Immunization Update 2017

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Learning Objectives

At the end of the presentation, the participant will be able to:

1. Identify important recent changes to the immunization schedules for adults and children in the United States.
2. Discuss the epidemiology of recent outbreaks of vaccine-preventable diseases in the United States.
3. Incorporate recent ACIP recommendations into your practice.
4. List promising new vaccines in the development pipeline

Self-Assessment Question #1

The new HPV9 vaccine schedule states that the 2 dose regimen should be given:

A. Now and 1-2 months later to all patients 9 to 26 years of age
B. now and 6-12 months later to all patients 9 to 26 years of age
C. now and 1-2 months later to all patients 9 to less than 15 years of age
D. now and 6-12 months later to all patients 9 to less than 15 years of age

Self-Assessment Question #2

Which high risk patients should be given meningococcal B vaccine?

A. All college students at age 18
B. All adolescents at age 18
C. All patients with complement deficiencies
D. All patients with HIV/AIDS

Self-Assessment Question #3

The FDA has approved meningococcal B vaccination with Trumenba as a:

A. A single dose
B. 2-dose series given at 0 and 1-2 months under certain circumstances
C. 2-dose series given at 0 and 6 months under certain circumstances
D. Must always be given as a 3 dose series at 0, 1-2 months, and 6 months.

Self-Assessment Question #4

The ACIP has recommended that vaccination with LAIV (Flumist®) in the 2016-2017 influenza season

A. Is preferred in children over IIV
B. Has no preference from the ACIP over IIV
C. Should not be given to anyone
D. Should be given to all age eligible patients 2-49 years-old

Self-Assessment Question #5

Vaxchora (Cholera vaccine Live, Oral- Pax Vax) is ACIP recommended for:

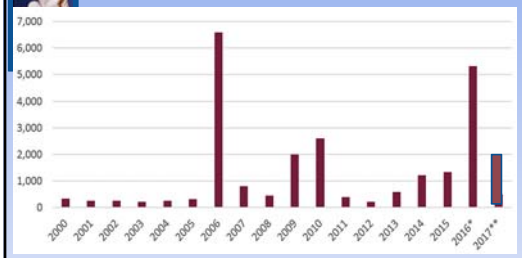
A. All traveler outside the U.S.
B. All traveler to countries with active cholera cases
C. All travelers likely to have direct contact with cholera cases
D. All travelers to countries with recent natural disasters

Vaccine-Preventable Diseases

Disease	Max. Cases	Year	Cases 2012	Cases 2013	Cases 2014	Cases 2015	Cases 2016
Diphtheria	206,939	1921	1	0	1	0	0
Hib	~20,000	1980's	30	18	27	16	30
Measles	894,134	1941	55	184	628	188	83
Mumps	152,209	1968	229	438	1,151	422	5311
Pertussis	265,209	1934	48,277	24,231	28,660	13,004	4,988
Rubella	2.5 Million	1964-1965	9	9	8	4	2
CRS	~30,000		3	0	1	1	0
Tetanus	601	1948	37	19	21	17	7
Varicella	221,983	1984	13,447	9,987	9,058	5,373	2,843

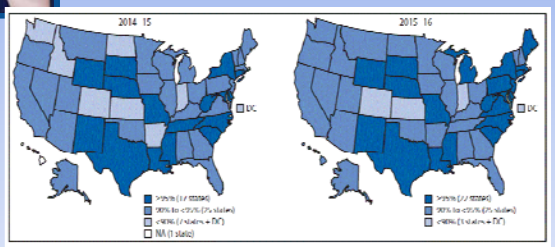
Epidemiology and Prevention of Vaccine-Preventable Diseases. 12th ed.; May 2012
JAMA. 2007;298:2155–263
MMWR. Weekly / April 21, 2017 /66(15)

Mumps Cases in U.S., by Year



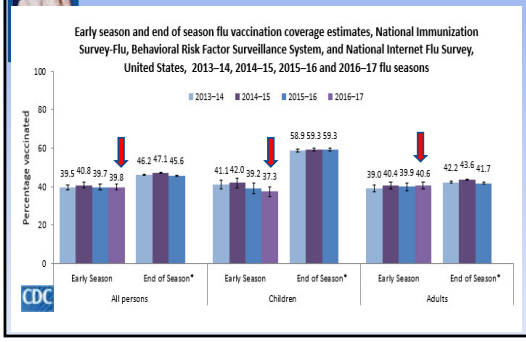
CDC

MMR Coverage by State



CDC

Influenza Coverage Estimates, 2013-2017



CDC

HPV9 Vaccine (Gardasil 9 – Merck)

