Vakcine

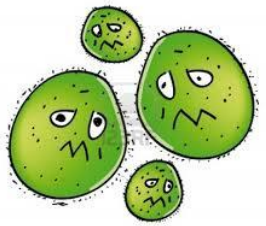
2. PREDAVANJE

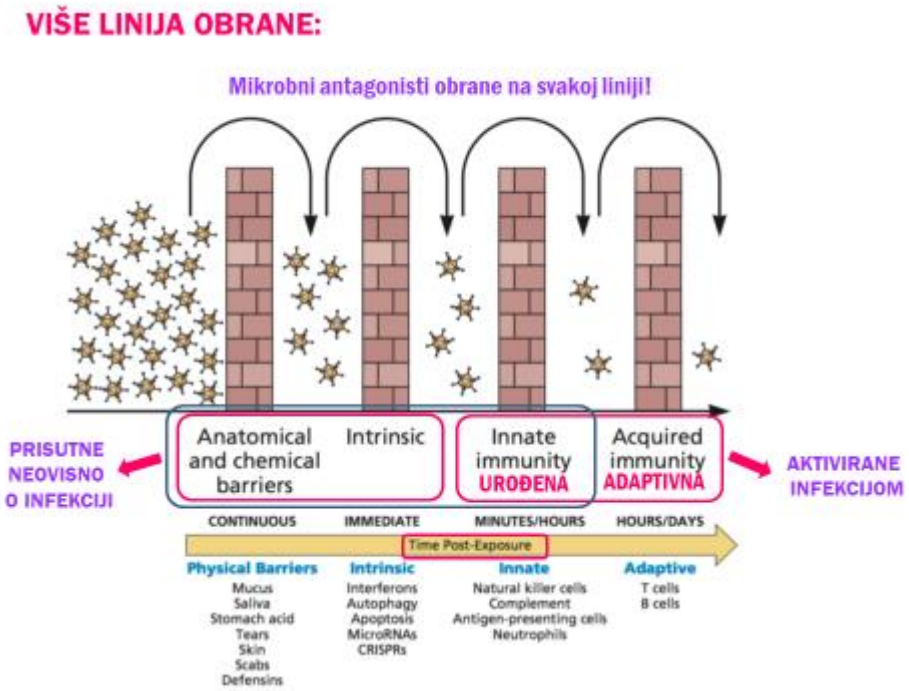
29.03.2024.

VAKCINE – princip djelovanja

Kako preživljavamo neprestane najezde patogena?

PRIRODNI OBRAMBENI SUSTAV – IMUNOSNI ODGOVOR





zatajenje

INFEKCIJA

INTRINZIČKA IMUNOST

- uvijek prisutna
- neovisna o infekciji

Intrinsic:
Ready to Go

NESPECIFIČNA IMUNOST

- inducirana infekcijom

Innate:
"Warming Up"
Required

ADAPTIVNA IMUNOST

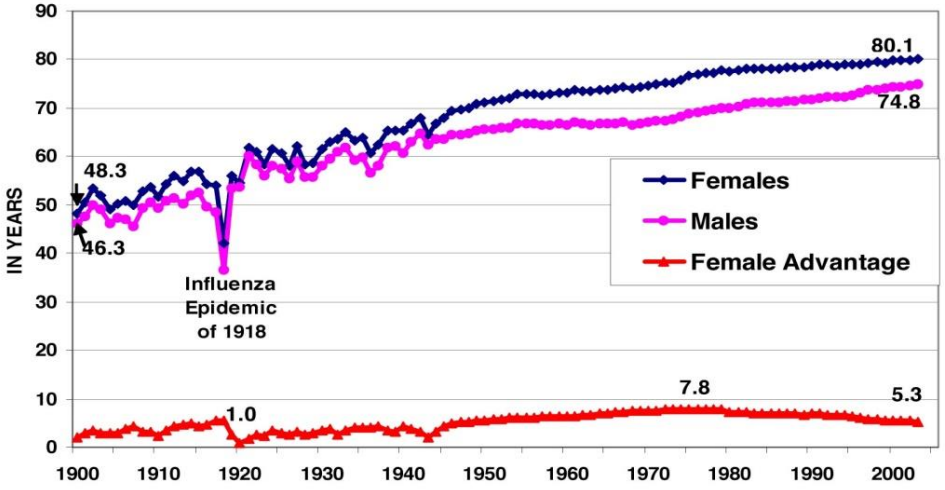
slow but efficient

VAKCINE – principi djelovanja

VAKCINE – dokazano najbolja obrana protiv infekcija

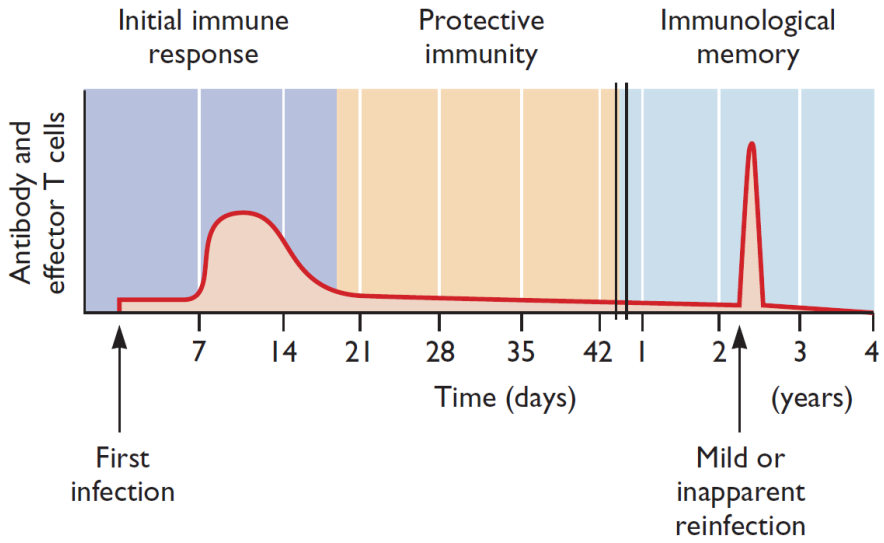
- simuliraju prirodnu infekciju bez patogenih učinaka
- mobiliziraju imunosni odgovor (memorijske stanice) kako bi spriječio prirodnu infekciju
- posljedično, remeti se lanac rasprostranjivanja patogena u populaciji

Figure 1. Life Expectancy at Birth, by Sex: 1900 to 2003.

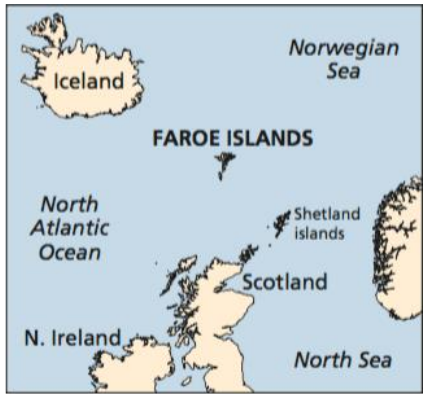


Source: For 1900-2002, CRS analysis based on data contained in NCHS, United States Life Tables, 2002, *National Vital Statistics Report*, vol. 53, no. 6, Nov. 10, 2004. For 2003, CRS analysis based on NCHS, Deaths: Final Data for 2003, *National Vital Statistics Report*, vol. 54, no. 13, Apr. 19, 2006.

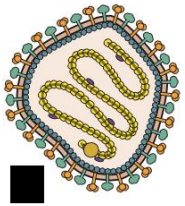
VAKCINE – princip djelovanja

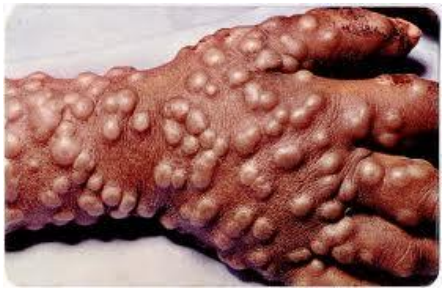


Količina protutijela i aktiviranih limfocita T opada nakon primarne infekcije, no reinfekcija istim antigenom (godinama kasnije) dovodi do snažnog imunosnog odgovora – IMUNOSNA MEMORIJA



Prirodni eksperiment – epidemije ospica 1781. i 1846. na Farskim Otocima (imunosna memorija dugotrajna i bez opetovanog izlaganja virusu)





VELIKE BOGINJE (smallpox)

najrazornija bolest u povijesti čovječanstva

(kroz povijest zaraženo 5% čovječanstva,

samo u 20. stoljeću 300 milijuna zaraženih)

Prva virusna bolest eradicirana ljudskom intervencijom!

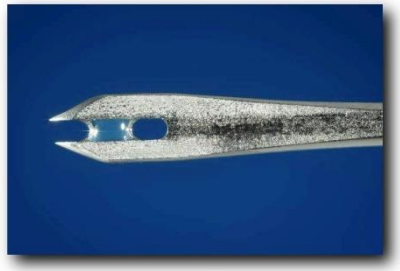
11. stoljeće – kineski i indijski liječnici provodili postupak "variolacije"

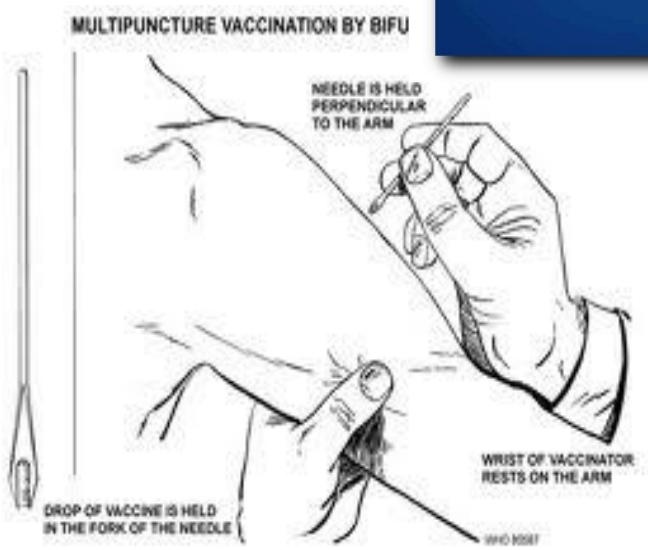
(sadržajem lezija inhalirali zdrave pojedince s ciljem izazivanja blage infekcije koja će pružiti dugotrajnu zaštitu – mnogo oboljelih)

18. stoljeće – "variolacija" u Europi (često zabranjena zakonom)

1796. – Edward Jenner

- opazio da mljekarice zaražene virusom kravljih boginja ne obolijevaju od velikih boginja!!!
- gnojem iz lezija kravljih boginja cijepio zdravog dječaka (James Phipps)
- dva tjedna kasnije izložio ga velikim boginjama – **nije obolio!**





1885. – Louis Pasteur

- **vakcina protiv virusa bjesnoće (suha kralješnička moždina inficiranog zeca)**

u čast Jenneru (lat. vacca – krava)

tek 1930-ih – vakcine za virus žute groznice i gripe

prvi “antivakcinacijski pokreti”

☺


DEGRADATIONEM VACCINUM
AstraZeneca

VAKCINACIJSKI PROGRAMI

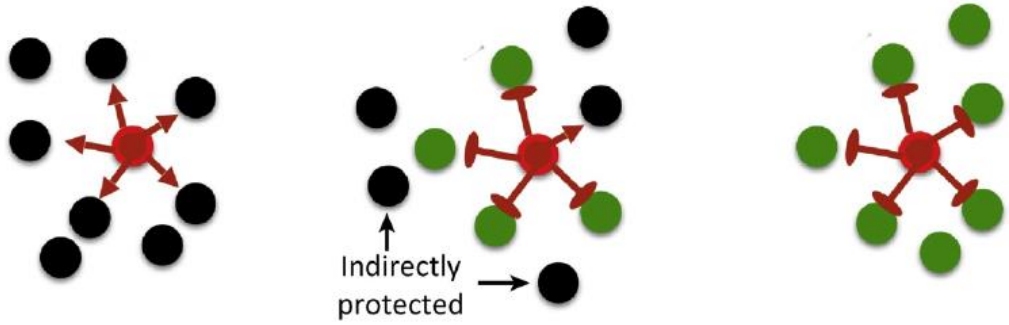
Danas – vakcinacija zakonska obveza (za ljude, ali i životinje)!

