Recent & Ongoing Advances in Vaccine Development

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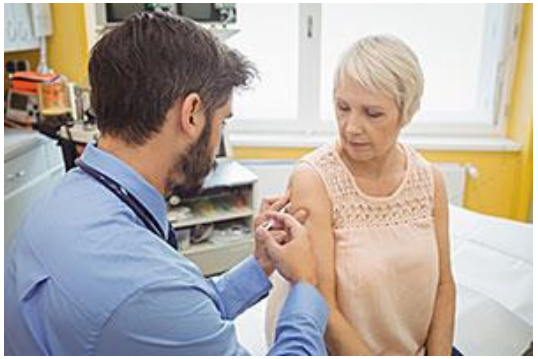
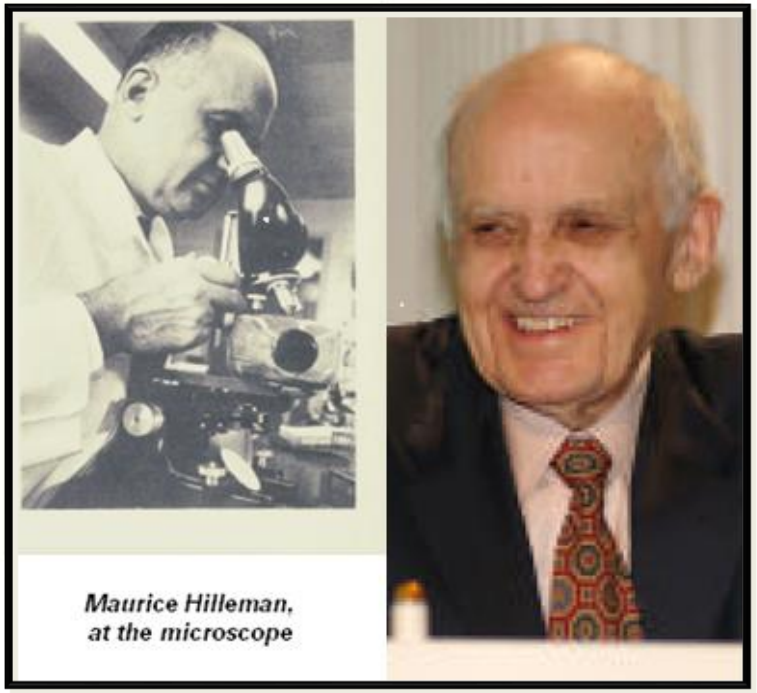


In honor and memory of the 100th anniversary of Dr. Hilleman's birth

- "Saved more lives than any other modern scientist"
  - Paul Offit, Children's Hospital of Philadelphia
- Developed more vaccines (27 licensed vaccines) than any other person



Overview

- The impact of vaccination on the health of people worldwide
- Opportunities/challenges for the vaccines of tomorrow
- How do vaccines mediate protection?
- Examples describing the design of new vaccines against the following diseases:
  - Herpes zoster
  - Influenza
  - Dengue
  - Ebola
- New technologies for vaccine delivery/administration
- Summary & questions

"The impact of vaccination on the health of the world's peoples is hard to exaggerate. With the exception of safe water, no other modality has had such a major effect on mortality reduction and population growth."

Susan and Stanley Plotkin, A Short History of Vaccination, in *Vaccines* 1st Edition, 1988

Vaccines provide the most cost-effective means to save lives, preserve good health, and maintain a high quality of life.

