Vaccination

"Artificially induced specific adaptive immunity"

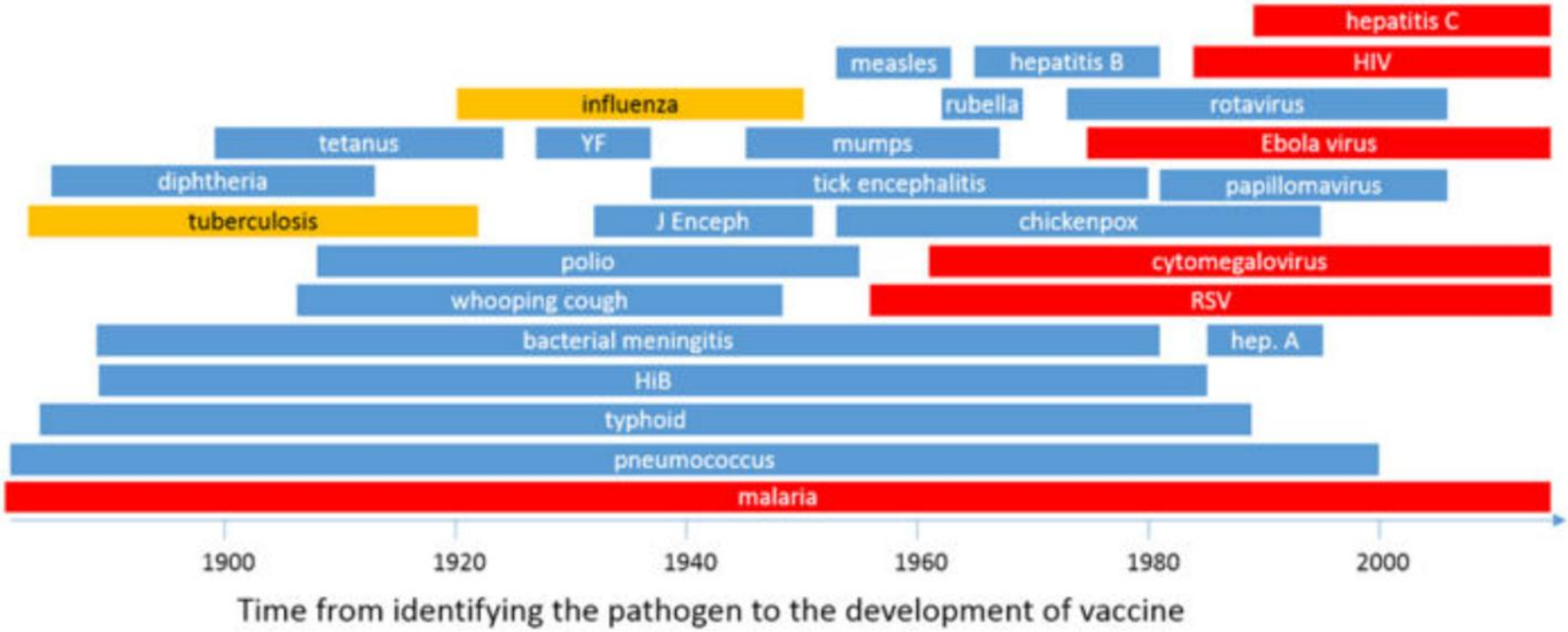
Is vaccination useful?

	Maximum Number of Annual Cases in Pre-vaccine Era (year)	Number of Cases in 2009	Percent Change
Diphtheria	12,641 (1899)	0	-100.00
Measles	52,866 (1952)	2	-99.99
Mumps	18,709 (1957)	13	-99.93
Pertussis[1]	13,333 (1937)	371	-97.22
Polio	3,950 (1955)	0	-100.00
Rubella	34,148 (1943)	1	-99.99
Tetanus	45 (1925)	0	-100.00
Hib [2] **(< 5 yrs of age)**	147 (1987)	1	-99.32
Chickenpox[1]	23,768 (1953)	2,219	-90.66

[1] Preliminary Data
[2] First became reportable in 1985

http://sphweb.bumc.bu.edu/otlt/MPH-Modules/PH/MA-Surveillance/MA-Surveillance7.html

Vaccines available today



Anti vaccination movement

(Conspiracy theory?)

Consequences of non vaccination

- **Japan (Rubella)**
- 2010. – 87 cases
- 01.01. - 01.05. 2013. – 5442 cases – Parents refuse to vaccinate their children

- **France 2018. (Measles)**
- – 4000 cases (4 deaths)

- **UK 2018. (Measles)**
- - 1000 cases (1 death)