- October 7, 2016 2 dose schedule approved by FDA
  - 2 doses may improve compliance
- Immunogenicity data presented to ACIP
  - Higher titers with vaccination than natural infections
  - Non-inferior antibody response in 9-14 year olds with 2 doses
    - Compared with 3 doses in 16-26 year olds
    - 0–6 months or 0–12 months schedule
    - 97.8%-100% seropositivity
    - Higher seroconversion in younger ages

2-Dose Schedules

- Minimum interval of 5 months for 2 doses mandatory
  - Memory B cells require 4-6 months to mature and differentiate into high-affinity B cells
  - 6-month interval allows last dose to efficiently reactivate memory B cells
- Persistence
  - No data from 2-dose studies

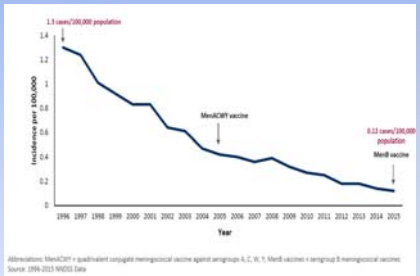
HPV Recommendation

- 2-dose schedule at age 11-12 years
  - Include "less than 15 years"
  - Second dose 6-12 months after first
  - If interval less than 6 months, give third dose 6 months from first
- 3-dose schedule after 15th birthday
  - 0,1-2,6 months
- Special situations
  - If interrupted, doses based upon age of first dose
  - Minimum interval 5 months (FDA Approved)
  - Immunocompromised – 3-dose series
- Vote: Approved
- Note: HPV2 and HPV4 no longer available

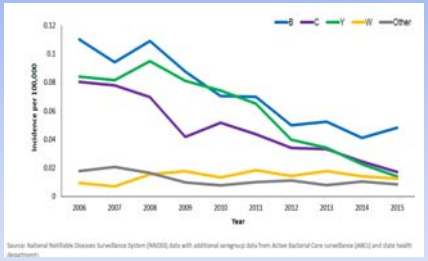
Meningococcal Vaccines

- Men ACWY Vaccines
  - Menomune – Sanofi Pasteur (MPSV4)
    - No longer available after last dose expires June-September 2017
  - Menactra – Sanofi Pasteur (MenACWY135-D)
  - Menveo – Novartis (MenACWY-135-CRM)
  - MenHibrix – GSK (HibMenCY-TT)
  - CDC-ACIP recommendations
    - Routine in adolescents
    - High-risk over 2 months of age
- MenB Vaccines
  - Both licensed by FDA for ages 10–25 years
  - Trumenba (Pfizer)
    - 3 dose series (0, 2, 6 months)
    - Components: FHBP subfamily Av2,3; subfamily B/v1
  - Bexsero (Novartis)
    - 2 dose series (0, 1–6 months)
    - Components: FHBP subfamily B/V1, NhbA, NadA, Por A1.4

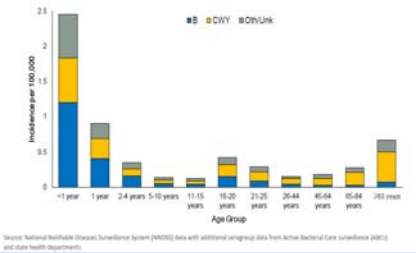
Meningococcal Disease Incidence- All types, U.S. 1996-2015



Meningococcal Disease Incidence, U.S. 1996-2015



Average Annual Incidence by Age-Group and Serogroup- U.S., 2006-2015



Estimated Average Annual Cases, Deaths, and Sequelae, 2009–2013

	Age Group	Cases	Deaths	Sequelae
Serogroup B	<5 years 11-24 years All ages 18-23 years (College) 18-23 years (Non-College)	74-94 54-67 203-260 14 22	7-14 5-10 20-39 2 3	7-19 5-13 20-52
Serogroups C and Y	<5 years 11-24 years All ages	34-43 62-77 307-393	3-6 6-12 31-59	3-9 6-15 31-79

The majority (80%) of MenB cases in the 11-24 age group occur in ages 16-24 years

Trumenba (Pfizer) Dosing Schedules Studied

3-dose schedule
- 0,2,6 months
- 0,1,6 months

2-dose schedule
- 0,6 months
- 0,4 months
- 0,2 months
- 0,1 month

- Short-term immunogenicity
  - Based upon reanalysis of earlier studies used for initial approval
  - Slightly lower with 2-dose 0,6 months highest
- Antibody persistence
  - Similar
- Similar response to booster dose
- Similar safety profiles