Nabel GJ. NEJM 2013

Increase in Life Expectancy

Vaccines of the 20th century

⇩

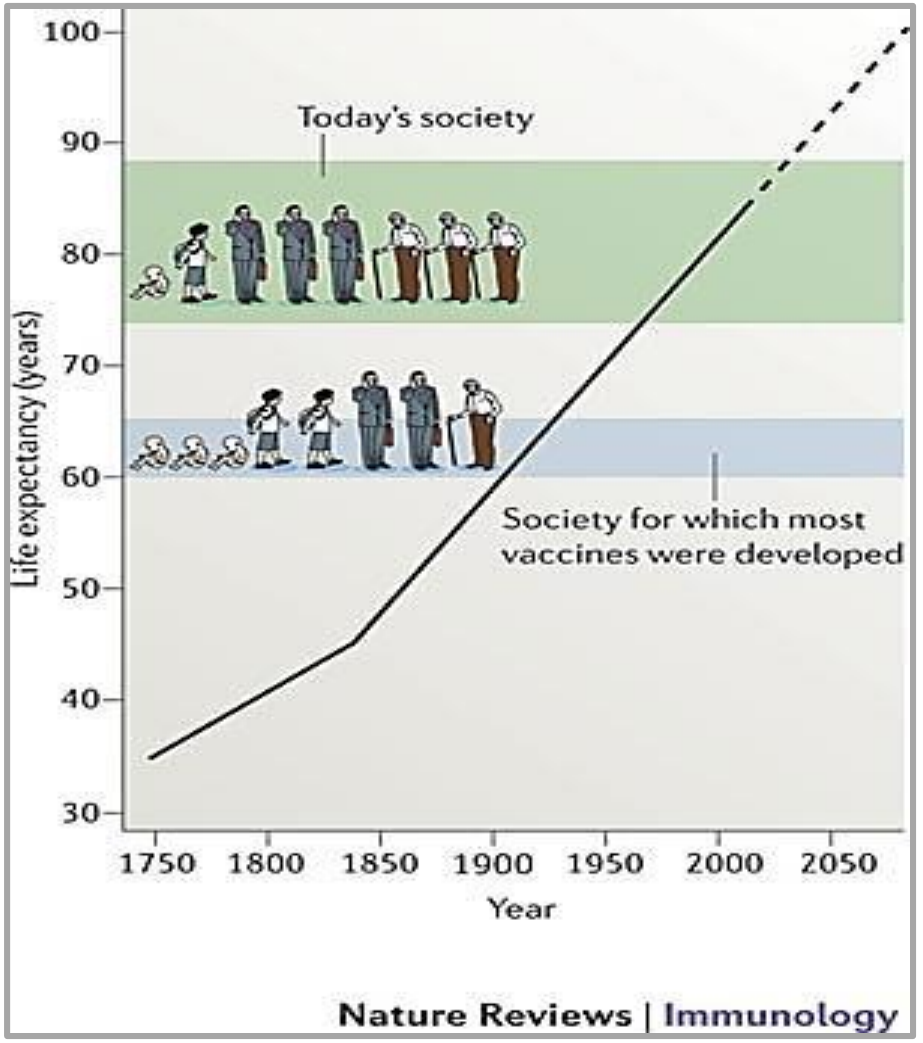
Eliminated many infectious diseases

⇩

Decreased early mortality

⇩

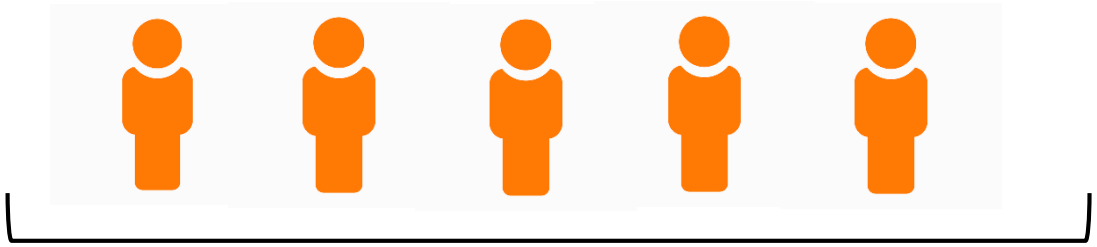
Increased life span in adults



Rappuoli R et al. Nat. Rev. Immunol 2011;11:865-872

Vaccines: An achievement of civilization, a human right, our health insurance for the future
J. Exp. Med 2018; 16 (1):7-9

- About 25 million deaths will be prevented through vaccination over a 10-year period (eg, 2010-2020)
  - This is equivalent to :



5 lives saved/minute

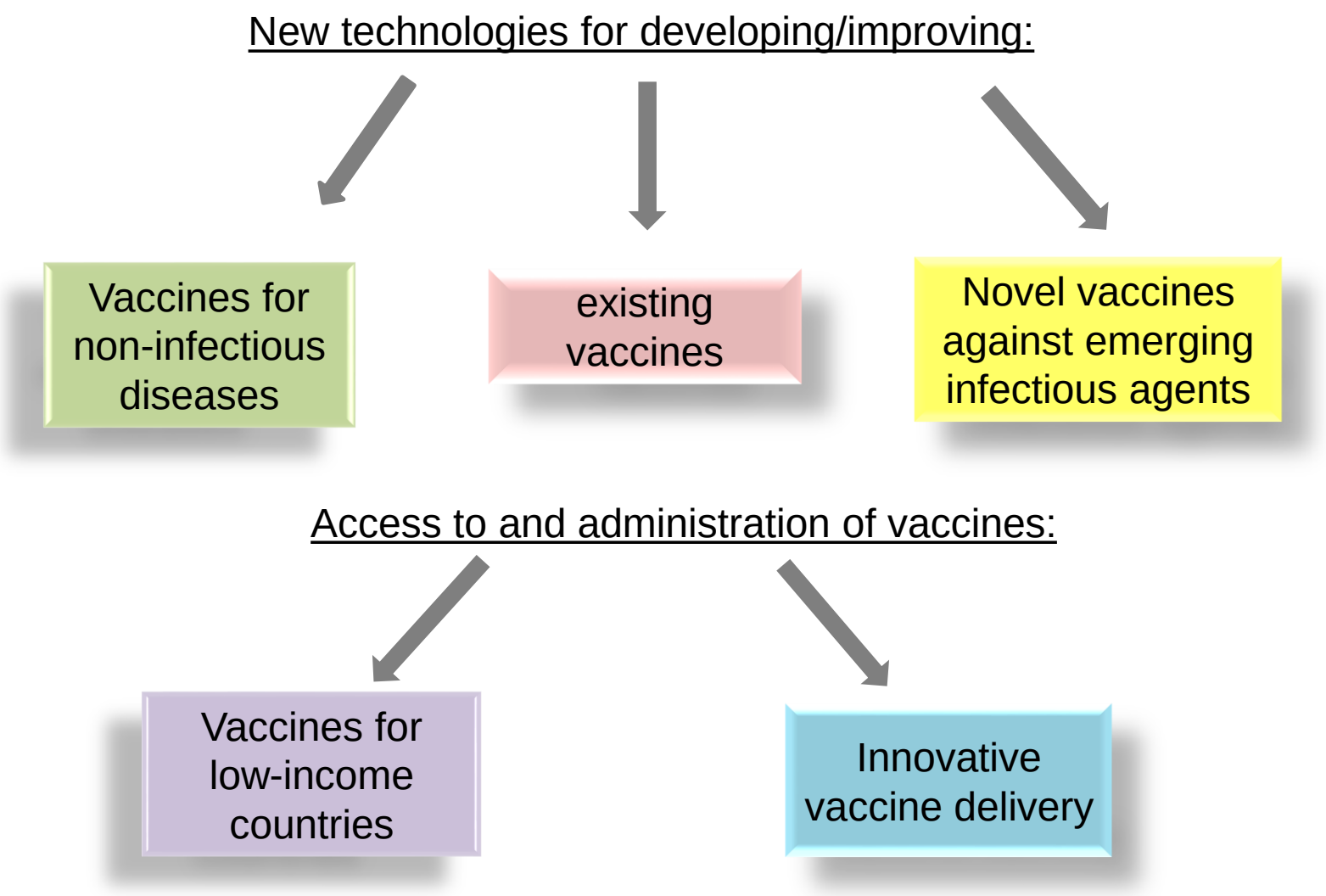
- WHO estimates that vaccinations for diphtheria, tetanus, whooping cough and measles currently prevent 2-3 million deaths/year

