Vaccinology 101

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History of Vaccine development

- Concept of Vaccination as a Public Health Tool
- Immunology of Protection
  - Development of Protection
  - Life-long vs. Transient immunity
  - Types of immungens:
    - Live vs. killed; whole vs. selected antigen; adjuvant; conjugated and combination vaccines
    - Mimic the natural route of infection vs. systemic administration
  - Active vs. passive protection

Principles of Vaccination

- Antigen (Immunogen)
  - A live or inactivated substance (e.g., protein, polysaccharide) capable of producing a (protective) immune response
- Antibody
  - Protein molecules (immunoglobulin) produced by B lymphocytes to help process and/or eliminate an antigen
- Cell-mediated response
  - e.g. T-helper or cytotoxic T cell response

Principles of Vaccination

- Active Immunity
  - Protection produced by the person's own immune system in response to infection, exposure or vaccination
  - Usually permanent, but may or may not be complete
- Passive Immunity
  - Protection transferred from another person or animal
  - Temporary protection that wanes with time

Vaccination

- Active immunity produced by a vaccine
  - Immunity and immunologic memory similar to natural infection but without risk or much lower risk of clinical disease

Passive Immunity

- Transfer of antibody produced by one human/animal to another person or animal
- Sometimes called Antiserum
- Temporary protection
- Transplacental maternal antibody is the most important source in infancy

Sources of Passive Immunity

- Almost all blood or blood products
- Pooled human antibody (immune globulin)
- Human hyperimmune globulin
- Heterologous hyperimmune serum (antitoxin) from another animal species
- Monoclonal antibody

Principles of Vaccination

- **General Rule:** the more similar a vaccine is to the disease-causing form of the organism, the "better" the immune response to the vaccine
- **Current Trend:** targeted immune response by exploiting conjugated carrier molecules, adjuvants, cytokines.....

Immunization Strategy

- **Prevention of infection vs. symptoms:**
  - **HIV vs. Measles**
- **Temporary vs. Long-lasting Immunity**
  - **Passive protection: specific antibodies**
    - **Immediate** Protection, but $t_{1/2} \approx 27$ days:
    - Antitoxins
      - » Antibodies to Tetanus, Diphtheria, Botulinum toxins
    - Hyperimmune antisera to specific pathogens:
      - » Hepatitis B, Varicella, Rabies, RSV
    - Pooled Human Immune Globulin: not specific
      - » Immune Serum Globulin & Intravenous IG
  - **Active: vaccination (Longer lag time, but long-lasting)**
  - **Active - Passive (HBIG+Hep B vac.; RIG+Rabies vac.)**
- **Pre-exposure (Polio) vs. Post-exposure (Rabies)**

Target Populations for Immunization

- **High-Risk Groups Only (ex: Rabies, Varicella in some countries)**
  - No effect on overall disease burden in the general population
  - Vaccine must be highly effective
  - Must be able to reach all members of high-risk group
  - Less expensive in the short term

Target Populations for Immunization

- **Universal Immunization (Polio, Rubella, Varicella in USA)**
  - Diminishes overall disease burden in general population
  - Pre-emptive immunization of healthy individuals who eventually become high-risk
  - Decreases risk of exposure for everyone
  - Planned access to target population
  - More cost-effective in long term
  - Requires extremely safe vaccines

Immunization of High Risk Groups

- **Travel**
  - Japanese Encephalitis, Yellow fever, Typhoid….
- **Occupation:**
  - Hepatitis B, Rabies, Anthrax, Plague, Rubella & Varicella
- **Age, illness, immunosuppression**
  - **High-risk for invasive pneumoccocal disease:**
    - Children < 6 years (Pneumococcal conjugate vaccine)
    - Elderly, high-risk kids ≥ 6 years (Pneumococcal polysaccharide vaccine)
  - **Influenza:** infants, elderly, or cardiac or pulmonary disease, pregnancy, obesity….
  - **Severe varicella (live attenuated varicella vaccine):**
    - leukemic children & HIV-infected kids with CD4 ≤ 15%
  - **HIV-infected children (Inactivated polio vaccine)**

Administration

- **Route**
  - Mimic route of natural infection: Oral polio, Live attenuated Intranasal Influenza vaccines
  - Parenteral (Intramuscular, subcutaneous)
- **Age at immunization**
  - **Age distribution of natural infection:**
    - In pre-vaccine era: ≥ 60% of invasive H.influenzae type b infections occurred at ≤ 18 months of age
  - **Age-dependent immune response:**
    - Polysaccaride antigens (HIB, Pneumo & Meningococcus) are poorly immunogenic at ≤ 2 years of age
  - **Ability to access population to be immunized:**
    - Hepatitis B & rubella vaccines in infants vs. adolescents

Immune Response to Immunization

- Primary response
  - 1st exposure to the antigen
  - 7-10 day lag time between exposure and production of antibody and cell-mediated responses
  - Initial antibody response is IgM, later switch to IgG
  - Establish populations of memory T & B cells
- Secondary response
  - After a repeat exposure to the antigen (or pathogen)
  - Shortened lag time between exposure and production of antibody and cell-mediated responses
  - Antibody response is almost all IgG
  - Rapid expansion/ Memory T & B cell populations

