VACCINES (IMMUNOPROPHYLAXIS)

INSTRUCTOR: Laura Kasman, PhD, kasmanL@musc.edu

OBJECTIVES: After studying this unit you should be able to

1. Name the type of vaccine (toxoid, subunit, live-attenuated, etc.) for each of the 17 routine vaccinations performed in the U.S at this time.
2. List contraindications to vaccination with live attenuated vaccines.
3. Explain what an adjuvant is, what types of vaccines are most likely to need one, and what they consist of in the United States.
4. Contrast polysaccharide and polysaccharide-conjugate vaccines in terms of efficacy in different age groups.
5. Explain what herd immunity is, what types of pathogens it applies to, and why the threshold of immunity needed to achieve it may vary for the same pathogen in different situations.
6. Explain how mRNA-based vaccines are able to induce immunity.

LECTURE OUTLINE:

I. Important definitions
II. Types of immunization
III. Goal of immunization
IV. Definition of important terms
    1. Attenuation
    2. Herd Immunity and R_0
V. Adjuvants
    1. Purpose
    2. Types
        I. Aluminum hydroxide / Aluminum phosphate
        II. Certain lipid emulsions (AS01B, MF59)
        III. CpG 1018, an adjuvant based on synthetic DNA sequences
VI. Vaccine strategies for active immunization
    1. Live attenuated microorganisms
    2. Intact killed / inactivated microorganisms
    3. Toxoids (formalin inactivated toxins)

4. Purified subcellular fragments/ antigens conjugated to protein (conjugate vaccines)
5. Proteins expressed from recombinant DNA
6. Lipid Nanoparticle mRNA

VII. Routine vaccination schedules for U.S. and vaccines in current use

1. Hepatitis B
2. RSV (passive or active)
3. Rotavirus
4. Diphtheria
5. Tetanus
6. Pertussis
7. Poliovirus
8. *Haemophilus influenza B* (Hib)
9. *Streptococcus pneumoniae*
10. Influenza
11. Measles
12. Mumps
13. Rubella
14. Chickenpox (Varicella)
15. Hepatitis A
16. Human papillomavirus
17. *Neisseria meningitidis*

VIII. Biological obstacles to vaccination

1. Factors affecting individual vaccine response
2. Contraindications to vaccination
3. Risk-group recommendations
4. Pathogen-specific obstacles to vaccination

IX. Future directions

READING REFERENCES:

http://www.cdc.gov/vaccines/schedules/

http://www.cdc.gov/vaccinesafety/index.html

Immunoprophylaxis (Vaccination)

- Laura Kasman, PhD
- kasmanl@musc.edu

Learning OBJECTIVES: After studying this unit you should be able to

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Bulletin of the World Health Organization

Vaccination greatly reduces disease, disability, death and inequity worldwide

FE Andre [a], R Booy [b], HL Bock [c], J Clemens [d], SK Datta [e], TJ John [e], RW Lee [f], S Lolekha [g], H Peltola [h], TA Ruff [i], M Santosham [j], HJ Schmitt [k]

Reduce infectious disease mortality
Reduce morbidity and long-term disability from infections
Prevent some cancers.
Reduce healthcare expenditures
Reduce development of antibiotic resistance
Ensure safer travel
Empower women by reducing child mortality
Promote economic growth
Protect against bioterrorism
Increase socioeconomic equity

The number of cases of vaccine-preventable diseases are decreased 70-100% from pre-vaccine numbers for **all** diseases for which we routinely vaccinate in childhood. This is despite a doubling of the world's population since most vaccines were released. Smallpox is extinct. Polio is close to extinct. However, many infectious diseases do not yet have a successful vaccine – we will discuss why at the end.

Outline

- Types of immunization
- Goal of immunization
- Definition of important terms
  - Attenuation
  - Herd Immunity and R_0
  - Adjuvants
- Vaccine strategies for active immunization
- Routine vaccination schedules for U.S. and vaccines in current use
- Obstacles to vaccination

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Types of immunization

- **Immunization = Immunoprophylaxis = Vaccination**
  - Use of cowpox virus to prevent smallpox gave the name vaccination to the practice from "vacca" meaning cow circa 1798 and Dr. Jenner's work.

- **Passive immunization** – immune effector cells or molecules (Ab) are transferred from an immune person (or animal) to a naïve one
- **Active immunization** – immune response is stimulated in the person being protected

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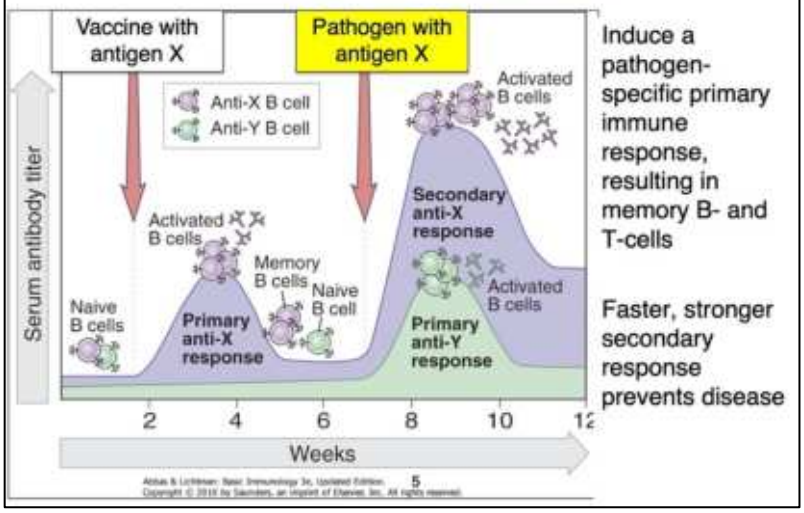
This lecture focuses on strategies for active immunization/ vaccination/ immunoprophylaxis.