Zemlje trećeg svijeta???

Cilj vakcinacijskih programa - imunizirati što veći dio populacije s ciljem onemogućavanja rasprostranjivanja virusa

tzv. "HERD" IMMUNITY

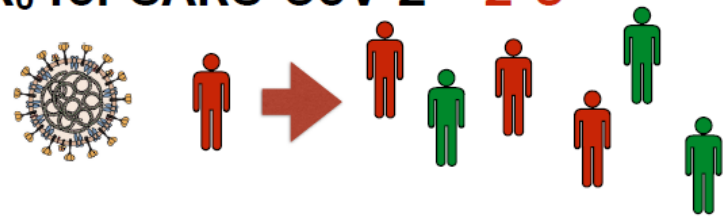
- **za zaštitu populacije nije nužno imunizirati svakog pojedinca, potrebno je imunizirati "dovoljno" ljudi (ovisno o virusu)**



- **rasprostranjivanje virusa zaustavljeno je kada vjerojatnost infekcije padne ispod određene razine 1-1/Ro (Ro – reprodukcijski broj virusa, govori o infektivnosti)**

  velike boginje 80-85%, ospice 93-95% populacije treba biti imunizirano
- **nijedna vakcina nije 100% efikasna (ako je 80% populacije imunizirano na virus ospica, 76% populacije je zaštićeno)**

R_0 for SARS-CoV-2 = 2-3



Number of people who must be vaccinated to prevent virus spread:

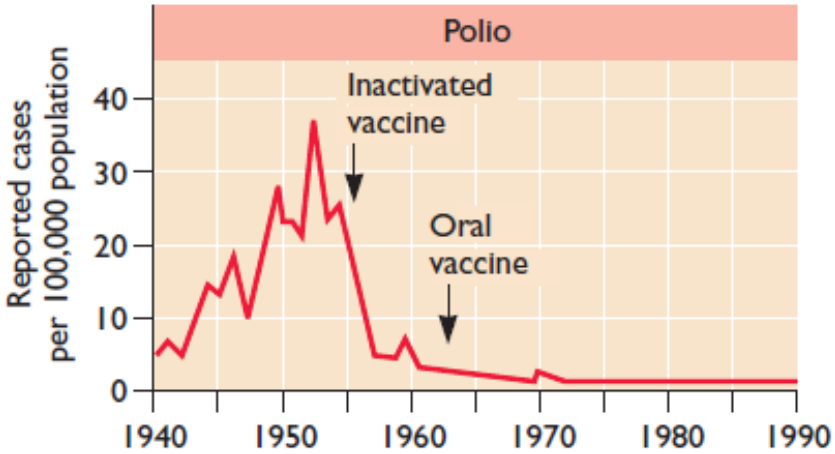
$$1 - 1/R_0$$

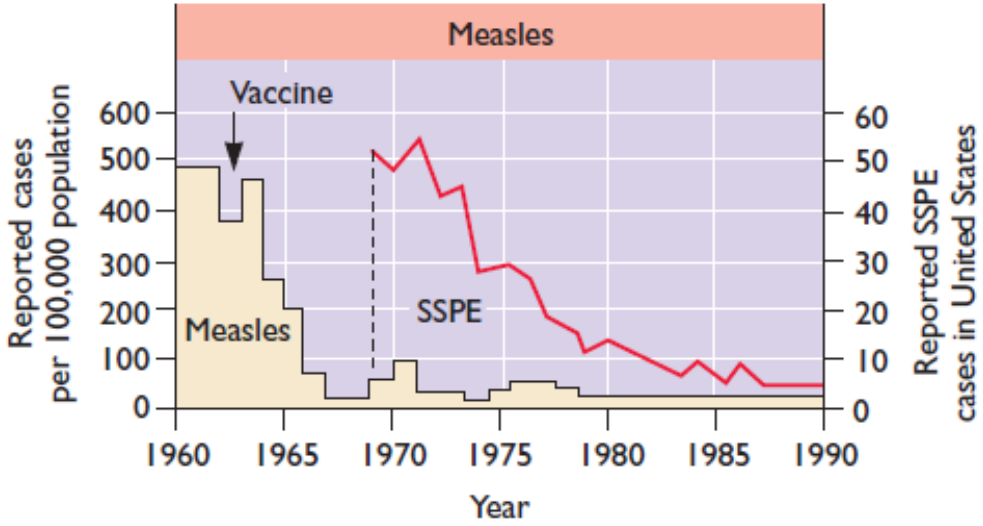
R_0 = tau * c * d

Tau = probability of infection given contact
C = average duration of contact between infected and uninfected host
D = duration of infectivity

Primjeri uspješnih vakcinacijskih programa:

- velike boginje (1978. WHO proglasio eradikaciju – od tada nisu zabilježeni slučajevi prirodnih infekcija)
- 1988. WHO – eradikacija poliomijelitisa i ospica do 2000. – *highest priority* (novi rok 2010., i danas slučajevi u nerazvijenim zemljama)





Brojni problemi!

Je li potpuna eradikacija moguća?

2 osnovna preduvjeta: samo jedan prirodni domaćin i doživotna imunost!!!

Laboratorijske zalihe virusa velikih boginja!!!

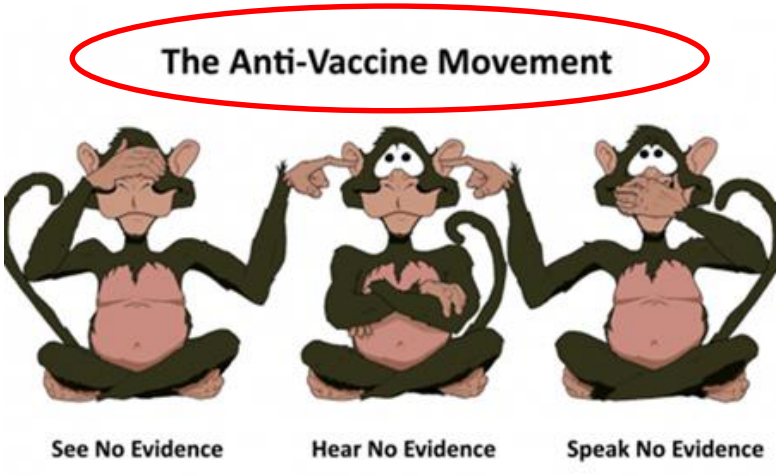
https://www.jutarnji.hr/life/zdravlje/smrtonosne-velike-boginje-sjedinjene-drzave-i-rusija-ne-zele-unistiti-571-ampulu-opakog-virusa/813151/

Važan je stav javnosti!

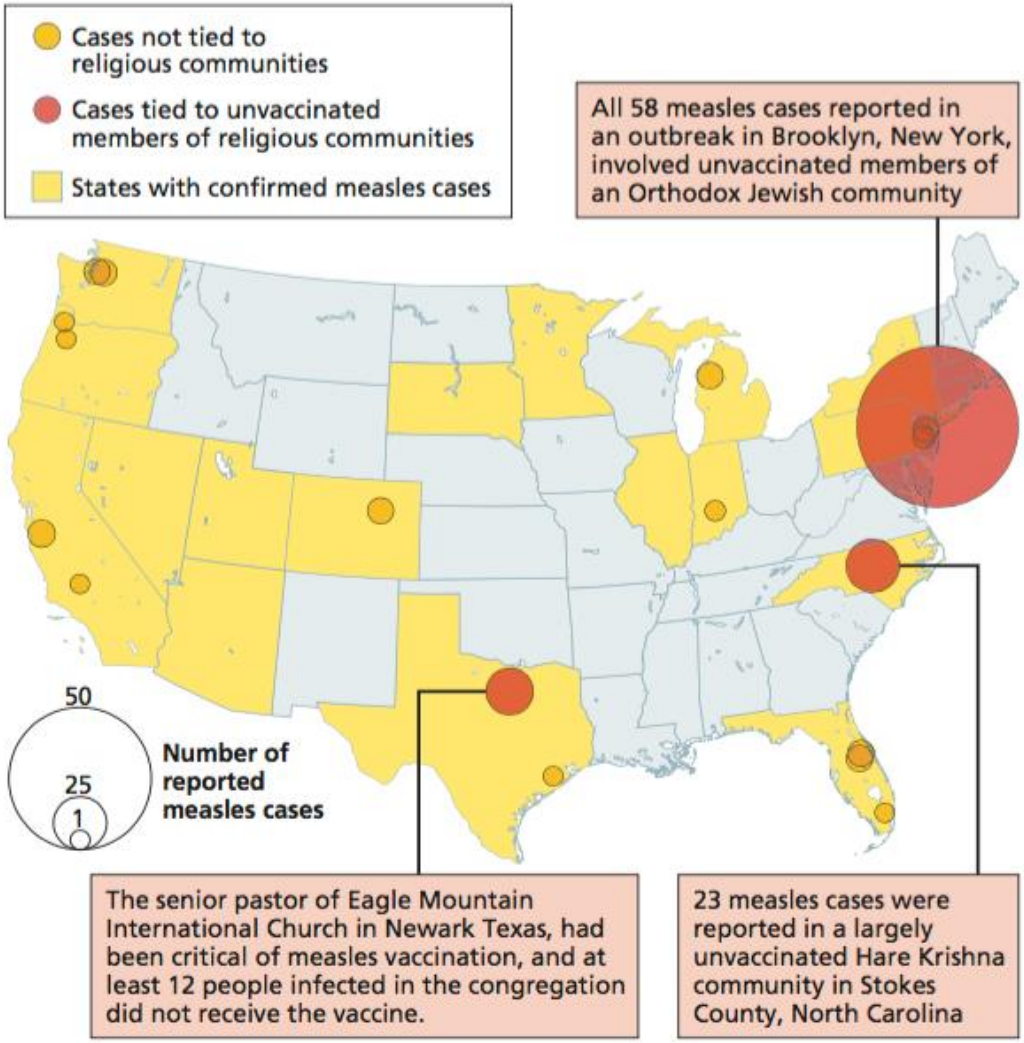
Najčešći argumenti:

- "Viral diseases are a thing of the past"
- "Polio is long gone"
- "I never get the flu"
- "Measles is just a trivial kid's disease"
- "Chicken pox only affects kids"
- "Kids should get infected naturally"
- "I'm not injecting anything into *my* body"
- "Vaccines make you sick, they cause autism, they cause multiple sclerosis, etc etc"
- "I know a guy who got the flu shot and then got the flu"
- "I can't afford to immunize my kids"
- "I don't have time this year"

Važan je stav javnosti!