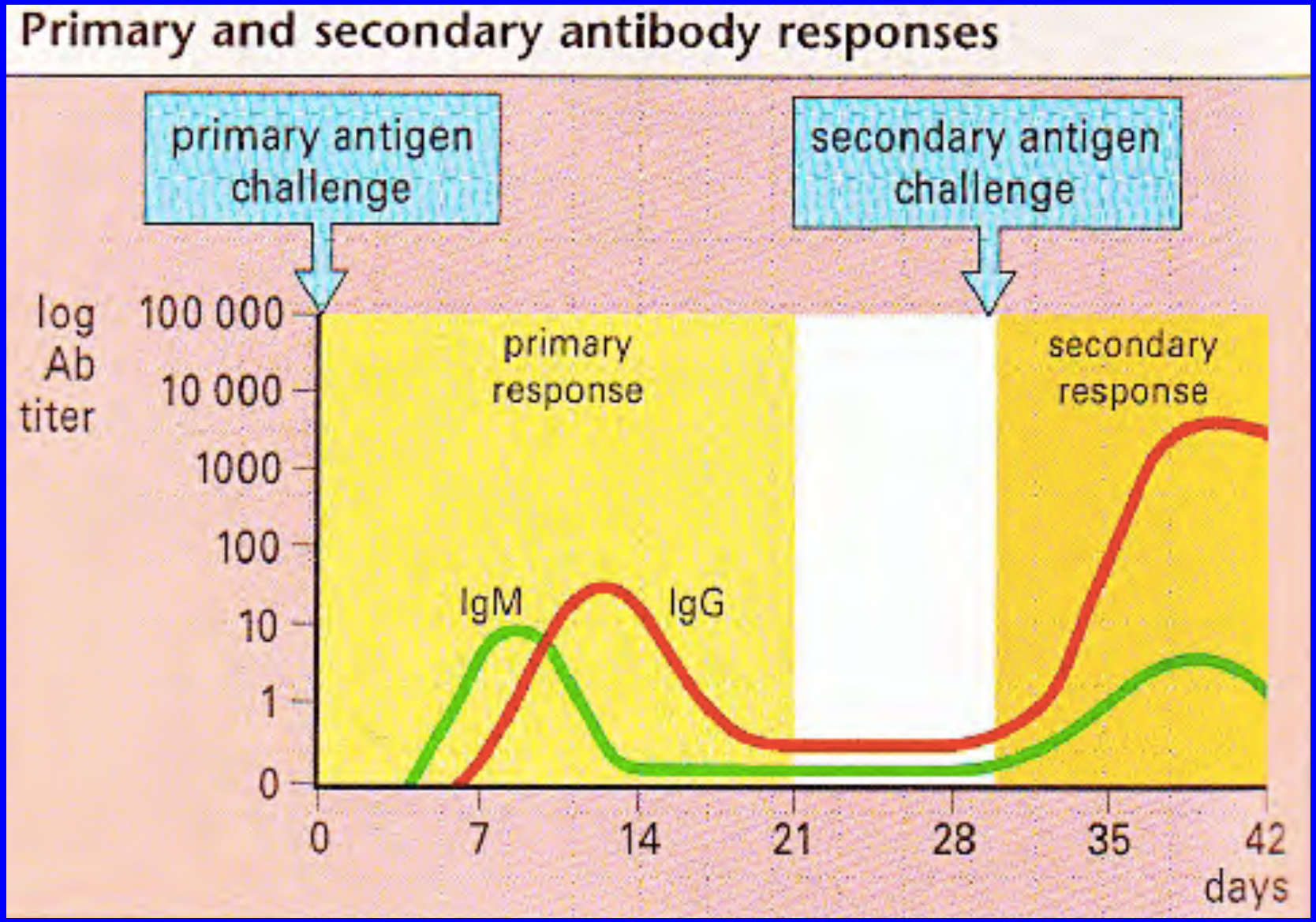


Fig. 9.14, Immunology, 8th ed, Male, et. al. 2013

How Does Immunization Strategy Influence the Choice of Vaccine?

