Beyond the Pediatric Vaccine Schedule

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Outline

- Current vaccine schedules for adolescents and adults
- Building adolescent and adult platforms
- Which vaccines might be added next?
  - Sexually transmitted infections (STIs)
  - Cytomegalovirus (CMV)
  - *Clostridium difficile* (C. diff)
  - Group B *streptococcus* (GBS)

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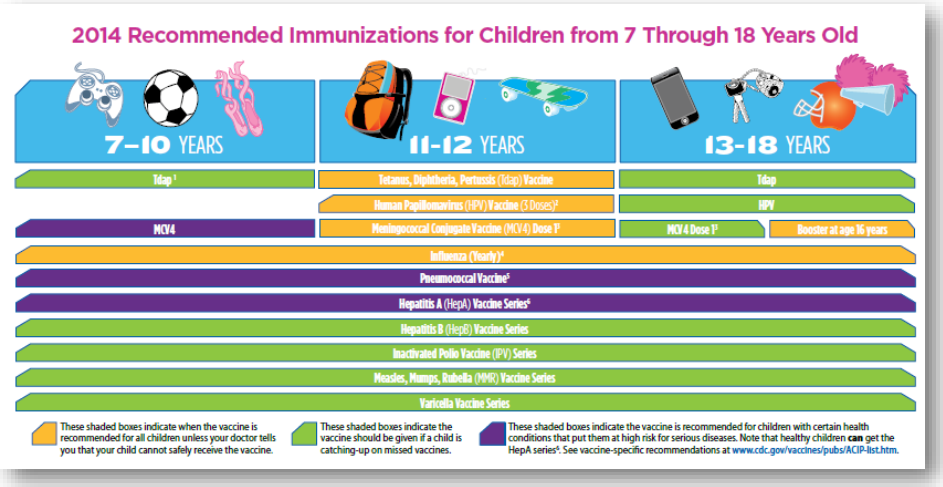

Recommended Adult Immunization Schedule—United States - 2014

Note: These recommendations must be read with the footnotes that follow containing number of doses, intervals between doses, and other important information.

Figure 1. Recommended adult immunization schedule, by vaccine and age group[1]

VACCINE ▼ AGE GROUP ►	19-21 years	22-26 years	27-49 years	50-59 years	60-64 years	≥ 65 years
Influenza [2,*]	1 dose annually					
Tetanus, diphtheria, pertussis (Td/Tdap) [3,*]	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs					
Varicella [4,*]	2 doses					
Human papillomavirus (HPV) Female [5,*]	3 doses					
Human papillomavirus (HPV) Male [5,*]	3 doses					
Zoster [6]					1 dose	
Measles, mumps, rubella (MMR) [7,*]	1 or 2 doses					
Pneumococcal 13-valent conjugate (PCV13) [8,*]	1 dose					
Pneumococcal polysaccharide (PPSV23) [9,10]	1 or 2 doses					1 dose
Meningococcal [11,*]	1 or more doses					
Hepatitis A [12,*]	2 doses					
Hepatitis B [13,*]	3 doses					
Haemophilus influenzae type b (Hib) [14,*]	1 or 3 doses					

*Covered by the Vaccine Injury Compensation Program

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STI Vaccine Roadmap
A long overdue intervention

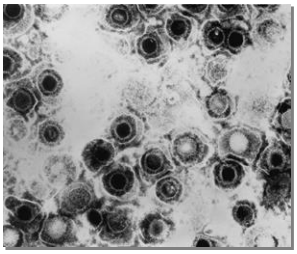
- **Decade of Vaccines and Global Vaccine Action Plan provide a global mandate to support vaccine development for neglected diseases**
- **WHO estimates 500 million people newly infected in 2008**
  - Chlamydia trachomatis
  - Neisseria gonorrhoeae
  - Treponema pallidum
  - Trichomonas vaginalis
- **HSV infection estimated at over 530 million people**
  - Increased risk of HIV acquisition associated with HSV-2 infection
  - A compelling public health argument for investment

STI Vaccine Roadmap
A long overdue intervention

- The investment case for development is a global imperative
- Each vaccine is at a different stage of development, yet there is progress in understanding all five
- Scientists attending the WHO consultation felt the time was right to exchange information and build consensus
- It is time to rekindle global interest for a neglected and yet critically important field
- If not now, when?