- Estimated that $1 invested in vaccination

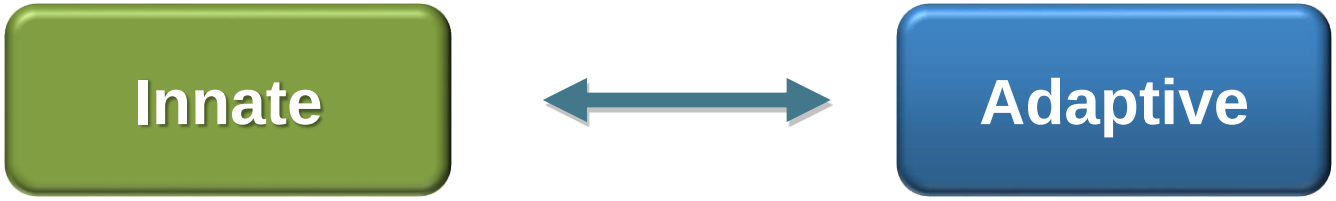
⇩

$10-44 healthcare saving

Despite the triumphs of conventional vaccines, a variety of opportunities/challenges remain for the vaccines of tomorrow



Components of the Host Immune Response

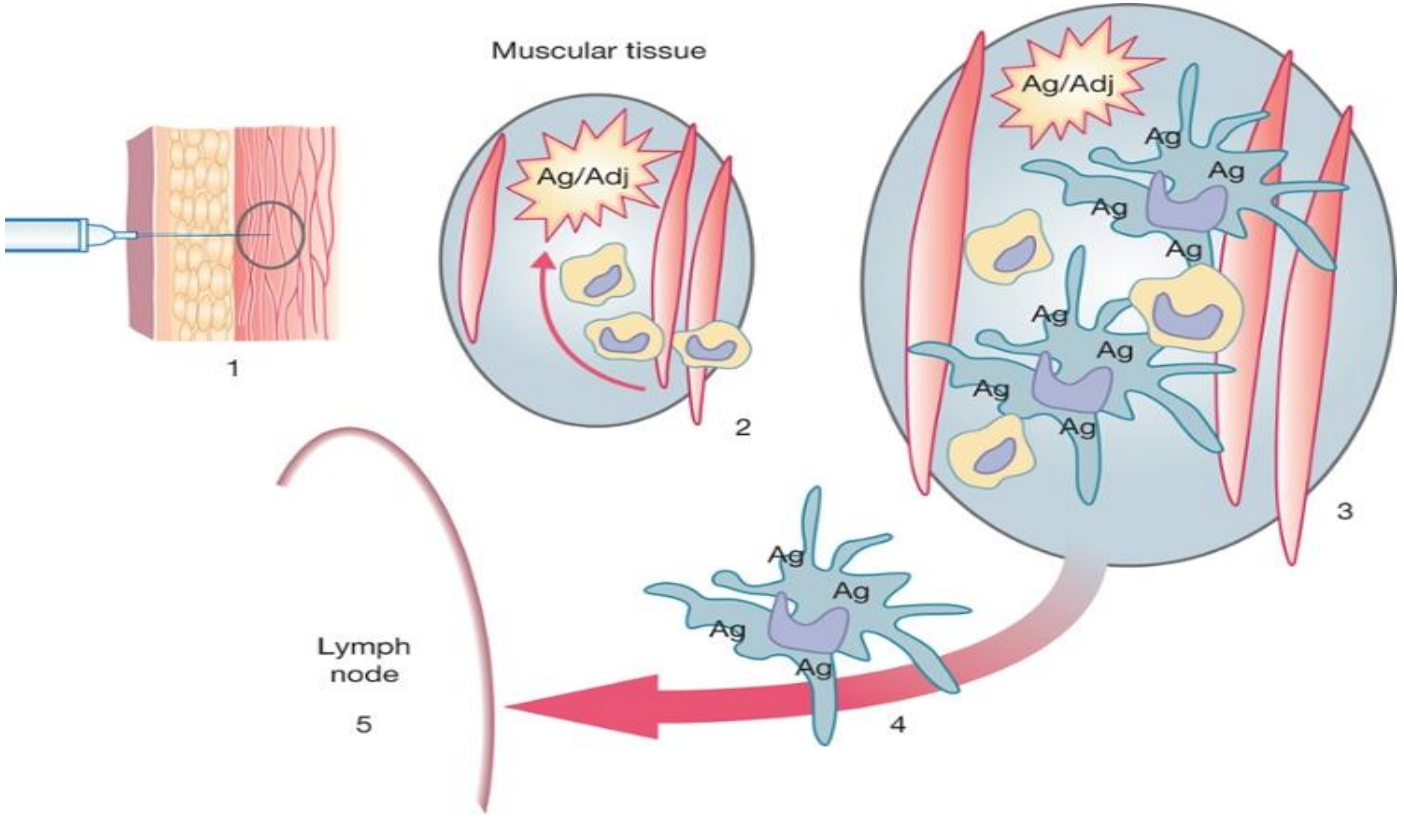


- Naturally present
- Not due to prior sensitization to an antigen (from infection or vaccination), it is NOT specific

- Develops when the body is exposed to various "danger signals" and mounts a defense that is **specific** to that "danger signal"
- Has **memory**

Initiation of the Immune Response to Vaccination

From innate to adaptive immunity activation



Vaccine Immunology in Plotkin's Vaccines 7th ed.; 2018:16-40

Vaccine-Induced Adaptive Immunity

Vaccine Immunology In: Plotkin's Vaccines 7th ed.; 2018:16-40

IMMUNE EFFECTORS

Cellular immunity

$CD8^+$ T lymphocytes

- Kill pathogen-infected cells through direct contact or cytokine production

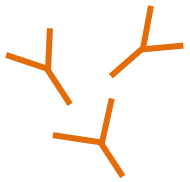
$CD4^+$

T-helper cells

Generation/maintenance of B and $CD8^+$ T-cell responses

Humoral immunity

B lymphocytes



Bind specifically to a toxin or pathogen

https://vaccinemakers.org/resources/videos-animations

New Vaccine Technologies

Conventional vaccines

- Killed or weakend pathogen
- Subunit
- Risk of reversion with live-attenuated
- Need to grow the pathogen in cell culture
- Aluminum (adjuvant)
- Mainly humoral immunity