Polio - today

Three countries: Afganistan, Pakistan, Nigerija

YEAR-TO-DATE 2018

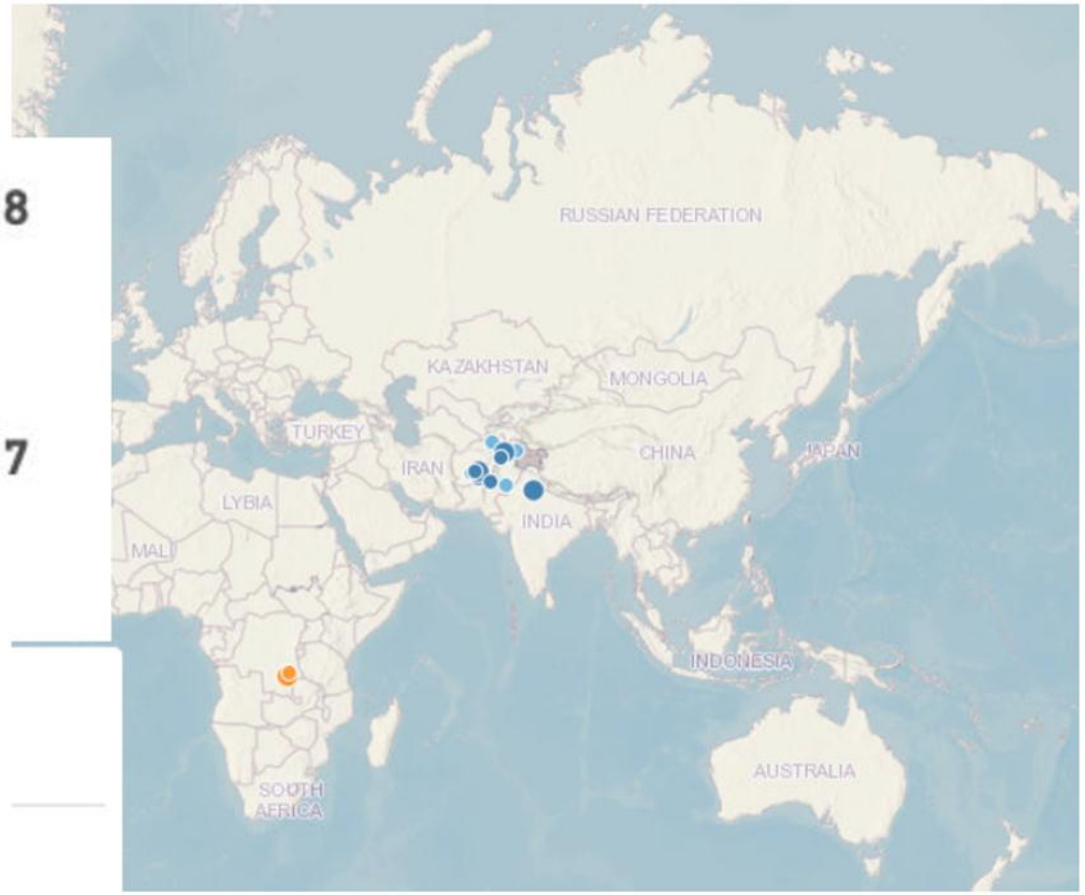
Jan 1 - Apr 5, 2018

8 WPV **3** cVDPV

YEAR-TO-DATE 2017

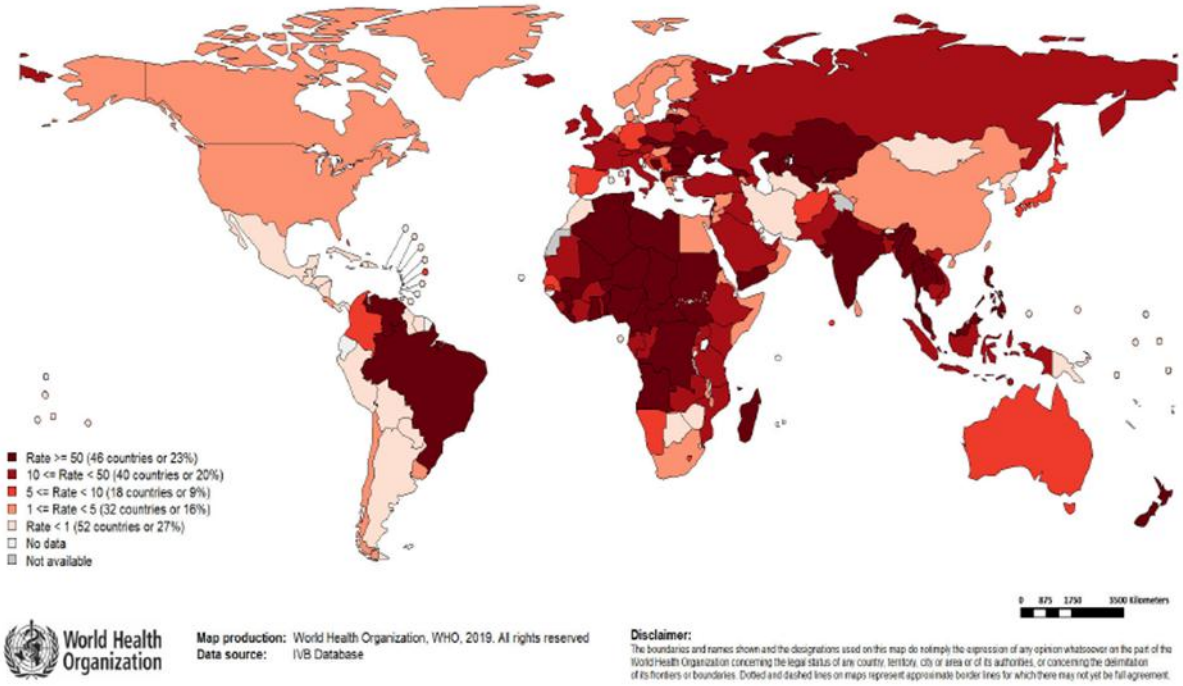
Jan 1 - Apr 5, 2017

5 WPV **0** cVPDV



Measles - today

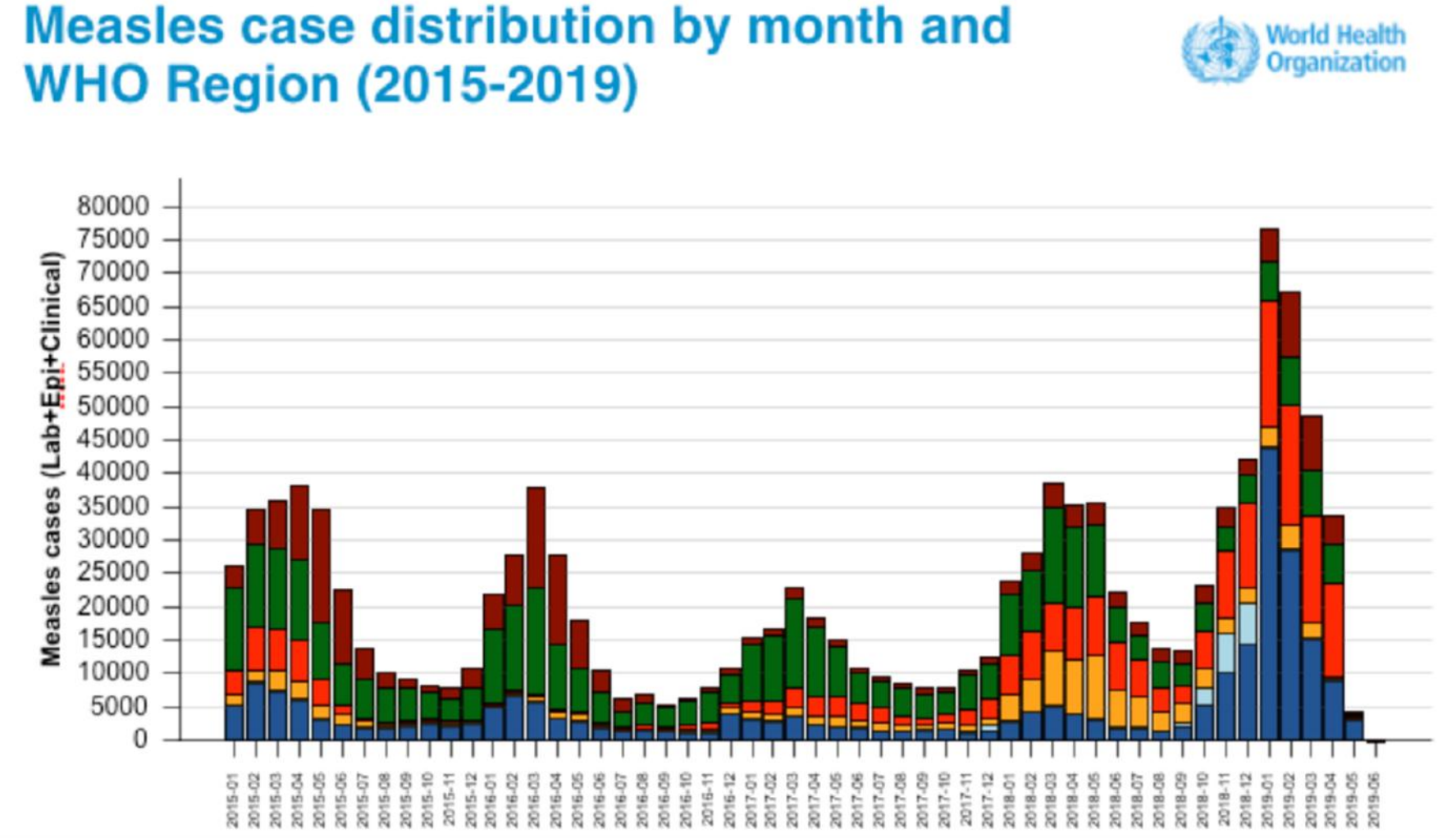
Top 10**		
Country	Cases	Rate
Madagascar	151026	6066.63
Ukraine	80184	1804.38
India****	71834	54.25
Philippines	48420	468.64
Nigeria	27396	147.3
Brazil	13605	65.52
Kazakhstan	10417	579.12
Yemen	10231	370.9
DR Congo	9495	120.59
Thailand	7713	112