Primjer posljedica antivakcinacijskih pokreta



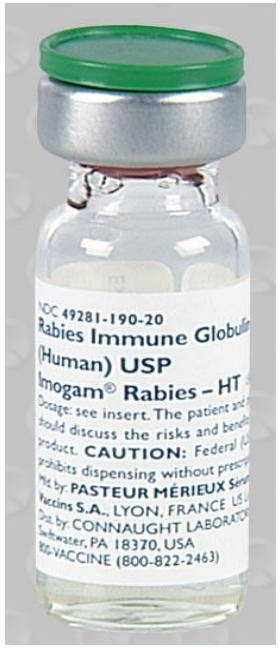
TIPOVI VAKCINA

Aktivne - modificirani patogeni ili njihovi dijelovi

↳ **dugotrajna imunost (memorijske stanice)**

Pasivne – gotovi proizvodi imunosnog odgovora (antitijela ili stimulirane stanice)

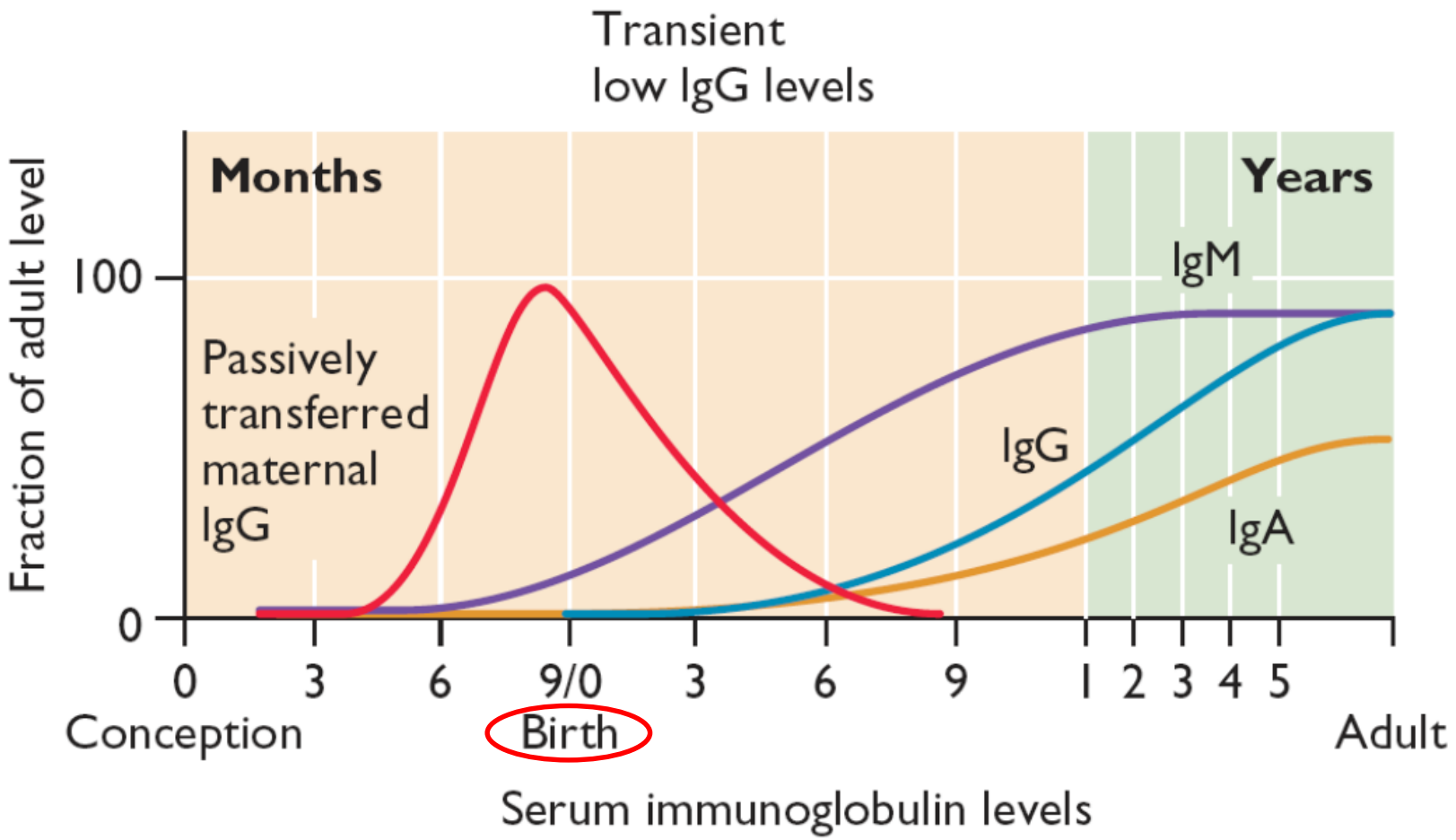
↳ **kratkotrajna imunost (post-exposure prophylaxis, npr. virus bjesnoće)**



Uses For Bayrab

Rabies immune globulin is used together with rabies vaccine to prevent infection caused by the rabies virus. Rabies immune globulin works by giving your body the antibodies it needs to protect it against the rabies virus. This is called passive protection. This passive protection lasts long enough to protect your body until your body can produce its own antibodies against the rabies virus. Rabies immune globulin is given to persons who have been exposed (e.g., by a bite, scratch, or lick) to an animal that is known, or thought, to have rabies. This is called post-exposure prophylaxis. Rabies immune globulin is used only in persons who have never before received the rabies vaccine.

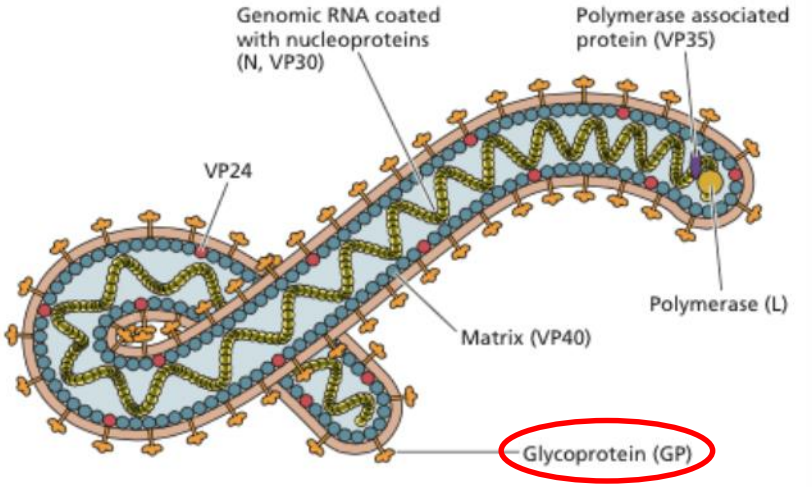
Pasivni transfer antitijela s majke na dijete

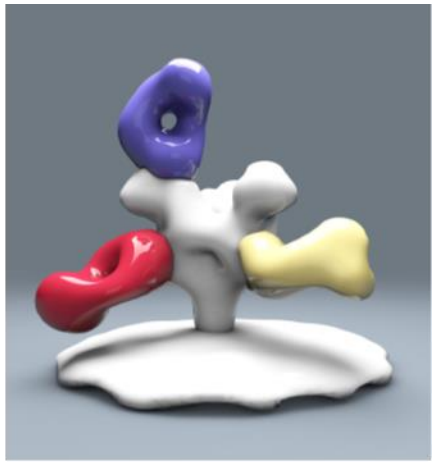


PASIVNE VAKCINE

„Zmapp” – trenutno najbolja pasivna vakcina

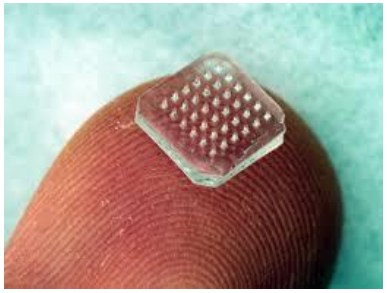
- **namijenjena terapiji infekcije virusom Ebola**
- **mješavina tri monoklonska antitijela (prepoznaju tri različita epitopa)**
- **proizvedena u miševima imuniziranim neinfektivnim „virus-like” česticama**
- **izolirana antitijela kimerizirana s humanim imunoglobulinom radi izbjegavanja imunosnog odgovora na mišje proteine (Fab fragmenti zadržani)**
- **masovna proizvodnja u biljkama duhana**
- **2014. tijekom epidemije u Africi - FDA odobrio upotrebu ove vakcine**





Uvjeti za uspješne vakcine:

- sigurnost (ne smije uzrokovati bolest, minimalne nuspojave)
- moraju pružiti zaštitnu imunost protiv virulentnog oblika patogena u velikom dijelu populacije (tzv. “herd immunity”, 80-95% populacije treba imati vakcinom-induciranu imunost)
- zaštita mora biti dugotrajna
- niska cijena (preporuka WHO <1$ doza, polio vakcina 5 centi)
- stabilnost (način skladištenja)
- poželjna ne-injekcijska primjena (oralno, sprejevi za nos, “flasteri” i sl.)

