Grading of Recommendations Assessment, Development, and Evaluation (GRADE): MenACWY-CRM Vaccine for Increased Risk Infants

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National Center for Immunization & Respiratory Diseases
Division of Bacterial Diseases

Outline

- **GRADE process for meningococcal vaccine, MenACYW-CRM**
  - Study question
  - Considerations for vaccine use
    - Assessment of evidence for outcomes (benefits and harms)
    - Overall evidence type
    - Values/Preferences
    - Economic Analysis

STUDY QUESTION

Study question

- **Should MenACWY-CRM be administered to 2, 4, 6, and 12 month olds at increased risk for meningococcal disease?**
  - Infants with persistent complement pathway deficiencies
  - Infants with anatomic or functional asplenia
  - Infants in communities with serogroup A, C, W, or Y disease outbreaks
  - Infants traveling to the Hajj or "meningitis belt" of sub-Saharan Africa

Considerations for vaccine use: MenACWY-CRM for increased risk infants

Key Factors	Comments
Balance between benefits and harms	
Evidence type for benefits and harms	
Values and preferences	
Economic analysis	

OUTCOMES (BENEFITS AND HARMS) EVIDENCE

Rank outcomes

Outcome	Ranking
1. Short-term efficacy for MenACWY-CRM (one month after vaccination)	**Critical**
2. Long-term efficacy for MenACWY-CRM (1, 3, and 5 years after vaccination)	**Critical**
3. Occurrence of mild adverse events after vaccination	**Not Important**
4. Occurrence of serious adverse events after vaccination	**Critical**
5. Interference with other co-administered vaccines	**Important**

Final outcomes to GRADE

	Outcome	Inclusion Criteria
Benefits	1. Short-term efficacy – MenACWY-CRM (one month after vaccination)	-US and non-US populations -Proposed US schedule
	2. Long-term efficacy – MenACWY-CRM (1, 3, and 5 years after vaccination)	
Harms	3. Occurrence of serious adverse events after vaccination	
	4. Interference with other co-administered vaccines	

MenACWY-CRM: Evidence for Outcomes

	Outcome	Evidence Type (# of studies) for MenACWY-CRM
Benefits	Short-term efficacy: MenACWY-CRM 1 month after 3 dose infant series 1 month after full series (infant and toddler dose)	 RCT(3) RCT(1), Obs (1)
	Long-term efficacy: MenACWY-CRM 28 months post-dose 4	RCT(1)
Harms	Serious adverse events	RCT(4)
	Interference with co-administered vaccines	RCT(3)

- 4 studies in total: all Randomized Controlled Trials (1 observational for full series short-term efficacy)
- 1 published, 2 conference posters, 1 unpublished
- Only healthy infants included in all studies

Evidence of Benefits: Correlates of Protection for Meningococcal Disease

- **Due to low incidence of meningococcal disease, pre-licensure clinical effectiveness studies of meningococcal vaccines not feasible**
- **Serum bactericidal antibody (SBA) titers are accepted as the immunologic correlate of protection**
- **Effectiveness demonstrated to correlate with SBA titers**
  - Adolescent MenACWY-D experience in the US
  - MenC conjugate vaccines in the UK

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: MenACWY-CRM Efficacy

- **Protective hSBA titers ≥1:8 present for all serogroups**
  - 67-89% (A) and 94-98% (C, W, Y) post-dose 3*
  - 89-94% (A) and 95-100% (C, W, Y) post-dose 4*

- **Duration of protection 28 months post 4th dose varies by serogroup****
  - 10% (A), 34% (C), 76% (W), 67% (Y) 40 months out
  - Waning immunity indicates vaccine unlikely to provide long-term protection

*Nolan, T. et al. IDSA ID Week, October 2012., Tregnaghi, M. et al 29th ESPID meeting, June 2011., Klein, NP et al. PIDJ 2012 Jan;31(1):64-71
**Dull, P. Presentation to ACIP Meningococcal Vaccines Work Group , July 2013.

Evidence of Harms: MenACWY-CRM Serious Adverse Events

- **Serious adverse events (SAE) reported from time of vaccination through 6-month post-vaccination***
- **Physician verified**
- **Over 5,000 infants in safety studies**
- **At least 1 SAE reported during the infant series**
  - 3% of study participants who received MenACWY-CRM with concomitant vaccines and 2% of controls
- **At least 1 SAE reported 1 month after 2, 4, or 6 months dose**
  - 1% of study participants who received MenACWY-CRM with concomitant vaccines and 1% of controls
- **At least 1 SAE reported 6 months after full series**
  - 2% of study participants who received MenACWY-CRM with concomitant vaccines and 2% of controls

*Defined as any medical occurrence that results in death, is life-threatening, requires hospitalization, results in disability/incapacity, is an important medical event.