Other countries with high incidence rates***		
Country	Cases	Rate
Georgia	4756	1211.59
The Republic of North Macedonia	1902	913.89
Kyrgyzstan	2896	486.25
Israel	3782	461.68
Bosnia and Herzegovina	1396	396.95

Measles cases from countries with known discrepancies between case-based and aggregate surveillance, as reported by country				
Country	Year	Cases in Case-based	Cases in Aggregate	Data Source for aggregate #s
DR Congo	2018	5597	67072	SITUATION EPIDEMIOLOGIQUE DE LA ROUGEOLE EN RDC, Week of 06/08/2019
	2019	6543	140,725	
Somalia	2018	131	9135	Somali EPI/POL Weekly Update Week 30
	2019	28	2397	

Measles - worldwide

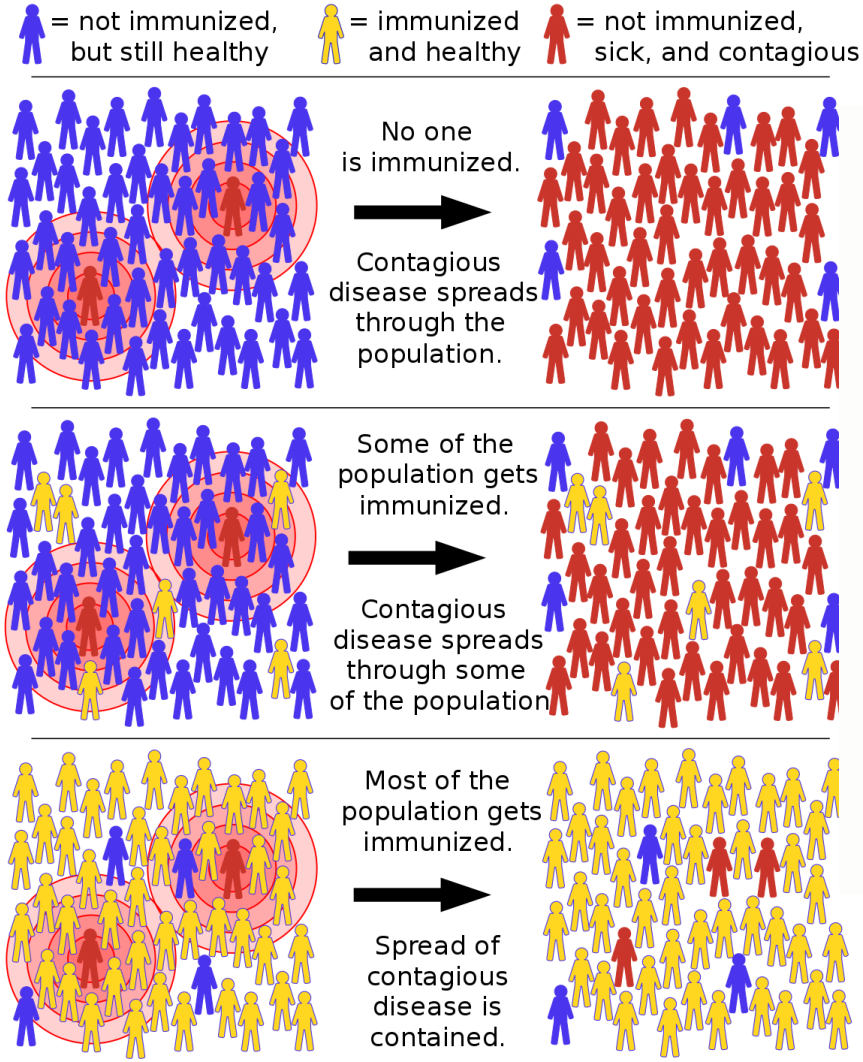


Measles - Europe

Table 1. Number of measles cases by month and notification rate per million population by country, EU/EEA, 1 September 2018–31 August 2019

	2018	2018	2018	2018	2019	2019	2019	2019	2019	2019	2019	2019			
Country	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Total cases	Cases per million	Total lab-positive cases
Austria	6	0	4	1	25	33	1	27	38	8	4	7	154	17.5	143
Belgium	14	4	6	6	20	87	67	34	94	66	28	14	440	38.6	341
Bulgaria	0	0	0	0	0	51	185	279	281	236	84	42	1158	164.2	1047
Croatia	0	0	0	0	0	1	0	0	4	6	10	4	25	6.1	25
Cyprus	0	0	0	0	0	1	0	1	3	1	0	0	6	6.9	5
Czech Republic	4	7	16	19	58	150	199	90	50	20	14	4	631	59.5	551
Denmark	2	0	0	1	2	5	4	2	1	1	0	0	18	3.1	18
Estonia	0	0	0	0	3	6	2	0	6	7	1	1	26	19.7	25
Finland	0	0	1	7	3	3	0	2	0	0	0	0	16	2.9	16
France	38	76	62	61	122	209	321	341	557	467	314	107	2675	40.0	1625
Germany	24	13	10	10	102	71	129	70	50	20	20	19	538	6.5	426
Greece	4	2	0	1	0	3	7	12	6	0	0	0	35	3.3	20
Hungary	0	0	0	1	2	5	4	2	9	0	1	0	24	2.5	24
Iceland	0	0	0	0	0	1	6	0	0	0	1	0	8	23.0	8
Ireland	2	1	1	0	2	18	23	6	10	2	3	1	69	14.3	36
Italy	57	82	58	76	180	173	229	309	237	217	152	77	1847	30.5	1544
Latvia	0	0	1	2	0	0	0	1	0	0	0	.	4	2.1	4
Lithuania	0	0	8	20	12	73	250	232	122	62	32	40	851	303.0	851
Luxembourg	0	0	1	0	0	0	15	7	1	1	0	0	25	41.5	25
Malta	0	0	0	0	0	0	3	13	11	3	0	1	31	65.2	31
Netherlands	0	0	0	2	4	4	10	2	13	16	9	9	69	4.0	60
Norway	0	0	0	0	0	1	7	3	3	1	0	2	17	3.2	14
Poland	9	21	79	114	164	239	287	256	244	122	40	7	1582	41.7	1056
Portugal	3	2	24	12	2	2	2	0	2	1	0	0	50	4.9	47
Romania	72	65	81	130	261	77	188	110	148	123	110	80	1445	74.0	1135
Slovakia	28	16	38	50	43	37	70	105	43	9	3	6	448	82.3	385
Slovenia	0	1	0	0	0	0	0	6	8	3	1	1	20	9.7	20
Spain	4	4	1	6	11	11	23	67	74	28	13	11	253	5.4	230
Sweden	4	1	0	3	0	1	4	6	4	2	2	0	27	2.7	24
United Kingdom	16	21	26	11	81	81	108	118	125	113	52	20	772	11.7	771
EU/EEA	**287**	**316**	**417**	**533**	**1097**	**1343**	**2144**	**2101**	**2144**	**1535**	**894**	**453**	**13264**	**25.6**	**10507**

