in insect cells:

- HPV16 ad HPV11 **(Kirnbauer et al. 1995; Rose et al. 1995)**

HPV vaccines available in 2006

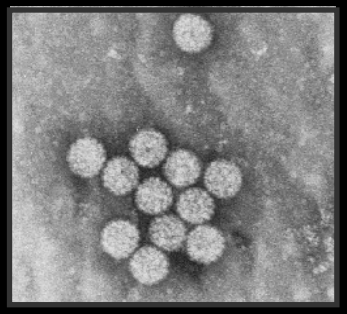
Lessons learned from Animal studies

Vaccines	Protection
L1 VLPs	++++
L1 + L2 VLPs	++++
Heterologous VLPs	-
L1 Capsomers	++
Denatured VLPs	-
anti-VLPs (passive transmission)	++

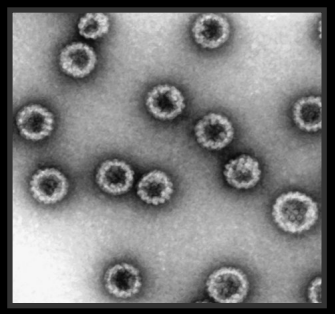
(Kirnbauer et al., 1992; Suzich et al., 1995; Kirnbauer et al., 1996; Christensen et al., 1996; Breitburd et al., 1997)

Production of recombinant Virus-like particles (VLPs)

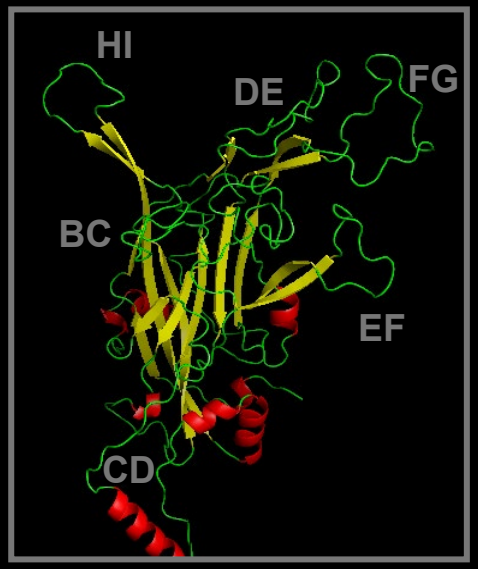
Viral capsid protein (L1 or L1+L2) when expressed in insect cells self-assembled into virus-like particles or VLPs



Virus

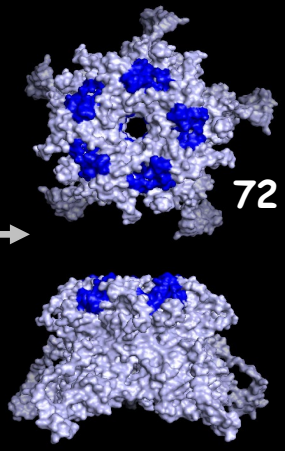


(VLPs)



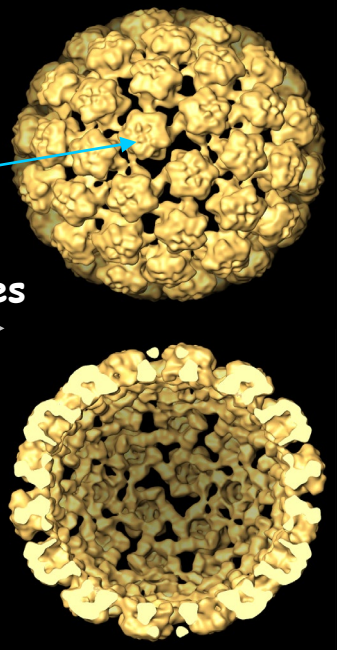
L1 protein
(Chen *et al.*, 2000)

5 L1



Capsomere

72 capsomeres



Capsid (360 L1)

Morphology and conformational epitopes are similar in VLPs and viruses

Licensed HPV L1 vaccines

Name	Gardasil®	Gardasil 9®	Cervarix®
Manufacturer	MSD	MSD	GSK
HPV types	6,11,16,18	6,11,16,18,31, 33,45,52,58	16,18
Protein	L1 (20-40 ug)	L1 (20-60 ug)	L1 (20 ug)
Expression system	Yeast	Yeast	Insect cells
Protection against non-vaccine types	31	?	31, 33, 45
Adjuvant	Al(OH)PO4	Al(OH)PO4	ASO4

aluminum Hydroxyphosphate

Al(OH)3 + 3D-MPL
(detoxified Lipid A from Salmonella minessota)

Cecolin, Xiamen Innovax Biotech, 2020, bivalent 16 & 18, express in E. coli, Al(OH)3.