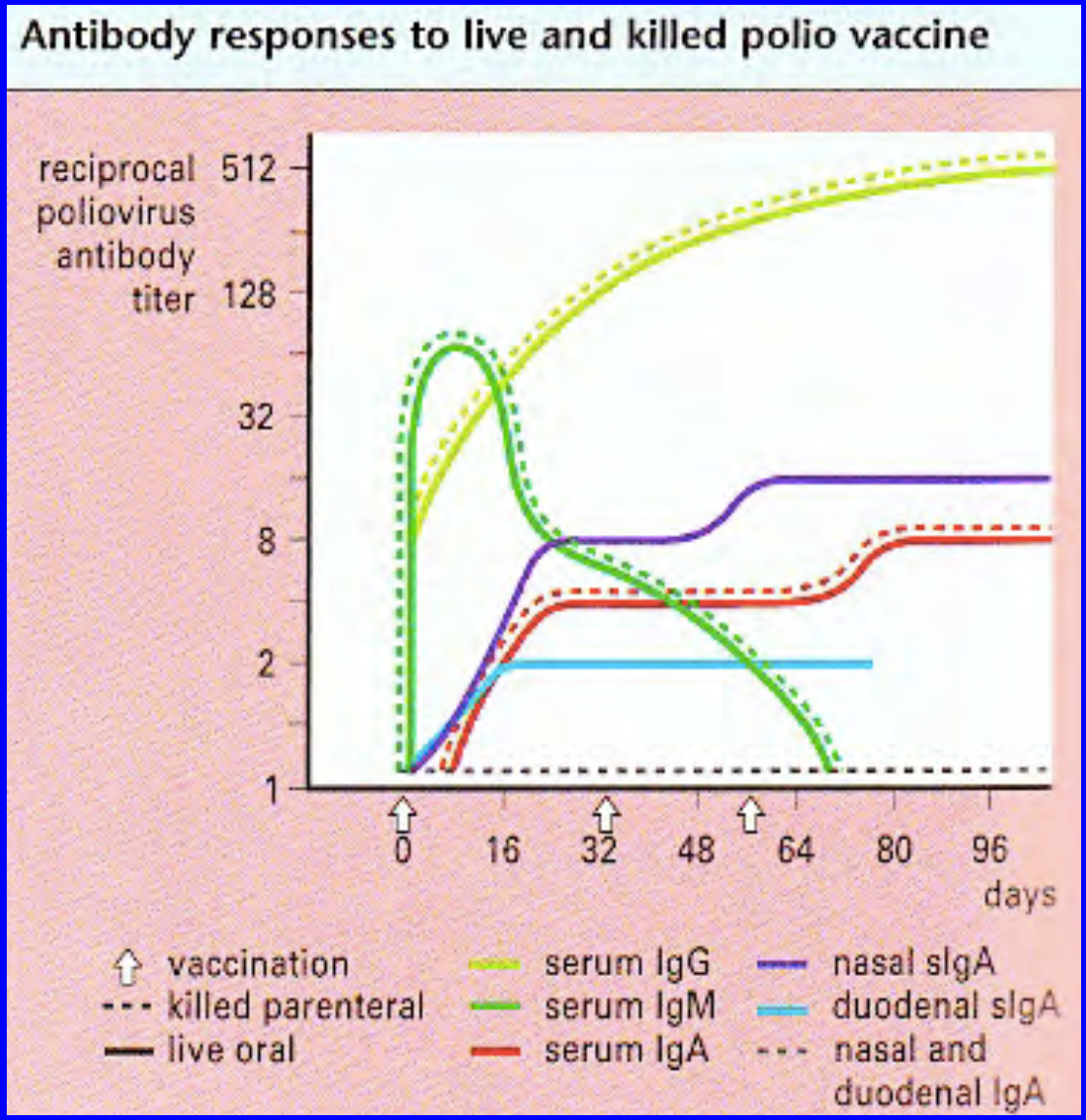
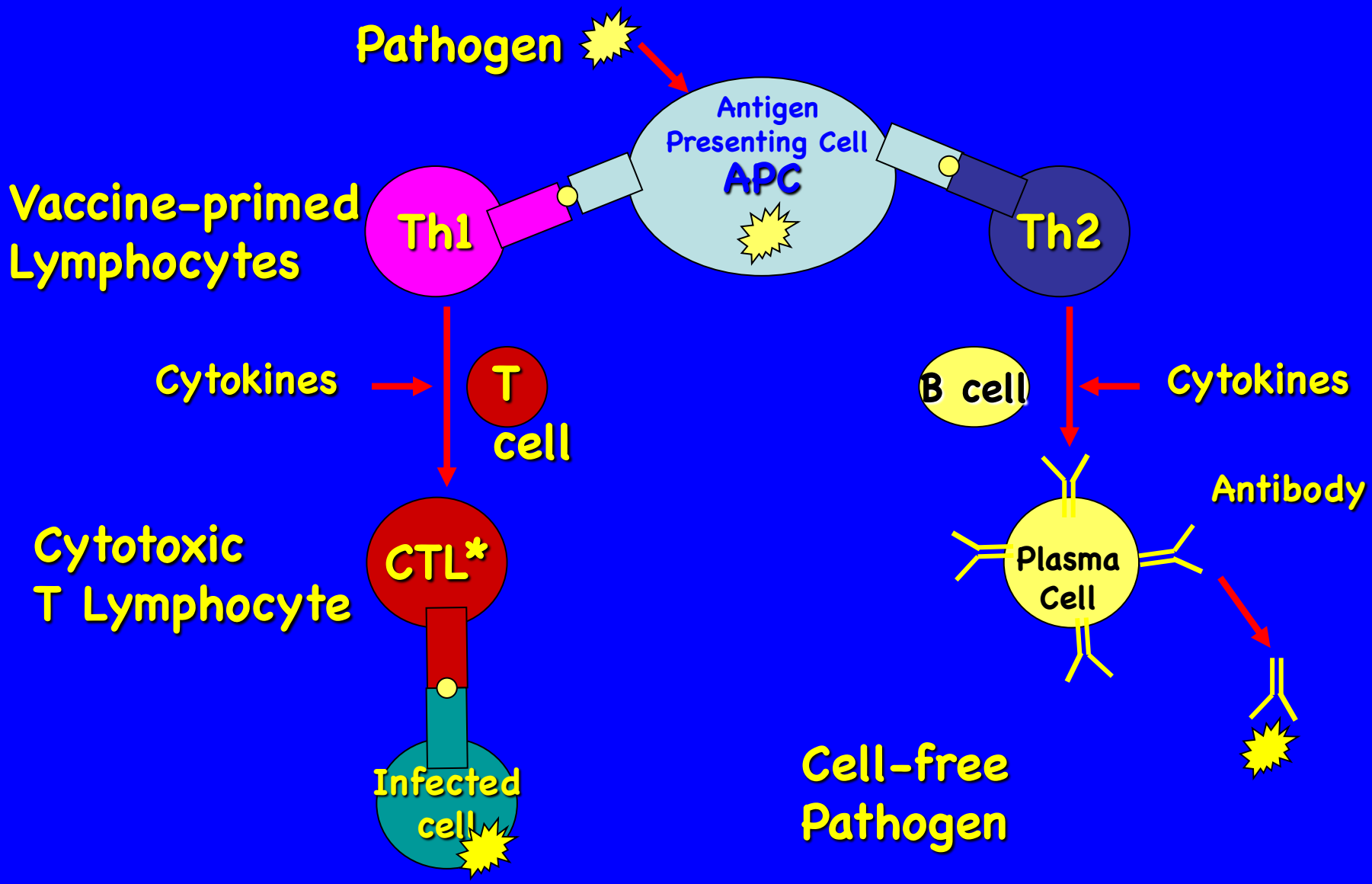


Fig. 18.10, Immunology, 8th ed, Male, et. al. 2013

What Happens When a Vaccinee is Exposed to a Pathogen after being Immunized?



