Considerations for Use of MenACWY Vaccines In HIV-Infected Persons

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National Center for Immunization & Respiratory Diseases
Division of Bacterial Diseases

Outline

- Evidence of increased risk
- MenACWY vaccine response
- Other considerations

Background

- HIV is an established risk factor for several bacterial infections
- A growing body of evidence supports an increased risk of meningococcal disease among HIV-infected persons
- ACIP does not currently include HIV-infected persons in the recommendations for routine vaccination of persons at increased risk of meningococcal disease
  - If a HIV-infected person aged ≥2 years is vaccinated they should receive a 2-dose primary series

Meningococcal Disease in HIV-Infected Persons

- Surveillance data from the 8-county metropolitan area of Atlanta from 1988-1993 found HIV-infected adults had a nearly 24-fold increased risk of meningococcal disease[1]
- GERMS* – South Africa study[2]
  - 45% of 308 meningococcal disease patients were HIV-infected
  - Age adjusted relative risk of 11.3 (95%CI 8.9-14.3)
  - Case-fatality ratio among HIV-infected cases was 20% vs. 11% among HIV-uninfected cases

[1]Stephens DS, Hajjeh RA, Baughman WS, Harvey RC, Wenger JD, Farley MM. Sporadic meningococcal disease in adults: results of a 5-year population-based study. Ann Intern Med. 1995: 123:937-40

[2]Cohen C, Singh E, Wu HM, Martin S, de Gouveia L, Klugman KP, et al; Group for Enteric Respiratory and Meningeal Disease Surveillance in South Africa (GERMS-SA). Increased incidence of meningococcal disease in HIV-infected individuals associated with higher case-fatality ratios in South Africa. AIDS. 2010; 24:1351-60.

*Group for Enteric Respiratory and Meningeal Disease Surveillance in South Africa (GERMS-SA)

Evaluation of Risk of Meningococcal Disease Among Persons Infected With HIV – Active Bacterial Core surveillance (ABCs)

- **Chart review of HIV-infected meningococcal disease cases reported through ABCs from 2000-2008**
  - Incidence calculations limited to cases that met the CDC-AIDS surveillance case definition
- **33 HIV-infected cases reported during 2000-2008**
  - 70% serogroup C, W, or Y
- **12 additional HIV-infected cases reported during 2009-2015**
  - 83% serogroup C, W, or Y

Harris CM et al. Meningococcal Disease in Patients with HIV Infection-A Review of Cases Reported Through Active Surveillance in the United States, 2000-2008. *Manuscript Under Preparation.*

HIV Related Clinical Data for Meningococcal Cases with HIV Infection Obtained from Expanded Chart Reviews, All Ages (N=32)

	N (%)
Concurrent CD4 count available	22 (69)
≥500 cells/µL	7 (32)
200-499 cells/µL	9 (41)
<200 cells/µL	6 (27)
CDC AIDS surveillance case definition met	18 (56)
Reported HAART use	
Currently taking at time of presentation	16 (64)
Previous use	7 (28)
Never use	2 (8)
Currently taking opportunistic infection prophylaxis at the time of presentation	7(23)

Harris CM et al. Meningococcal Disease in Patients with HIV Infection-A Review of Cases Reported Through Active Surveillance in the United States, 2000-2008. *Manuscript Under Preparation.*

Increased Incidence of Meningococcal Disease in Persons Aged 25-64 Years Meeting the CDC-AIDS Case Definition, ABCS, 2000-2008

	CDC-AIDS criteria met		CDC-AIDS criteria not met	
	Cases	Incidence (95% CI)*	Cases	Incidence (95% CI)*
Total	17	3.5 (2.1-5.6)	474	0.3 (0.3-0.3)

*per 100,000 person years

RR = 12.9 (95%CI 7.9-20.9)

Harris CM et al. Meningococcal Disease in Patients with HIV Infection-A Review of Cases Reported Through Active Surveillance in the United States, 2000-2008. *Manuscript Under Preparation.*

Similar Increase in Risk for Men and Women Aged 25-64 Years Meeting the CDC-AIDS Case Definition, ABCs, 2000-2008

