Grading of Recommendations Assessment, Development, and Evaluation (GRADE): Meningococcal Conjugate Vaccines in HIV-Infected Persons

Introduction

A growing body of evidence demonstrates an increased risk of meningococcal disease among HIV-infected persons; risk increases further with a low CD4 count or high viral load (1-3). Meningococcal vaccination has previously been recommended for certain groups with medical conditions that increase risk for meningococcal disease (4), including persons with persistent complement component deficiencies, persons receiving eculizumab (Soliris®, Alexion Pharmaceuticals), or persons with functional or anatomic asplenia. Three meningococcal conjugate vaccines are licensed for use in the United States: two quadrivalent (serogroups A, C, W, and Y) vaccines (MenACWY-D [Menactra®, Sanofi Pasteur] and MenACWY-CRM [Menveo®, GlaxoSmithKline]) and one bivalent (serogroups C and Y) vaccine (Hib-MenCY-TT [MenHibrix®, GlaxoSmithKline]).

GRADE was used to evaluate routine vaccination of HIV-infected persons with meningococcal conjugate vaccine. The primary policy question was "Should meningococcal conjugate vaccines be administered routinely to all HIV-infected persons aged ≥2 months for prevention of meningococcal disease?" Evidence of benefits and harms were reviewed in accordance with GRADE methods (5).

Methods for GRADE

Immunogenicity and safety data from two open-label observational studies of MenACWY-D (6-8) were considered in the assessment. No studies of immunogenicity or safety of MenACWY-CRM or Hib-MenCY-TT in HIV-infected persons were available.

The benefits outcomes considered for each vaccine included short-term immunogenicity (1 month after both the first dose of vaccine [week 4] and after the second dose of vaccine [week 28]) and persistence of immunogenicity (48 weeks after the second dose of vaccine [week 72]). The harms outcome considered included occurrence of serious adverse events (SAEs) after vaccination. The evidence type for each outcome was derived through a review of study design, risk of bias, inconsistency, indirectness, imprecision and other considerations (strength of association, dose response gradient and opposing plausible residual confounding or bias).

Clinical effectiveness studies of meningococcal vaccines among HIV-infected persons are not feasible because of low incidence of disease. Estimates of short-term immunogenicity and persistence of immunogenicity were based on demonstration of immune response, as measured by serum bactericidal assay using a baby rabbit complement source (rSBA) against each meningococcal serogroup (A, C, W,

and Y). Immunogenicity was assessed by the proportion of subjects who achieved a ≥4-fold increase in rSBA titer for each of the strains tested and the proportion of subjects who achieved an rSBA titer ≥1:128.

Results:

Table 1: Evidence Table: Use of MenACWY vaccines in HIV-infected persons aged ≥2 months

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

Table 1b: Considerations for Vaccine Use: MenACWY vaccines in HIV-infected persons aged ≥2 months

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 percentage and higher viral loads. Low disease burden lowers overall benefits.
Evidence type for benefits and harms	
MenACWY vaccines in HIV-infected persons aged ≥2 months	**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**

Summary:

The evidence type for use of meningococcal conjugate vaccine in HIV-infected persons aged ≥2 months was determined to be type 3 (low level of evidence). After reviewing the result of the GRADE analysis and other data demonstrating increased risk of meningococcal disease among HIV-infected persons, the Advisory Committee on Immunization Practices (ACIP) recommended that HIV-infected persons aged ≥2 months be routinely vaccinated with a MenACWY vaccine to prevent meningococcal disease (recommendation Category A). The full recommendations for the use of MenACWY vaccines in HIV-infected persons aged ≥2 months are available on the ACIP website.

References

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