Trumenba Revised Dosing

- Approved by FDA (April 4, 2016)
  - 0, 6 months
  - 0, 1-2, 6 months
  - Choice depends upon risk of exposure and patient's susceptibility to MenB disease
    - High-Risk Patients
      - Persons with compliment deficiencies
      - Persons presently taking Eculizumab (Soliris®)
      - Persons that are asplenic
      - Microbiologist
      - Those exposed during outbreaks of disease.
- ACIP voted to agree with FDA recommendation

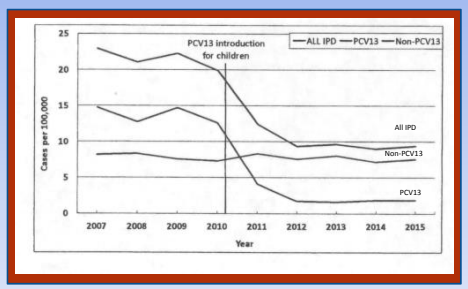
Final Wording

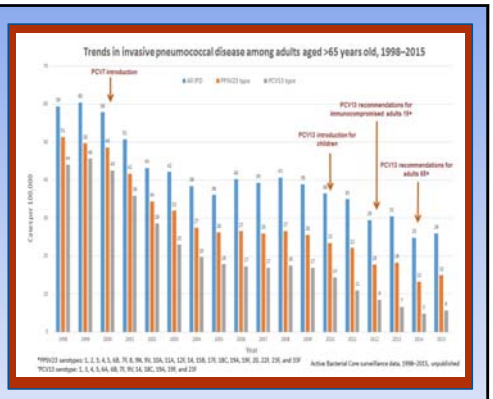
- For a person at increased risk for meningococcal disease and for use during serogroup B outbreaks, 3 doses of MenB-FHbp should be administered at 0, 1-2, 6 months
- When given to healthy adolescents who are not at increased risk for meningococcal disease, 2 doses of MenB-FHbp should be administered at 0 and 6 months
- If the second dose is given at an interval of <6 months, a third dose should be given at least 6 months after the first dose

Challenges

- Meningococcal B Vaccine
  - Number of cases of MenB that could be prevented with vaccine unknown
  - Limited duration of protection – Booster doses recommended
    - Recommended intervals under discussion
  - Strain coverage not clinically proven
  - Effectiveness data not available
    - Licensure based upon immunological studies
  - Impact on carriage unknown
  - Impact on circulating strains unknown
- Menomune (MPSV4) – Removed from Market
  - FDA approval included age 56 years and older
  - No vaccine FDA approved for this age group
  - CDC still recommends MCV4 for high-risk groups over 55 years of age

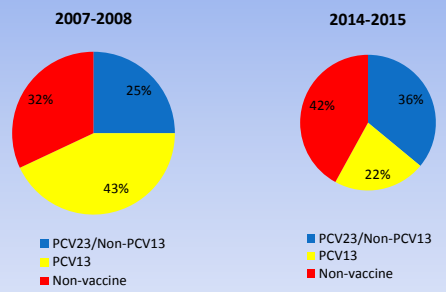
Annual Trends in IPD Incidence Children <5 years old, 2007-2015



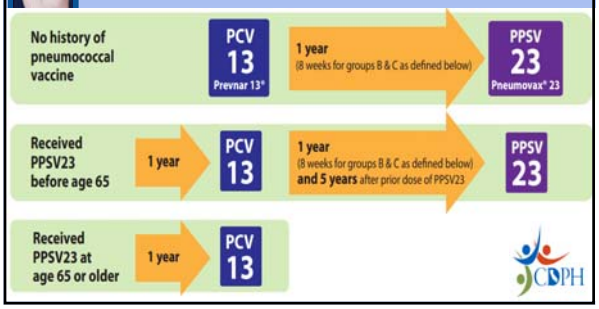


Source: ACIP Meeting, October 2016

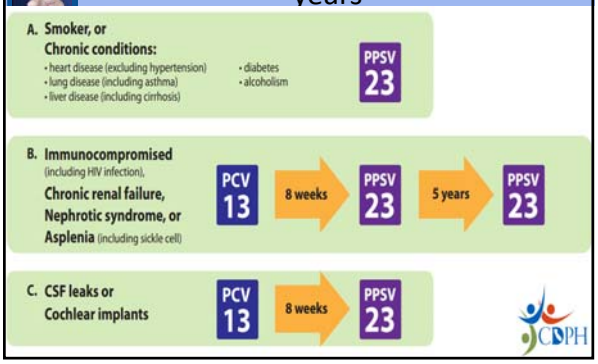
Serotype Distribution among Adults ≥65 Years Old