The goal of vaccination



Induce a pathogen-specific primary immune response, resulting in memory B- and T-cells

Faster, stronger secondary response prevents disease

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The secondary immune response is larger and faster because a higher percentage of circulating cells recognizes that antigen and the lymphocytes are already matured into full-fledged effector cells (which takes 7-14 days in the primary infection or exposure). If a vaccine is effective, this prevents disease/symptoms

This diagram shows a humoral response, but the same pattern occurs for a cell-mediated response.

Definition: immune memory

- Clonal selection theory (1957)
- Discovery of T and B lymphocytes (1965)

The key mechanism became clear: the antigen(s) of a vaccine must induce clonal expansion in specific T and B cells, leaving behind a population of memory cells, which enable a stronger, *more rapid* and therefore effective response when the pathogen is next encountered.

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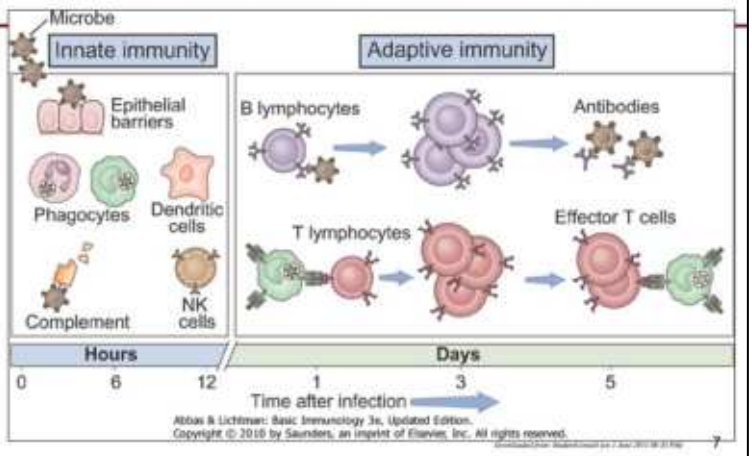
Additional exposures further boost the memory population, so additional doses of vaccine are sometimes called "booster shots"

Induction of memory requires activation of innate and adaptive immunity



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Recall that activation of T-cells requires activation of dendritic cells of the innate immune system to present antigen and co-stimulator molecules.

Therefore, vaccines must activate both the innate and adaptive immune systems to induce immune memory.

Definitions: Attenuation

- Late 19th century: Louis Pasteur discovers the basic principal of **attenuation**, the basis for the most modern vaccines in use.

  If a human pathogen is grown in a different host species or in vitro culture system, it acquires mutations over multiple passages that enable it to adapt to the new environment. Often these mutations reduce (attenuate) pathogenicity in the original host.

- It wasn't understood at the time, but the attenuated strains must maintain the same *antigenic* determinants as virulent strains to be useful as a vaccine.

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Attenuated strains are replication-competent but non-pathogenic versions of an infectious agent
In 2013, researchers in France and Australia successfully applied a novel attenuation method of vaccine creation to Chikungunya virus (CHIKV) using a technique called large scale random codon re-encoding. Using this approach, they demonstrated that the engineered viruses exhibited a stable phenotype with a significantly decreased viral fitness (i.e., replication capacity), making it a new vaccine candidate for this emerging viral disease.

Attenuation on the molecular level

- Example: Sequencing of the Sabin attenuated poliovirus vaccine strains revealed
  - Type I has 57 mutations
  - Type 2 has only 2 key mutations
  - Type 3 has only 2 key mutations
  - Both 2 and 3 have occasionally reverted and caused paralytic polio
  - Recombinant DNA techniques could improve safety by allowing site-directed mutagenesis

Why take this risk?

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There are only 3 serotypes of poliovirus that infect humans, named 1, 2 and 3. The Sabin vaccine is the live-attenuated polio vaccine. The Salk vaccine contained wildtype virus of all 3 serotypes inactivated with formalin.

Live-attenuated organisms produce stronger immunization

- Longer antigenic challenge
- Induction at appropriate site
- More antigens (less likely to be subject to MHC restriction)
- T-cell dependent

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So live attenuated vaccines give stronger, longer lasting protection at the cost of slightly higher risk.

Herd Immunity

- Herd immunity describes a situation where so many individuals in a population are immune to an infectious disease agent that the disease cannot maintain itself in that group.
- Put another way, there are too few susceptible individuals to maintain a chain of infection.

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Herd Immunity

- Herd immunity is critically important to protect those who cannot or have not had the opportunity to develop immunity to these diseases
  - Newborns and pregnant women
  - The immunocompromised
- Usually determined empirically

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Estimated at 70-90% for most infectious diseases for which we have vaccines.