What Is Immunologic Memory?
B cell Clonal Expansion

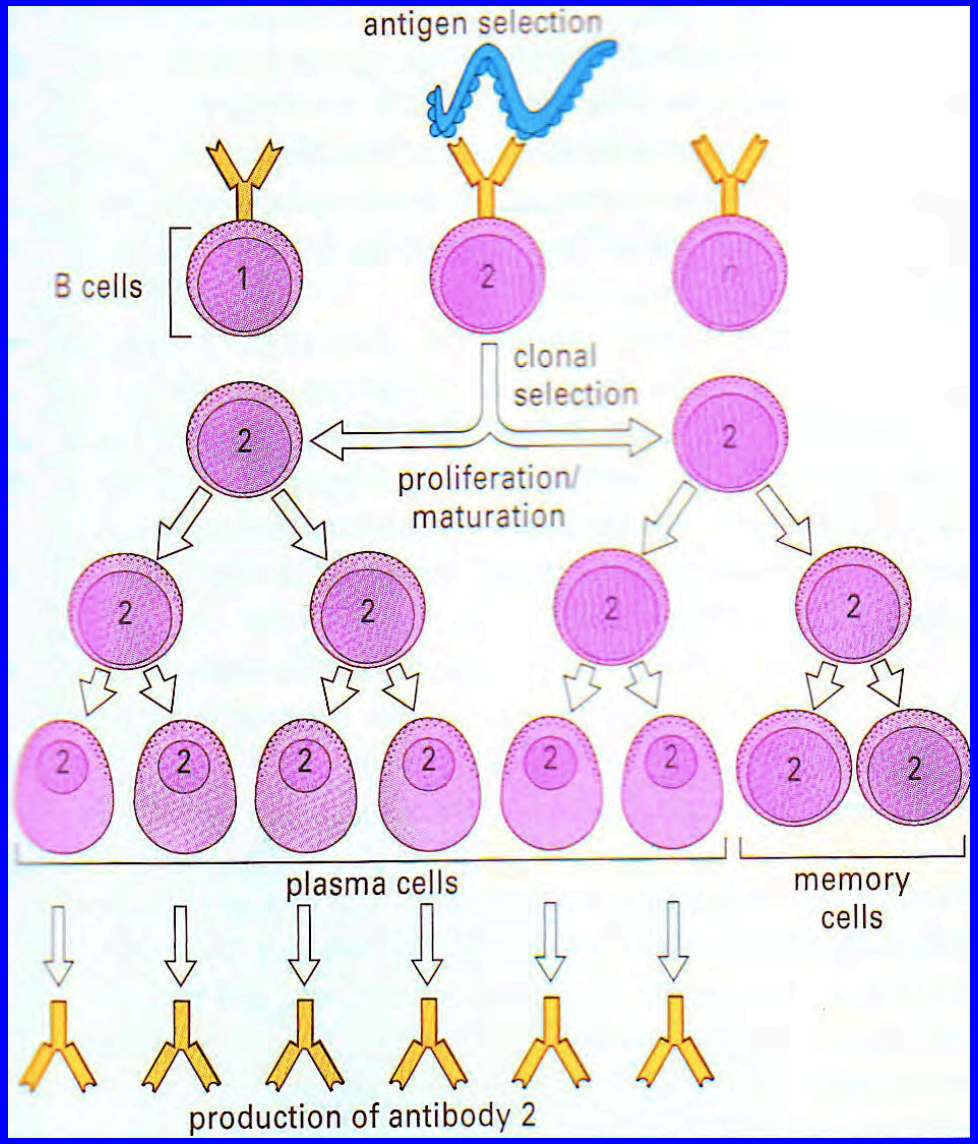


Fig. 1.13, Immunology, 8th ed, Male, et. al. 2013

Factors That Influence Vaccine Effectiveness

- HLA types
- Physiologic condition of vaccinee
  - Age, nutritional status, immune status
- Type of vaccine
  - Live attenuated vs. killed
- Dose and route of administration
- Adjuvants

Influence of Host Genetic Factors on Response to Vaccination

- 5-10% of healthy subjects do not mount an antibody response (anti-HBs) to Hepatitis b Vaccine
- Non-response is associated with different HLA-DR alleles and impaired Th(1?) cell response:
  - increased incidence of non-responsiveness in subjects with HLA-DR3(+) or -DR7(+) haplotypes

Current Technology

- **Inactivated whole organism:**
  - Whole cell Pertussis, eIPV, Hepatitis A, Rabies, Influenza(detergent-treated), plasma-derived Hepatitis B (no longer available in US)
- **Live organism from a related or different species:**
  - Vaccinia, Bacille Calmette-Guerin (BCG, also attenuated by serial passage)
- **Live attenuated organism:**
  - Oral Polio, Measles, Mumps, Rubella, Varicella, Cold-adapted Influenza, Yellow fever
  - Attenuated by passage in tissue culture
- **Toxoids:** inactivated Diphtheria, Tetanus toxins
- **Combination Vaccines:**
  - DTP, MMRV, DTP-HIB, HIB-Hep.B, DTaP- Hep.B-IPV

Current Technology

- **Specific subunit/antigen(s), extracted, purified:**
  - **Acellular Pertussis Vaccines:**
    - PT (Pertussis toxoid), FHA (filamentous hemagglutinin), Pertactin, Agglutinogens
  - **Polysaccarides (T-cell independent antigens):**
    - Hæmophilus (no longer available), Meningococcus, Pneumococcus
  - **Influenza surface glycoproteins (HA, NA)**
- **Conjugated antigens (T-cell dependent):**
  - **HiB:** PRP-D, PRP-T, PRP-OMP, HBoC (crm197)
  - **Pneumococcal Conjugate-13 valent: CRM 197- 1, 3,** 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F
  - **Meningococcus A, C, W-135 & Y** conjugated to diphtheria toxoid