Gaps in Knowledge
Herpes simplex virus

- Candidate prophylactic vaccines have been disappointing
- Second generation vaccines are in development and in early clinical trials
- Limited understanding of different immunological responses between discordant couples and between sexes
- Future candidates need to protect against HSV 1 or 2
- Complete immunity may be challenging but advances could demonstrate reduction in viral shedding and disease



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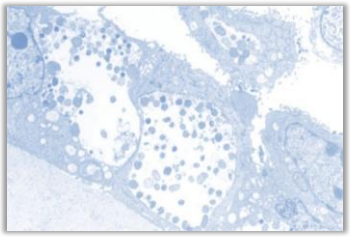
Gaps in Knowledge
Chlamydia trachomatis

- Screening programs have been difficult to bring to scale
- Limited understanding of protective immunological responses
- Reverse vaccinology has identified a large selection of target antigens
- Vaccine candidates in basic and early preclinical development
- Recent ability to genetically manipulate *Chlamydia* may advance the field



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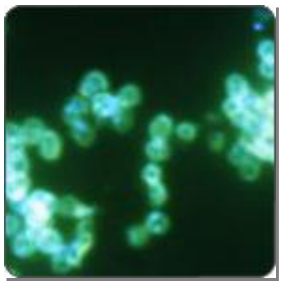
Gaps in Knowledge
Neisseria gonorrhoeae

- Rising antimicrobial resistance globally increases the urgency
- Evades the host immune response through antigenic variation and immunosuppression
- Vaccines against GroupB *Neisseria meningitidis* may provide insight
- Vaccine candidates in basic and early preclinical development
- Diagnosing PID is a barrier to assessing it as a clinical trial endpoint



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Gaps in Knowledge
Treponema pallidum

- **Syphilis is a generalized problem in parts of the world and a resurgent problem in high risk groups**
- **Causes adverse pregnancy outcomes and enhances HIV transmission**
- **Modeling is needed to understand the benefits and economic rational of a vaccine versus screening programs**
- **Technical difficulties in experiments with *T. pallidum* and limited number of researchers**

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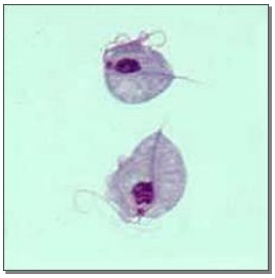
Gaps in Knowledge
Trichomonas vaginilas

- **Lack of diagnostic tests hampers identification and control**
- **Need to improve understanding of epidemiology and natural history**
- **Risks of sequelae need to be better defined**
- **Host-pathogen interaction in the genital tract is not well defined**
- **No correlates of immunity are known**



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Cytomegalovirus

- CMV is a common infection that is usually harmless.
- Among every 100 adults in the United States, 50–80 are infected with CMV by the time they are 40 years old.
- Congenital CMV
  - About 1 of every 5 children born with congenital CMV will develop permanent problems (such as hearing loss or developmental disabilities).
- CMV in transplant patients
  - Up to 60 percent of transplant recipients develop symptomatic disease.

http://www.cdc.gov/CMV/overview.html

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NIAID-Supported Research

- Sanofi Pasteur's CMV glycoprotrein B (CMV gB)
  - Three trials:
  - Women within 1 year after giving birth
    - Women who received the vaccine were 50% less likely to later become infected with CMV throughout the 42-month follow up.
  - Volunteers awaiting liver or kidney transplants
    - Vaccination reduced posttransplant duration of viremia and the number of days of required treatment in patients who were seronegative at transplant but who received organs from donors who were CMV-positive.
  - Healthy adolescent girls
    - Analysis is ongoing

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C. difficile infection (CDI)

- *C. difficile* is the most commonly reported pathogen for health care-associated infections[1]
- The rate of CDI has increased three fold in the last 10 years [2]
- US mortality rates from CDI > quadrupled 1999-2004 [3]
- CDI estimated cause $7 B healthcare costs in US + EU [4]

Spectrum of disease

- Asymptomatic colonization
- Diarrhea - Colitis
- Pseudomembranous colitis
- Toxic megacolon

Magill 2014 NEJM 370:13[1]; Rupnik 2009; 7:526/McDonald EID 2006;12:409 /Redelings EID 2007;13:1417

NIAID-Supported Research

Protection against *C. difficile* disease and recurrence correlates with the presence of antitoxin antibodies making vaccination a viable prevention strategy or possible therapeutic intervention

- Novel adherence factors and quorum sensing molecules to be developed as potential subunit vaccine candidates
  - Recently identified Type IV pilin proteins
  - Based on the agr quorum sensing system of C. *difficile*
- Novel subunit vaccine candidates
  - Flagellin-toxin genetic fusions
  - Nontoxic genetic fusions of Toxin A and toxin B
- Live vector vaccines against C. difficile
  - Salmonella typhi-based delivery of nontoxic versions of toxin A, toxin B and binary toxin

