Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): MenACWY Vaccines for HIV-Infected Persons

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National Center for Immunization & Respiratory Diseases
Meningitis & Vaccine Preventable Disease Branch

Outline

- **GRADE process for MenACWY conjugate vaccines for HIV-infected persons**
  - Study question
  - Modified assessment of disease burden data
  - Assessment of evidence for outcomes (benefits and harms)

STUDY QUESTION

Study Question

- **Should MenACWY vaccine be administered routinely to all HIV-infected persons aged ≥2 months for prevention of meningococcal disease?**

Meningococcal Conjugate Vaccines

- **Menactra®**
  - Serogroups A, C, W, Y
  - Sanofi Pasteur
  - 9 months–55 years
- **Menveo®**
  - Serogroups A, C, W, Y
  - Novartis Vaccines/GlaxoSmithKline (GSK)
  - 2 months–55 years
- **MenHibrix®**
  - Serogroups C, Y and *Haemophilus influenzae* type b
  - GSK
  - 6 weeks–18 months

Overview of Critical Outcomes

Assessment	Outcome
Modified assessment of disease burden data	Cases/Incidence
	Mortality
Quality of evidence assessed using standard GRADE approach	Short-term immunogenicity against serogroups A, C, W, Y -4 weeks after 1st dose (week 4) -4 weeks after 2nd dose (week 28)
	Persistence in immunogenicity against serogroups A, C, W, Y -48 weeks after 2nd dose (week 72)
	Serious adverse events

MODIFIED ASSESSMENT OF DISEASE BURDEN DATA

Quality of Data on Meningococcal Disease Burden Among HIV-Infected Persons

- **Unable to use GRADE format to evaluate data**
  - Surveillance
  - No intervention tested
- **Important to objectively assess these data**
  - Representativeness
  - Completeness

MENINGOCOCCAL DISEASE AMONG HIV-INFECTED PERSONS

U.S. Meningococcal Disease Incidence

- **Active Bacterial Core surveillance (ABCs)**
  - Population-based active surveillance in 10 sites
  - Covers 43 million persons, ~14% of U.S. population
  - Contains HIV status
- **National Notifiable Diseases Surveillance System (NNDSS)**
  - Passive reporting by all U.S. states/territories
  - Does not contain HIV status
- **Not independent surveillance systems**

Meningococcal Disease Among HIV-Infected Persons, ABCs, 1995–2014

- **62 cases reported among HIV-infected persons**
  - 2% of 3951 total cases reported

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Age (years)	n (%)	Serogroup					
		B	C	W	Y	Non-groupable	Unknown
0–9	1 (2%)				1		
10–19	2 (3%)	1			1		
20–29	10 (16%)	3	4	1	1		1
30–39	19 (31%)	3	7		6		3
40–49	20 (32%)	4	8	2	4	1	1
50–59	8 (13%)	2	3		3		
60–69	2 (3%)		1		1		
≥70	0 (0%)						
Total n (%)	**62 (100%)**	**13 (21%)**	**23 (37%)**	**3 (5%)**	**17 (27%)**	**1 (2%)**	**5 (8%)**

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Chart Review of Meningococcal Disease Among HIV-Infected Persons, ABCs, 2000–2008

- 33 cases among HIV-infected persons included
- HIV-infected population unknown
  - Incidence calculations limited to 17 cases that met CDC-AIDS surveillance case definition