New vaccine technologies

- Examples:
  - Novel adjuvants
  - Genomic vaccines
    - Viral vector-based

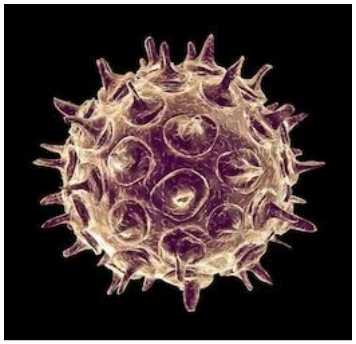
- Enhance the immune response
- Stimulate both humoral and cellular immunity
- Simpler, faster and less expensive manufacturing process than conventional vaccines

RS et al. Frontiers in Immunology; 2018 (9):1-24

https://www.scientificamerican.com/article/genomic-vaccines/, accessed November 24, 2019

Herpes Zoster (HZ) or Shingles

- Herpes Zoster (HZ) caused by reactivation of latent varicella zoster virus from a prior chickenpox infection
- HZ is a painful rash that develops on one side of the face or body
- About 50% of herpes zoster cases (HZ) in adults ≥60 years of age
- About 40% who get HZ feel a burning shooting pain for months or years after the rash is gone (PHN)
- Severity of illness and its complications increase with age

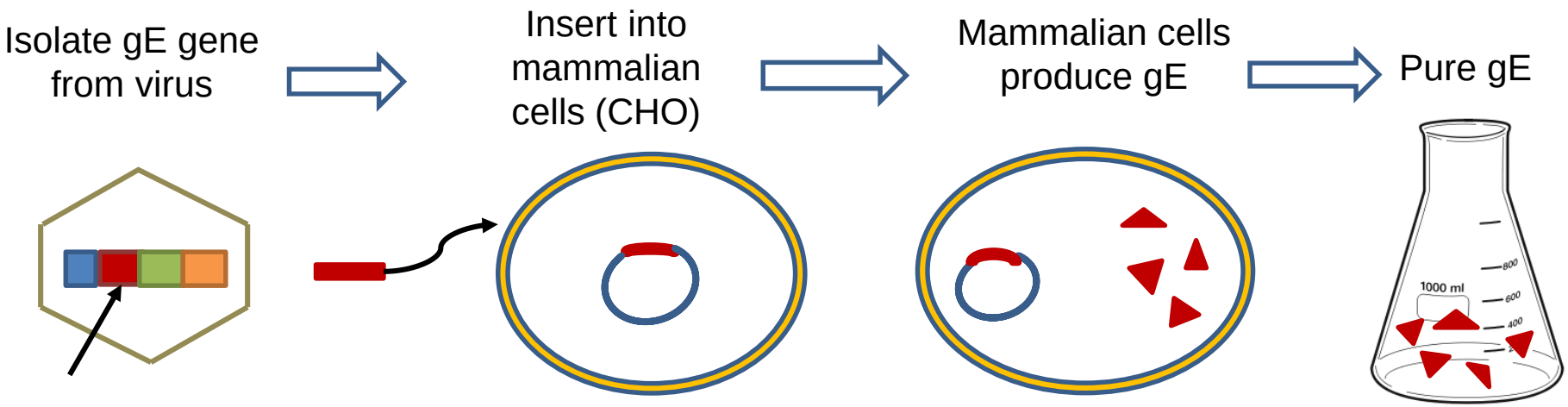


Varicella Zoster Virus

http://www.immunize.org/askexperts/experts_zos.asp, accessed December 2, 2019
https://www.webmd.com/skin-problems-and-treatments/shingles/ss/slideshow-shingles-myths-facts, accessed December 3, 2019

Overcoming an unmet medical need for a better zoster vaccine

- Recombinant zoster vaccine,(RZV) Shingrix, approved by FDA in 10/17
- RZV: recombinant glycoprotein E + novel adjuvant ($AS01_B$)



Cunningham AL et al. JID 2018;217:1750-1760
https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Shingrix/pdf/SHINGRIX.PDF, accessed December 3, 2019

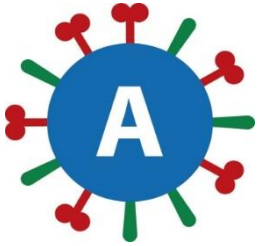
Zoster Vaccine Live (ZVL) vs Recombinant Zoster Vaccine (RZV)

ZVL	RZV
Live-attenuated	Subunit, recombinant
Licensed in 2006	Licensed in 2017
• FDA-approved for ≥50 years • ACIP-recommended for ≥60 years	• FDA-approved for ≥50 years • ACIP-recommended for immunocompetent ≥50 years
Single SC dose	2-doses by IM

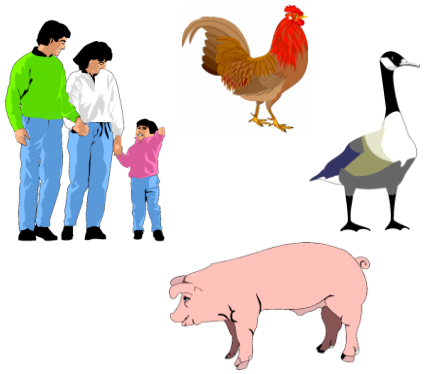
Efficacy against shingles:
• Overall: 51%
  • 70% in 50-59 years
  • 64% in 60-69 years
  • 38%in ≥70 years
• By 6 years postvaccination protection <35%
	Efficacy against shingles:
	  • 97% in 50-59 years
	  • 97% in 60-69 years
	  • 91% in ≥70 years
	• Four years postvaccination efficacy was 85% in ≥70 years