	CDC-AIDS criteria met		CDC-AIDS criteria not met		
	Cases	Incidence (95% CI)*	Cases	Incidence (95% CI)*	Rate Ratio (95% CI)
Men	13	3.5 (2.0-5.7)	249	0.3 (0.3-0.3)	11.8 (6.7-20.6)
Women	4	3.9 (1.3-9.3)	225	0.3 (0.2-0.3)	15.1 (5.6-40.6)

*per 100,000 person years

Harris CM et al. Meningococcal Disease in Patients with HIV Infection-A Review of Cases Reported Through Active Surveillance in the United States, 2000-2008. *Manuscript Under Preparation.*

Evaluation of Risk of Meningococcal Disease Among Persons Infected With HIV – New York City

- **Match of meningococcal disease surveillance data from 2000-2011 to death and HIV registries in New York City**
  - Age-matched case-control analysis including a subset of HIV-infected cases with CD4 count and viral load measurements near the time of meningococcal disease
- **40 HIV-infected cases reported during 2000-2011**
  - 87% serogroup C, W, or Y

Miller L, Arakaki L, Ramautar A, Bodach S, Braustein S, et al. Elevated Risk for Invasive Meningococcal Disease Among Persons with HIV. Ann Intern Med. 2014; 160:30-38.

Incidence of Meningococcal Disease in Persons Aged 15-64 Years, New York City, 2000-2011

	HIV-infected (Incidence per 100,000) (n=40)	HIV-uninfected (Incidence per 100,000) (n=223)	Risk Ratio (95% CI)
Incidence per 100,000	3.4	0.34	10.0 (7.2, 14.1)
Case Fatality Ratio (%)	10	23	

Miller L, Arakaki L, Ramautar A, Bodach S, Braustein S, et al. Elevated Risk for Invasive Meningococcal Disease Among Persons with HIV. Ann Intern Med. 2014; 160:30-38.

Declining Risk of Meningococcal Disease Among Persons Aged 15-64 Years, New York City, 2000-2011

Interval	HIV-infected (Incidence per 100,000)	HIV-uninfected (Incidence per 100,000)	Risk Ratio (95% CI)
2000-2002 (n=78)	4.7	0.41	11.4 (6.2-21.1)
2003-2005 (n=69)	4.2	0.35	11.8 (6.4-22.0)
2006-2008 (n=71)	3.3	0.36	8.9 (4.6-17.4)
2009-2011 (n=45)	1.9	0.23	8.2 (3.5-19.3)

Miller L, Arakaki L, Ramautar A, Bodach S, Braustein S, et al. Elevated Risk for Invasive Meningococcal Disease Among Persons with HIV. Ann Intern Med. 2014; 160:30-38.

Incidence of Meningococcal Disease by Gender in Persons Aged 15-64 Years, New York City, 2000-2011

Gender	HIV-infected (Incidence per 100,000)	HIV-uninfected (Incidence per 100,000)	Risk Ratio (95% CI)
Men	3.6	0.29	12.2 (8.1, 18.5)
Women	2.9	0.38	7.6 (4.0, 14.5)

Miller L, Arakaki L, Ramautar A, Bodach S, Braustein S, et al. Elevated Risk for Invasive Meningococcal Disease Among Persons with HIV. Ann Intern Med. 2014; 160:30-38.

Increased Risk of Meningococcal Disease Among HIV-Infected Persons, New York City, 2005-2011

	Case Patients with Meningococcal Disease an HIV (n)	Control Patients (HIV Only) (n)	Matched Odds Ratio (95% CI)
$CD4^+$ Count			
⩾0.200x10^9 cells/L	6	35	Ref
<0.200x10^9 cells/L	10	13	5.3 (1.4-20..4)
HIV Viral Load			
0-399 copies/mL	4	24	Ref
≥400 copies/mL	10	18	4.5 (0.9-22.2)

Miller L, Arakaki L, Ramautar A, Bodach S, Braustein S, et al. Elevated Risk for Invasive Meningococcal Disease Among Persons with HIV. Ann Intern Med. 2014; 160:30-38.

Risk of Meningococcal Disease in Children and Adults with HIV in England, 2011-2013

	HIV-infected (n=14)	HIV-uninfected (n=2,339)
Incidence per 100,000	6.6	1.5

RR = 4.5 (95 % CI 2.7–7.5)

Simmons RD. et al. Risk of invasive meningococcal disease in children and adults with HIV in England: a population-based cohort study. BMC Med. 2015; 13: 297.