Current Technology

- Recombinant antigens:
  - HBsAg/ yeast
  - Meningococcus B:
    - Bexsero: recombinant proteins adhesin A, Heparin Binding Antigen, factor H binding protein, Outer Membrane Vesicles, aluminum hydroxide
    - Trumemba: recombinant lipidated factor H binding protein variants from serogroup B, subfamilies A & B, aluminum phosphate

Current Technology

- Virus-like particles:
  - HPV Quadrivalent Vaccine:
    - Major capsid proteins of human papillomavirus(HPV) serotypes 6, 11, 16 & 18 expressed in eucaryotic cells
    - 99-100% vs HPV 16/18 related Cervical Intraepithelial Neoplasia (CIN) 2/3 in uninfected women
    - 27% efficacy in women who are recently infected
    - No efficacy in those with established infection
    - FDA-approved for use in females 9-26 years in 2006
      - Males and a bivalent 16/18 vaccine later on
      - Younger age groups to follow

Rotavirus Vaccine

- RotaTeq Vaccine Study:
  - Pentavalent bovine-human reassortant vaccine
    - VP7 genes of serotypes G1, G2, G3, G4 and P-type P1A)
  - 70,000 placebo-controlled study:
    - 70% efficacy vs. any vaccine-serotype-related disease
    - 98% vs. severe disease
    - 85, 94, 96% ↓ in office visits, ED & hospitalizations
    - Intussuception:
      - 6 & 5 cases in the overall vaccine & placebo groups
      - 0 & 1 in vaccine & placebo groups after the 1st dose
  - 3 doses at 2, 4, & 6 months of age
  - Added to the 2007 Recommended childhood schedule

Zoster Vaccine Recombinant Adjuvated (Shingrix)

- Varicella virus recombinant gE antigen component + AS01B adjuvant suspension
- FDA-approved on Oct. 20, 2017
- Indication: adults ≥50 years of age including all who received prior live attenuated Zoster vaccine (Zostavax)
- 2 doses, with 2nd dose 2-6 months after the 1st

Newer Vaccine Technologies

- 2015: Malaria (RTS,S/AS01)
  - Repeat T-cell Epitope, HBsAg/Adjuvant
- 2019: Ebola vaccines
  - rVSV-ZEBOV: VSV replication competent vectored-expressing Kikwit strain surface glycoprotein
  - Ad26.ZEBOV/MVA-BN-Filo:
    - Prime (adenovirus expressing Mayinga variant surface glycoprotein)
    - Boost (Modified Vaccinia Ankara expressing expressing GP from EBOV, SUDV, and MARV as well as TAFV NP
- 2019: COVID-19 vaccines:
  - mRNA constructs

Adjuvants

- Non-pathogen related additives that improve immunogenicity
- Aluminum salts are most common
  - Hepatitis b vaccine, tetanus and diphtheria toxoids
- Mechanisms of action?
  - Formation of an antigen depot at the inoculation site
    - Water/oil emulsions & alum
  - Mobilization of Th cell response:
    - Protein carriers, polyA/polyU
  - Up-regulation of Ig receptors on B cells:
    - B-cell mitogens, antigen polymerizing agents
  - Increased uptake by Antigen-presenting cells:
    - MDP (muramyl dipeptide) derivatives, LPS, Lipid A
  - Cytokine induction & secretion

Invasive Pneumococcal Disease

FIGURE 1. Changes in incidence rate* of invasive pneumococcal disease (IPD) among children aged <5 years before and after introduction of 7-valent pneumococcal conjugate vaccine (PCV7), by age and year — Active Bacterial Core surveillance, eight states,† 1998–2005

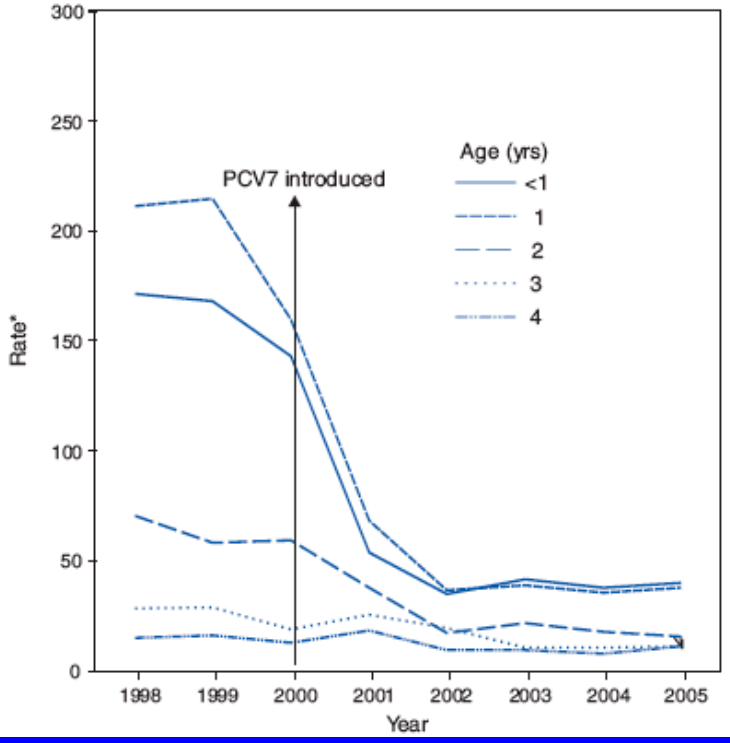
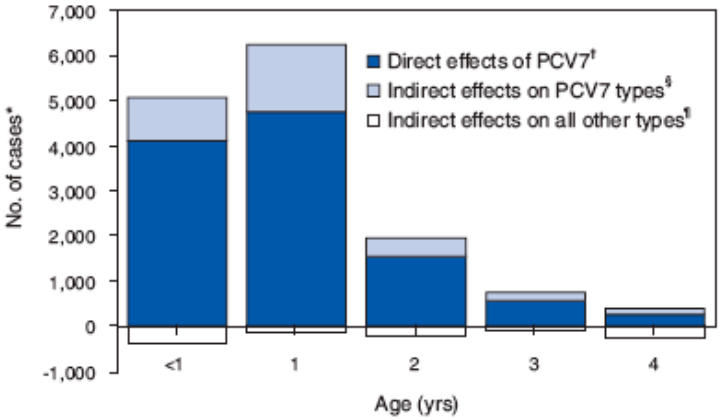