“Herd immunity”



Disease	Threshold (%)
Mumps	75–86
Polio	80–86
Smallpox	80–85
Diphtheria	85
Rubella	83–85
Pertussis	92–94
Measles	83–94

Vaccination schedule in Republic of Croatia

REPUBLIKA HRVATSKA
Ministarstvo zdravstva

KALENDAR CIJEPLJENJA ZA 2019. GODINU

NAVRŠENA DOB / CJEPIVO	MJESECI				GODINE		RAZRED OSNOVNE ŠKOLE			GODINE		
	0	2	4	6	1	5	I	VI	VIII	19	24	60
BCG	BCG											
Hib		Hib	Hib	Hib	Hib							
Di-Te-Per		DTPa	DTPa	DTPa	DTPa	DTPa	*					
Polio		IPV	IPV	IPV	IPV		IPV		IPV	*		
Di-Te							*		dT	*	*	
Mo-Pa-Ru					MRP		MRP					
Hepatitis B[1]		HBV	HBV	HBV			*	*				
Pneumokok[2]		Pn	Pn		Pn							
Ana-TE												Te

[1] Cijepi se i novorođenčad HBsAg pozitivnih majki odmah po rođenju uz primjenu imunoglobulina prema postekspozicijskoj shemi
[2] Novorođenčad rođena prije 37. tjedna gestacije cijepi se pneumokoknim konjugiranim cjepivom po shemi 3 + 1
* Provjera cjepnog statusa i nadoknada propuštenog cijepljenja, prema potrebi

Good vaccine characteristics

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

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

Fighting infectious diseases

Some infections for which effective vaccines are not yet available	
Disease	**Estimated annual mortality**
Malaria	618,248
Schistosomiasis	21,797
Intestinal worm infestation	3304
Tuberculosis	934,879
Diarrheal disease	1,497,724
Respiratory infections	3,060,837
HIV/AIDS	1,533,760
Measles*	130,461

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

Type of vaccine

Type of vaccine	Examples	Form of protection
Live attenuated, or killed, bacteria	BCG, cholera	Antibody response
Live attenuated viruses	Polio, rabies	Antibody response; cell-mediated immune response
Subunit (antigen) vaccines	Tetanus toxoid, diphtheria toxoid	Antibody response
Conjugate vaccines	*Haemophilus influenzae, Streptococcus pneumoniae* (pneumococcus)	Helper T cell–dependent antibody response to polysaccharide antigens
Synthetic vaccines	Hepatitis virus (recombinant proteins)	Antibody response
Viral vectors	Clinical trials have been done	Cell-mediated and humoral immune responses
DNA vaccines	Clinical trials ongoing for several infections	Cell-mediated and humoral immune responses

Live attenuated vaccine

- Microbes are weak but alive
- Mimics natural immunization (infection): strong cellular and humoral immune response
- Limitations /downsides:
  - Possibility of mutation (back) to virulent forms
  - Not absolutely safe for everyone
  - Requires cooling during storage

Examples: **morbilli, parotitis, varicella, influenza, rotavirus, rubella**…

Inactivated (killed) vaccines

- Dead microbes: - whole or fractionated; killed by chemicals, temperature, irradiation
- Microbes can not mutate into virulent form
- Do not require cooling during storage

Limitations /downsides:

  - Weaker immune response in comparison to live vaccines (revaccinations (booster dose) are needed)

Examples: **influenza, polio, pertussis, HAV, cholera, typhoid, diphtheria (toxoid), tetanus (toxoid)**,…

Conjugated vaccines

- Antigens are usually polysaccharide
- Conjugated with protein carrier to stimulate

T-cell immune response

- Strong immune response to a week antigen

Examples: **Hemophilus, meningococcus, streptococcus**, …

Recombinant vaccines

- Antigens (epitopes) that are the most potent in stimulating immune response
- Usually contains several antigens
- Recombinant DNA technology is used for genetic cloning

Limitations /downsides:

- It is not easy to determine the most immunogenic antigens for the population

Examples: **HBV, HCV, HPV, Ebola**?, **HIV**?,…

Genetic engineering – recombinant DNA technology

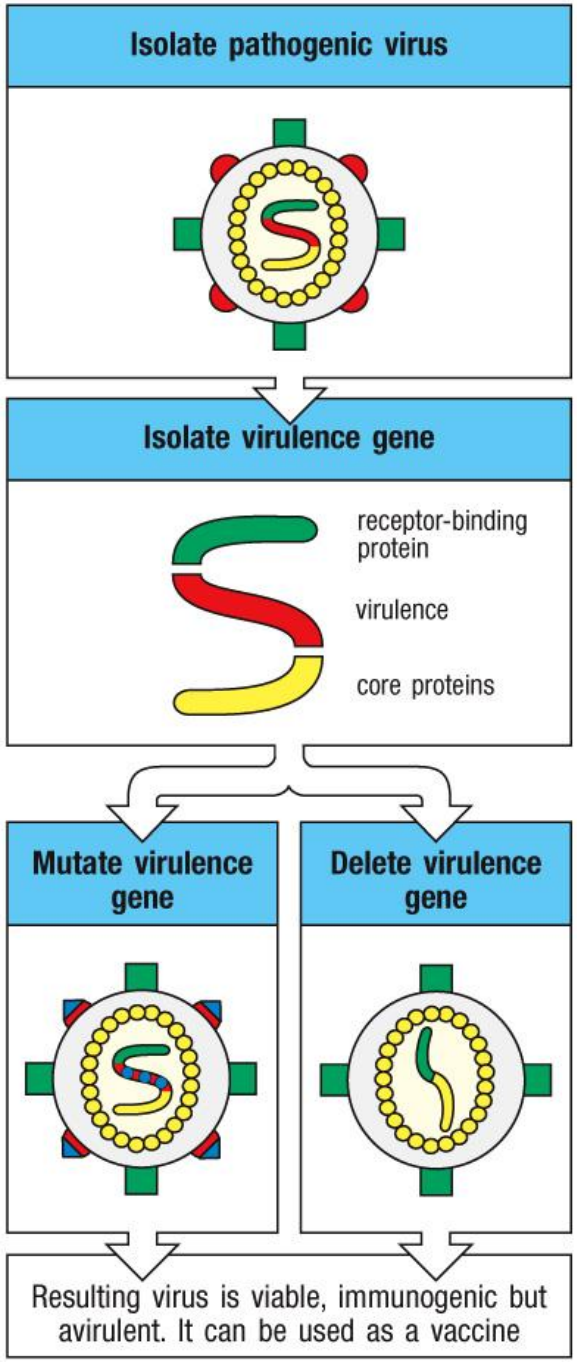
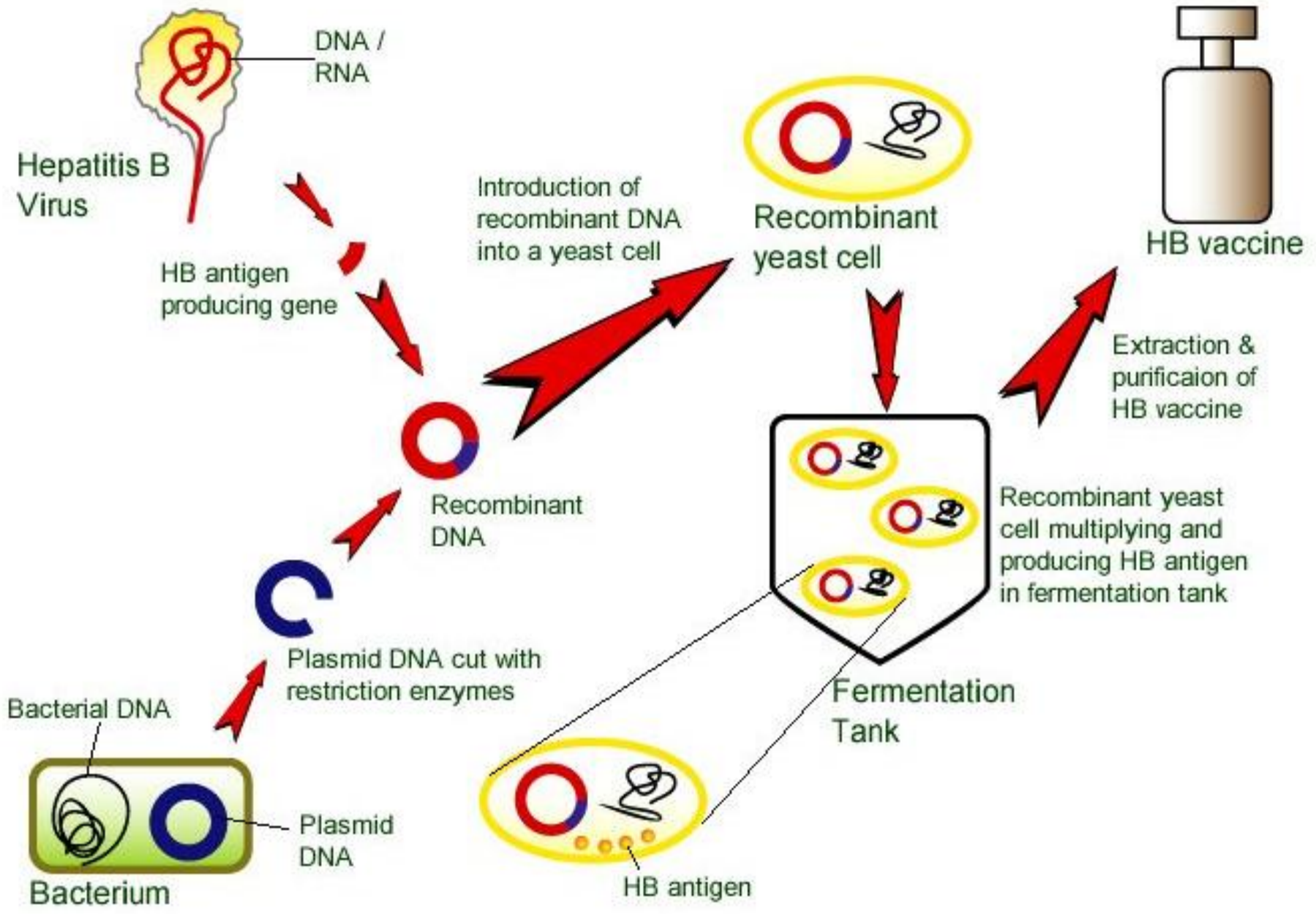
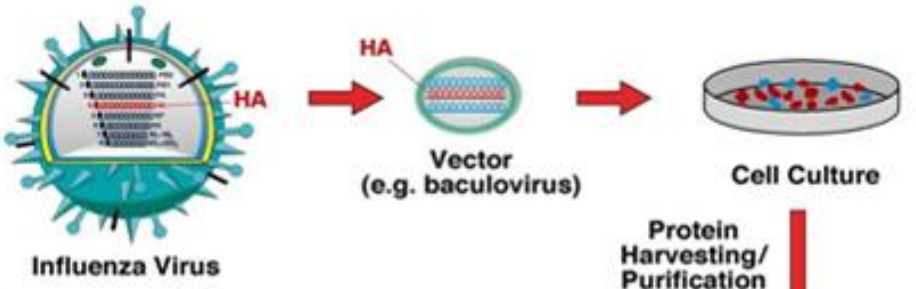


Figure 16.25 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Production of recombinant HBV vaccine