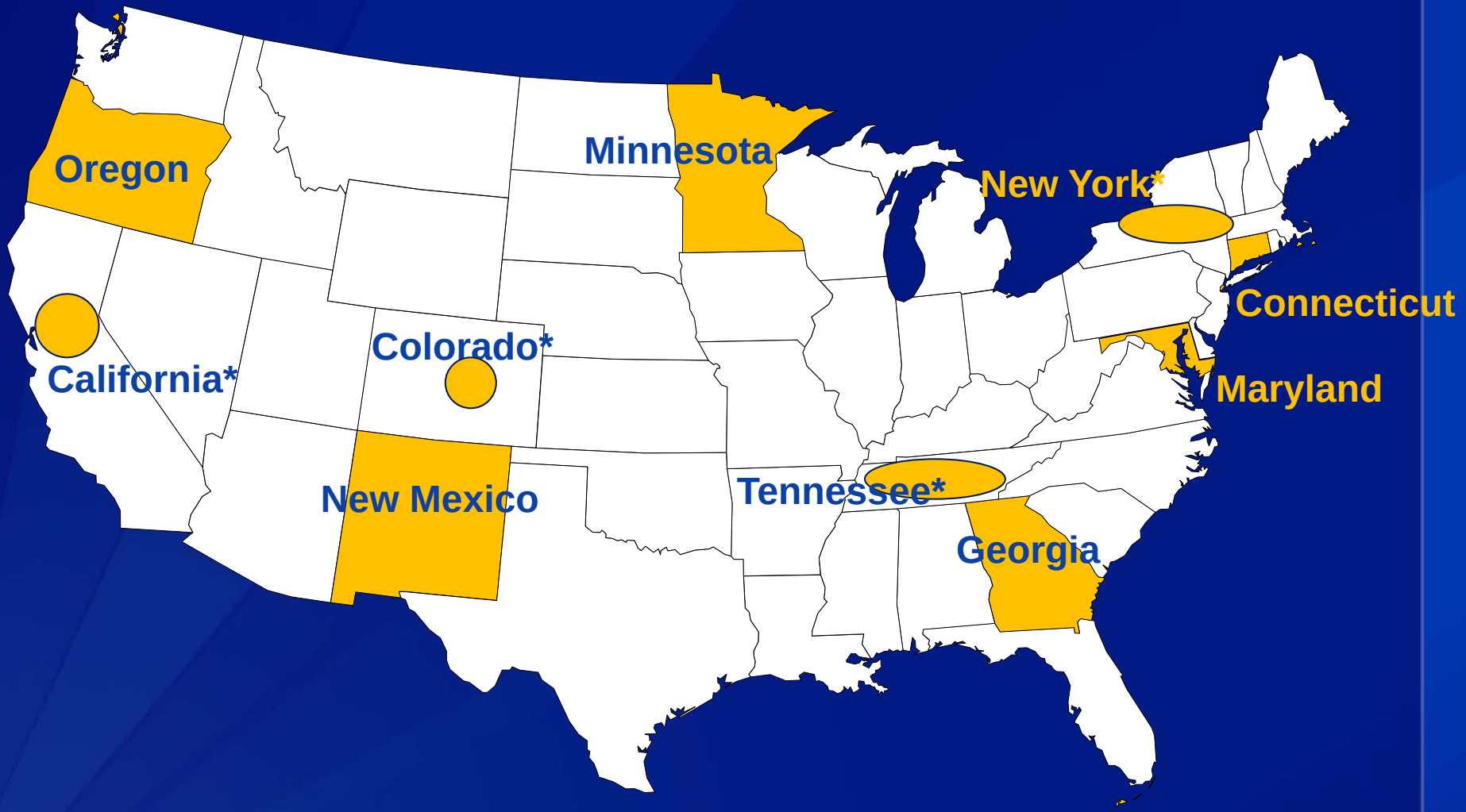
Time Period	HIV-infected Cases that Met CDC-AIDS Criteria		HIV-infected Cases that Did not Meet CDC-AIDS Criteria -and- HIV-uninfected Cases	
	Cases	Incidence (95% CI)*	Cases	Incidence (95% CI)*
2000–2008	17	3.5 (2.1–5.6)	474	0.3 (0.3–0.3)

*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.*

ABCs–2014



*Includes 3 counties (Alameda, Contra Costa, San Francisco) in California, 5 Denver counties in Colorado, 20 counties in Tennessee, and 15 Albany and Rochester counties in New York.

ABCs Catchment Area, 2000–2008

State	2000	2001	2002	2003	2004	2005	2006	2007	2008
California	3 counties								
Colorado		5 counties							
Connecticut									
Georgia	whole state					20 counties			
Maryland									
Minnesota									
New Mexico									
New York									
Oregon									
Tennessee	11 counties								

CDC. HIV Surveillance Report, 2014; vol. 26. http://www.cdc.gov/hiv/library/reports/surveillance/. Published November 2015. Accessed April 27, 2016.
CDC. HIV Surveillance Report, 2000-2008; vol. 12–20. http://www.cdc.gov/hiv/library/reports/surveillance/pastIssues.html/. Accessed April 27, 2016.

