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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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
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

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
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

Gaps in Knowledge
Trichomonas vaginalis

- 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
NIAID-Supported Research

- Sanofi Pasteur's CMV glycoprotein 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 infections¹
- The rate of CDI has increased three fold in the last 10 years²
- US mortality rates from CDI > quadrupled 1999-2004³
- CDI estimated cause $7 B healthcare costs in US + EU⁴

**Spectrum of disease**

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

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

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**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](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

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
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.

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.
# Recommended Childhood and Adolescent Immunization Schedule

![Immunization Schedule Image](#)

**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 notes 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.