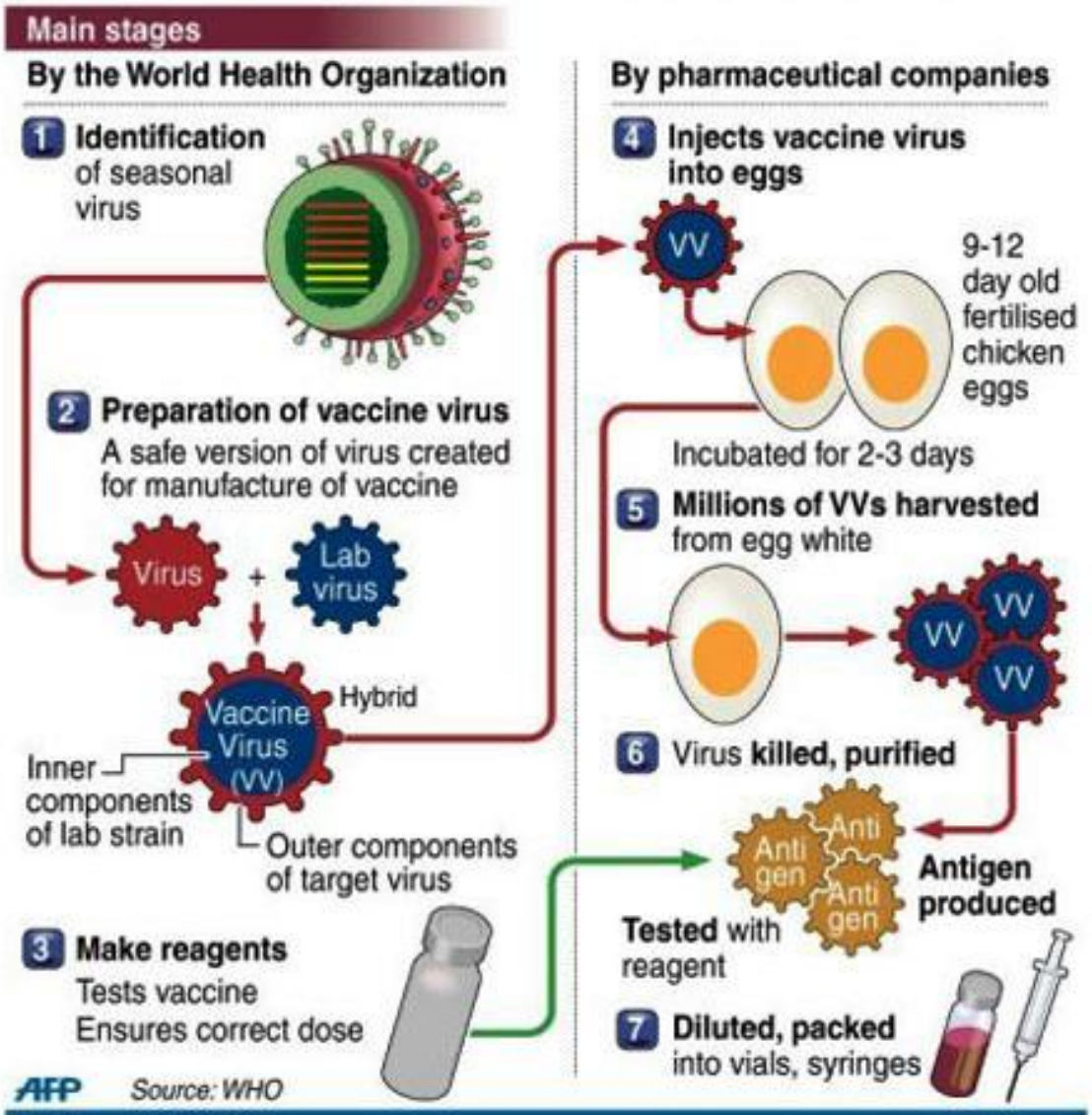
Flu vaccine production



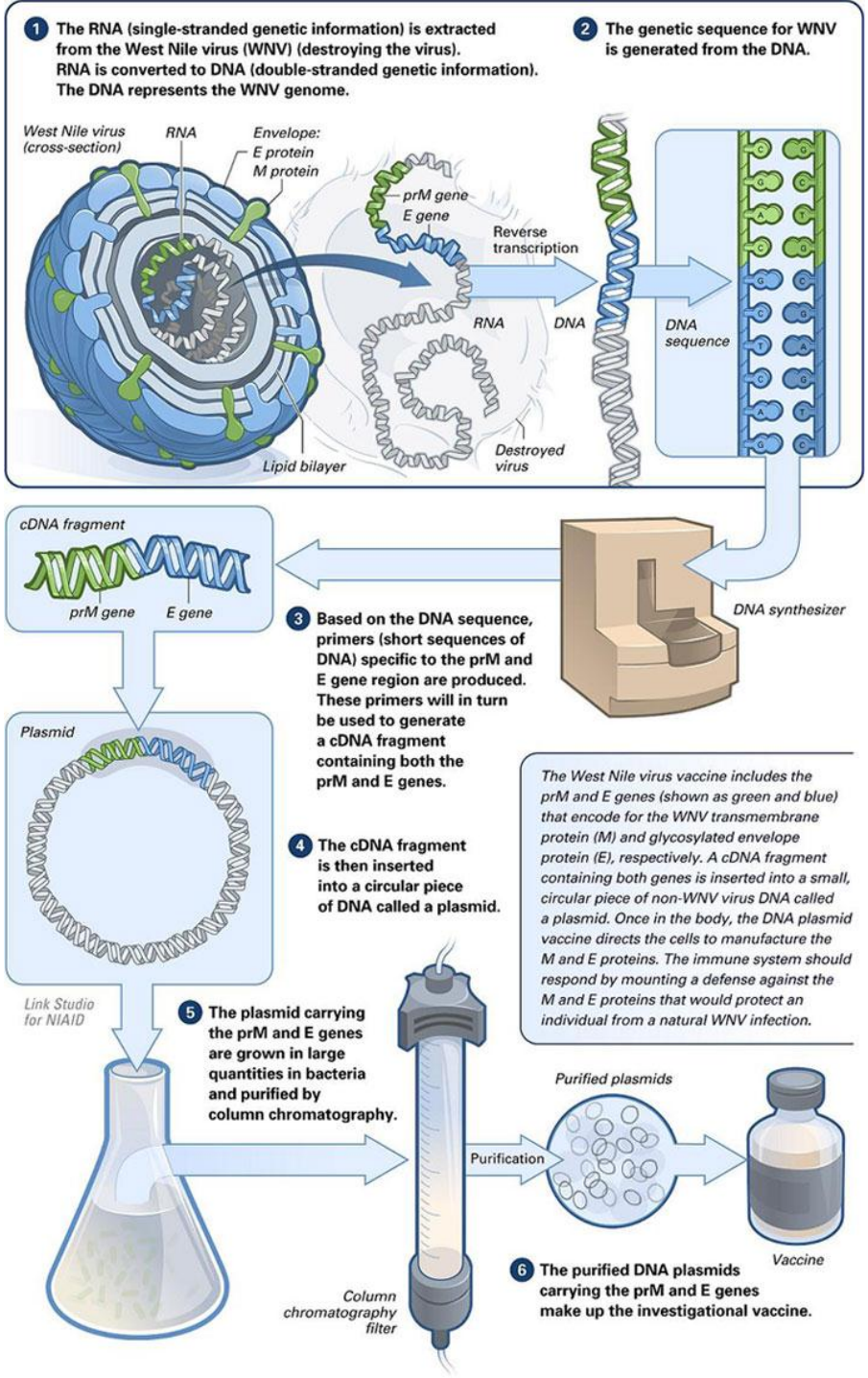
Recombinant DNA vaccine

← **Traditional method**

(with technology based on chicken eggs 5 to 6 months in average is needed for mass production of influenza vaccine)