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Oregon									
Tennessee	11 counties								
Proportion (%) of HIV-infected U.S. population ≥14 years represented in ABCs catchment area	9.0	12.2	12.6	10.6	10.9	11.2	11.3	12.3	17.0

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Proportion (%) of HIV-infected U.S. children (0–13 years) represented in ABCs catchment area	-	9.1	6.0	6.1	5.8	8.0	9.8	8.9	8.5

CDC. HIV Surveillance Report, 2014; vol. 26. http://www.cdc.gov/hiv/library/reports/surveillance/. Published November 2015. Accessed April 27, 2016.
CDC. HIV Surveillance Report, 2000-2008; vol. 12–20. http://www.cdc.gov/hiv/library/reports/surveillance/pastIssues.html/. Accessed April 27, 2016.

Limitations of Meningococcal Disease Among HIV-infected Persons Surveillance Data

- **HIV testing rates suboptimal**
  - Adults: 37% in 2000 to 45% in 2008
  - Adolescents: 12% in 2005, 13% in 2007

Centers for Disease Control and Prevention. HIV Testing Trends in the United States, 2000-2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; January 2013:17,28.

Meningococcal Disease Among HIV-Infected Persons Compared to HIV-Uninfected Persons

Year	Site	Population	No. cases	HIV-infected compared to HIV-uninfected	Serogroup
1996–1999	Australia	All ages	60	5-fold increased rate	B, C
1990–2000	London	All ages	2900	14-fold increased rate	B, C
1988–1993	Atlanta	18–45 years	132	24-fold increased risk	B, C, Y
2003–2007	South Africa	All ages	504	11-fold increased risk	A, B, C, W, Y
2000–2011	New York City	15–64 years	265	10-fold increased risk	C, Y
2011–2013	England	All ages	2353	5-fold increased risk	A, B, C, W, Y

Couldwell DL. Invasive meningococcal disease and HIV coinfection. Commun Dis Intell Q Rep. 2001;25(4):279-280.
Pearson IC, et al. Meningococcal infection in patients with the human immunodeficiency virus and acquired immunodeficiency syndrome. International journal of STD & AIDS. 2001;12(6):410-411.
Stephens DS, et al. Sporadic meningococcal disease in adults: results of a 5-year population-based study. Annals of internal medicine. 1995;123(12):937-940.
Cohen C, et al. Increased incidence of meningococcal disease in HIV-infected individuals associated with higher case-fatality ratios in South Africa. Aids. 2010;24(9):1351-1360.
Miller L, et al. Elevated risk for invasive meningococcal disease among persons with HIV. Annals of internal medicine. 2014;160(1):30-37.
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.

MORTALITY AMONG HIV-INFECTED PERSONS WITH MENINGOCOCCAL DISEASE

Case-Fatality Ratios Among HIV-Infected and HIV-Uninfected Persons with Meningococcal Disease, ABCs

Time Period	Population	Case-fatality Ratio		P-value
		HIV-infected	No HIV Infection Reported	
2000–2008	25–64 years	13% (4/30)	11% (49/461)	.55
1995–2014	All ages	16% (10/62)	11% (420/3889)	.13

Mortality Among HIV-Infected Persons with Meningococcal Disease

Year	Site	Mortality Among HIV-infected	Mortality Among HIV-uninfected
1996–1999	Australia	67%	5%
2003–2007	South Africa	20%	11%
2000–2011	New York	10%	23%
2011–2013	England	0%	6%

- **Lower mortality among HIV-infected persons**
  - Engaged in healthcare services
  - Antibiotic prophylaxis
  - Antiretroviral therapy

Representativeness of Meningococcal Disease Among HIV-Infected Persons Disease Burden Data

- **Cases/Incidence**
  - 9–17% of U.S. HIV-infected population represented in ABCs
  - Findings from ABCs similar to other analyses of surveillance data
    - Diverse group of HIV-infected individuals
    - Multiple countries
    - Long time period with variable HIV testing, care, and treatment
- **Mortality**
  - Small numbers
  - Few studies
  - Mixed results

Completeness of Meningococcal Disease Among HIV-Infected Persons Disease Burden Data

- **Cases/Incidence**
  - Potential for missed cases
  - 9–17% of U.S. HIV-infected population represented in ABCs
  - NNDSS does not collect HIV status of cases
  - Suboptimal HIV testing
  - Data likely underestimate true incidence and risk ratio
- **Mortality**
  - Missed cases = missed deaths
  - Few studies