http://www.immunize.org/askexperts/experts_zos.asp, accessed December 18, 2019

Types of Seasonal Influenza Viruses



Widespread in nature; found in birds and mammals

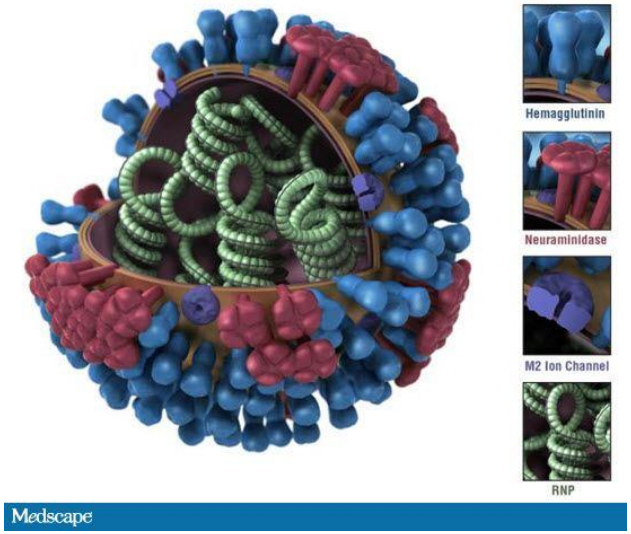


Found mainly in humans

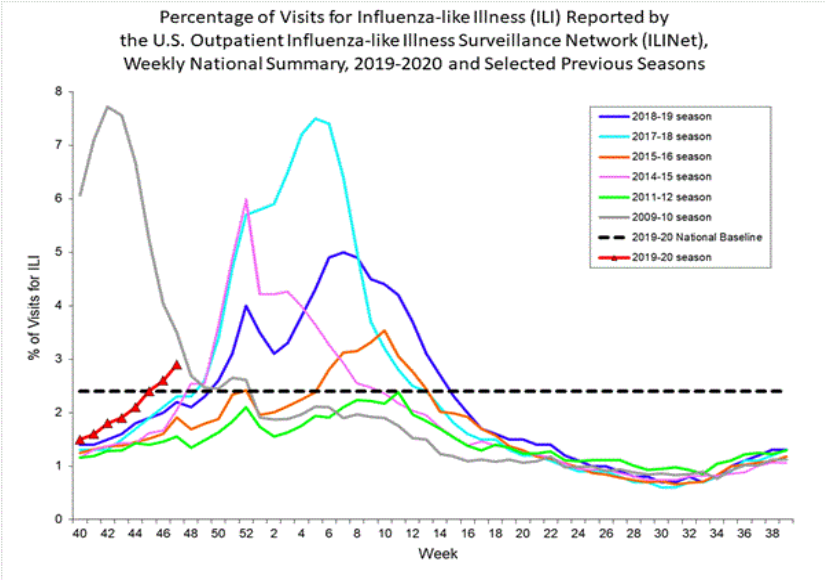
Only found in humans

Type A viruses are further classified into subtypes (eg, H1N1 and H3N2)

A challenging 2017-2018 flu season



Influenza A virion
Photo credit: Public Health Institute Library



https://www.cdc.gov/flu/weekly/index.htm#OISmap, accessed December 5, 2019

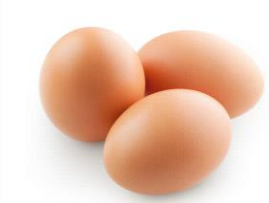
2017-2018 Influenza Vaccine Effectiveness (VE) for All Ages

- Overall VE against influenza A and B viruses: 38% (95%CI: 31%-43%)
- Most infections caused by A(H3N2) viruses
- VE against infections caused by:
  - A(H3N2): 22% (95%CI:12%-31%)
  - A(H1N1): 62% (95%CI:50%-71%)
  - B/ Yamagata: 48% (95%CI:39%-55%)
  - B/Victoria: 76% (95% CI:45%-89%)

https://www.cdc.gov/flu/vaccines-work/2017-2018.html, accessed December 5, 2019

Improving the performance of influenza vaccines

Egg-based production



- Growing flu viruses in eggs triggers mutations, especially in H3N2 viruses
- Slow manufacturing time
- Poor response in certain populations

Cell-based flu vaccine

- Candidate vaccine viruses grown in mammalian cells
- Faster start-up of the manufacturing process

Recombinant flu vaccine

Isolate HA gene from CVV

↓

Combine with a portion of the genetic material of another virus

↓

Grow "recombinant" vaccine virus in insect cells

Adjuvanted egg-based approach

- MF59 adjuvant (≥65 yrs)

- ➢ Shorter manufacturing
- ➢ Consistent efficacy
- ➢ Strong response in all vaccinees

https://www.cdc.gov/flu/about/qa/advances.htm, accessed July 21, 2018
Vaccines (Basel). 2018 Mar 30;6(2). pii: E19. doi: 10.3390/vaccines6020019.