Risk of Meningococcal Disease in Children and Adults with HIV in England, 2011-2013

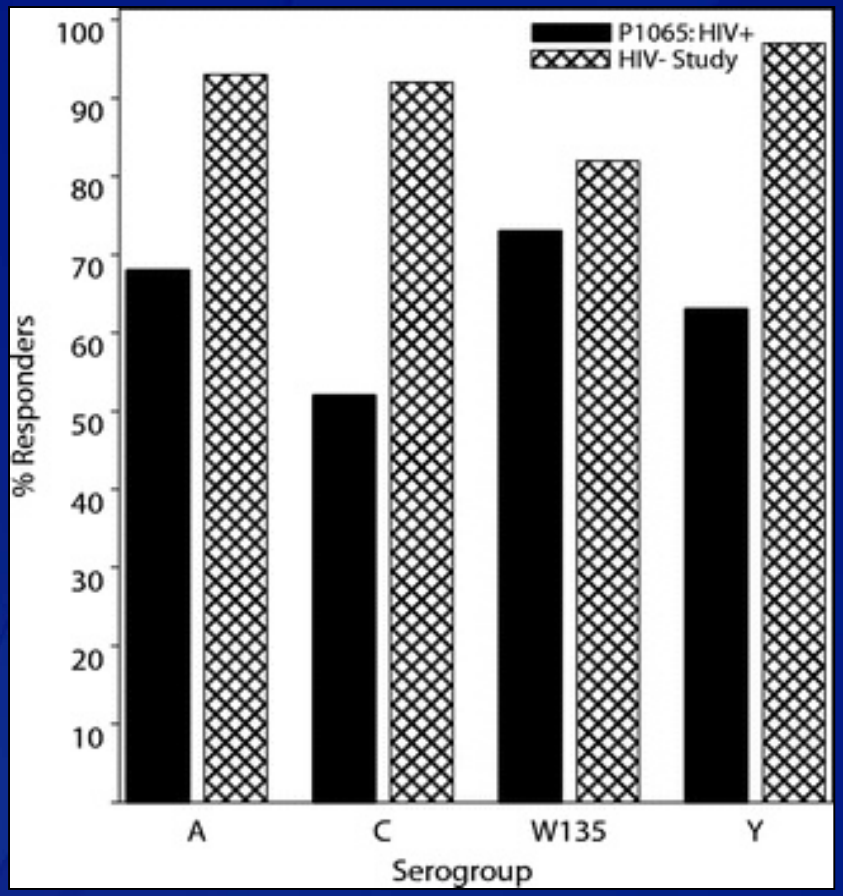
- All but one case occurred in adults aged 16–64 years
  - 22.7-fold increased risk compared with the HIV-uninfected adults
- 14 HIV-infected cases reported during 2011-2013
  - 71% serogroup C, W, or Y
- Most HIV-infected cases were aware of their HIV status and were receiving antiretroviral treatment
- The most common clinical presentation was septicemia and, although intensive care admission was common, none died

Simmons RD. et al. Risk of invasive meningococcal disease in children and adults with HIV in England: a population-based cohort study. BMC Med. 2015; 13: 297.

Summary

- **Increased risk of meningococcal disease in HIV-infected persons**
  - Among HIV-infected persons, low CD4 count or high viral load increases risk
  - Similar increase in risk for both males and females
  - Overall, risk declining along with meningococcal disease incidence in the United States
- **Meningococcal disease in HIV-infected persons primarily due to serogroups C, W, and Y**
- **Mixed data on case-fatality ratio**

Rates of Response (≥4-Fold Increase in rSBA Titer) to a Single Dose of MenACWY-D at Week 4 by Serogroup in HIV-Infected and Healthy Adolescents



P1065 Study Population:

- 11 to 24 years of age
- 324 subjects enrolled
- 305 had entry and week 4 serology results

≥4-fold increase in rSBA titer at week 4:

- Serogroup A: 68%
- Serogroup C: 52%
- Serogroup W: 73%
- Serogroup Y: 63%

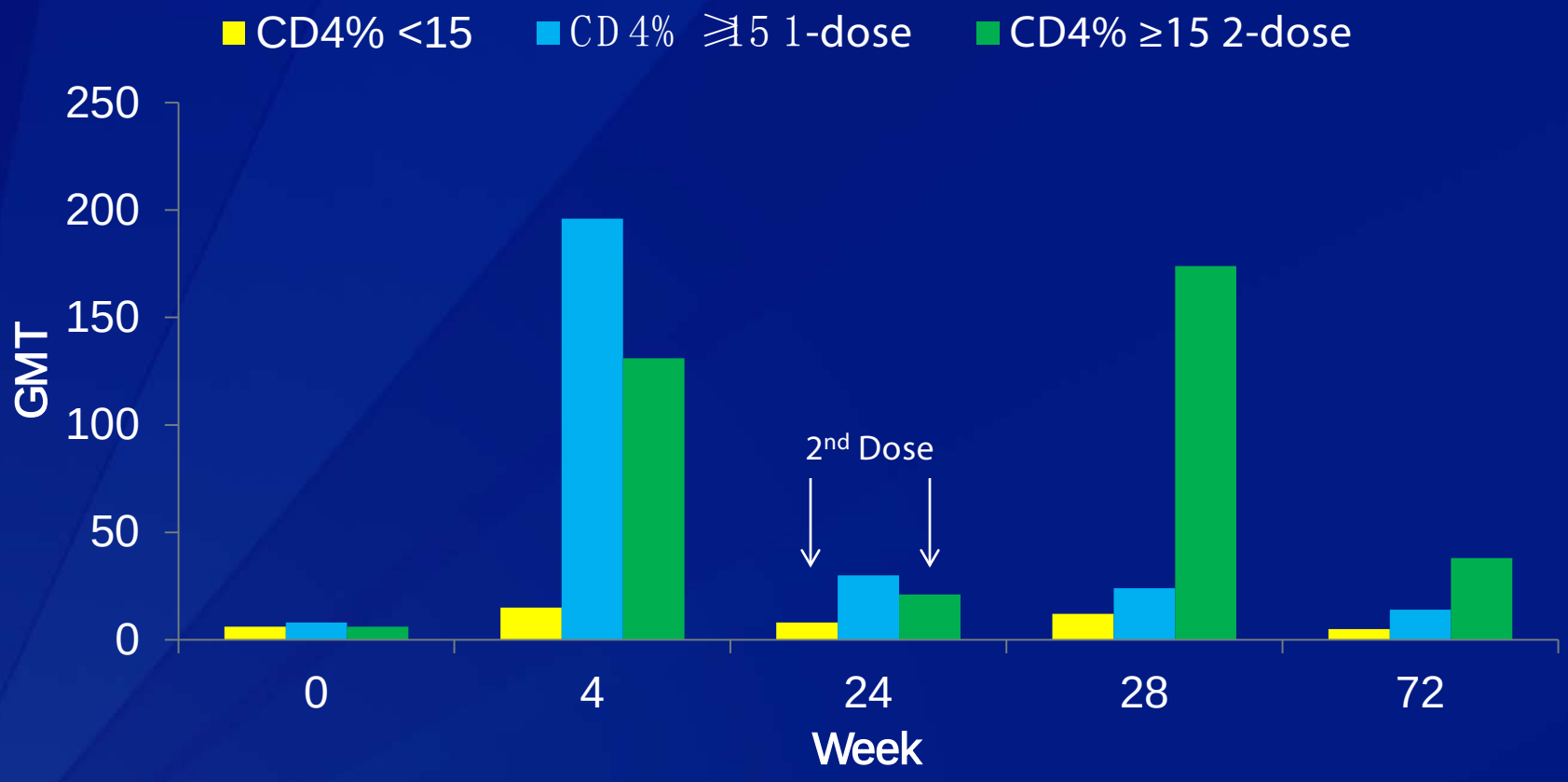
Phase I/II, Open-Label Trial of Safety and Immunogenicity of Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine in Human Immunodeficiency Virus-Infected Adolescents. Pediatric Infectious Disease Journal. 29(5):391-396, May 2010.