Pneumococcal Vaccine for 65 years and older



Pneumococcal Vaccine for 19-64 years



Vaccine Effectiveness – US Flu VE Network (all ages)

2015-2016

- Any Vaccine – Overall Adjusted VE – 47%
  - A/H1N1pdm09 – 41%
  - A/H3N2 – 45%
  - B/Yamagata – 55%
  - B/Victoria – 55%
- IIV – Overall Adjusted VE – 49%
  - A/H1N1pdm09 – 44%
  - A/H3N2 – 43%
  - B/Yamagata – 59%
  - B/Victoria – 58%

2016-2017 – Estimates

- Any Vaccine – Overall Adjusted VE – 48%
- A (H3N2) – 43%
- Influenza B – 73%

Results of VE (%) since 2009

2-17 years (U.S. Flu Network)

Any Flu A or B

	2010-11 Mixed	2011-12 H3N2	2012-13 H3N2	2013-14 H1N1	2014-15 H3N2	2015-16 H1N2
IIV	71	55	45	60	15	63
LAIV3	71	67	46			
LAIV4				-1	3	3

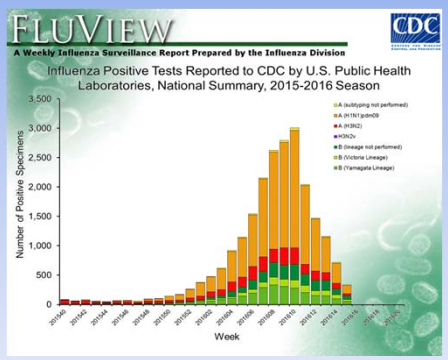
Possible Explanations

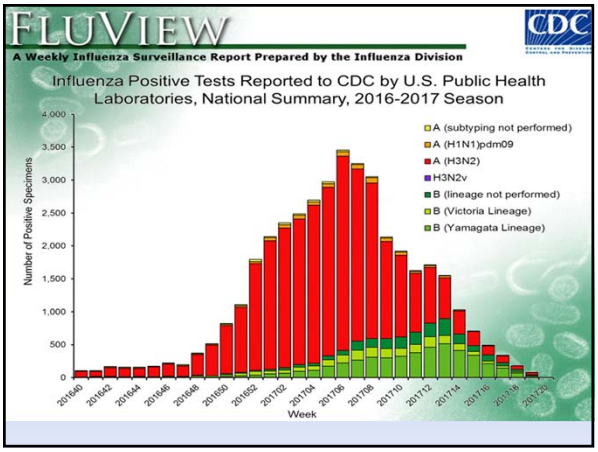
- Suboptimal performance of A/H1N1 vaccine strain
- Interference among virus when additional B strain added to quadrivalent
- Reduce immunogenicity of LAIV as a result of more highly vaccinated population in later years; more children were vaccine naïve in earlier years
- **Vote**
  - **"In light of the evidence for poor effectiveness of LAIV in the United States over the last three influenza seasons (2013-2016), for the 2016-17 season, the ACIP makes the interim recommendation that LAIV should not be used."**
- MedImmune studying new vaccine strain
  - LAIV has 6 internal genes and 2 external genes (HA & NA) from circulating strains

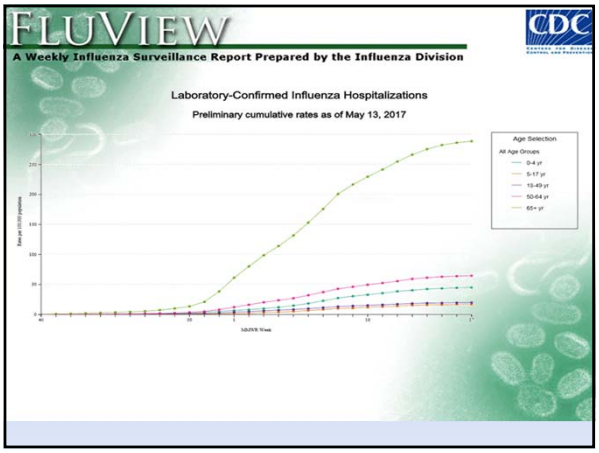
Recommendations for 2016-17 Influenza Season