Herd Immunity and R_0 (R-nought)

- R_0 (R-nought) is the average number of new infections started by an infected individual during the course of their illness
- Difficult to determine with precision because depends on many factors:
  - infectivity of the agent
  - duration of shedding
  - environmental conditions
  - health status and behavior of population
- In theory, the proportion of the population that needs to be vaccinated to prevent sustained spread of the infection is given by $1 - 1/R_0$

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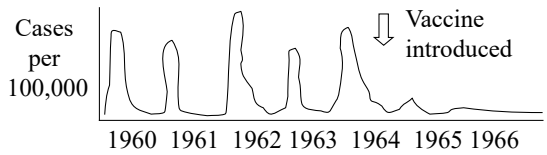
R nought stands for basic reproduction number. Notice that the higher R_0 is, the greater the percentage of vaccine coverage needed for effective herd immunity.

Uncertainties of herd immunity

- Duration can be complicated chronic carriers, or common sources of contamination
- Infectivity is affected by population density
  - Example: measles and the start of school



- Susceptibility varies with the general state of health of the population

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There was a resurgence of measles in the U.S. between 1989 and 1990 (with 41 deaths per year)- reduced vaccination rates most likely reason.

And there are some diseases for which no herd immunity is possible – ones caused by organisms that can survive in the environment without need for a human host. Can you think of one that is routinely vaccinated against?

Adjuvants

- Immunological adjuvants are substances added to vaccines to enhance the immune response
- Adjuvants act by aggregating antigen or by inducing inflammation (second signal)
- Choice of adjuvant and route of vaccination can be used to influence the type of immune response

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In other words, adjuvants enhance inflammation at the injection site.

Aggregation is important for engaging multiple Ag receptors on B-cells.

Adjuvants in currently licensed vaccines in the U.S.

- Three types of vaccine adjuvants currently licensed for use in the United States
  - Aluminum hydroxide / Aluminum phosphate
  - Certain lipid emulsions, for example:
    - AS01B (Monophosphoryl lipid A)
    - MF59 (squalene-based oil-in-water)
  - CpG 1018, an adjuvant based on synthetic DNA sequences

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In case you are curious, adjuvant AS01B (currently only in Cervarix HPV vaccine and Shingrix™ vaccine) (Glaxo Smith Kline) is composed of 3-O-desacyl-4-monophosphoryl lipid A (MPL) from *Salmonella minnesota* and QS-21 and a saponin purified from a plant extract, formulated as liposomes. You do not need to memorize that.

MF59 is a Novartis proprietary product

Adjuvants
Non-living vaccines often require an adjuvant

- Aluminum **adjuvants are present** in the following U.S. childhood vaccines:
  - hepatitis A
  - hepatitis B
  - DTaP, Tdap
  - Hib
  - HPV
  - *S. pneumonia* (pneumococcus)

- **No adjuvant** in these:
  - measles-mumps-rubella
  - Varicella/chickenpox
  - rotavirus
  - inactivated polio vaccine (IPV)*
  - *most* seasonal influenza vaccines

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*IPV and seasonal influenza are not live vaccines, but they consist of whole virus and are effective. IPV is also often given in a combination injection that contains adjuvant.

Fate of aluminum adjuvants in vivo: Dissolved by α-hydroxycarboxylic acids in interstitial fluid, absorbed into the blood, distributed to tissues, and eliminated in the urine. Studies with aluminum isotopes showed that aluminum was present in the blood 1hr after IM injection.

Stanley Hem. Elimination of aluminum adjuvants. *Vaccine* Volume 20, Supplement 3, 31 May 2002, Pages S40-S43 Aluminum Adjuvants in Vaccines: Workshop Summary

Vaccine types for active vaccination

1. Live attenuated microorganisms
2. Intact killed / inactivated microorganisms
3. Toxoids (formalin inactivated toxins)
4. Purified subcellular fragments/ antigens conjugated to protein (conjugate vaccines)
5. Proteins expressed from recombinant DNA
6. Lipid Nanoparticle mRNA