Multivariable Logistic Regression Results for Immunogenicity Response to Serogroup C as Predicted by Clinical Characteristics

Predictor	Adjusted Odds Ratio for Response	95% CI	P value
CD4 stratum			0.003
<15%	0.14	(0.04, 0.45)	
15-<25%	0.61	(0.36, 1.04)	
≥25%	1.00	Ref	
Viral load: (copies/mL)			0.005
<400	1.00	Ref	
400-10,000	0.62	(0.33, 1.17)	
>10,000	0.33	(0.17, 0.64)	
CDC Clinical Classification			<0.001
Class N/A	1.00	Ref	
Class B/C	0.38	(0.23, 0.64)	

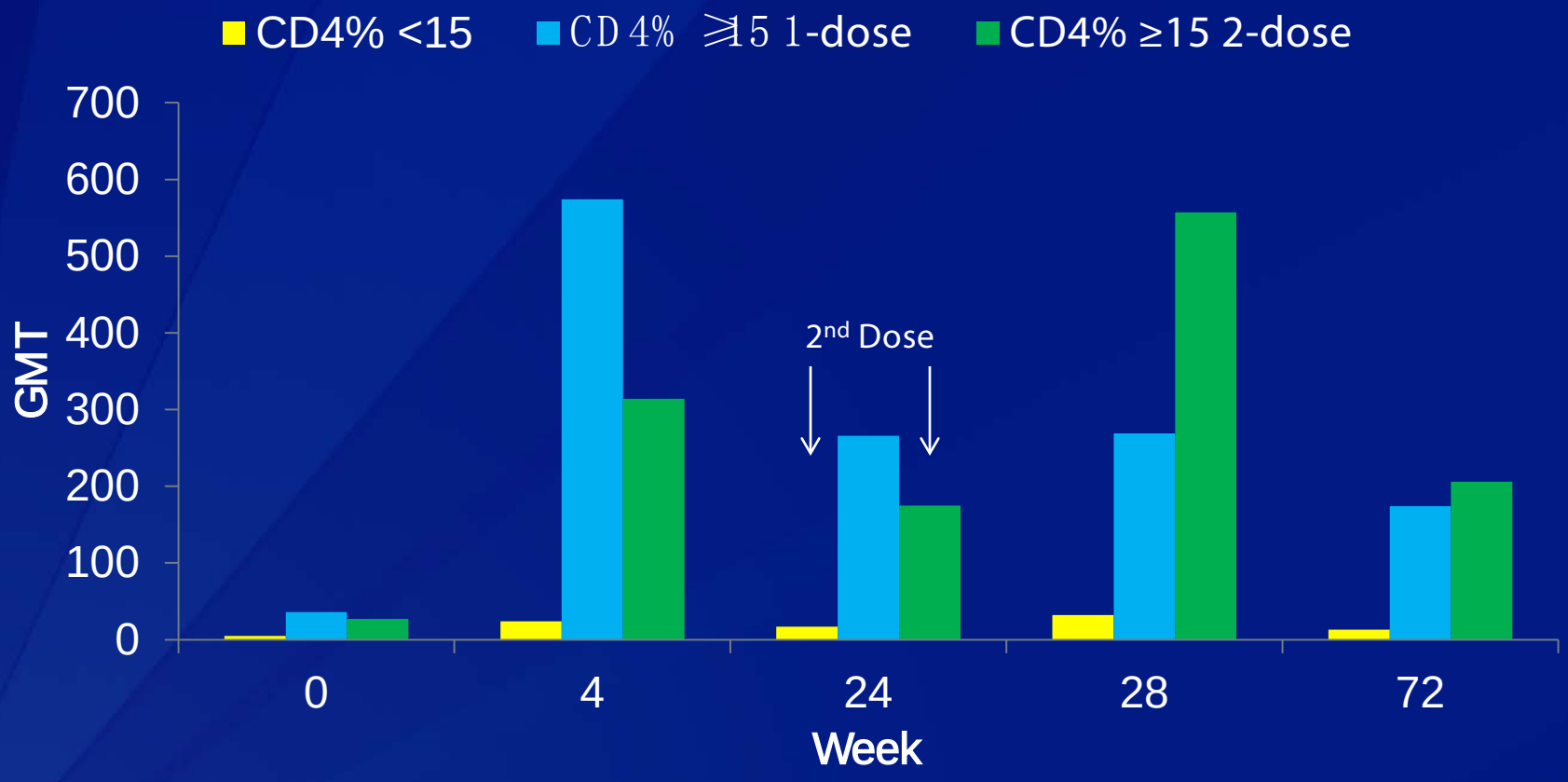
Phase I/II, Open-Label Trial of Safety and Immunogenicity of Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine in Human Immunodeficiency Virus-Infected Adolescents. Pediatric Infectious Disease Journal. 29(5):391-396, May 2010.