FIGURE 2. Projected number of invasive pneumococcal disease (IPD) cases prevented among children aged <5 years by 7-valent pneumococcal conjugate vaccine (PCV7), by age and direct or indirect effects — United States, 2005



* National projections of IPD cases calculated applying ABCs age- and race-specific rates to the age and racial distribution of the U.S. population using U.S. Census 2000 data.

† Calculated as a product of national projections of PCV7-type IPD cases among children aged <5 years in 1998–1999, PCV7 coverage (≥3 doses) for each birth cohort in 2001–2005, and PCV7 efficacy against PCV7-type IPD.

§ Calculated by subtracting national projections of PCV7-type cases in 2005 from average national projections of PCV7-type IPD cases in 1998–1999 and then subtracting PCV7-type IPD cases prevented directly.

¶ Calculated by subtracting national projections of non-PCV7-type cases in 2005 from average national projections of non-PCV7–type IPD cases in 1998–1999.

←19A

- Also ↓ pneumonia, otitis media

Comparison of 20th Century Annual Morbidity and Current Morbidity: Vaccine-Preventable Diseases

Disease	20th Century Annual Morbidity†	2019 Reported Cases ††	Percent Decrease
Smallpox	29,005	0	100%
Diphtheria	21,053	2	> 99%
Measles	530,217	1,287	> 99%
Mumps	162,344	3,509	98%
Pertussis	200,752	15,662	92%
Polio (paralytic)	16,316	0	100%
Rubella	47,745	3	> 99%
Congenital Rubella Syndrome	152	0	100%
Tetanus	580	19	97%
Haemophilus influenzae	20,000	14*	> 99%

† JAMA. 2007;298(18):2155-2163

†† National Notifiable Disease Surveillance System, Week 52 (2019 Provisional Data), Unpublished. Atlanta, GA. CDC Division of Health Informatics and Surveillance, 2020. Accessed on January 21, 2020.

* *Haemophilus influenzae* type b (Hib) < 5 years of age. An additional 12 cases of Hib are estimated to have occurred among the 243 notifications of Hi (< 5 years of age) with unknown serotype.

https://www.cdc.gov/ncird/surveillance/materials-resources.html

Comparison of Pre-Vaccine Era Estimated Annual Morbidity with Current Estimate: Vaccine-Preventable Diseases

Disease	Pre-Vaccine Era Annual Estimate	2016 Estimate (unless otherwise specified)	Percent Decrease
Hepatitis A	117,333 †	4,000 *	97%
Hepatitis B (acute)	66,232 †	20,900 *	68%
Pneumococcus (invasive)			
all ages	63,067 †	30,400 #	52%
< 5 years of age	16,069 †	1,700 #	89%
Rotavirus (hospitalizations, < 3 years of age)	62,500 ††	30,625 ##	51%
Varicella	4,085,120 †	102,128 ###	98%

† JAMA. 2007;298(18):2155-2163
†† CDC. MMWR. February 6, 2009 / 58(RR02):1-25
* CDC. Viral Hepatitis Surveillance - United States, 2016
# CDC. Unpublished, Active Bacterial Core Surveillance, 2016
New Vaccine Surveillance Network 2017 data (unpublished); U.S. rotavirus disease now has biennial pattern
CDC. Varicella Program 2017 data (unpublished)

https://www.cdc.gov/ncird/surveillance/materials-resources.html

Questions?