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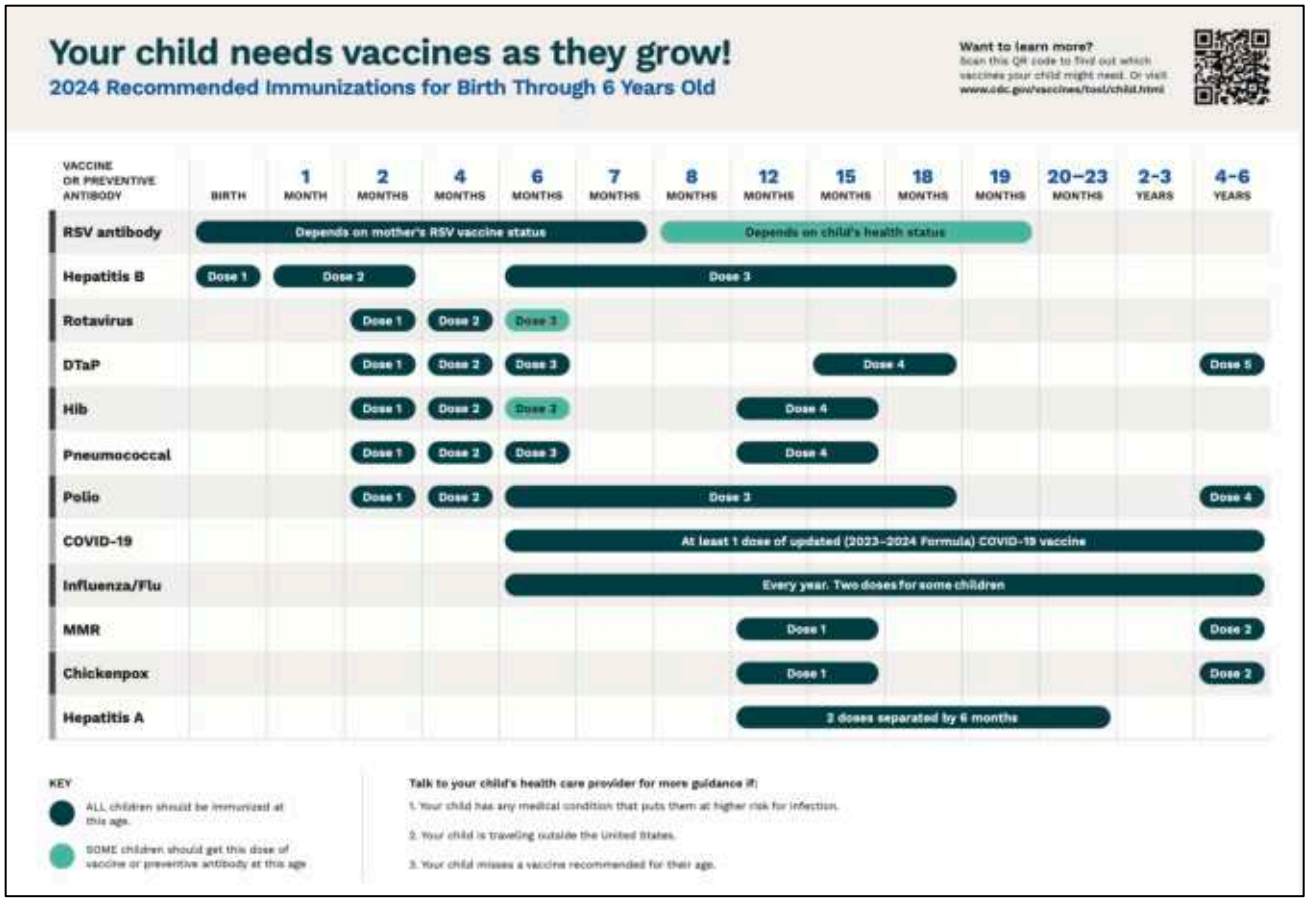
17 diseases routinely vaccinated against in the U.S. (Active vaccines)

In order by recommended age at first dose

1. Hepatitis B
2. RSV (passive or active)
3. Rotavirus
4. Diptheria
5. Tetanus
6. Pertussis
7. Poliovirus
8. *Haemophilus influenza B*
9. *Streptococcus pneumoniae*
10. Influenza
11. Measles
12. Mumps
13. Rubella
14. Chickenpox (Varicella)
15. Hepatitis A
16. Human papillomavirus
17. *Neisseria meningitidis*

20



This is the "Parent-friendly" summary of an ACIP report that is 191 pages long with hundreds of references.

- Hepatitis B recombinant vaccine – only vaccine given at birth (injection)
- RV = rotavirus: ONLY live-attenuated vaccine given before 1 year of age (oral)
- Pneumococcal conjugate vaccine (Prevnar-20, or PCV) (injection)
- IPV = inactivated polio vaccine injection
- Influenza/Flu = inactivated virus (live attenuated vaccine not given until *after* age 2)
- MMR = measles-mumps-rubella live attenuated (injection)
- Chickenpox live–attenuated (injection) of Varicella zoster virus often in combination with MMR

Hepatitis B vaccine (pure surface Ag)

- Consists of purified HBsAg protein + adjuvant
- Proteins are expressed in yeast by recombinant DNA technology and purified
- Advantages:
  - Absolutely no chance of disease transmission
  - Microbial components are very well defined
- Disadvantages:
  - Limited number of epitopes means some individuals do not respond.
  - Yeast allergies.

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Recombinant vaccines are very safe. There has been considerable research on using naked DNA as a vaccine as well, with appropriate promoters and adjuvant molecules also expressed. So far, none have been approved for use in humans.

Recent studies suggest that people with yeast allergies can safely receive this vaccine, as the amount of yeast allergen in the vaccination is usually undetectable.

RSV (Respiratory Syncytial Virus) vaccines

- Active vaccine: recombinant vaccines containing RSV fusion protein in the pre-fusion conformation
  - Pfizer vaccine (Abrysvo) is approved for adults over 60 and pregnant individuals at 32 through 36 weeks gestation from Sept to January (to protect the infant)
  - GSK Arexvy for adults over 60 only
- Passive vaccine: **nirsevimab** for recommended for all infants younger than 8 months of age who are born during—or who are entering—their first Respiratory Syncytial Virus (RSV) season without maternal antibodies

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Old passive RSV protection was called Pavilizumab. It is also antibody injected intramuscularly, but monthly during RSV season. Likely phased out now that nirsevimab is available and **single dose.**

RSV (Respiratory Syncytial Virus) vaccines

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Getting kind of complicated for RSV…

Rotavirus vaccines (live attenuated)

- Live attenuated rotaviruses given orally as as a suspension
- *Only* live-attenuated vaccine given before 1 yr of age
- Induces protective IgA

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Virus is made in tissue culture.
No catch-up vaccination for children over 6 months of age.