DNA vaccines



DNA vaccines

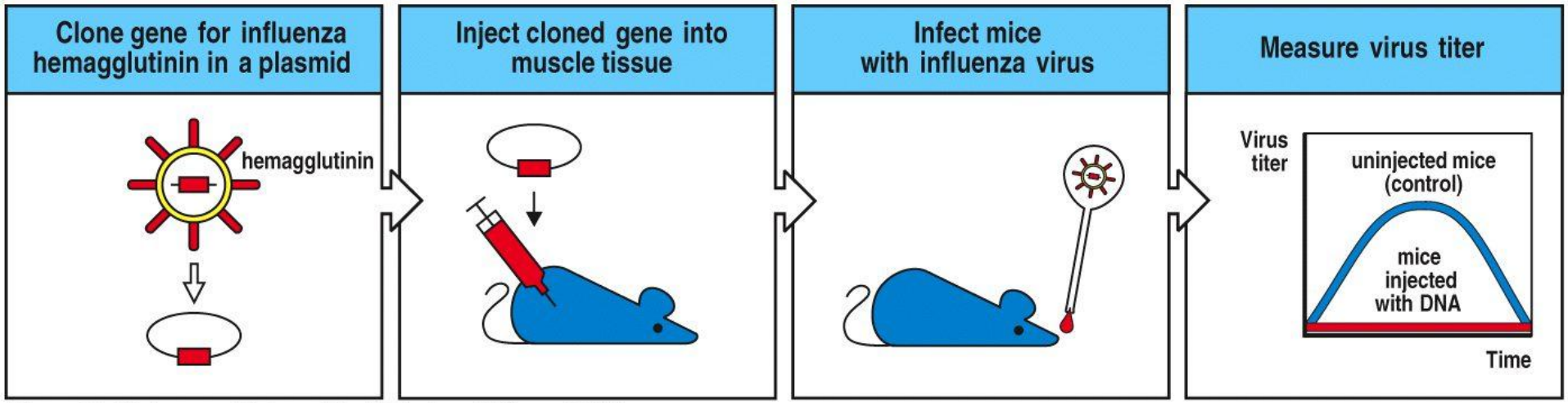
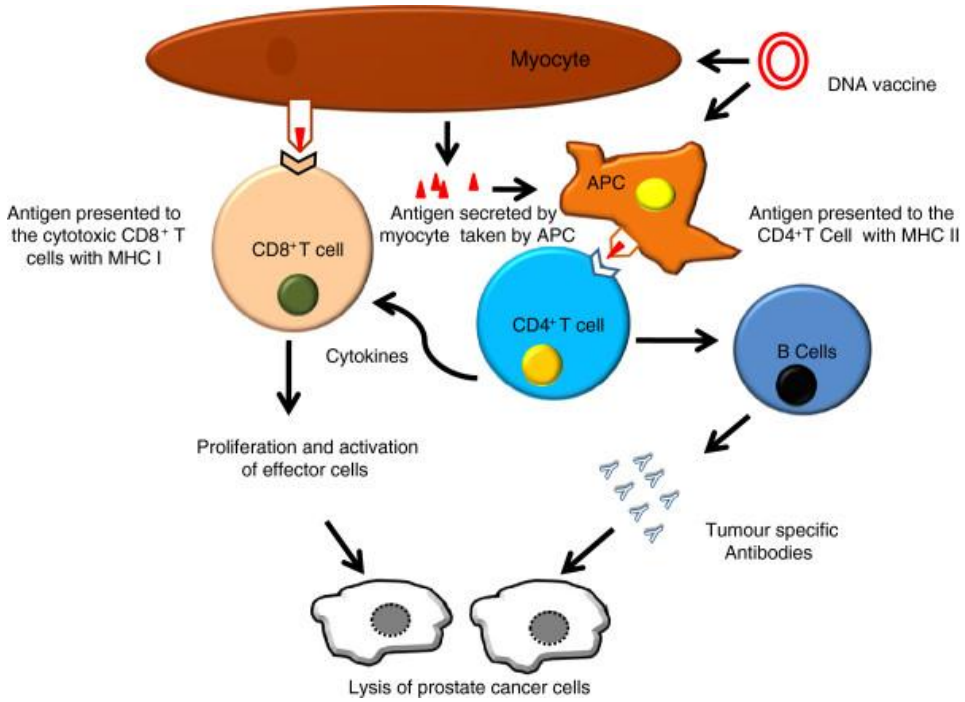


Figure 14-28 Immunobiology, 6/e. (© Garland Science 2005)



Adjuvans

Adjuvans are added to vaccines to stimulate immune response for specific antigen, while they do not induce specific immunity themselves

Immune stimulation mechanism of adjuvans:

- Increase availability of antigen in the blood and tissue
- Increase adsorptions of antigen via APC
- Activate macrophages and lymphocytes
- Stimulate the production of cytokines

Types of adjuvans

- **Anorganic components**: aluminium salts, aluminium hydroxide, aluminium phosphate, calcium phosphate and hydroxide
- **Mineral oils:** paraffin oil (for „Depo" vaccines)
- **Bacterial products**: dead bacteria *Bordetella pertussis, Mycobacterium bovis*, toxoids
- **Nonbacterial organic compounds**: skvalen, thimerosal
- **Substances that facilitate delivery**: detergens (Quil A)
- **Plant saponins:** quillaja, Soy, Polygala senega,…
- **Cytokins**: IL-1, IL-2, IL-12
- **Combination**: Freund's complete adjuvans (exicated *M. tuberculosis* emulsified in mineral oil)
- **Other**: (adjuvant 65) – peanut oil

New vaccines development

- Develop better adjuvanses
  - ISCOMs (Immune Stimulatory Complexes) transfer peptides for MHC I presentation
  - Mucose adjuvans (modified pertusis toxin)

- The aim is to act on APC during simultaneous admission of cytokines

- Developing nasal or oral vaccines

(molecular pharming)

Vaccine Adverse Reactions

Adverse reaction is extraneous effect caused by vaccine (side effect)

- **Adverse event:**
  - any medical event following vaccination
  (may be true adverse reaction or may be only coincidental)
- **Local adverse reactions:**
  - pain, swelling, redness at site of injection
  (occur within a few hours of injection; usually mild and self-limited)
- **Systemic adverse reactions:**
  - fever, malaise, headache
  (nonspecific; may be unrelated to vaccine)
- **Severe allergic: (anaphylaxis)**
  - due to vaccine or vaccine component
  - rare
  - risk minimized by screening

Contraindications and Precautions to Vaccination

Contraindication

- A condition that increases the likelihood of a serious adverse reaction to a vaccine for a patient with that condition

Precaution

- A condition in a recipient that might increase the chance or severity of an adverse reaction, or
- Might compromise the ability of the vaccine to produce immunity

Contraindications and precautions for vaccination

Condition	Live	Inactivated
Allergy to component	C	C
Encephalopathy	---	C
Pregnancy	C	V*
Immuno-suppression	C	V
Severe illness	P	P
Recent blood product	P**	V

C=contraindication

P=precaution

V=vaccinate if indicated

*except HPV

**MMR and varicella containing (except zoster vaccine) only

Permanent contraindications to vaccination

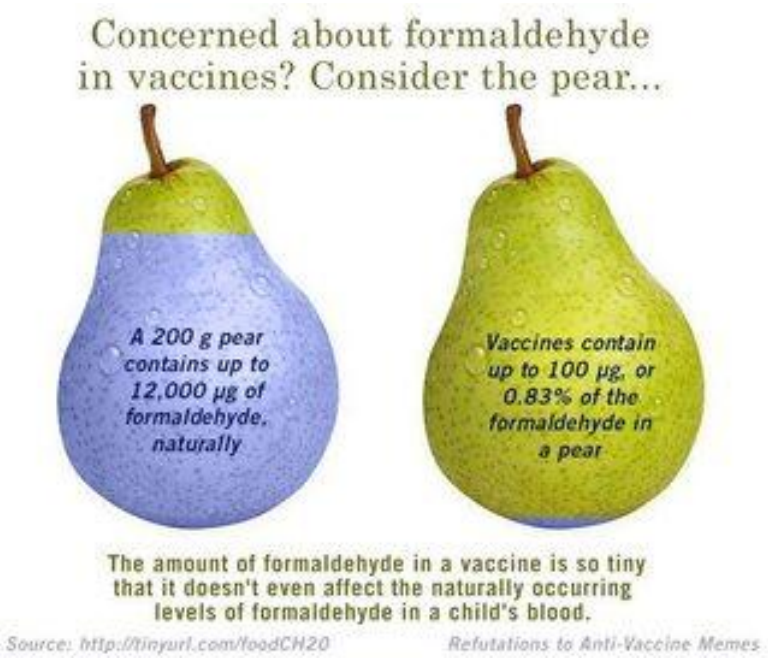
- Severe allergic reaction to a vaccine component or following a prior dose
- Encephalopathy not due to another identifiable cause occurring within 7 days of pertussis vaccination
- Severe combined immunodeficiency (rotavirus vaccine)
- History of intussusception (rotavirus vaccine)