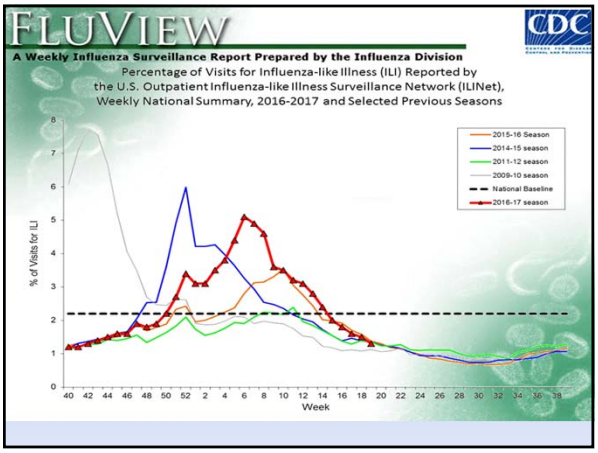
- **No LAIV**
- Reiteration of vaccination of all persons 6 months and older
- Minor change in wording of vaccination timing
  - "Healthcare providers should offer vaccination by October, if possible. Vaccination should continue to be offered as long as influenza viruses are circulating."
- Changes to egg allergy recommendations
- New vaccines
  - Flublok quadrivalent approved
- No vaccine preferences for one vaccine over another

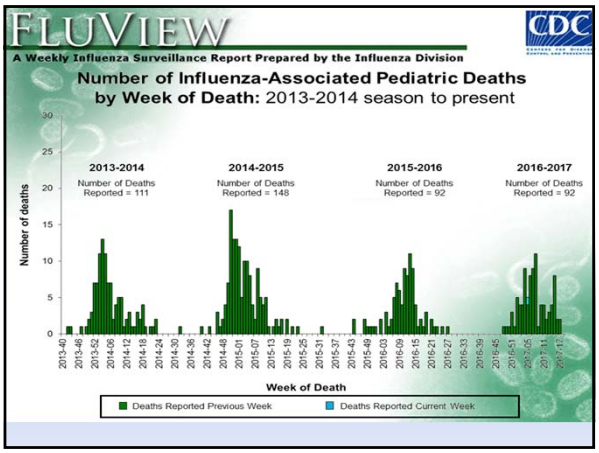
2015-2016

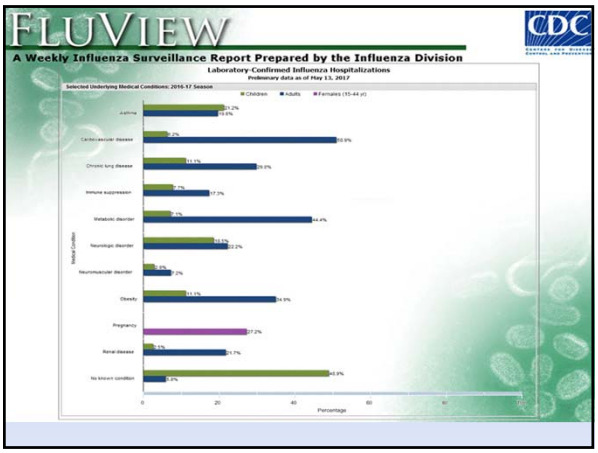












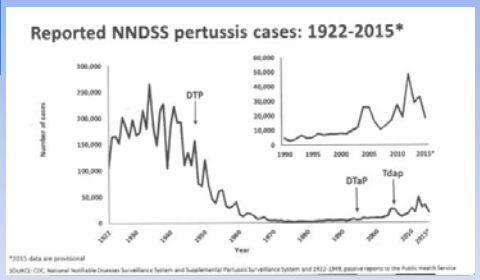
Adjuvanted IIV3 Vaccine

- Developed by Novartis (now Seqirus)
- MF59 Adjuvant
  - Approved in Europe and Canada (30 countries)
    - 17 years of use with 76 million doses distributed
  - Enhances immune response
    - Squalene and surfactants
    - Recruits immune cells and activates T cells and B cells
    - 39 studies available
      - Immunological studies non-inferior
      - Generated higher AB titers
      - Higher immune response to drifted strains
  - Safety profile similar to non-adjuvanted vaccine
    - No narcolepsy reported
- Favorable by VERPAC for 65 years and older