Rotavirus vaccines

- Two rotavirus vaccines are currently licensed for infants in the United States:
  - RotaTeq® (RV5) is given at ages 2 months, 4 months, and 6 months
  - Rotarix® (RV1) is given at ages 2 months and 4 months
- The first dose of either vaccine should be given before a child is 15 weeks of age. Children should receive all doses of rotavirus vaccine *before* they turn 8 months old.

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No catch-up vaccination for children over these recommended ages for rotavirus vaccines.

(Older children seem to have an increased risk of intussusception)

DTaP (toxoid vaccine)

- D is for Diphtheria toxoid
- T is for Tetanus toxoid
- aP is for acellular Pertussis fragments which include pertussis toxoid

Baby with neonatal tetanus. His mom was not immune.

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Pertussis antigens in DTaP:

- Pertussis Toxoid (PT)
- Filamentous Haemagglutinin (FHA)
- Pertactin (PRN)
- Fimbriae Types 2 and 3 (FIM)

DTaP protects against 3 bacteria

vaccine	organism	remarks
Tetanus toxoid	*Clostridium tetani*	Average of 600 U.S. cases/yr pre-vaccine, 8 post-vaccine
Diphtheria toxoid	*Corynebacterium diptheriae*	>50,000 annual U.S cases of diphtheria to <100 within 10 years of introducing the vaccine
Acellular pertussis (aP vaccine)	*Bordetella pertussis*	Original whole killed cell vaccine caused seizures in a small number of children.

Tetanus toxin is a protease. Diphtheria toxin is an ADP-ribosylating enzyme

DTaP

- Toxoids are chemically modified toxins which are no longer toxic but are still antigenic and can be used as a vaccine.
- Current method: inactivated with formalin
- Multiple doses are required for lasting immunity
- TdaP booster given to adults. Same ingredients, different ratio

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Formalin cross-links amino acid residues. Many toxins are enzymes or must undergo other conformational changes to have their toxic effect. Formalin prevents this.

Inactivated polio vaccine (IPV)

- Old technology – same as the Salk polio vaccine
- Consists of purified pathogenic virus inactivated with heat or formalin
- Oral vaccine replaced it until polio was eradicated in the U.S., such that the live vaccine was the main source of poliovirus in the U.S.
- U.S. switched to IPV, and WHO is now also

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Routinely given vaccines consisting of whole (intact) killed microorganisms

vaccine	organism	remarks
Inactivated polio (Salk vaccine)	Polioviruses 1, 2, and 3	Only polio vaccine used in the U.S.
Rabies	Rabies virus	Usually given *after* exposure, but recommended for all veterinarians
Influenza (inactivated)	Influenza virus	Must be revaccinated every year, starting at age 6 mos.
Inactivated Typhoid	*Salmonella* serotype Typhi	Only for travelers to certain regions. A live attenuated oral vaccine is also available.

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Sal**k** vaccine is **k**illed virus

Hib (*Haemophilus influenza type B*) vaccine

- *H. influenza* is most pathogenic when it expresses a polysaccharide capsule
- *H. influenza type B* is especially pathogenic in children under 5
- Antibodies to capsular polysaccharide are protective, but polysaccharides are poorly immunogenic in persons under 24 months of age
- < 24 mos old *must* receive conjugate vaccine for effective protection

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Bacterial capsules inhibit phagocytosis because they mask PAMPS that would bind to PRRs on phagocytes. However, if the capsule is bound by antibodies, the inhibition is overcome because the phagocytes can now recognize the bacterium via Fc-gammaR1 receptors and complement fragments generated by the classical pathway.

Why conjugate vaccines for polysaccharide antigens?

- They elicit T-cell help, for immune memory

	Protein antigen	**Non-protein antigen**
T-cell	Recognized in the context of MHC*	Not recognized
B-cell	Recognized as long as it is multivalent or aggregated	Recognized as long as it is multivalent or aggregated

*MHC II for helper T-cells which are CD4+

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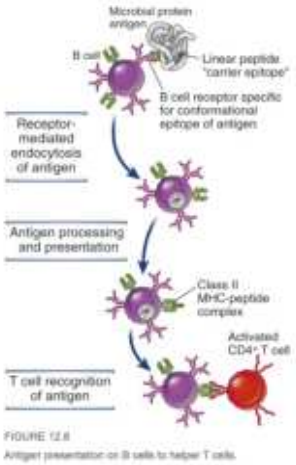
Learned from initial HiB polysaccharide-only vaccine trials that responses to T-independent antigens are very weak in children under 2 years of age.

Incidence of invasive *H. influenza disease* declined >99% in children under 5 since conjugate vaccine introduced, given at 2, 4, and 6 mos of age.

Conjugate vaccine mechanism



- B-cell is activated by the polysaccharide, but processes conjugate and presents peptide from protein part on MHC II along with B-7 and CD40
- CD4 T-cell that recognizes the peptide is activated to make CD40L and CD28
- B-cell isotype switches and makes memory cells - acts as both APC and humoral effector cell

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Same for any non-protein antigen conjugated to a protein, including haptens.