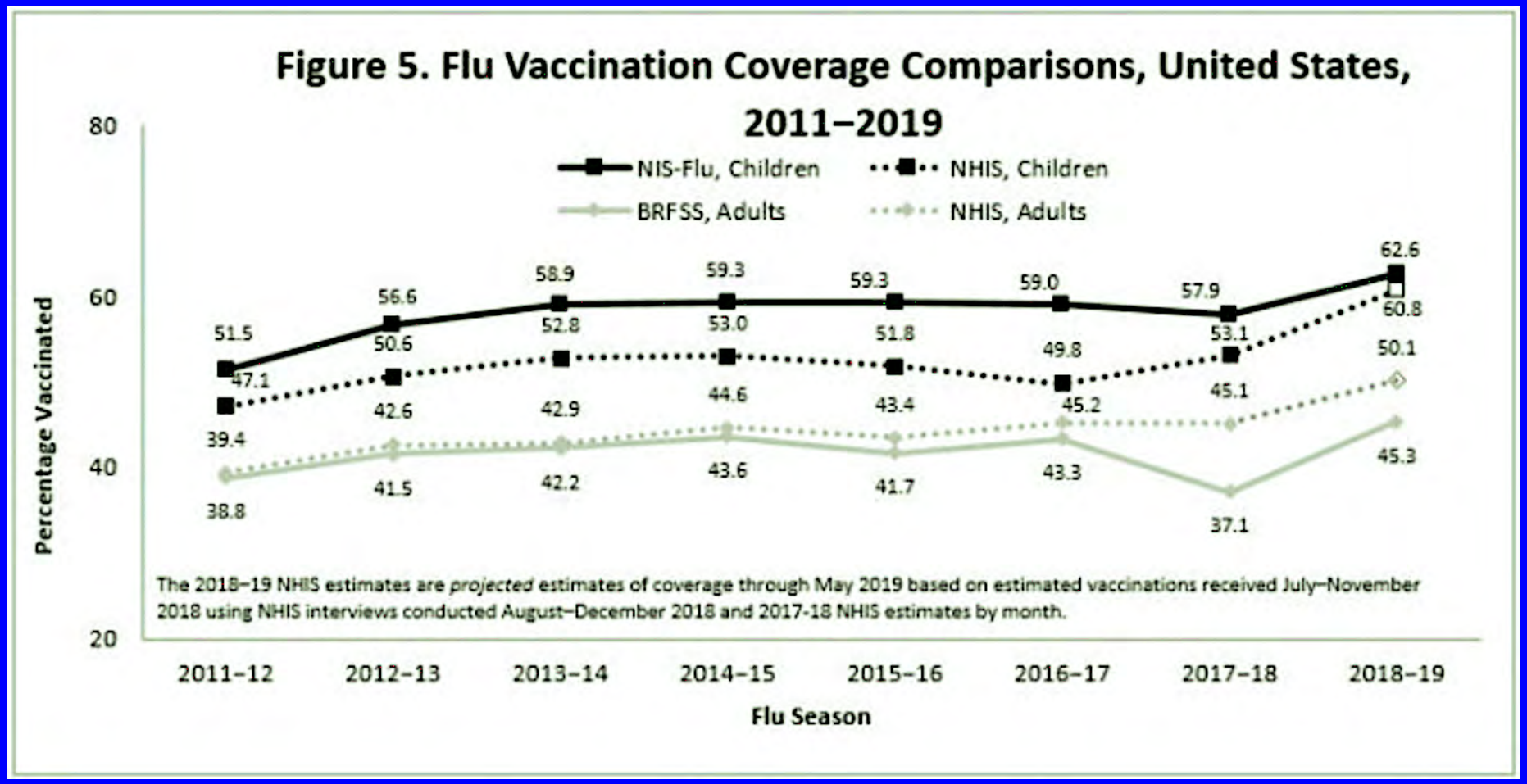
Vaccine Coverage Levels – United States, 1962-2016

Year	DTP 3+	DTP4+	Polio 3+	MMR*	Hib3+	Var	PCV3+	HepB3+	Rota	Combined 4-3-1	Combined 4-3-1-3
1962	67.3										
1963	71.4										
1964	74.6										
1965	72.7										
1966	74.0										
1967	77.9			60.0							
1968	76.8			61.5							
1969	77.4			61.4							
1970	76.4			58.4							
1971	77.8			62.2							
1972	74.1			62.8							
1973	71.7		59.5	61.0							
1974	72.4		60.0	63.4							
1975	73.2		63.6	65.5							
1976	72.7		61.3	66.3							
1977	69.6		62.6	65.0							
1978	66.6		59.5	63.6							
1979	64.4		59.7	66.5							
1980	66.0		58.9	66.6							
1981	68.1		59.2	66.8							
1982	67.1		57.0	67.6							
1983	65.4		56.9	66.3							
1984	65.0		53.2	65.8							
1985	63.6		53.6	61.2							
1986†											
1987†											
1988†											
1989†											
1990†											
1991	68.8		53.2	82.0							
1992	83.0	59.0	72.4	82.5	28.2			8.0		68.7	55.3
1993	88.2	72.1	78.9	84.1	55.0			16.3		67.1	
1994	93.0	77.7	83.0	89.0	86.0			37.0		75.0	
1995	94.7	78.5	87.9	87.6	91.7			68.0		76.2	74.2
1996	95.0	81.1	91.1	90.7	91.7	16.0		81.8		78.4	76.5
1997	95.5	81.5	90.8	90.5	92.7	25.9		83.7		77.9	76.2
1998	95.6	83.9	90.8	92.0	93.4	43.2		87.0		80.6	79.2
1999	95.9	83.3	89.6	91.5	93.5	57.5		88.1		79.9	78.4
2000	94.1	81.7	89.5	90.5	93.4	67.8		90.3		77.6	76.2
2001	94.3	82.1	89.4	91.4	93.0	76.3		88.9		78.6	77.2
2002	94.9	81.6	90.2	91.6	93.1	80.6	40.8	88.9		78.5	77.5
2003	96.0	84.8	91.6	93.0	93.9	84.8	68.1	92.4		82.2	81.3
2004	95.9	85.5	91.6	93.0	93.5	87.5	73.2	92.4		83.5	82.5
2005	96.1	85.7	91.7	91.5	93.9	87.9	82.8	92.9		83.1	82.4
2006	95.8	85.2	92.9	92.4	93.4	89.3	87.0	93.4		83.2	82.3
2007	95.5	84.5	92.6	92.3	92.6	90.0	90.0	92.7		82.8	81.1
2008	96.2	84.6	93.6	92.1	90.9	90.7	92.8	93.5		82.5	79.6
2009	94.0	83.9	92.8	90.0	92.1	89.6	92.6	92.4	43.9	81.5	50.6
2010	95.0	84.4	93.3	91.5	90.4	90.4	92.6	91.8	59.2	82.0	78.8
2011	95.5	84.6	93.9	91.6	94.0	90.8	93.6	91.1	67.3	82.6	81.9
2012	94.3	82.5	92.8	90.8	93.0	90.2	92.3	89.7	68.6	80.5	76.0
2013	94.1	83.1	92.7	91.9	92.8	91.2	92.4	90.8	72.6	81.5	77.1
2014	94.7	84.2	93.3	91.5	92.6	91.0	92.6	91.6	71.7	82.6	77.7
2015	95.0	84.6	93.7	91.9	93.2	91.8	93.3	92.6	73.2	83.2	77.7
2016	93.7	83.4	91.1	91.1	91.6	90.6	91.8	90.5	74.1	81.9	76.8