Evaluation of Meningococcal Disease Burden Data: Overall Good Quality

Criteria	Cases/ Incidence	Mortality
Representativeness	Minor	Moderate
Completeness	Minor	Moderate

OUTCOMES (BENEFITS AND HARMS) EVIDENCE

Study Question

- **Should MenACWY vaccine be administered routinely to all HIV-infected persons aged ≥2 months for prevention of meningococcal disease?**

Overview of Critical Outcomes

	Outcome
Benefits	Short-term immunogenicity (4 weeks after 1st dose [week 4])
	Short-term immunogenicity (4 weeks after 2nd dose [week 28])
	Persistence in immunogenicity (48 weeks after 2nd dose [week 72])
Harms	Serious adverse events

MenACWY in HIV-infected Persons: Evidence for Outcomes

	Outcome	Evidence Type (# of studies)
Benefits	Short-term immunogenicity (4 weeks after 1st dose [week 4])	Observational (2)
	Short-term immunogenicity (4 weeks after 2nd dose [week 28])	Observational (2)
	Persistence in immunogenicity (48 weeks after 2nd dose [week 72])	Observational (2)
Harms	Serious adverse events	Observational (2)

- **2 studies in total**
  - Both observational, open-label trials
  - Both assessed Menactra®
    - 2- to 10-year-old children
    - 11- to 24-year-old adolescents and young adults
  - No data for Menveo® or MenHibrix®

Siberry GK, et al. Safety and immunogenicity of quadrivalent meningococcal conjugate vaccine in 2- to 10-year-old HIV-infected children. PIDJ. 2012;31(1):47-52.
Siberry GK, et al. Phase I/II, open-label trial of safety and immunogenicity of meningococcal polysaccharide diphtheria toxoid conjugate vaccine in human immunodeficiency virus-infected adolescents. PIDJI. 2010;29(5):391-396.
Lujan-Zilbermann J, et al. Immunogenicity and safety of 1 vs 2 doses of quadrivalent meningococcal conjugate vaccine in youth infected with HIV. J Pediatr. 2012;161(4):676-681 e672.

Evidence of Benefits: Short-term Immunogenicity and Persistence of Immunogenicity

- **Clinical effectiveness studies of meningococcal vaccines are not feasible**
  - Low incidence of meningococcal disease among HIV-infected persons
- **Serum bactericidal antibody (SBA) titers are accepted as the immunologic correlate of protection in healthy persons**

Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med. 1969 Jun 1;129(6):1307-26.

Andrews N, Borrow R, Miller E. Validation of serological correlate of protection for meningococcal C conjugate vaccine by using efficacy estimates from postlicensure surveillance in England. Clin Diagn Lab Immunol. 2003 Sep;10(5):780-6

Evidence of Benefits: Short-term Immunogenicity

- ≥4-fold increase in rSBA titer

Serogroup	4 weeks after 1st dose			4 weeks after 2nd dose		
	2- to 10-year-olds	11- to 24-year-olds		2- to 10-year-olds	11- to 24-year-olds	
	CD4%≥25% N=49	CD4%≥15% N=220	CD4%<15% N=20	CD4%≥25% N=49	CD4%≥15% N=220	CD4%<15% N=20
A	92%	76%	25%	88%	67%	40%
C	43%	61%	17%	80%	62%	17%
W	98%	83%	32%	100%	80%	42%
Y	76%	67%	40%	84%	70%	40%

- MenACWY immunogenic in HIV-infected youth
  - Suppressed in HIV-infected adolescents compared to HIV-infected children and healthy adolescents
  - Suppressed further if low CD4 count or high viral load
  - Serogroup C demonstrated lowest rates of response

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Evidence of Benefits: Persistence of Immunogenicity

- **rSBA titer ≥1:128 at Week 72**

Serogroup	2- to 10-year-olds	11- to 24-year-olds		
	CD4%≥25% 2 doses	CD4%≥15% 1 dose	CD4%≥15% 2 doses	CD4%<15% 2 doses
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W	95%	60%	66%	6%
Y	91%	63%	71%	28%

- **Higher levels of seroprotection among children**
- **Seroprotection wanes rapidly in adolescents**
  - Suppressed further if low CD4 count or high viral load
- **Serogroup C had lowest rates of response**
- **Boost response seen to second dose**

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Evidence of Harms: Serious Adverse Events

- Serious adverse events (SAE) reported from time of vaccination through 6 weeks post-vaccination*