C. difficile Toxoid Vaccine

- NIAID-supported Phase I trial showed that the vaccine was safe and generally well-tolerated
- Now in Phase III trials supported by Sanofi Pasteur
  - Population: Age 50 +
  - For more information, see: http://clinicaltrials.gov/show/NCT01887912

Kotloff 2001 I&I 69:988; Aboudola 2003 I&I 71:1608

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Maternal Immunization

- Global:
  - WHO Maternal and Neonatal Tetanus (MNT) Elimination Initiative
    - Aims to reduce MNT cases to such low levels that the disease is no longer a major public health problem
    - MNT deaths can be easily prevented by hygienic delivery practices and by immunizing mothers with the tetanus vaccine
- Domestic:
  - The CDC Advisory Committee on Immunization Practices now recommends a dose of Tdap during each pregnancy
- Considerations for the future: Group B Strep

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Group B Streptococcus (GBS)

- GBS is a type of bacteria that causes illness in people of all ages.
- About 25% of pregnant women carry group B strep in the rectum or vagina. Group B strep may be present without symptoms.
- In the U.S., GBS is the leading cause of meningitis (infection of the fluid and lining around the brain) and sepsis (infection of the blood) in a newborn's first week of life.

http://www.cdc.gov/groupbstrep/about/fast-facts.html

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GBS Vaccines - History

- Since the early 1990s, NIAID has funded contracts supporting GBS vaccine design studies and more than 20 Phase I and Phase II trials.
- Studies indicated that the conjugate vaccines are safe and capable of inducing functional antibody responses.
- A GBS conjugate vaccine has the potential to prevent early- and late-onset infant GBS disease and invasive disease in pregnant women.

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Current Research

- NIAID-supported research of cellular signaling pathways and molecular regulatory networks that mediate GBS infections as potential novel vaccine target candidates (Lakshmi Rajagopal, Seattle Children's Hospital).
- Novartis is supporting the development of a GBS vaccine that is currently being tested in a Phase II clinical trial.

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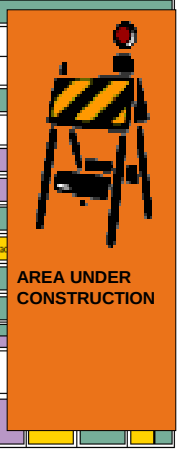
Recommended Childhood and Adolescent Immunization Schedule

Figure 1. Recommended immunization schedule for persons aged 0 through 18 years – United States, 2014.

(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE [FIGURE 2]).

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are in bold.

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19–23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13–15 yrs	16–18 yrs
Hepatitis B[1] (HepB)	1st dose	← 2nd dose →			← 3rd dose →											
Rotavirus[2] (RV) RV1 (2-dose series); RV5 (3-dose series)			1st dose	2nd dose	See footnote 2											
Diphtheria, tetanus, & acellular pertussis[3] (DTaP: <7 yrs)			1st dose	2nd dose	3rd dose			← 4th dose →				5th dose				
Tetanus, diphtheria, & acellular pertussis[4] (Tdap: ≥7 yrs)																
Haemophilus influenzae type b[5] (Hib)			1st dose	2nd dose	See footnote 5		← 3rd or 4th dose, See footnote 5 →									
Pneumococcal conjugate[6] (PCV13)			1st dose	2nd dose	3rd dose		← 4th dose →									
Pneumococcal polysaccharide[6] (PPSV23)																
Inactivated poliovirus[7] (IPV) (<18 yrs)			1st dose	2nd dose	← 3rd dose →							4th dose				
Influenza[8] (IIV; LAIV) 2 doses for some: See footnote 8					Annual vaccination (IIV only)						Annual vac					
Measles, mumps, rubella[9] (MMR)							← 1st dose →					2nd dose				
Varicella[10] (VAR)							← 1st dose →					2nd dose				
Hepatitis A[11] (HepA)							← 2-dose series, See footnote 11 →									
Human papillomavirus[12] (HPV2: females only; HPV4: males and females)																
Meningococcal[13] (Hib-MenCY ≥ 6 weeks; MenACWY-D ≥9 mos; MenACWY-CRM ≥ 2 mos)			See footnote 13													



Range of recommended ages for all children

Range of recommended ages for catch-up immunization

Range of recommended ages for certain high-risk groups

Range of recommended ages during which catch-up is encouraged and for certain high-risk groups

Not routinely recommended