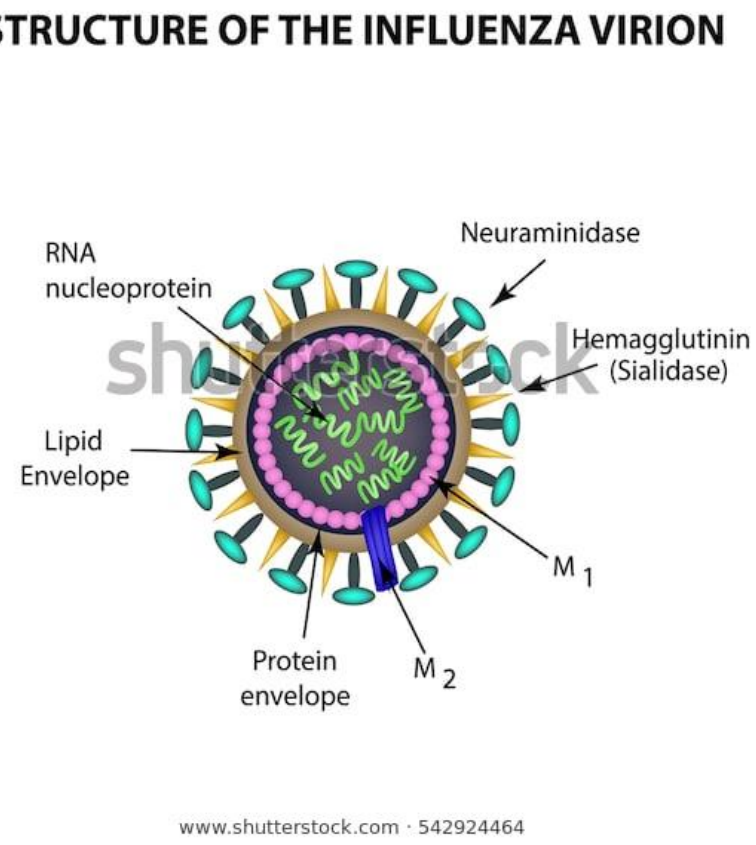
What is the long-term goal to improve flu vaccines?

- A single vaccine that would provide safe, effective and long-lasting immunity against a broad spectrum of influenza viruses, both seasonal and novel.
- A vaccine with these qualities is referred to as a “universal flu vaccine”
- Government agencies and private companies are working on the development of a universal flu vaccine

https://www.cdc.gov/flu/about/qa/advances.htm, accessed July 21, 2018

Target Antigens for a “Universal Flu Vaccine”

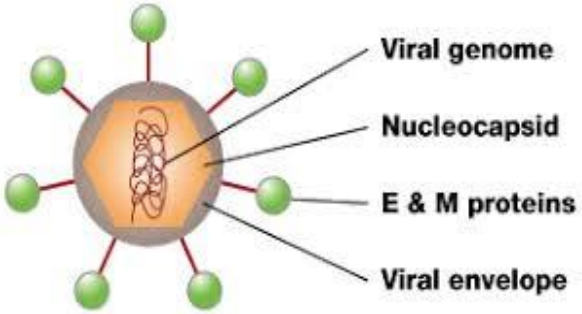
- Candidate vaccines are based on conserved viral proteins
- Examples include: hemagglutinin stem, nucleoprotein, and matrix (M1 and M2)



Dengue-Disease & Epidemiology

- Caused by four antigenically distinct viruses: Dengue 1 through 4 which spread through the bite of an infected mosquito
- >390 million infections globally each year; of those >95 million are clinically apparent
- Dengue is common in >100 countries worldwide; ~ 3 billion live in areas with a risk of dengue
- Endemic in the US territories of American Samoa, Guam, Puerto Rico and the US Virgin Islands

Aedes aegypti mosquito



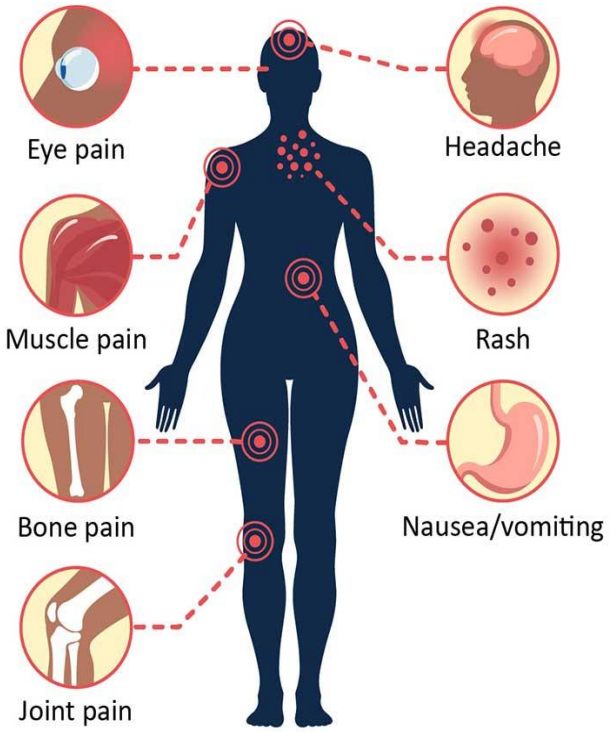
Dengue virus structure

Source: 2011 Nature Education

https://www.cdc.gov/dengue/about/index.html, accessed November 13, 2019
Thomas SJ. Human Vaccines & Immunotherapeutics 2019; 15(10):2295-2314

Dengue- Symptoms

- About 1 in 4 who get infected will get sick
- Symptoms can be mild or severe
- Severe dengue can be life-threatening (more likely following a previous infection)
- Most common symptom is fever with any of the following:
  - Nausea, vomiting
  - Rash
  - Aches and pains
- Duration of illness: 2-7 days



https://www.cdc.gov/dengue/symptoms/index.html, accessed November 13, 2019

Dengue-Vaccine

- The Immune response to Dengue viruses
  - Infection with one type affords long-term protection against the same type
  - Subsequent infection by any of the other 3 types increases the risk for developing severe disease