	2- to 10-year-olds	11- to 24-year-olds		
	CD4%≥25% 2 doses	CD4%≥15% 1 dose	CD4%≥15% 2 doses	CD4%<15% 2 doses
Overall	5% (3/59)	2% (7/319)	0% (0/128)	7% (2/31)
Laboratory	2 (neutropenia)	2 (leukopenia, neutropenia)	0	0
Signs/ symptoms	1 (fever)	5 (headache, fever, pain, psychiatric)	0	2 (ocular pain, lip lesion)

- SAE rates inversely related to entry CD4%
- 2 deaths† reported, unrelated to vaccine
- 1 SAE (ocular pain) judged related to vaccine

*Defined as Guillain Barre Syndrome, death, new grade 3 or higher AE according to Dec 2004 Division of AIDS AE Grading Table.
†Deaths were due to methamphetamine overdose and HIV-related complications

Considerations for Men ACWY vaccine use in HIV-infected persons

Key Factors	Comments
Balance between benefits and harms	Vaccine is immunogenic in HIV-infected children and adolescents in the short-term and safe. Immunogenicity persists in HIV-infected children but wanes rapidly in adolescents and young adults. Immune responses are suppressed with lower CD4% and higher viral loads. Low disease burden lowers overall benefits.

GRADE Criteria

- Risk of Bias (methodological limitations)
- Inconsistency
- Indirectness
- Imprecision
- Other considerations (publication bias, strength of association, dose response)

Algorithm for determining final evidence type

Study design	Initial evidence type	Criteria for moving down*	Criteria for moving up*^	Possible final evidence type
Randomized controlled trials	1	**Risk of bias** -1 Serious -2 Very serious **Inconsistency** -1 Serious -2 Very serious **Indirectness** -1 Serious -2 Very serious **Imprecision** -1 Serious -2 Very serious **Publication bias** -1 Likely -2 Very likely	**Strength of association** + 1 Large + 2 Very large **Dose response** + 1 Evidence of a gradient **Direction of all plausible residual confounding** + 1 Would reduce a demonstrated effect, or + 1 Would suggest a spurious effect when results show no effect	1 2
Observational studies	3			3 4

* 1= move up or down 1 level, 2= move up or down 2 levels
^Observational studies that were moved down cannot be moved up.

Evidence Table: Routine administration of MenACWY vaccines to HIV-infected persons

Outcomes	Design (# studies)	Initial Evidence	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Others	Final Evidence	Overall Evidence Type
Benefits										
Short-term immunogenicity after 1 dose (week 4)	2 Obs	3	Not Serious							
Short-term immunogenicity after 2 doses (week 28)	2 Obs	3	Not Serious							
Persistence of immunogenicity after 2 doses (week 72)	2 Obs	3	Not Serious							
Harms										
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*SBA titers for serogroups A C W Y not well-defined correlate of protection in HIV-infected persons

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Persistence of immunogenicity after 2 doses (week 72)	2 Obs	3	Not Serious	Not Serious	**Serious*(-1)**	Not Serious				
Harms										
Serious adverse events (after any dose)	2 Obs	3	Not serious	Not serious	Not Serious	**Serious†(-1)**				

*SBA titers for serogroups A C W Y not well-defined correlate of protection in HIV-infected persons
†Total sample size not sufficient to detect rare adverse events

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Outcomes	Design (# studies)	Initial Evidence	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Others	Final Evidence	Overall Evidence Type
Benefits										
Short-term immunogenicity after 1 dose (week 4)	2 Obs	3	Not Serious	Not Serious	**Serious*(-1)**	Not Serious	Not Serious			
Short-term immunogenicity after 2 doses (week 28)	2 Obs	3	Not Serious	Not Serious	**Serious*(-1)**	Not Serious	Not Serious			
Persistence of immunogenicity after 2 doses (week 72)	2 Obs	3	Not Serious	Not Serious	**Serious*(-1)**	Not Serious	Not Serious			
Harms										
Serious adverse events (after any dose)	2 Obs	3	Not serious	Not serious	Not Serious	**Serious†(-1)**	Not Serious			

*SBA titers for serogroups A C W Y not well-defined correlate of protection in HIV-infected persons
†Total sample size not sufficient to detect rare adverse events

Evidence Table: Routine administration of MenACWY vaccines to HIV-infected persons