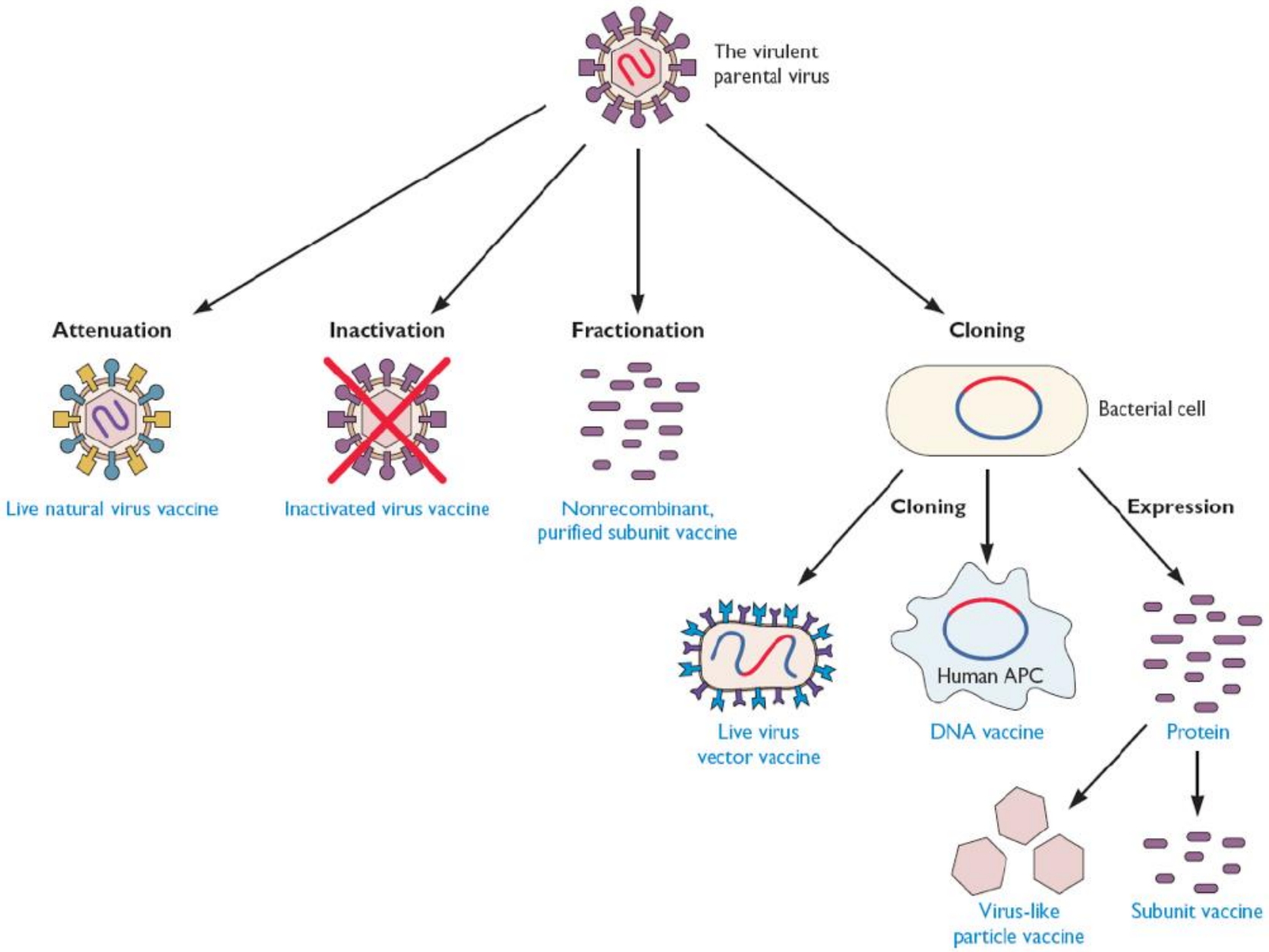


Efikasnost vakcina ovisi i o:

- poticanju odgovarajućeg imunosnog odgovora (humoralna ili stanična imunost)
- strukturi populacije (npr. starosna dob)
- genetičkoj strukturi virusa sadržanih u vakcini (praćenje mutanata - sigurnost)

Malo registriranih vakcina!

PRIPREMA VAKCINA



LICENCIRANE VAKCINE

Disease or virus	Type of vaccine	Indications for use	Schedule
Adenovirus	Live attenuated, oral	Military recruits	One dose
Hepatitis A	Inactivated whole virus	Travellers, other high-risk groups	0, 1, and 6 mo
Hepatitis B	Yeast-produced recombinant surface protein	Universal in children, exposure to blood, sexual promiscuity	0, 1, 6 and 12 mo
Influenza	Inactivated viral subunits	Elderly and other high-risk groups	Two-dose primary series, then one seasonal dose
Influenza	Live attenuated	Healthy children and adults 5–49 yr old	Two-dose primary series, then one seasonal dose
Japanese encephalitis	Inactivated whole virus	Travelers to or inhabitants of high-risk areas in Asia	0, 7, and 30 days
Measles	Live attenuated	Universal vaccination of infants	12 mos of age; 2nd dose, 6 to 12 yr of age
Mumps	Live attenuated	Universal vaccination of infants	Same as measles, given as MMR
Papilloma (human)	Yeast- or SF9-produced virus-like particles	Females 9–26 yr old	Three doses
Rotavirus	Live reassortant	Healthy infants	2, 3, and 6 mo or 2 and 4 mo of age depending on vaccine
Rubella	Live attenuated	Universal vaccination of infants	Same as measles, given as MMR
Polio (inactivated)	Inactivated whole viruses of types 1, 2, and 3	Changing: commonly used for immunosuppressed where live vaccine cannot be used	2, 4, and 12–18 mo of age, then 4 to 6 yr old
Polio (live)	Live, attenuated, oral mixture of types 1, 2, and 3	Universal vaccination; no longer used in United States	2, 4, and 6–18 mo of age
Rabies	Inactivated whole virus	Exposure to rabies, actual or prospective	0, 3, 7, 14, and 28 days postexposure
Smallpox	Live vaccinia virus	Certain laboratory workers	One dose
Varicella	Live attenuated	Universal vaccination of infants	12 to 18 mo of age
Varicella-zoster	Live attenuated	Adults 60 yr old and older	One dose
Yellow fever	Live attenuated	Travel to areas where infection is common	One dose every 10 yr

VAKCINE S INAKTIVIRANIM VIRUSIMA

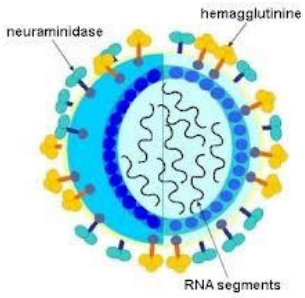
- virioni inaktivirani kemijskom obradom (formaldehid, neionski detergenti i sl.)
- infektivnost eliminirana, zadržana antigeničnost
- primjeri inaktiviranih vakcina: inaktivirani poliovirus (Salkova vakcina)
  gripa (do 50.000 smrti godišnje u SAD-u)
  hapatitis A
  bjesnoća

ZA

- sigurne za upotrebu

PROTIV

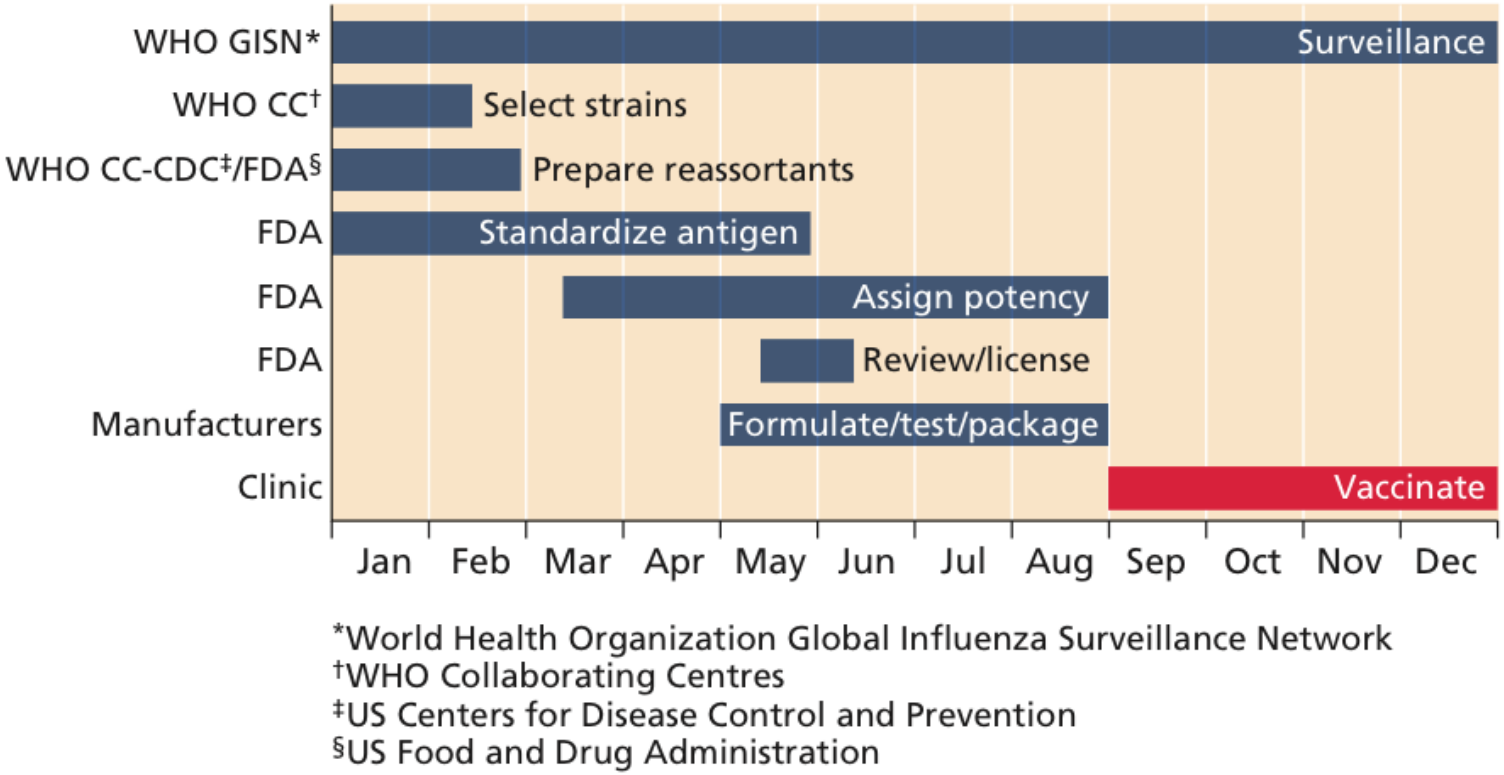
- u tijelu se zadržavaju kratko pa ne potiču adekvatnu imunosnu memoriju
- za postizanje dugoročne imunosti potrebna vakcinacija s više doza
- rijetko potiču staničnu imunost



VAKCINE S INAKTIVIRANIM VIRUSIMA

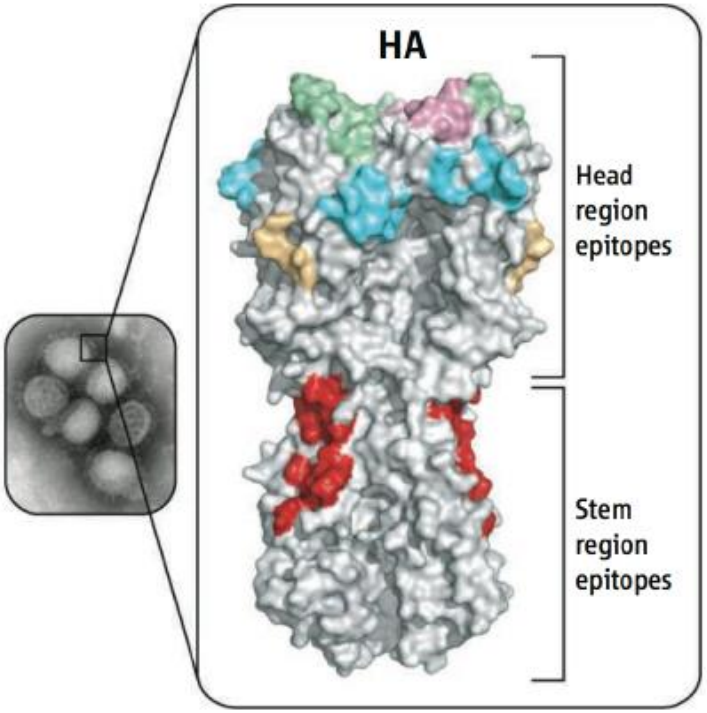
Vakcina za gripu (sojevi A i B) – produkcija antitijela na varijante glikoproteina HA i NA prisutne u populaciji prethodne godine (FDA i WHO)