High-dose (HD) vs Standard Dose (SD) Presented at Feb 2017 ACIP

- 50,000 residents in 823 nursing homes
  - Review of records- Not a prospective study
  - Study flaws noted
    - Severity of season
    - 10% of residents not vaccinated
    - H1N1 circulating (No difference if TIV or QIV)
    - Reduced hospitalizations not the only benefit of vaccination
  - Roughly equal numbers of HD and SD
- Number Need to Treat with HD to prevent 1 hospitalization = 81
  - 81 HD vaccines cost about $2430 (81 x approximately $30/vaccine)
  - Much less than one hospitalization

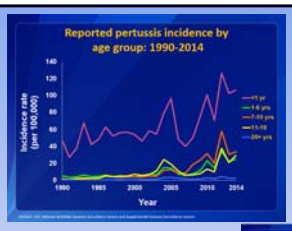
Pertussis



CDC

Source: CDC ACIP Meeting, October 2016

Pertussis



Source: CDC ACIP Meeting, October 2016

Tdap in Pregnant Women

- Current recommendations 27-36 weeks
  - First passed in 2011
  - Coverage range 14-48% in United States
  - Safety monitoring reassuring – no increased risk
- New data on earlier vaccine administration
  - High maternal antibody concentrations
  - Higher anti-pertussis antibody in infant cord blood when vaccine given to mothers earlier
    - Perhaps due to longer exposure time during pregnancy
    - Vaccinating too early may not allow for sustained antibodies during first 2 months of life

Tdap Recommendations

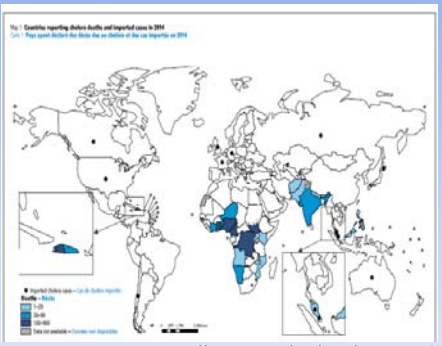
"Tdap should be administered between 27-36 weeks gestation, although it may be given at any time during pregnancy. Currently available data suggest that vaccinating earlier in the 27 through 36 week window will maximize passive antibody transfer to the infant."

CDC

New Influenza Vaccine Licensures

- Afluria (Seqirus)
  - **Quadrivalent**
    - Approved August 24, 2016 for ≥18 year olds
    - Studies for ≥6 months underway
  - TIV and QIV approved for PharmaJet
- Fluad (Seqirus)
  - **Trivalent**
    - Approved for adults 65 years and older
  - Adjuvanted with MP59
- Flucelvax **Quadrivalent** (Seqirus)
  - Approved May 23, 2016 for ≥ 4 years
- Flublok **Quadrivalent**
  - Approved October 7, 2016
- FluLaval **Quadrivalent**
  - Approved November 18, 2016 for use in younger children
  - Now persons **6 months** and older
  - Same dose (15mcg of each strain)

Cholera

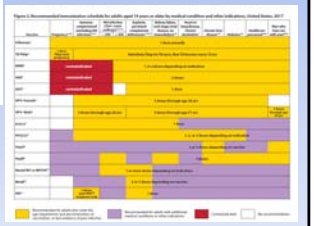


http://www.who.int/wer/2015/wer9040.pdf

Vaxchora (PaxVax)

- Single oral dose given 10 days before travel
- Approved June 2016 for persons aged 18-64 years
  - Aid, refugee, and health care workers likely to have direct contact with bodily fluids in proximity to displaced populations, especially in crowded camps or impoverished areas
- Adverse effects
  - Tiredness, headache, abdominal pain, N/V, lack of appetite, diarrhea
- No data on this vaccine in:
  - Pregnancy, breastfeeding, immunocompromised, children, shedding/household transmission
- 80-90% effectiveness
  - Duration of protection: 3-6 months
  - No activity against E Coli for Travelers diarrhea

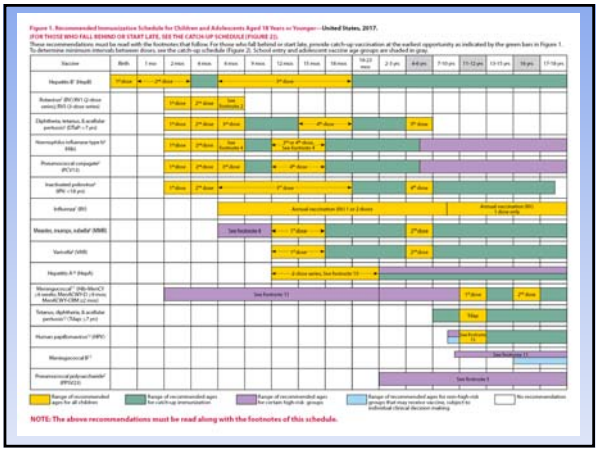
ACIP Immunization Schedule for Adults, 2017