CDC, Epidemiology & Prevention of Vaccine-Preventable Diseases, 13th Ed., March 2018

TABLE 1. Estimated coverage with selected vaccines and doses among adolescents aged 13–17* years, by age at interview — National Immunization Survey–Teen (NIS-Teen), United States, 2018

	Age at interview (yrs), % (95% CI)†					Total	
	13	14	15	16	17	2018	2017
Vaccine	(n = 3,852)	(n = 3,875)	(n = 3,741)	(n = 3,751)	(n = 3,481)	(n = 18,700)	(n = 20,949)
Tdap§ ≥1 dose	87.1 (85.0–89.0)	87.7 (85.4–89.7)	89.7 (87.8–91.4)	89.0 (87.1–90.6)	91.0 (89.5–92.4)¶	88.9 (88.0–89.7)	88.7 (87.8–89.6)
MenACWY**							
≥1 dose	86.3 (84.2–88.1)	86.2 (84.0–88.1)	86.1 (83.7–88.2)	86.3 (84.0–88.3)	88.1 (86.3–89.6)	86.6 (85.6–87.5)††	85.1 (84.2–86.1)
≥2 doses§§	NA	NA	NA	NA	50.8 (47.7–53.8)	50.8 (47.7–53.8)††	44.3 (41.4–47.2)
HPV¶¶ vaccine							
All adolescents							
UTD***	39.9 (37.0–42.9)	50.3 (47.3–53.2)¶	54.0 (51.0–56.9)¶	54.5 (51.5–57.5)¶	57.5 (54.4–60.5)¶	51.1 (49.8–52.5)††	48.6 (47.3–49.9)
≥1 dose	62.6 (59.7–65.4)	66.9 (64.1–69.6)¶	69.7 (66.9–72.3)¶	71.2 (68.5–73.8)¶	70.1 (67.3–72.8)¶	68.1 (66.8–69.3)††	65.5 (64.3–66.7)
Females							
UTD	38.9 (35.0–42.9)	52.7 (48.5–56.8)¶	54.7 (50.4–59.0)¶	57.5 (53.3–61.6)¶	66.0 (61.8–70.1)¶	53.7 (51.8–55.6)	53.1 (51.2–55.0)
≥1 dose	61.1 (56.9–65.2)	68.6 (64.4–72.5)¶	70.7 (66.5–74.5)¶	73.5 (69.8–76.8)¶	76.3 (72.2–80.0)¶	69.9 (68.1–71.6)	68.6 (66.9–70.2)
Males							
UTD	40.9 (36.5–45.3)	47.7 (43.6–51.8)¶	53.2 (49.1–57.3)¶	51.8 (47.5–56.1)¶	50.0 (45.7–54.3)¶	48.7 (46.8–50.6)††	44.3 (42.6–46.0)
≥1 dose	64.0 (59.9–67.9)	65.1 (61.3–68.7)	68.7 (65.0–72.1)	69.2 (65.2–73.0)	64.7 (60.7–68.5)	66.3 (64.6–68.0)††	62.6 (60.9–64.2)
MenB ≥1 dose†††	NA	NA	NA	NA	17.2 (14.9–19.9)	17.2 (14.9–19.9)	14.5 (12.3–17.1)
MMR ≥2 doses	93.5 (92.1–94.7)	93.0 (91.6–94.2)	91.8 (89.9–93.3)	90.5 (88.4–92.2)¶	90.9 (89.2–92.4)¶	91.9 (91.2–92.6)	92.1 (91.3–92.8)
Hepatitis B vaccine ≥3 doses	93.1 (91.5–94.5)	93.0 (91.5–94.3)	91.6 (89.1–93.5)	91.1 (89.3–92.6)	91.8 (90.1–93.2)	92.1 (91.3–92.8)	91.9 (91.1–92.6)
Varicella vaccine							
History of varicella disease§§§	9.8 (8.1–11.9)	10.3 (8.5–12.4)	11.8 (10.0–13.9)	12.4 (10.7–14.3)	15.0 (13.2–17.1)¶	11.9 (11.0–12.7)††	13.2 (12.3–14.2)
No history of varicella disease							
≥1 dose vaccine	95.4 (94.2–96.5)	95.4 (94.2–96.3)	94.1 (92.1–95.6)	94.3 (92.7–95.5)	95.2 (93.9–96.3)	94.9 (94.3–95.4)	95.5 (94.8–96.1)
≥2 doses vaccine	92.1 (90.5–93.4)	91.3 (89.6–92.8)	89.8 (87.4–91.8)	86.6 (84.3–88.7)¶	87.9 (85.4–90.1)¶	89.6 (88.7–90.4)	88.6 (87.6–89.5)
History of varicella or ≥2 vaccine doses	92.9 (91.4–94.1)	92.2 (90.6–93.5)	91.0 (88.9–92.7)	88.3 (86.2–90.1)¶	89.7 (87.5–91.6)¶	90.8 (90.0–91.6)	90.1 (89.3–90.9)



https://www.cdc.gov/flu/fluvaxview/coverage-1819estimates.htm

Table 1–A: Influenza vaccination coverage estimates by age group — United States,* 2007–08 through 2010–11

Age Groups	Estimate†	2007-08‡	2008-09‡	2009-10 Seasonal (Trivalent)§	2010-11
6 months–17 years	n			149,872	116,799
	%	NA	NA	43.7	51.0
18–64 years	n	140,955	235,800	246,461	244,933
	%	30.7	33.6	34.4	34.8
≥65 years	n	58,987	106,402	115,018	132,636
	%	72.3	74.0	69.6	66.6

https://www.cdc.gov/flu/fluvaxview/trends/age-groups.htm