Outcomes	Design (# studies)	Initial Evidence	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Others	Final Evidence	Overall Evidence Type
Benefits										
Short-term immunogenicity after 1 dose (week 4)	2 Obs	3	Not Serious	Not Serious	**Serious*(-1)**	Not Serious	Not Serious	**Yes‡§ (+1)**		
Short-term immunogenicity after 2 doses (week 28)	2 Obs	3	Not Serious	Not Serious	**Serious*(-1)**	Not Serious	Not Serious	**Yes‡§ (+1)**		
Persistence of immunogenicity after 2 doses (week 72)	2 Obs	3	Not Serious	Not Serious	**Serious*(-1)**	Not Serious	Not Serious	**Yes§ (+1)**		
Harms										
Serious adverse events (after any dose)	2 Obs	3	Not serious	Not serious	Not Serious	**Serious†(-1)**	Not Serious	None		

*SBA titers for serogroups A C W Y not well-defined correlate of protection in HIV-infected persons
‡Total sample size not sufficient to detect rare adverse events
‡Very strong strength of association: relative risk ranges between 5 and 49
§Strong dose response

Evidence Table: Routine administration of MenACWY vaccines to HIV-infected persons

Outcomes	Design (# studies)	Initial Evidence	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Others	Final Evidence	Overall Evidence Type
Benefits										
Short-term immunogenicity after 1 dose (week 4)	2 Obs	3	Not Serious	Not Serious	**Serious*(-1)**	Not Serious	Not Serious	**Yes‡§ (+1)**	3	
Short-term immunogenicity after 2 doses (week 28)	2 Obs	3	Not Serious	Not Serious	**Serious*(-1)**	Not Serious	Not Serious	**Yes‡§ (+1)**	3	
Persistence of immunogenicity after 2 doses (week 72)	2 Obs	3	Not Serious	Not Serious	**Serious*(-1)**	Not Serious	Not Serious	**Yes§ (+1)**	3	
Harms										
Serious adverse events (after any dose)	2 Obs	3	Not serious	Not serious	Not Serious	**Serious‡(-1)**	Not Serious	None	4	

*SBA titers for serogroups A C W Y not well-defined correlate of protection in HIV-infected persons
‡Total sample size not sufficient to detect rare adverse events
‡Very strong strength of association: relative risk ranges between 5 and 49
§Strong dose response

Evidence Table: Routine administration of MenACWY vaccines to HIV-infected persons

Outcomes	Design (# studies)	Initial Evidence	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Others	Final Evidence	Overall Evidence Type
Benefits										3
Short-term immunogenicity after 1 dose (week 4)	2 Obs	3	Not Serious	Not Serious	**Serious*(-1)**	Not Serious	Not Serious	**Yes‡§ (+1)**	3	
Short-term immunogenicity after 2 doses (week 28)	2 Obs	3	Not Serious	Not Serious	**Serious*(-1)**	Not Serious	Not Serious	**Yes‡§ (+1)**	3	
Persistence of immunogenicity after 2 doses (week 72)	2 Obs	3	Not Serious	Not Serious	**Serious*(-1)**	Not Serious	Not Serious	**Yes§ (+1)**	3	
Harms										
Serious adverse events (after any dose)	2 Obs	3	Not serious	Not serious	Not Serious	**Serious‡(-1)**	Not Serious	None	4	

*SBA titers for serogroups A C W Y not well-defined correlate of protection in HIV-infected persons
‡Total sample size not sufficient to detect rare adverse events
‡Very strong strength of association: relative risk ranges between 5 and 49
§Strong dose response

Considerations for vaccine use: MenACWY vaccines in HIV-infected persons

Key Factors	Comments
Balance between benefits and harms	Vaccine is immunogenic in HIV-infected children and adolescents in the short-term and safe. Immunogenicity persists in HIV-infected children but wanes rapidly in adolescents and young adults. Immune responses are suppressed with lower CD4% and higher viral loads. Low disease burden lowers overall benefits.
	Evidence type for benefits and harms
MenACWY vaccines in HIV-infected persons	**Overall Evidence Type: 3** **Benefits:** Short term immunogenicity after 1 dose (week 4): **Evidence Type 3** Short term immunogenicity after 2 doses (week 28): **Evidence Type 3** Persistence in immunogenicity (week 72): **Evidence Type 3** **Harms:** Serious Adverse Events: **Evidence Type 4**

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