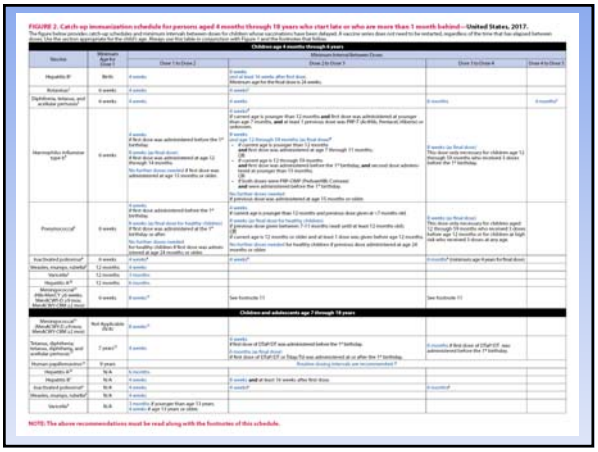


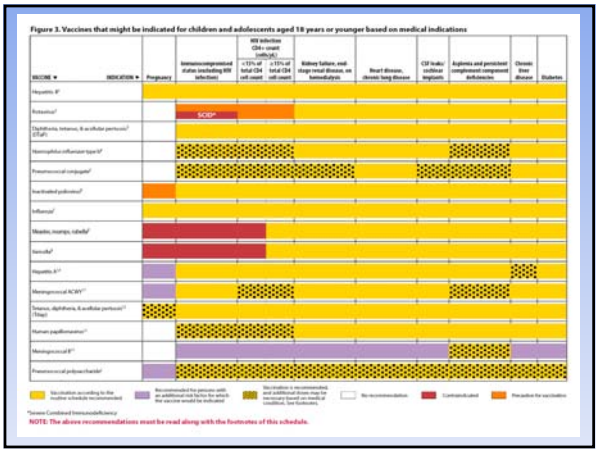
Contraindications and Precautions

Adult Schedule Changes

- Influenza
  - No LAIV for 2016-2017
  - History of Egg Allergy with only hives can receive any IIV
- HPV
  - 2 dose series before age 15 years
- Hepatitis B
  - Updates chronic liver disease conditions
- Meningococcal
  - Separate ACWY-135 and B into two rows
  - MenB for high-risk vs Category B
  - HIV not a routine indication for MenB
    - Men ACWY added as recommended for HIV infected adults
  - 2 or 3 doses MenB depending on vaccine
- Footnote Changes







Childhood and Adolescent Schedule Changes

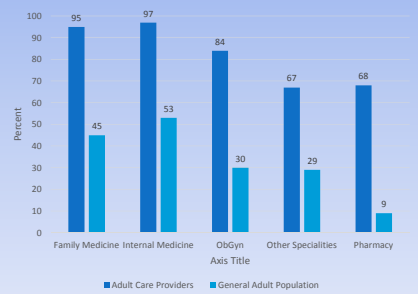
- New Figure Three - Contraindications
- 16 year-old column added for MenB
- Influenza
  - No LAIV for 2016-2017
- Hep B
  - Change permissive birth dose recommendation to recommend
- Tdap
  - Give closer to 27 weeks than 36 weeks
- HPV
  - 2 dose series at least 5 months apart if started before age 15 years
  - HPV2 and HPV4 gone
- Foot Note Changes

Pharmacist Administered Influenza Vaccine

- Study using prescription database and BFRSS 2007-2013
- Results
  - Number vaccinations increased from 3.2 million to 20.9 million
  - No significant difference in adult vaccination rates
  - No observed difference in high-risk adult vaccination rates
- Conclusion
  - "…we do not observe substantial increases in adult immunizations vaccination rates……which suggest that most of the people vaccinated by pharmacists would have been vaccinated anyway. The main benefit…a more convenient and flexible way to obtain an important health service"

McConeghy KW, Wing C. A national examination of pharmacy-based immunization statutes and their association with influenza vaccinations and preventive health. *Vaccine* 2016;34:3463-3468

Comparison of Adult Vaccination Assessments Reported by HCPs and Pharmacists, and General Adult Populations, United States, 2016