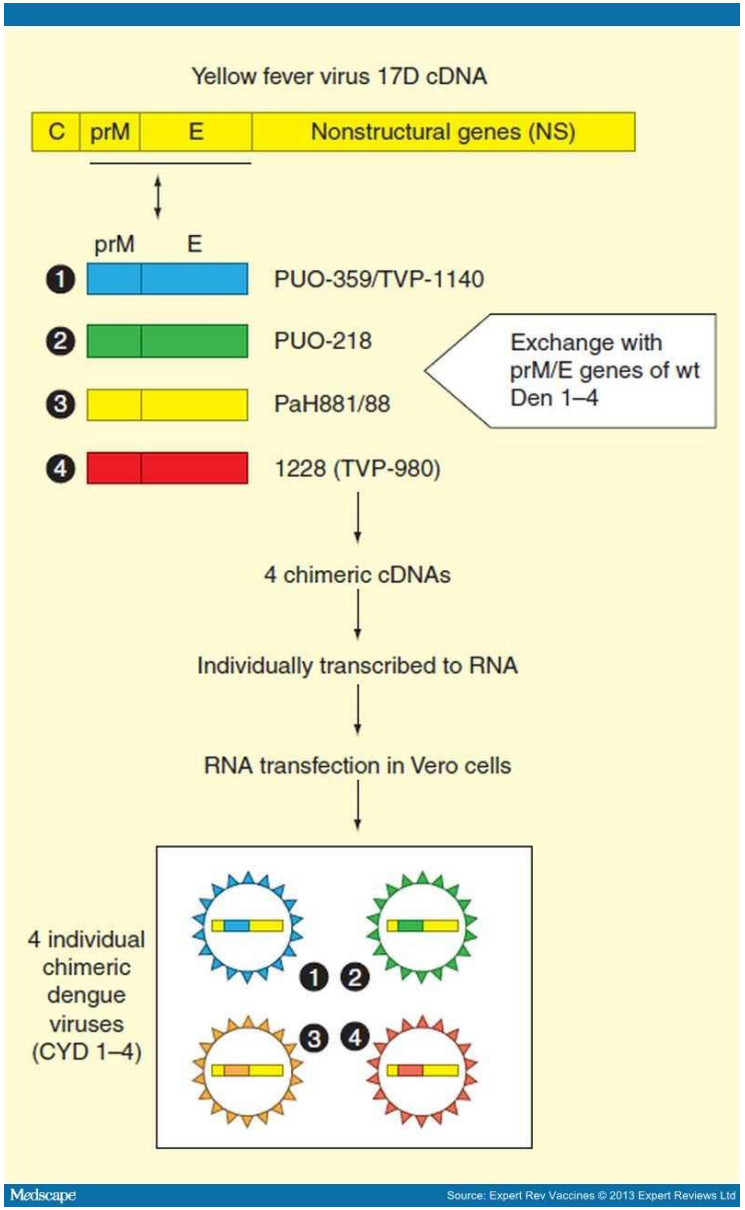
- The only licensed Dengue vaccine is Dengvaxia®,
  - Registered in 20 dengue endemic countries
  - Approved by the European Union and FDA

- Indications:
  - Dengvaxia is a vaccine indicated for the prevention of dengue disease caused by dengue virus serotypes 1,2,3 and 4. Dengvaxia is approved for use in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

https://www.fda.gov/news-events/press-announcements/first-fda-approved-vaccine-prevention-dengue-disease-endemic-regions, accessed November 14, 2019
Thomas SJ. Human Vaccines & Immunotherapeutics 2019; 15(10):2295-2314

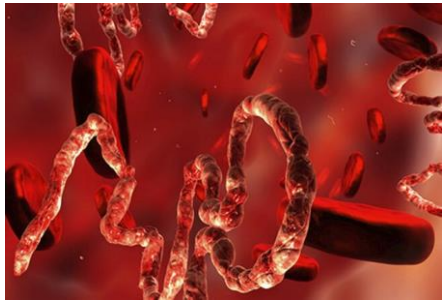
How is Dengvaxia® (chimeric yellow fever dengue-CYD) made?

- Construction of a live-attenuated tetravalent vaccine
  - prM and E genes from each of the 4 dengue virus serotypes replace the corresponding yellow fever virus (YFV) 17D genes in the live attenuated YFV17D vaccine strain
  - Four chimeric dengue viruses are produced. The envelope contains the immunizing Ag from each dengue serotype; replication machinery is from YFV17D



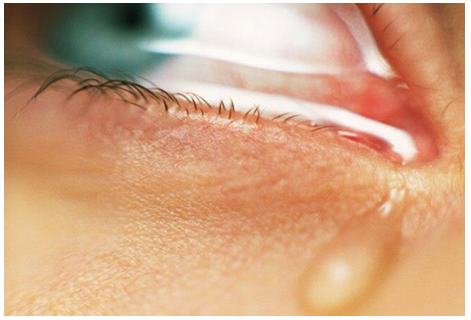
Ebola

(The Virus, Transmission, Symptoms, Prevention)



A deadly viral disease (RNA virus). Five strains; 4 can make people sick.

Ebola outbreaks concentrated in West Africa.



Transmission through body fluids.

Initial symptoms: fever, fatigue, myalgia, headache, sore throat

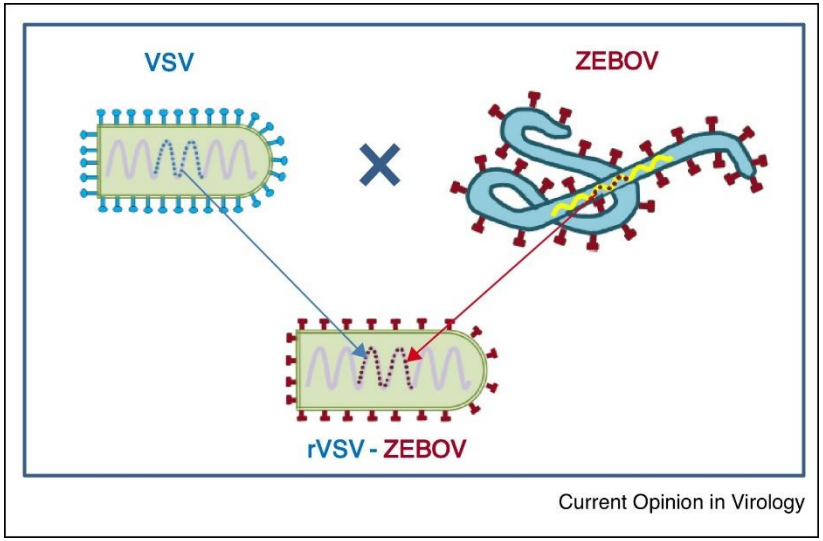
Strain-specific antibodies in survivors

Hand washing, avoid contact with infected people and certain wild animals.