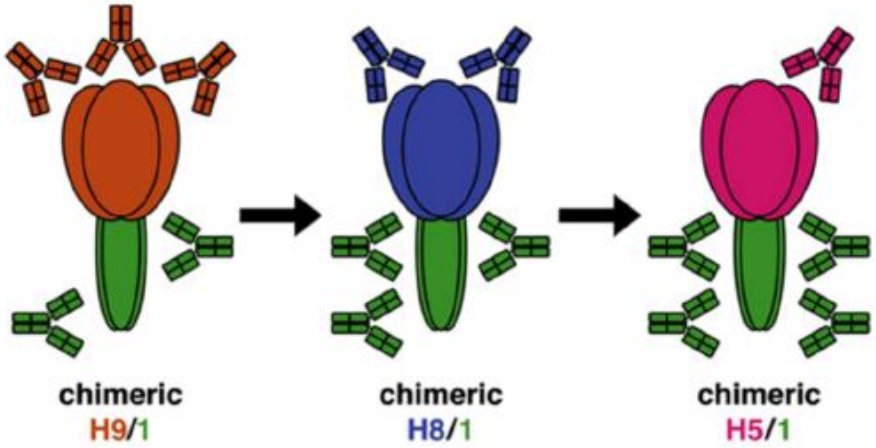
→ **zaštita nije zagarantirana!**



*World Health Organization Global Influenza Surveillance Network
†WHO Collaborating Centres
‡US Centers for Disease Control and Prevention
§US Food and Drug Administration

Univerzalna vakcina za gripu?

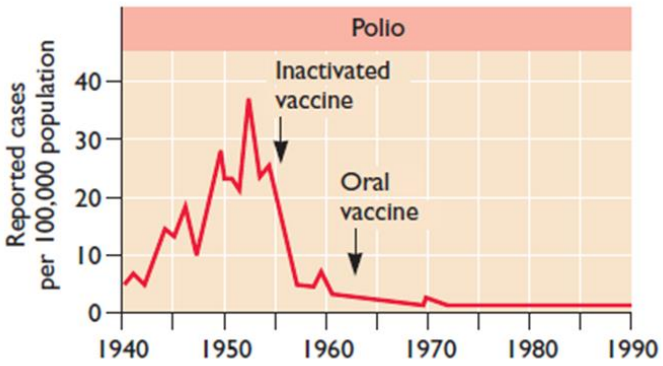




By exchanging the HA head domains, but retaining the same HA stalk domain, the antibody response can be redirected towards the otherwise immuno-subdominant stalk region.

NPJ Vaccines. 2017; 2: 26.

VAKCINE S INAKTIVIRANIM VIRUSIMA



Inaktivirana polio-vakcina, IPV (Salkova vakcina)

1954. Jonas Salk – najveći klinički pokus ikada

1.800000 djece cijepio inaktiviranom vakcinom

zaštita >50 posto (licenca)

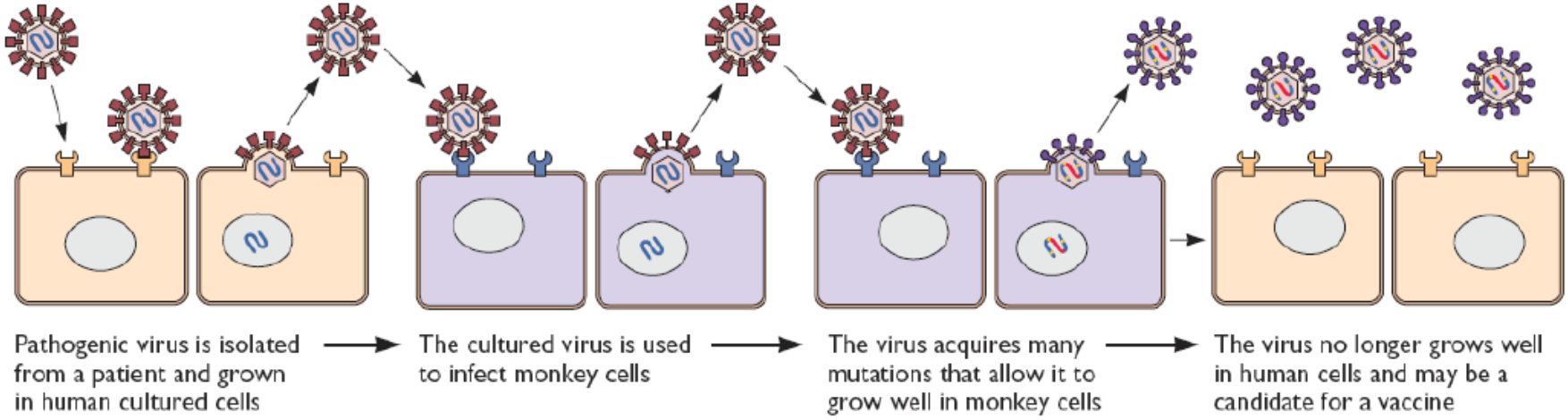
nedugo zatim – 260 oboljelih (propust u proizvodnji – Cutter Laboratories)

vakcinacija u mišić → krv

crijevni epitel nije imun → rasprostranjivanje virusa

VAKCINE SA "ŽIVIM" OSLABLJENIM VIRUSIMA

- **virus oslabljen laboratorijskom manipulacijom (npr. pasažiranje)**



- **selekcija replikativno sposobnih oslabljenih mutanata (blaga ili asimptomatska infekcija)**

- **primjeri atenuiranih vakcina:** **oslabljeni poliovirus (Sabinova oralna vakcina)**
  ospice
  mums
  rubela
  rotavirus…

VAKCINE SA "ŽIVIM" OSLABLJENIM VIRUSIMA

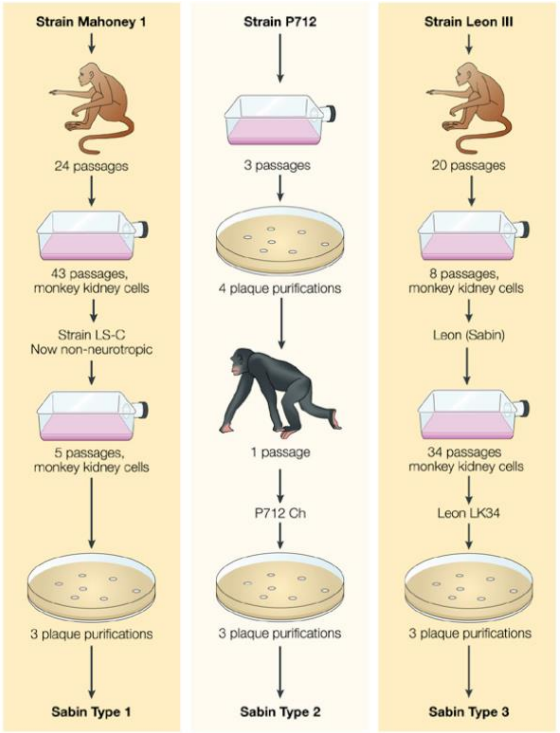
- **FluMist** (nazalna vakcina protiv gripe) – mutante dobivene pasažiranjem u uvjetima snižene temperature (niža od fiziološke) → replikacija samo u gornjem dišnom sustavu

- **Sabinova vakcina** - "živa" oslabljena vakcina protiv poliomijelitisa (1961. OPV)

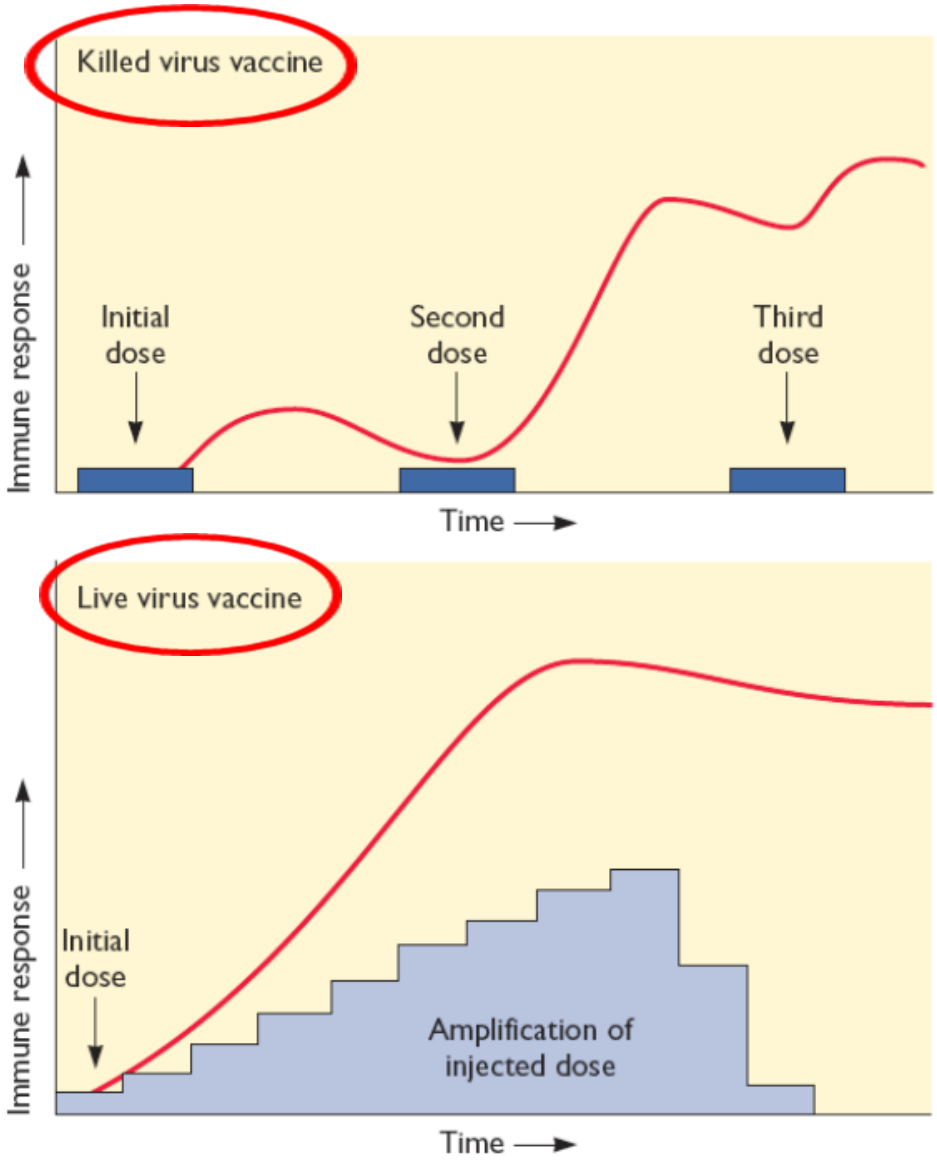
  kombinacija 3 oslabljena soja

  dobivena empirijski, mali broj mutacija

Virus	Mutation (location/nucleotide position)
P1/Sabin	5'-UTR nt 480 VP1 aa 1106 VP1 aa 1134 VP3 aa 3225 VP4 aa 4065
P2/Sabin	5'-UTR nt 481 VP1 aa 1143
P3/Sabin	5'-UTR nt 472 VP3 aa 3091