CDC

VACCINES IN THE PIPELINE

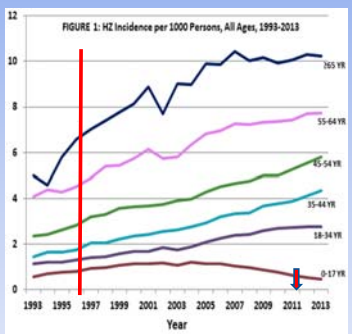
Ebola Vaccine Trials

- Guinea and Sierra Leone Trial
  - recombinant vesicular stomatitis virus vaccine expressing the glycoprotein of Zaire Ebola virus
    - Protects against 1 or 5 strains of Ebola
  - Phase 3 trial –ring vaccination
    - Not placebo controlled- offered immediate vaccination or 21 day delay
  - 100% effective after 10 days
- Sierra Leone Trial – China CDC
  - Recombinant adenovirus type-5 vector based vaccine
  - Phase 2 trial
  - Safe and highly immunogenic
  - 85% decrease in response after 6 months
- Developed after peak of outbreaks
- Other vaccine trials ongoing which may interfere with overall result
- Duration of protection unknown

RSV Vaccine

- No successful vaccine since virus discovery 1956
  - Monoclonal antibodies for high-risk infants
- First vaccine 1966
  - Formalin inactivated
  - More severe RSV disease than unvaccinated
- Novavax, Inc.
  - Completed Phase 3 trials in older adults
    - Initial results not good
    - Trials ongoing – differing formulations
  - Multiple studies ongoing
    - Maternal immunizations
    - Pediatrics

Zoster Incidence



Rafael Harpaz. 2015 Centers for Disease Control and Prevention, Atlanta, GA. ID Week

Zoster Vaccines

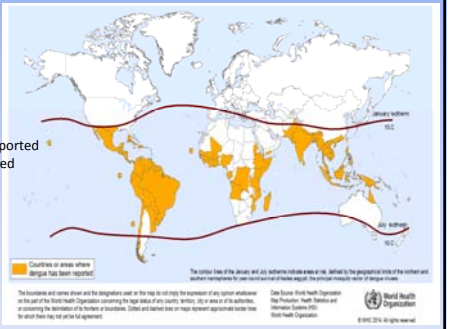
- V212 (Merck)
  - Inactivated formulation of Zostavax
  - 4-dose series in persons >18 years of age
  - Ongoing Phase 3 efficacy trials
- HZ/su (GSK) – Shingrix
  - Inactivated, 2-dose series in persons
  - Efficacy
    - 97.2% ≥50 years
    - 89% ≥ 70 years
      - 70-79 years – 90.0%
      - ≥80 years – 89.1%
  - Submitted BLA to FDA October 2016

Planned Studies With HZ/su

- Revaccination
  - Boostability at 5 and 10 years
  - Booster after live vaccine
- Co-administration
- Duration of protection
- Efficacy in select immunocompromised patients
- Impact on daily life
- Comparison study with live vaccine

Dengue – Global 2013

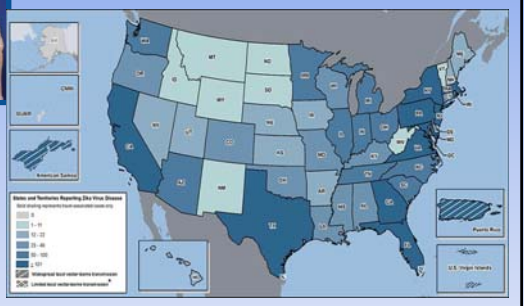
- 3.2 million cases reported
- 50-100 mill estimated
- 9,000+ deaths



Dengue Vaccine

- Ideal vaccine must cover DENV 1-4 strains
- Dengvaxia (CYD-TDV)
  - Registered in several dengue endemic countries (not the US)
  - Live attenuated, recombinant, tetravalent
  - 3 SC doses 6 month intervals
  - 53%-93% vaccine efficacy for up to 3 years (early estimates)
  - May make infections worse in areas of low disease incidence.
- Several other candidate vaccines
  - Recombinant, DNA, VLP, virus-vectored, live-attenuated

Zika Virus Update



- 4,835 cases in United States

https://www.cdc.gov/zika/intheus/maps-zika-us.html. Accessed January 5, 2017

Inactivated Zika Vaccine Trial Started

- Induced neutralizing antibodies in rhesus monkeys
- First of 5 phase 1 trials (Military)
- 75 participants with no previous infections by flaviviruses
- To be completed by fall 2018
- Additional trials to start soon

Health Agencies Update. *JAMA* 2016;316(24):2588