„Dangerous adjuvans” in vaccines

- Aluminium

A cup of tea contains as much aluminum as one vaccine shot.

- Formaldehyde



- Hg – 1 µg in 1 dose = 10 g of canned tuna fish

Mo-Pa-Ru vs. autism

Annals of Internal Medicine®

ORIGINAL RESEARCH | 16 APRIL 2019

Measles, Mumps, Rubella Vaccination and Autism: A Nationwide Cohort Study FREE

Anders Hviid, DrMedSci; Jørgen Vinsløv Hansen, PhD; Morten Frisch, DrMedSci; Mads Melbye, DrMedSci

Article, Author, and Disclosure Information

FULL ARTICLE

Abstract

Methods

Results

Discussion

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Figures

Tables

Supplements

Summary for Patients

Comments

MORE

Abstract

Background: The hypothesized link between the measles, mumps, rubella (MMR) vaccine and autism continues to cause concern and challenge vaccine uptake.

Objective: To evaluate whether the MMR vaccine increases the risk for autism in children, subgroups of children, or time periods after vaccination.

Design: Nationwide cohort study.

Setting: Denmark.

Participants: 657 461 children born in Denmark from 1999 through 31 December 2010, with follow-up from 1 year of age and through 31 August 2013.

Mo-Pa-Ru vs. autism

Annals of Internal Medicine®

Conclusion: The study strongly supports that MMR vaccination does not increase the risk for autism, does not trigger autism in susceptible children, and is not associated with clustering of autism cases after vaccination. It adds to previous studies through significant additional statistical power and by addressing hypotheses of susceptible subgroups and clustering of cases.

Summary for Patients

Comments

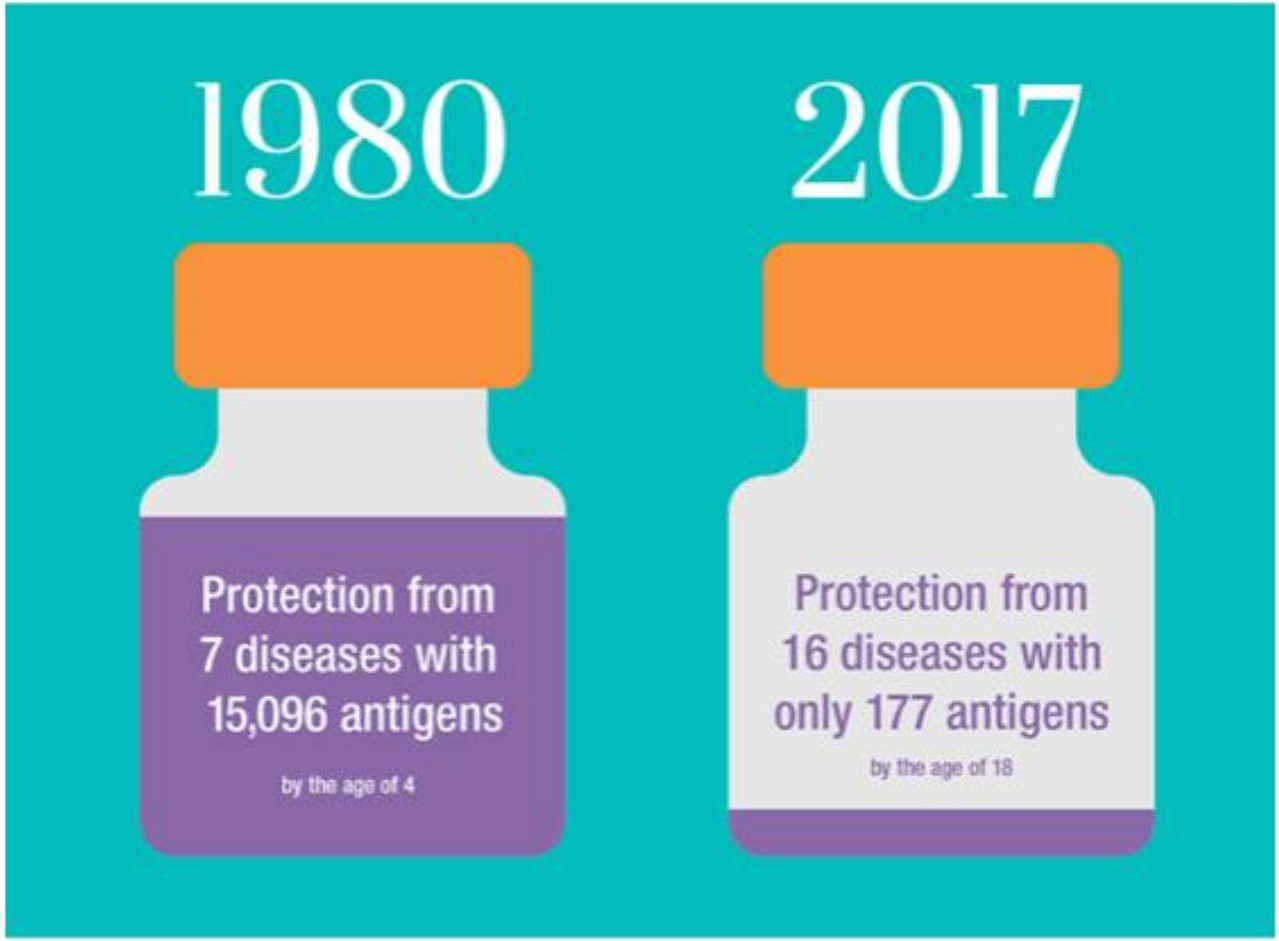
MORE

Setting: Denmark.

Participants 657 461 children born in Denmark from 1999 through 31 December 2010, with follow-up from 1 year of age and through 31 August 2013.

Vaccines Today Work Better Than Ever

Since 1980: More protection, fewer antigens.



Literature:

Epidemiology and Prevention of Vaccine-Preventable Diseases: **The Pink Book**: Course Textbook - 13th Edition (2015)

http://www.cdc.gov/vaccines/pubs/pinkbook/index.html