Usporedba imunosnog odgovora na vakcine s inaktiviranim i oslabljenim virusima



VAKCINE SA "ŽIVIM" OSLABLJENIM VIRUSIMA

ZA

- potiču jak i dugotrajan imunosni odgovor (humoralnu i staničnu imunost)

PROTIV

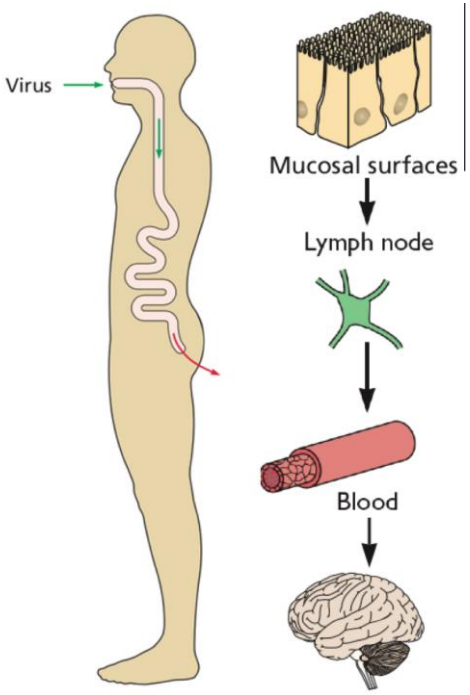
-mogućnost reverznih mutacija (osobito RNA-virusi) →
infekcija nevakciniranih pojedinaca

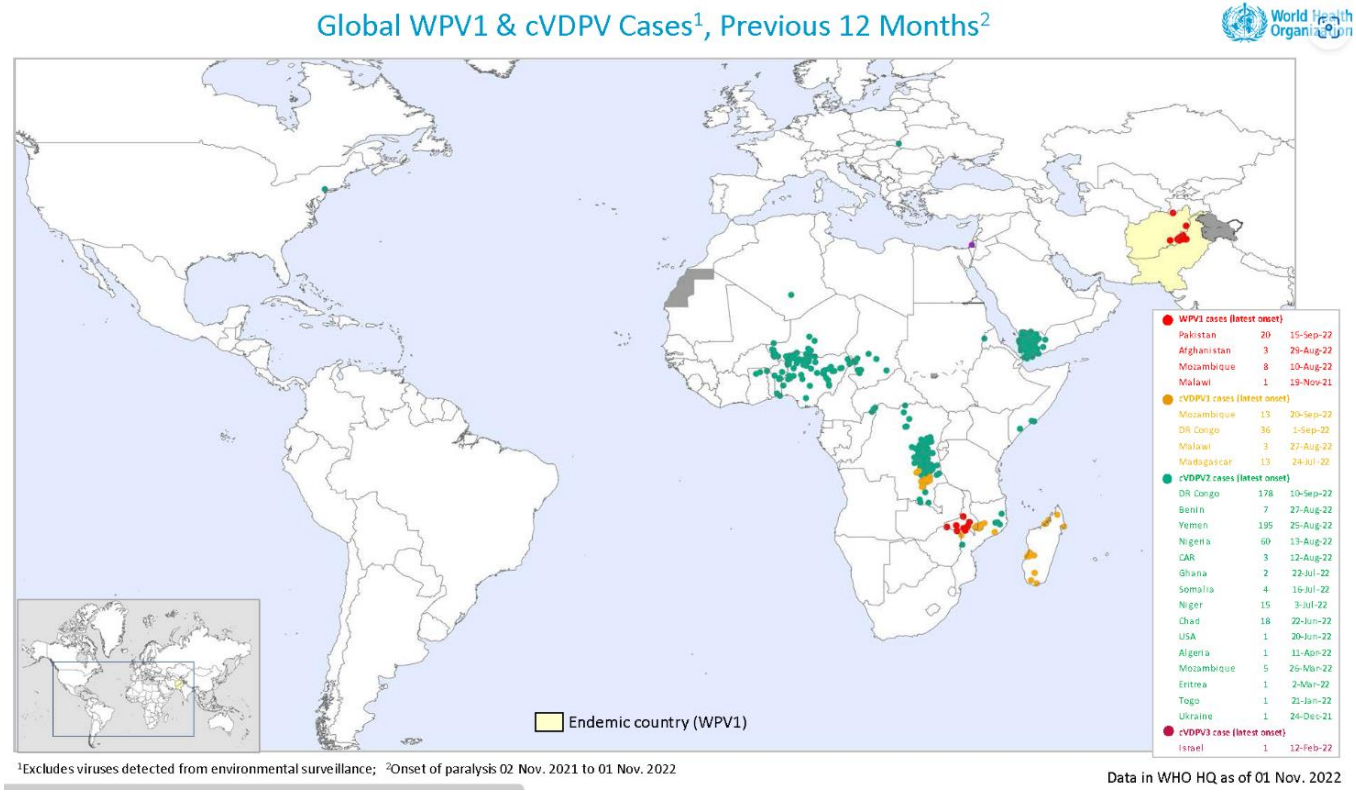
-imunosuprimirani pacijenti?

Budućnost u rekombinantnim vakcinama!

SABINOVA VAKCINA

- **“živa”atenuirana vakcina (Sabin) → reverzija u neurovirulentni soj identičan divljem soju**
- **cjepni sojevi cirkuliraju u populaciji → pojava bolesti u nevakciniranih pojedinaca (2017. epidemije u Siriji i Kongu)**



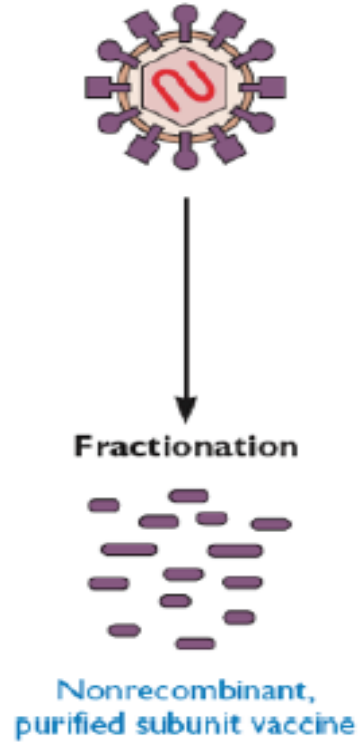


http://polioeradication.org/polio-today/

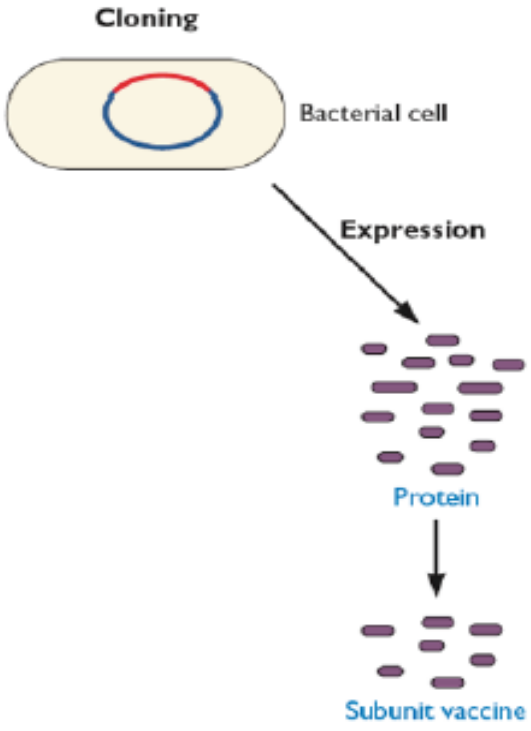
Vakcinacija protiv vakcine? IPV vs OPV?

VAKCINE S VIRUSNIM PODJEDINICAMA

2 pristupa:



nerekombinantne



rekombinantne

fragmentiranje virusa → imunizacija pročišćenim komponentama

antigen najčešće komponenta kapsidnog ili membranskog proteina

VAKCINE S VIRUSNIM PODJEDINICAMA

ZA

- **ne sadrže virusne genome (sigurne)**
- **nema “kontaminacije” stranim proteinima**

PROTIV

- **skupa proizvodnja**
- **slab imunosni odgovor – nema replikacije (potrebni adjuvansi)**
- **ne stimuliraju staničnu imunost**
- **apliciraju se injekcijski**

ADJUVANSI

- **imunogeničnost inaktiviranih i podjediničnih vakcina često se pojačava dodatkom supstanci koje stimuliraju upalnu reakciju (ADJUVANSI)**

- **stimuliraju rane procese imunosnog prepoznavanja i upalnu reakciju**

- **minimalno tri načina djelovanja:**
  prezentacija antigena kao čestice
  lokalizacija antigena na mjesto inokulacije (sporije otpuštanje)
  direktna stimulacija imunosnog odgovora

Različit sastav: **mrtve mikobakterije (ligandi receptora TLR)**
mineralna ulja
aluminijevi spojevi (bolji ulazak u APC-stanice)

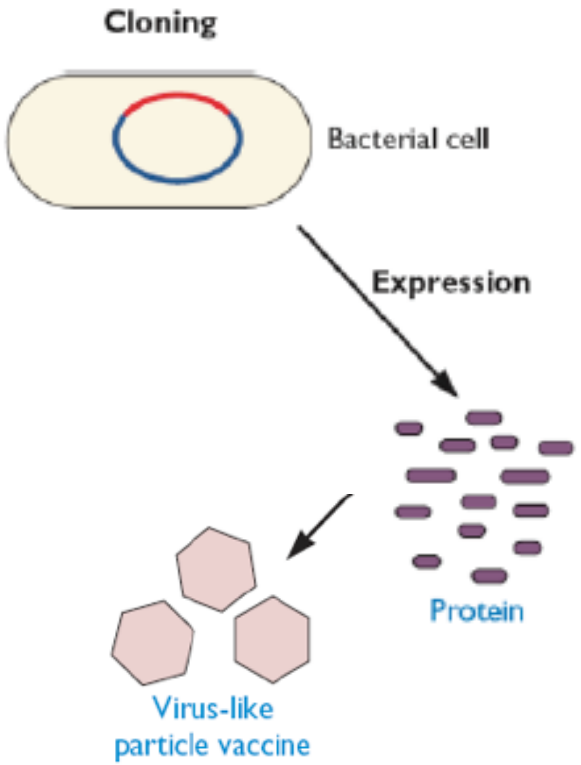
Moderni adjuvansi omogućuju prezentaciju egzogenih proteina u sklopu MHC I