GMT rSBA Titers for Serogroup C for Subjects with Serology Data at Weeks 0, 4, 24, 28 and 72



Immunogenicity and Safety of 1 vs 2 Doses of Quadrivalent Meningococcal Conjugate Vaccine in Youth Infected with Human Immunodeficiency Virus. The Journal of Pediatrics. 161(4):676-681. October 2012.

GMT rSBA Titers for Serogroup Y for Subjects with Serology Data at Weeks 0, 4, 24, 28 and 72



Immunogenicity and Safety of 1 vs 2 Doses of Quadrivalent Meningococcal Conjugate Vaccine in Youth Infected with Human Immunodeficiency Virus. The Journal of Pediatrics. 161(4):676-681. October 2012.

Antibody Persistence in Subjects with CD4% ≥15 at Week 72 by Serogroup

Serogroup	Group	% subjects with rSBA titer ≥1:128 at Wk 72	% subjects with rSBA titer ≥1:8 at Wk 72
A	1-dose	57%	59%
	2-dose	71%	76%
C	1-dose	21%	24%
	2-dose	35%	49%
W	1-dose	60%	69%
	2-dose	66%	77%
Y	1-dose	63%	80%
	2-dose	71%	84%

Immunogenicity and Safety of 1 vs 2 Doses of Quadrivalent Meningococcal Conjugate Vaccine in Youth Infected with Human Immunodeficiency Virus. The Journal of Pediatrics. 161(4):676-681. October 2012.

Summary

- **Seroresponse to MenACWY-D conjugate vaccine in HIV-infected adolescents suppressed compared to healthy adolescents**
  - Low CD4 count or high viral load suppresses response further
- **Immune response to MenACWY-D wanes rapidly**
  - Boost response seen to second dose, however duration of protection still an issue

Programmatic Considerations

- **Approximately 1.2 million persons aged >13 years living with HIV in the U.S.[1]**
  - 50,000 new HIV infections each year[1]
- **About 50% of persons diagnosed with HIV receive regular HIV care[2]**
  - Of those retained in care, 89% are prescribed antiretroviral therapy and 77% achieve viral suppression[2]
- **For HIV-infected persons in care:**
  - HIV clinics may administer other vaccines recommended for HIV-infected persons
  - May be more likely to have CD4 counts and viral loads favorable for immunogenicity

[1] http://www.cdc.gov/hiv/statistics/overview/ataglance.html
[2] http://www.cdc.gov/hiv/prevention/programs/pwp/linkage.html

Vaccine Coverage in HIV-Infected Persons From The HIV Outpatient Study (HOPS)

- **Among active patients in HOPS clinics:**
  - Annual influenza vaccination* rates were 26-51% during 1999-2013[1,2]
  - 32% of eligible patients were vaccinated* with least 1 dose of hepatitis B vaccine during 1992-2002[3]
  - 23% of eligible patients were vaccinated* ≥1 dose of hepatitis A vaccine during 1992-2002[3]

*Documentation of receipt in the medical record

[1]Durham MD. Rates and correlates of influenza vaccination among HIV-infected adults in the HIV Outpatient Study (HOPS), USA, 1999–2008. Preventive Medicine 53 (2011) 89–94.

[2]Durham MD. Seasonal Influenza Vaccination Rates in the HIV Outpatient Study—United States, 1999–2013. CID 60 (2015) 976-7.

[3]Tedaldi EM. Hepatitis A and B Vaccination Practices for Ambulatory Patients Infected with HIV. CID 38 (2004) 1483-9.