https://www.webmd.com/a-to-z-guides/ebola-fever-virus-infection, accessed November 20, 2019

Ervebo- The First Approved Ebola Vaccine

- Two decades of research (virus discovered in 1976)
- A priority following the 2014-16 outbreak in West Africa
  - > 28,000 infected and > 11,000 died
- Initially engineered at Canada's National Microbiology Laboratory
  - Merck responsible for the research, development, manufacturing and regulatory efforts
- Approved in Europe, Nov. 2019
  - Active immunization of persons ≥18 yrs to protect against Ebola virus disease caused by Zaire Ebola virus
- Vesicular stomatitis virus (VSV)-based vector vaccine
- Consists of a live attenuated recombinant VSV
  - VSV envelope glycoprotein (GP) replaced with Zaire Ebolavirus surface

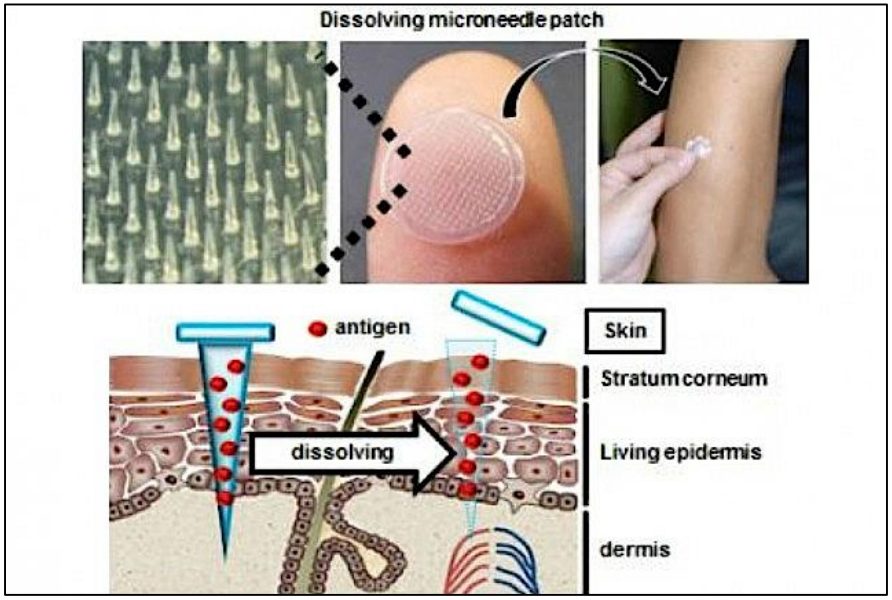


https://www.scientificamerican.com/article/ebola-vaccine-approved-in-europe-in-landmark-moment/, accessed November 25. 2019
https://www.mrknewsroom.com/news-release/ebola/mercks-ervebo-ebola-zaire-vaccine-rvsvdg-zebov-gp-live-granted-conditional-approv, accessed November 25, 2019
https://www.ema.europa.eu/en/medicines/human/summaries-opinion/ervebo, accessed November 25, 2019

New technologies for Vaccine Delivery/Administration

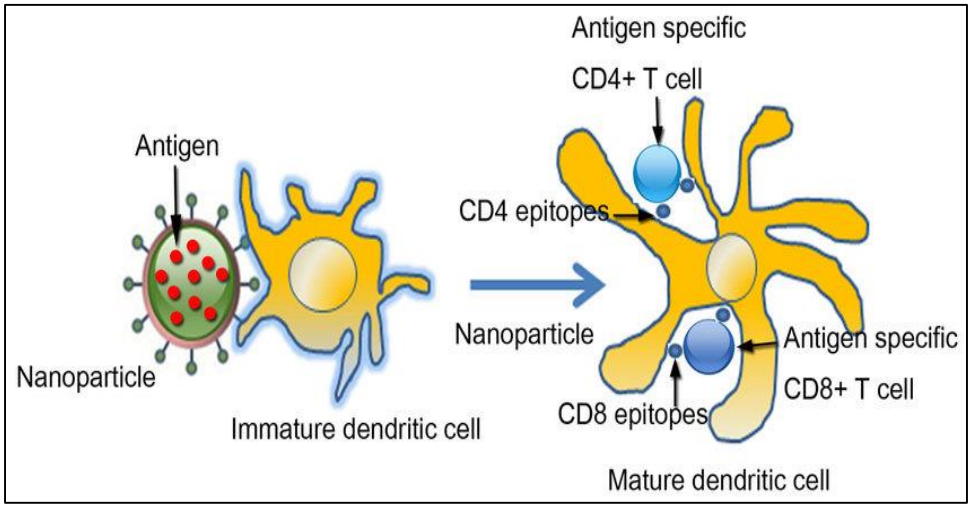
Microneedle Patch

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



Suh H et al. Clin Exp Vaccine Res. 2014

Nanoparticle-Based Vaccine Delivery



https://www.researchgate.net/figure/Application-of-nano-sized-delivery-systems-A-virus-like-nanoparticles-B-ligand_fig2_258337493

Summary

- To date, vaccination has significantly contributed to the health of people worldwide, by eliminating many infectious diseases, reducing mortality and increasing life expectancy.
- New technologies are necessary to design effective vaccines against emerging infectious agents, non-infectious diseases and improve existing vaccines.
- Shingrix, a recombinant zoster vaccine consisting of a novel adjuvant, has shown to afford >90% protection against zoster in persons ≥50 years of age.
- Recent advances in vaccines against influenza include a cell-based, recombinant and novel adjuvanted vaccines. Efforts are underway to develop a universal flu vaccine with a focus on conserved viral proteins across flu viruses.
- The design of the vaccines against Dengue fever and Ebola is based on the use of a live-attenuated recombinant virus as a vector of the gene expressing the “immunizing antigen” derived from the target pathogen.
- New technologies for vaccine delivery/administration include a microneedle patch and nanoparticles.

For your tireless work in promoting the health and well-being of your communities via immunizations !

QUESTIONS?