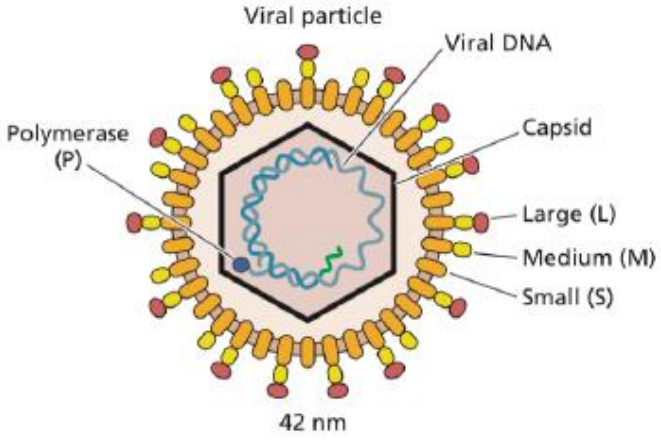
VIRUS-LIKE PARTICLES

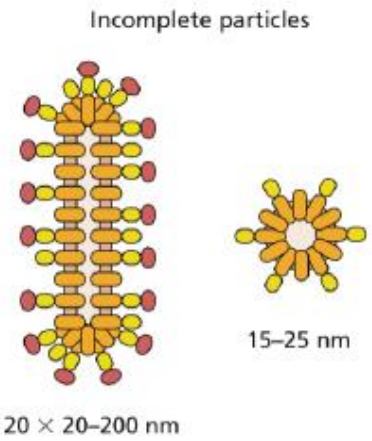
- **ponekad izolirani virusni proteini spontano formiraju prazne kapside →**
  izvorna prostorna struktura epitopa

Primjeri vakcina:

- **hepatitis B (u kvascu)**
  monomerni protein nije imunogeničan!







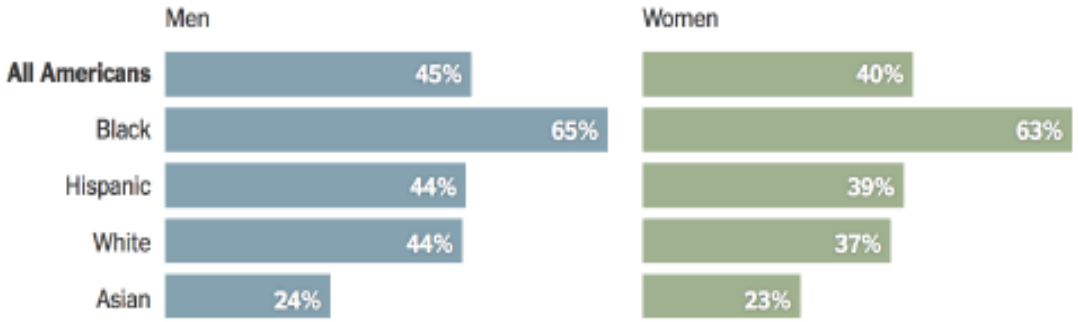
humani papiloma virusi

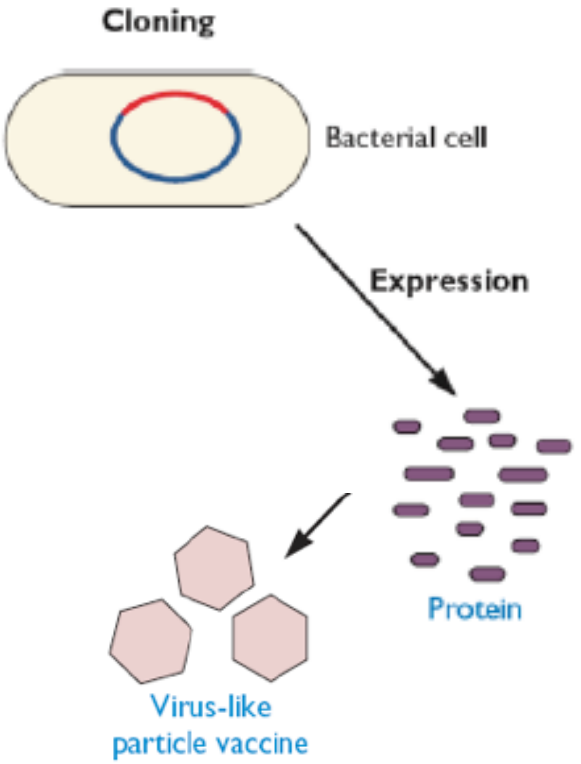
serotipovi 16,18 – visok rizika za razvoj karcinoma (cerviks, vagina, penis, anus)

Dostupno više vakcina:

u kvascu - Merck

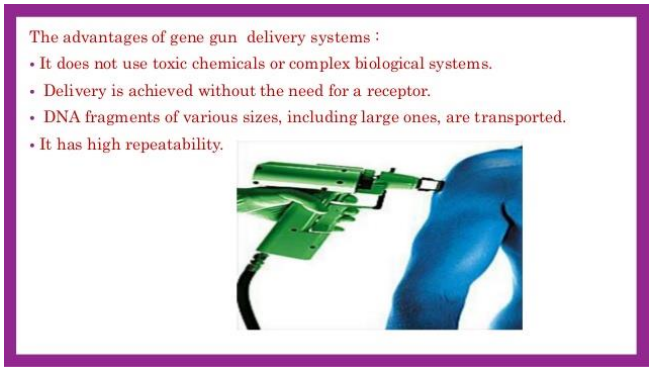
u kukcima - GlaxoSmithKline





DNA-vakcina = DNA-plazmid koji kodira virusne proteine

ekspresija virusnih gena unutar stanice → imunizacija



- **inokulacija injekcijski u mišić ili kožu**
- **“gene gun” pristup – direktno u stanice kože**

- **u stanicana sinteza proteina *de novo (*MHC I prezentacija)**
- **plazmid se ne replicira u vakciniranoj osobi**

ZA

-nisu potrebni adjuvansi

-ne unosi se čitav virusni genetički materijal

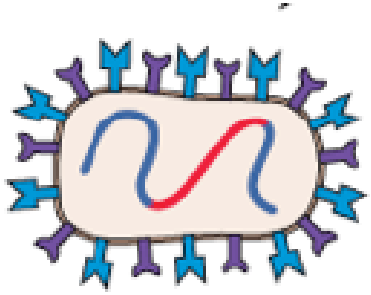
PROTIV

-eventualna integracija plazmida u genom (mutageneza, autoimuni odgovor)

VIRUSNI VEKTORI

Kloniranje gena patogenih virusa u genome nepatogenih virusa

hibridni virusi



Live virus
vector vaccine

npr. oralna vakcina protiv bjesnoće
korištena za divlje životinje
ili
virus vezikularnog stomatitisa + HIV

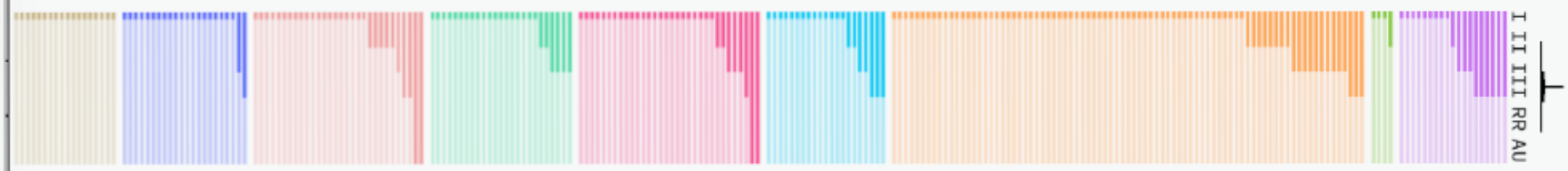
ZA

potiču jak i dugotrajan imunosni odgovor (humoralnu i staničnu imunost)

PROTIV

potencijal razvoja infekcije, imunizacija protiv vektora!

SARS-CoV-2 virus vaccines



251 vaccines in development, 61 in clinical testing, 11 in use

Leading Vaccines

BioNTech/Pfizer	Authorized
Moderna	Authorized
Oxford/AstraZeneca	Authorized
Janssen Pharma	Authorized
Sinovac/Instituto Butantan	Phase III
Wuhan Inst./Sinopharm	Phase III
Beijing Inst./Sinopharm	Phase III
Gamaleya Research Inst.	Phase III
CanSino Biologics	Phase III
Novavax	Phase III

VACCINE CATEGORIES

- Inactivated Virus
- Live Attenuated Virus
- Protein Subunit
- DNA-Based
- RNA-Based
- Replicating Viral Vector
- Non-Replicating Viral Vector
- Virus-Like Particle
- Other Vaccines

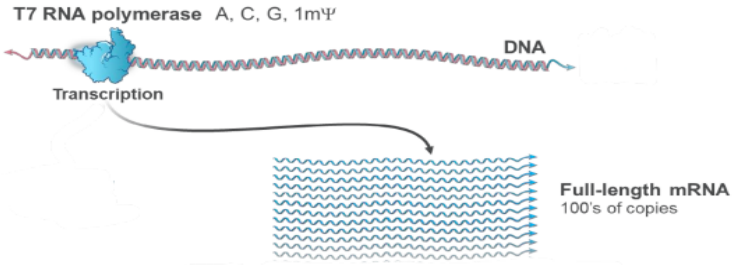
PHASES

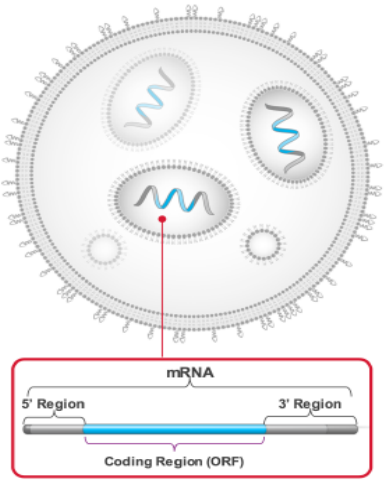
I	Phase One
II	Phase Two
III	Phase Three
RR	Regulatory Review
AU	Authorized