Vaccine Considerations

- **Current consideration is for MenACWY conjugate vaccine only**
  - In HIV-infected persons, risk primarily due to serogroups C, W, and Y
  - No safety or immunogenicity data is available for use of serogroup B meningococcal vaccines in HIV-infected persons
- **Includes all HIV-infected persons aged ≥2 months**
- **Increased risk from HIV-infection is life long, therefore regular booster doses would be recommended for HIV-infected persons**
  - Current booster recommendations: 3 years if age <7 years at previous dose and 5 years if age ≥7 years at previous dose

AAP Recommendations

- AAP currently recommends MenACWY for HIV-infected children ≥2 years of age
  - 2015 Red Book:

> • The risk of meningococcal disease in HIV-infected individuals is not well defined. People with HIV infection who are 2 years or older should receive a 2-dose primary series at least 8 weeks apart.

- Current AAP and ACIP recommendations are not harmonized for HIV-infected children aged ≥2 years

Meningococcal Disease Among HIV-Infected Men Who Have Sex With Men (MSM)

- Risk of meningococcal disease in MSM will be discussed in detail during the next presentations
- Of meningococcal disease cases among MSM for whom HIV status is known, the majority (59%) are HIV-infected
  - Makes disentangling the relative contribution of HIV and MSM status to the increase in risk challenging in MSM populations
- Vaccinating HIV-infected persons offers an opportunity to also potentially impact meningococcal disease risk among MSM

Conclusions

- A growing body of evidence supports an increased risk of meningococcal disease among HIV-infected persons
  - Incidence of meningococcal disease in HIV-infected persons ranges from 3.4-6.6 per 100,000, relative risk 4.5-12.9.
  - In HIV-infected persons, risk primarily due to serogroups C, W, and Y
- Suboptimal vaccine response and programmatic challenges may limit the impact of vaccination on disease burden in HIV-infected persons
- HIV-infected persons represent a relatively small, defined population who are already recommended to receive specialized medical care

Work Group Discussion

- **Strong support for including HIV-infected persons in groups at increased risk of meningococcal disease**
  - Evidence of increased risk of meningococcal disease
  - Benefit to targeted group
  - Persons with specialized medical care
  - Recognition of suboptimal vaccine response and duration of protection

Current MenACWY Conjugate Vaccine Recommendations for Persons at Increased Risk

- Routine vaccination of persons aged ≥2 months at **increased risk of meningococcal disease, including:**
  - Persons with persistent complement component deficiencies[1]
  - Persons with anatomic or functional asplenia[2]
  - Microbiologists who are exposed routinely to isolates of *Neisseria meningitidis*
  - Persons at risk during a community outbreak attributable to a vaccine serogroup
  - Persons who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic
  - Unvaccinated or incompletely vaccinated first-year college students living in residence halls
  - Military recruits

[1]Including inherited or chronic deficiencies in C3, C5-9, properdin, factor D, or factor H,

[2]Including sickle cell disease

Proposed Change to MenACWY Conjugate Vaccine Recommendations for Persons at Increased Risk

- Routine vaccination of persons aged ≥2 months at **increased risk of meningococcal disease, including:**
  - Persons with persistent complement component deficiencies[1]
  - Persons with anatomic or functional asplenia[2]
  - Persons with human immunodeficiency virus (HIV) infection
  - Microbiologists who are exposed routinely to isolates of *Neisseria meningitidis*
  - Persons at risk during a community outbreak attributable to a vaccine serogroup
  - Persons who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic
  - Unvaccinated or incompletely vaccinated first-year college students living in residence halls
  - Military recruits

[1]Including inherited or chronic deficiencies in C3, C5-9, properdin, factor D, or factor H,

[2]Including sickle cell disease

Guidance for Use of MenACWY for HIV-Infected Persons

- Persons aged ≥2 years with HIV who have not been previously vaccinated should receive a two dose primary series of MenACWY (0, 2 months)
  - Multi-dose schedule for children aged <2 years
- Persons with HIV who have been previously vaccinated should receive a booster dose at the earliest opportunity, and then continue to receive boosters at the appropriate interval
  - Current booster recommendations: 3 years if age <7 years at previous dose and 5 years if age ≥7 years at previous dose

Analyses in Progress

- Cost-effectiveness analysis
- GRADE for routine use of MenACWY in HIV-infected persons ≥2 months of age

Discussion

- In addition to the cost-effectiveness analysis and GRADE, are there additional analyses that ACIP would like to see?
- Is ACIP in agreement with the Meningococcal Vaccines Work Group proposal to consider routine use of MenACWY in HIV-infected persons ≥2 months of age?