Evidence of Harms: MenACWY-CRM Serious Adverse Events

- **11 SAE considered possibly related* to MenACWY-CRM by non-blinded investigators**
  - acute encephalomyelitis, cellulitis, complex partial seizure, epilepsy, febrile seizure (3), fever, Kawasaki Disease (3)

* The administration of the investigational vaccine and an AE were considered reasonably related in time **and** the AE could be explained by causes other than exposure to the investigational vaccine.

Evidence of Harms: MenACWY-CRM Serious Adverse Events

- **No deaths considered related to MenACWY-CRM**
  - 10 deaths occurred among subjects who previously received MenACWY-CRM
    - auto accident, cardiac arrest, cardiorespiratory failure, lung infection/bronchopneumonia, respiratory failure, sepsis/septic shock, sudden death
  - 2 deaths occurred among subjects who received only routine vaccines
    - cardiac arrest, anomalous pulmonary venous connection
  - Randomization (3:1 or 2:1) and control arm cross-over to receive MenACWY-CRM at 12 mos weighted data to MenACWY-CRM recipients

Evidence of Harms: MenACWY-CRM Interference

- Antibody responses for diphtheria, tetanus, HBV, Hib antigens and all poliovirus serotypes met criteria for non-inferiority*

*Nolan, T. et al. IDSA ID Week, October 2012., Tregnaghi, M. et al 29th ESPID meeting, June 2011., Klein, NP et al. PIDJ 2012 Jan;31(1):64-71

Evidence of Harms: MenACWY-CRM Interference

- **Non-inferiority criteria not met for pertussis antigens in 2 of 3 studies**
  - Pertussis toxin (PT) and FIM* - PT met after adjusting for center differences
  - Pertactin † – met using GMC ratios, not seroresponse
- **Pneumococcal IgG antibody met criteria for non-inferiority for all serotypes post-dose 3 except for serotypes 6B* and 23F†**
  - 6B and 23F met criteria after adjusting for center differences
- **Pneumococcal IgG antibody met criteria for non-inferiority for all serotypes post-dose 4 in all 3 studies****

*In 2 of 3 studies (Nolan, T. et al. IDSA ID Week, October 2012; Klein, NP et al. PIDJ 2012 Jan;31(1):64-71) † In 1 of 3 studies (Klein, NP et al. PIDJ 2012 Jan;31(1):64-71)
**Nolan, T. et al. IDSA ID Week, October 2012., Tregnaghi, M. et al 29th ESPID meeting, June 2011., Klein, NP et al. PIDJ 2012 Jan;31(1):64-71

Considerations for vaccine use: MenACWY-CRM for increased risk infants

Key Factors	Comments
Balance between benefits and harms	**Vaccine is immunogenic in the short-term. Duration of protection 2 years post-4th dose varies by serogroup. Vaccine is safe.**
Evidence type for benefits and harms	
Values and preferences	
Economic analysis	

GRADE criteria

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

Risk of Bias – MenACWY-CRM

- **Blinding**
  - Risk of bias more likely with subjective outcome
  - Serious adverse events outcome: downgrade for single/no blinding
  - Efficacy/interference outcomes: no downgrade for single/no blinding

MenACWY-CRM for increased risk infants Evidence Table

Outcome (# and Study design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other (Publication Bias)	Evidence Type	Overall Evidence Type
Short-term efficacy (infant series) (3 RCT)	Minor*						
Short-term efficacy (full series) 1 RCT 1 Obs	 Minor* Minor*						
Long-term efficacy 28 mos - 1 RCT	Minor*						
Serious Adverse Events (4 RCT)	Serious*						
Coadmin Vaccines (3 RCT)	Minor*						

*No blinding, large losses to follow-up/withdrawals

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Short-term efficacy (full series) 1 RCT 1 Obs	 Minor* Minor*	 NA NA					
Long-term efficacy 28 mos - 1 RCT	Minor*	NA					
Serious Adverse Events (4 RCT)	Serious*	No serious					
Coadmin Vaccines (3 RCT)	Minor*	Minor**					

*No blinding; **Data for Hepatitis B antigen showed inconsistency and imprecision

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Short-term efficacy (full series) 1 RCT 1 Obs	 Minor* Minor*	 NA NA	 Serious† Serious†				
Long-term efficacy 28 mos - 1 RCT	Minor*	NA	Serious†				
Serious Adverse Events (4 RCT)	Serious*	No serious	Serious†				
Coadmin Vaccines (3 RCT)	Minor*	Minor**	Serious†				