Other bacterial polysaccharide vaccines

vaccine	organism	remarks
Pneumococcal vaccine conjugate	Invasive *Streptococcus pneumoniae*	Polysaccharide conjugate vaccine is PCV-20 (Prevnar) = 20 serotypes of capsule conjugated to Diphtheria toxoid.
Pneumococcal vaccine	Invasive *Streptococcus pneumoniae*	Polysaccharide-only version is Pneumovax 23 = 23 serotypes of capsule, no protein
Meningococcal vaccine	*Neisseria meningitidis*	Polysaccharide and conjugate vaccines: Groups A C,W, Y. Group B vaccines separate.

PCV-20, like Hib, is given at 2,4,6, and 12 mos of age.

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There are 3 polysaccharide-conjugate vaccines among routine U.S. vaccinations: Hib, PCV-13, and the meningococcal vaccine.

Meningococcal vaccine is given to adolescents.

Pentavalent vaccines reduce shots

- In the U.S.: Pentacel
  - DTaP-IPV-Hib
- Globally (U.N.I.C.E.F.)
  - DTaP-Hib-HepB

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At 12-15 months

- Last doses of DTaP-Hib-IPV-Hep B
- Start hepatitis A vaccine two-dose series
  - HAV vaccines are inactivated whole virus
- Start live-attenuated MMRV vaccine two -dose series

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Live attenuated vaccines are not recommended until 1 year of age except rotavirus.

Measles-Mumps-Rubella-Varicella

Disease	Remarks
Measles	Introduced 1963
Mumps	Introduced 1967
Rubella	Introduced 1967
Varicella	1995 –produces a latent VZV infection, but reduced risk of shingles compared to wild-type infection*

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Two dose series: first at 12-15 months, the second at 4-6 years old.

*Gershon AA, Gershon MD, Shapiro ED. Live Attenuated Varicella Vaccine: Prevention of Varicella and of Zoster. J Infect Dis. 2021 Sep 30;224(12 Suppl 2):S387-S397. doi: 10.1093/infdis/jiaa573. PMID: 34590140; PMCID: PMC8482020.

Other live attenuated vaccines in U.S.

Disease	Remarks
Rotavirus	Introduced 1995
Yellow Fever	Introduced 1937
Typhoid	An inactivated vaccine also available
Tuberculosis	(BCG) Stable since 1921, some protection against leprosy
Influenza	Intranasal, live-attenuated influenza vaccine for ages 2 yrs- 65 yrs

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You only need to know the ones shaded in gray – the 16 routine vaccines.

Age 11-12 years old

1) **Human papillomavirus vaccine**
   - Gardasil 9®: consists of purified viral capsid protein L1 produced in recombinant yeast
   - Two doses if series is started before age 15, but 3 doses if started at age 15 or later

2) **Meningococcal vaccine (Menactra)**
   - Two dose series of polysaccharide serotypes A, C, Y and W-135 conjugated to diphtheria toxoid
   - Serotype B vaccine (Bexsero® and Trumenba®) is a separate vaccination

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There are 12 serotypes of meningococcus. Most illness is caused by serotypes A, B, C, Y and W-135 Menactra has been approved for use from ages 9 months- 55 years.

In addition, a yearly influenza vaccine and a single Tdap booster vaccine is recommended for adolescents.

Adult vaccines

1) Tdap or Td booster every 10 years
2) Influenza every year
3) Pneumococcal vaccines
   - **Prevnar-20 (PCV20)** once after age 65
   - Prevnar 15 once after age 65, followed by Pneumovax 23
4) Shingles vaccine (Varicella booster)

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Tdap boosters are especially important for adults who are in contact with infants too young to be fully immunized against pertussis.

Shingles vaccines (adults)

- Zostervax live-attenuated vaccine
  - Approved 2006 for adults 50 and over
  - 40-50% effective at preventing shingles
  - Now largely replaced by the recombinant vaccine
- Shingrix™ (Zoster recombinant, adjuvanted)
  - Approved in 2017 for adults 50 and over
  - Two-dose series, >90% effective
  - Consists of purified recombinant glycoprotein E viral antigen + AS01B adjuvant suspension

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Shingrix is an anti-shingles vaccine for people 50 and older who had chickenpox as children. Prior chickenpox does not need to be confirmed in any way, though, to give the vaccine.

COVID vaccines- new vaccine strategies

- Vectored vaccines
  - Adenovirus vectors modified to transduce human cells with the Covd-19 spike gene
- Recombinant spike protein vaccine made in insect cells
- Lipid nanoparticles (LNP) mRNA vaccines

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The adenovirus vaccines are **not** replication competent in humans.

Lipid nanoparticle mRNA vaccines

- Strategy: Deliver in vitro transcribed mRNA molecules encoding microbial antigens into the cytoplasm of cells for translation into protein
- Requires overcoming natural barriers
  - Optimizing mRNA 5'cap, UTR, poly-A tail for high efficiency translation
  - Reducing RNA instability
  - Improving in vivo delivery efficiency
  - Preventing activation of innate immune nucleic acid sensors

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Technology was developed many years before the COVID-19 pandemic.

Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics--developing a new class of drugs. Nat Rev Drug Discov. 2014 Oct;13(10):759-80. doi: 10.1038/nrd4278. Epub 2014 Sep 19. PMID: 25233993. https://pubmed.ncbi.nlm.nih.gov/25233993/

Key steps for mRNA-based vaccines were known in 2015

- Optimize mRNA 5'cap, UTR, poly-A tail for high efficiency translation
- Improve delivery and reduce RNA instability with lipid nanoparticles that fuse with host cell membranes
- Make the in vitro transcribed mRNAs immunologically silent with modified nucleosides (e.g. incorporate 1-methylpseudouridine) to evade innate immune receptors and type I interferon response

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Type I interferon response inhibits protein synthesis, so it is essential that the vaccine mRNA not trigger the innate nucleotide receptors like RIG, PKR, etc.

Modified nucleoside LNP mRNA vaccines are immunogenic

- Injection trauma is sufficient to activate dendritic cells?
- Can incorporate TLR agonists in the lipid nanoparticles
- Both B and T-cell responses are detected

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Vaccines for healthcare personnel

- **Advisory Committee on Immunization Practices (ACIP)** was established under Section 222 of the Public Health Service Act (42 U.S.C. § 2l7a) and is governed by its charter.
- Consists of 14 medical and public health experts and 1 consumer advocate who **develop recommendations on the use of vaccines in the civilian population of the United States**. Also 8 *ex officio* members and 30 non-voting representatives from liaison organizations.
- Meets three times per year at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. Meetings are open to the public and available online via webcast.

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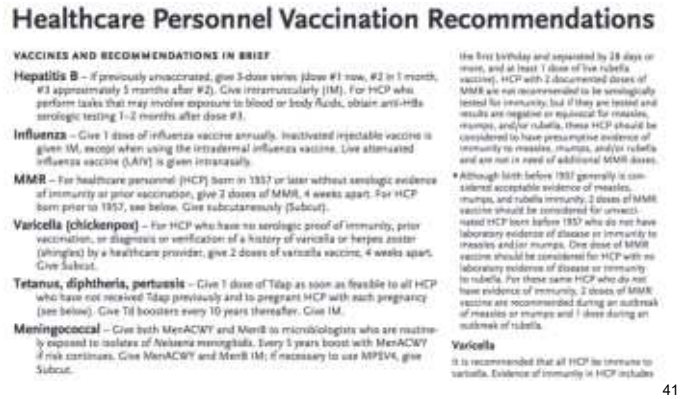
This report has 329 references



Healthcare Personnel Vaccination Recommendations

VACCINES AND RECOMMENDATIONS IN BRIEF

Hepatitis B – If previously unvaccinated, give 3-dose series (dose #1 now, #2 in 1 month, #3 approximately 5 months after #2). Give intramuscularly (IM). For HCP who perform tasks that may involve exposure to blood or body fluids, obtain anti-HBs serologic testing 1–2 months after dose #3.

Influenza – Give 1 dose of influenza vaccine annually. Inactivated injectable vaccine is given IM, except when using the intradermal influenza vaccine. Live attenuated influenza vaccine (LAIV) is given intranasally.

MMR – For healthcare personnel (HCP) born in 1957 or later without serologic evidence of immunity or prior vaccination, give 2 doses of MMR, 4 weeks apart. For HCP born prior to 1957, see below. Give subcutaneously (Subcut).

Varicella (chickenpox) – For HCP who have no serologic proof of immunity, prior vaccination, or diagnosis or verification of a history of varicella or herpes zoster (shingles) by a healthcare provider, give 2 doses of varicella vaccine, 4 weeks apart. Give Subcut.

Tetanus, diphtheria, pertussis – Give 1 dose of Tdap as soon as feasible to all HCP who have not received Tdap previously and to pregnant HCP with each pregnancy (see below). Give Td boosters every 10 years thereafter. Give IM.

Meningococcal – Give both MenACWY and MenB to microbiologists who are routinely exposed to isolates of *Neisseria meningitidis*. Every 5 years boost with MenACWY if risk continues. Give MenACWY and MenB IM; if necessary to use MPSV4, give Subcut.

the first birthday and separated by 28 days or more, and at least 1 dose of live rubella vaccine). HCP with 2 documented doses of MMR are not recommended to be serologically tested for immunity, but if they are tested and results are negative or equivocal for measles, mumps, and/or rubella, these HCP should be considered to have presumptive evidence of immunity to measles, mumps, and/or rubella and are not in need of additional MMR doses.

* Although birth before 1957 generally is considered acceptable evidence of measles, mumps, and rubella immunity, 2 doses of MMR vaccine should be considered for unvaccinated HCP born before 1957 who do not have laboratory evidence of disease or immunity to measles and/or mumps. One dose of MMR vaccine should be considered for HCP with no laboratory evidence of disease or immunity to rubella. For these same HCP who do not have evidence of immunity, 2 doses of MMR vaccine are recommended during an outbreak of measles or mumps and 1 dose during an outbreak of rubella.