Efficacy against invasive cervical cancer

In 1,672,983 Swedish girls and women from 2006-2017

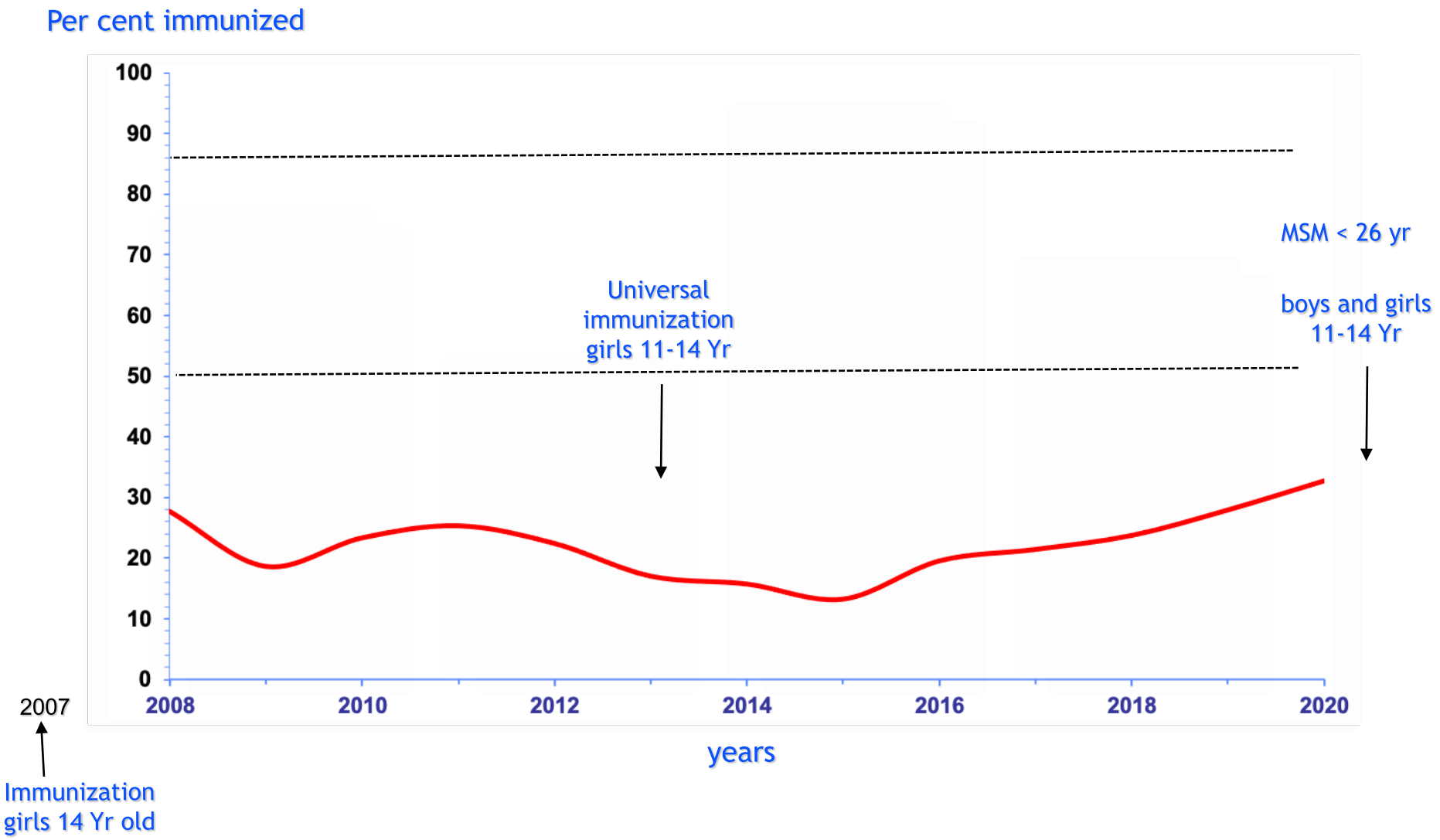
Vaccine status	N° cases of cervical Ca	Incidence rate /100,000 person-Yr	Vaccine efficacy*
Unvaccinated	538	5.27	-
Vaccinated (Gardasil)	19	0.73	63%
Before age 17 yr	2	0.10	88%
At age 17 - 30 yr	17	3.02	53%

(* Adjusted for age, county, year, education level, income level, previous CIN3+ diagnosis in mothers)

Lei et al., NEJM, 2020

HPV Vaccine Coverage in France)

Percent of 16 year-old girls fully vaccinated



(adapted from Fonteneau et al, Santé Publique France, 2019, InVs 2010, Santé Public France 2020)

Conclusions

Efficacy of HBV and HPV vaccines was demonstrated against acute and chronic Infections and associated cancers

Both vaccines have been confronted to misinformation concerning their safety and benefit, with as a consequence the very low coverage observed in the French population.

However, after 30 years, the HBV vaccine coverage in France became satisfactory due to an universal immunization early in life, the production of a combined vaccine and the immunization free of charge.

Do the same solutions be applied to HPV immunization to reach a vaccine coverage observed since many years in other industrial countries?