Data as of 3/24/21

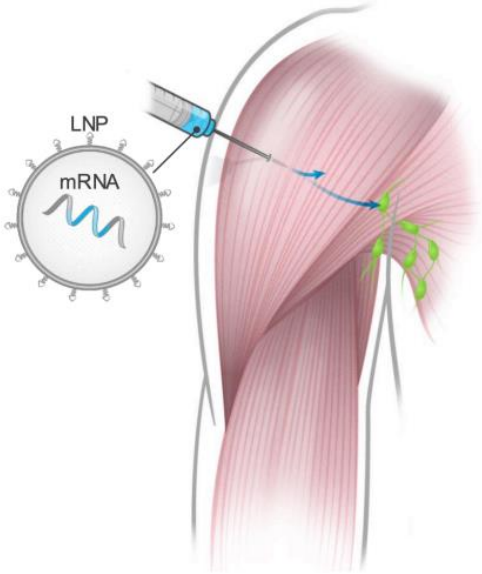
Moderna mRNA-1273

mRNA VAKCINE

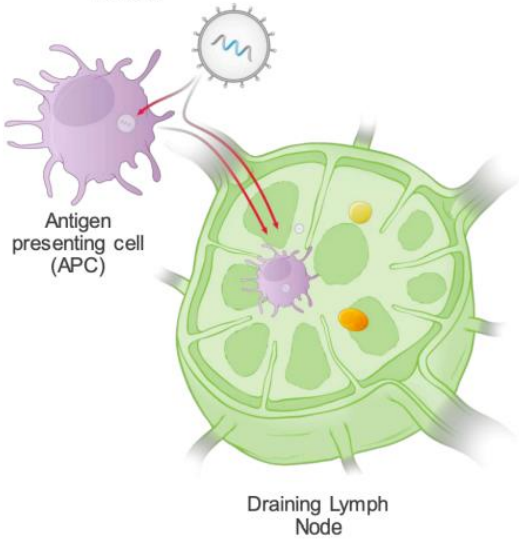




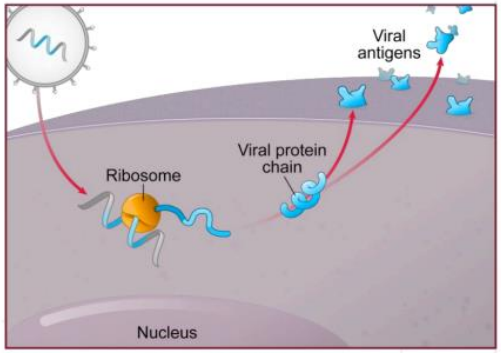
1 Recruitment of immune cells to the site of administration



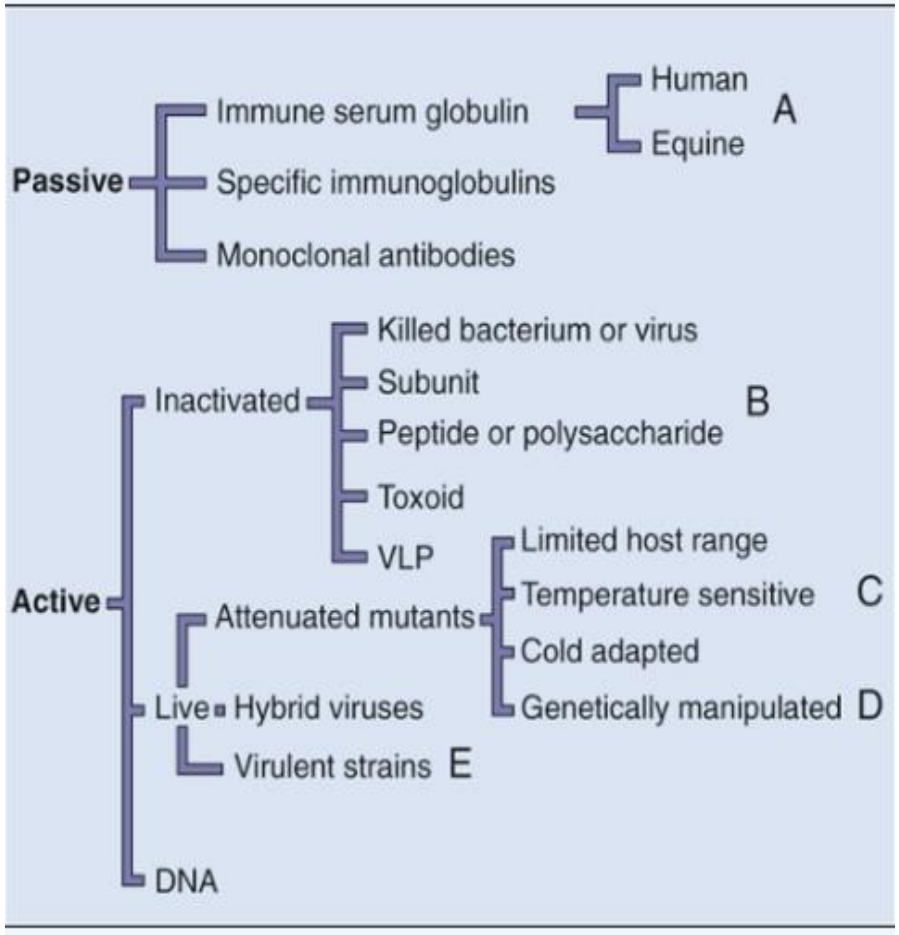
2 Migration of LNPs and APC to the draining lymph node



3 LNP uptake and antigen expression in cells at the injection site and in draining lymph nodes



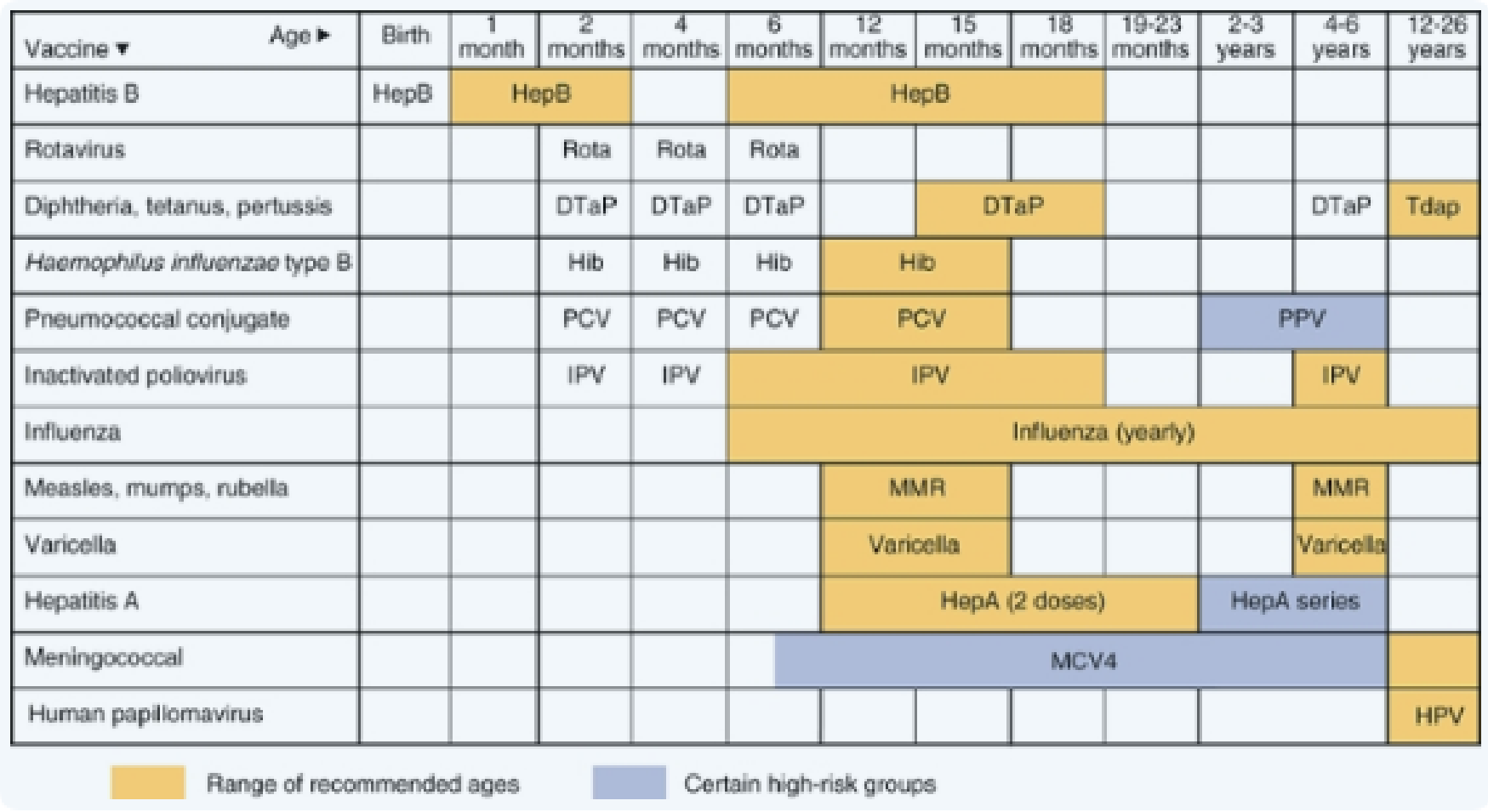
Antigen presenting cell (APC)



Types of immunizations. Antibodies (passive immunization) can be provided to block the action of an infectious agent, or an immune response can be elicited (active immunization) by natural infection or vaccination. The different forms of passive and active immunization are indicated. A, Equine antibodies can be used if human antibody is not available. B, Vaccine can consist of components purified from the infectious agent or can be developed through genetic engineering (virus-like particle [VLP]). C, Vaccine selected by passage at low or high temperature in animals, embryonated eggs, or tissue culture cells. D, Deletion, insertion, reassortment, and other laboratory-derived mutants. E, Vaccine composed of a virus from a different species that has a common antigen with the human virus.

TABLE 11-8 Bacterial Vaccines*†

Bacteria (Disease)	Vaccine Components	Who Should Receive Vaccinations
Corynebacterium diphtheriae (diphtheria)	Toxoid	Children and adults
Clostridium tetani (tetanus)	Toxoid	Children and adults
Bordetella pertussis (pertussis)	Acellular	Children and teens
Haemophilus influenzae B (Hib)	Capsule polysaccharide-protein conjugate	Children
Neisseria meningitidis A, C, Y, W135 (meningococcal disease) *N. meningitidis* B (protein vaccine)	Capsule polysaccharide-protein conjugate, capsule polysaccharide	People at high risk (e.g., those with asplenia), travelers to epidemic areas (e.g., military personnel), children
Streptococcus pneumoniae (pneumococcal disease; meningitis)	Capsule polysaccharides; capsule polysaccharide-protein conjugate	Children, people at high risk (e.g., those with asplenia), the elderly
Vibrio cholerae (cholera)	Killed cell	Travelers at risk to exposure
Salmonella typhi (typhoid)	Killed cell; polysaccharide	Travelers at risk to exposure, household contacts, sewage workers
Bacillus anthracis (anthrax)	Killed cell	Handlers of imported fur, military personnel
Yersinia pestis (plague)	Killed cell	Veterinarians, animal handlers
Francisella tularensis (tularemia)	Live attenuated	Animal handlers in endemic areas
Coxiella burnetii (Q fever)	Inactivated	Sheep handlers, laboratory personnel working with *C. burnetii*
Mycobacterium tuberculosis (tuberculosis)	Live attenuated bacillus Calmette-Guérin *Mycobacterium bovis*	Not recommended in United States



Recommended childhood immunization schedule from the Centers for Disease Control and Prevention. Vaccines are listed at the ages routinely recommended for their administration. Bars indicate the range of acceptable ages for vaccination. DTaP, Diphtheria, tetanus, and acellular pertussis; HepA, hepatitis A; HepB, hepatitis B; Hib, Haemophilus influenzae type B; IPV, inactivated poliovirus; MCV4, quadrivalent conjugated meningococcal; MMR, measles, mumps, rubella; PCV, pneumococcal conjugate; PPV, pneumococcal polysaccharide; Rota, rotavirus.


ASK
QUESTIONS