Varicella

It is recommended that all HCP be immune to varicella. Evidence of immunity in HCP includes

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Biological obstacles to vaccination

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https://www.cdc.gov/vaccines/hcp/conversations/downloads/vacsafe-acip-color-office.pdf

Immunization of Health-Care Personnel: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Factors affecting vaccine response in normal individuals

- Immunogenetic differences
  - HLA type, immunoglobulin genes, T-cell receptor genes, cytokine genes, NK cell receptor genes
- Prior antigenic exposures, circulating Ab
- Current co-infections
- Daily variation in circulating T-cell, B-cell clones
- Age

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Contraindications to vaccination

- **Live attenuated vaccines** are contraindicated in the immunocompromised*
  - congenital immunodeficiencies
  - HIV/AIDS
  - Iatrogenic immunosuppression (e.g. transplant, chemotherapy, anti-TNF therapy…)
  - Pregnant women
- Allergy (vaccines produced in eggs/yeast should not be given to people allergic to eggs/yeast)

*and care taken when vaccinating contacts of these risk groups

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Contraindication means conditions in a recipient that increase the risk for a serious adverse reaction to the vaccine. (www.cdc.gov)

People who cannot be vaccinated due to age or co-morbidities can be passively immunized with antibodies purified from blood of immune humans or animals.

Risk group recommendations

People with increased susceptibility to encapsulated bacteria…

- Asplenia (usually due to surgery)
- Sickle-cell anemia
- Congenital deficiencies of humoral immunity

….should receive some capsular polysaccharide vaccines earlier than usual:

- pneumococcal vaccine
- meningococcal vaccine

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Obstacles to vaccination success

1. Pathogen is too genetically and/or antigenically diverse (many serotypes)
2. Genetic diversity is geographical and/or continuously generated within an infected individual
3. High levels of immune response are present in naturally infected individuals – but the response is not protective.

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Example of too diverse: rhinoviruses

Examples of genetic variation continuously generated in an infected individual: HIV, HCV

Examples: syphilis, gonorrhea, HIV

Major diseases for which no vaccines are available

- HIV
- Hepatitis C
- Herpes simplex, CMV
- Adenoviruses, rhinoviruses
- Staphylococci, Streptococci
- Leprosy
- Syphilis *
- Chlamydia
- Candida *
- Pneumocystis *
- Malaria
- Trypanosomiasis (and other protozoa) *
- Schistosomiasis
- Onchocerciasis *

*ignorance of effective immunity

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What is meant by ignorance of effective immunity? Natural infection does not confer protection.

Future directions

- Needle free vaccines
  - Needle-free vaccines (nasal, skin patch, oral) example - an adenovirus expressing tetanus toxin C fragment given intranasally protected mice from tetanus (J. Virol. 75(23): 11474)
  - Epidermal powder injection delivered non-replicating antigen to Langerhans cells of the skin, stimulating CTL response, unlike needle injection IM (J. Virol 75(23) 11630)
- More sophisticated adjuvants are in trials
- Genetically engineered attenuated strains
- Anti-cocaine and anti-meth vaccines

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Practice questions

Question: One formulation of Hib-conjugate vaccine contains Hib polysaccharide covalently bound to diphtheria toxoid (DT). Which of the following statements best describes the primary antigen presentation mechanism that results in anti-Hib polysaccharide IgG antibodies?

A. B-cells present diphtheria toxoid fragment to T-helper cells
B. B-cells present Hib polysaccharide to T-helper cells
C. Dendritic cells present Hib polysaccharide to T-helper cells
D. Dendritic cells present diphtheria toxoid fragment to T-helper cells
E. Follicular dendritic cells present whole conjugate to B-cells

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Question: Adjuvants are used with non-living vaccines because they

A. Are cytotoxic
B. Increase vaccine shelf-life
C. Increase co-stimulatory molecule expression
D. Reduce uptake of vaccine by phagocytic cells
E. Reduce injection site irritation

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Question: For which of the following disease types is a high vaccination rate (herd immunity) **not** effective in preventing infection in an unvaccinated individual?

A. Transmitted by aerosols, person to person
B. Transmitted by blood products
C. Transmitted by fecal-oral contamination
D. Transmitted by sexual contact, person to person
E. Transmitted by spores in the environment

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Question: Which of the vaccine types listed describes the type of vaccine used in the United States for poliovirus ?

A. Attenuated live virus
B. Conjugate of viral polysaccharide
C. Recombinant viral protein
D. Toxoid
E. Whole killed virus

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Question: Which of the following vaccines is not recommended for an immunosuppressed individual?

A. Diphtheria-acellular pertussis-tetanus
B. Diphtheria toxoid-Hib conjugate
C. Hepatitis B
D. Measles-mumps-rubella
E. Polio (inactivated)

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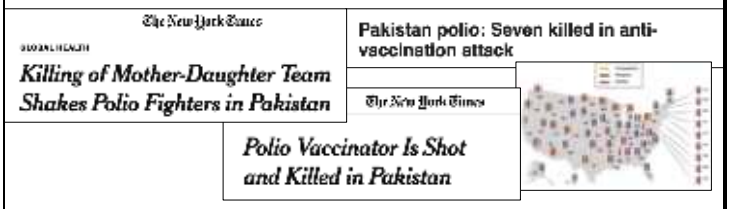
Non-biological obstacles to vaccination



Advocacy resource: Voices for vaccines

- https://www.voicesforvaccines.org/
- Podcast
- Email newsletter "This week in vaccine hesitancy"

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The CDC is also a great resource for vaccine information, however "Voices for Vaccines" watches social media for the latest circulating rumors and misinformation and publishes the facts.