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Short-term efficacy (full series) 1 RCT 1 Obs	 Minor* Minor*	 NA NA	 Serious† Serious†	 No serious No serious			
Long-term efficacy 28 mos - 1 RCT	Minor*	NA	Serious†	Serious‡			
Serious Adverse Events (4 RCT)	Serious*	No serious	Serious†	No serious			
Coadmin Vaccines (3 RCT)	Minor*	Minor**	Serious†	Minor**			

**No blinding; **Data for Hepatitis B antigen showed inconsistency and imprecision. †Data from healthy infants
‡Sample size <300, lower limit of CI shows only small difference

MenACWY-CRM for increased risk infants Evidence Table

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Short-term efficacy (full series) 1 RCT 1 Obs	 Minor* Minor*	 NA NA	 Serious† Serious†	 No serious No serious	 NA NA		
Long-term efficacy 28 mos - 1 RCT	Minor*	NA	Serious†	Serious‡	NA		
Serious Adverse Events (4 RCT)	Serious*	No serious	Serious†	No serious	No serious		
Coadmin Vaccines (3 RCT)	Minor*	Minor**	Serious†	Minor**	No serious		

**No blinding; **Data for Hepatitis B antigen showed inconsistency and imprecision. †Data from healthy infants ‡Sample size <300, lower limit of CI shows only small difference

MenACWY-CRM for increased risk infants Evidence Table

Outcome (# and Study design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other (Publication Bias)	Evidence Type	Overall Evidence Type
Short-term efficacy (infant series) (3 RCT)	Minor*	No serious	Serious†	No serious	No serious	2	3
Short-term efficacy (full series) 1 RCT 1 Obs	 Minor* Minor*	 NA NA	 Serious† Serious†	 No serious No serious	 NA NA	 2 4	
Long-term efficacy 28 mos - 1 RCT	Minor*	NA	Serious†	Serious‡	NA	3	
Serious Adverse Events (4 RCT)	Serious*	No serious	Serious†	No serious	No serious	3	3
Coadmin Vaccines (3 RCT)	Minor*	Minor**	Serious†	Minor**	No serious	2	

**No blinding; **Data for Hepatitis B antigen showed inconsistency and imprecision. †Data from healthy infants. ‡Sample size <300, lower limit of CI shows only small difference

Considerations for vaccine use: MenACWY-CRM for increased risk infants

Key Factors	Comments
Balance between benefits and harms	Vaccine is immunogenic in the short-term. Duration of protection 2 years post-4th dose varies by serogroup. Vaccine is safe.
Evidence type for benefits and harms	**Benefits: Evidence Type: 3** **Harms: Evidence Type: 3** **Overall Evidence Type: 3**
Values and preferences	
Economic analysis	

VALUES AND PREFERENCES

Vaccination of increased risk infants is standard of care

- **June 2011 ACIP meeting**
  - Vote to recommend routine vaccination of high-risk toddlers 9-23 months with meningococcal vaccine (MenACWY-D)
- **October 2012 ACIP meeting**
  - Vote to recommend routine vaccination of high-risk infants 2-23 months with meningococcal vaccine (HibMenCY)

Considerations for vaccine use: MenACWY-CRM for increased risk infants

Key Factors	Comments
Balance between benefits and harms	Vaccine is immunogenic in the short-term. Duration of protection 2 years post-4th dose varies by serogroup. Vaccine is safe.
Evidence type for benefits and harms	Benefits: Evidence Type: 3 Harms: Evidence Type: 3 Overall Evidence Type: 3
Values and preferences	**Vaccination of high-risk infants is standard of care. MenACWY-CRM provides an additional vaccine option for high-risk infants.**
Economic analysis	

ECONOMIC ANALYSIS

Vaccinating increased risk infants with MenACWY-CRM meningococcal vaccine has low overall cost

- **An estimated 5000 infants per year at increased risk for meningococcal disease**

Vaccine	Doses Recommended	Estimated cost per dose
MenACWY-CRM	4	$80-115
MenACWY-D	2	$80-115
HibMenCY	4	$9-25

Summary

Key Factors	Comments
Balance between benefits and harms	Vaccine is immunogenic in the short-term. Duration of protection 2 years post-4th dose varies by serogroup. Vaccine is safe.
Evidence type for benefits and harms	Benefits: Evidence Type: 3 Harms: Evidence Type: 3 Overall Evidence Type: 3
Values and preferences	Vaccination of high-risk infants is standard of care. MenACWY-CRM provides an additional vaccine option for high-risk infants.
Economic analysis	Vaccinating infants with MenACWY-CRM meningococcal vaccine has low overall cost.

GRADE evidence tables on ACIP website

- MenACWY-D and HibMenCY evidence tables presented at past ACIP meetings currently on ACIP website: http://www.cdc.gov/vaccines/acip/recs/GRADE/table-refs.html
- Evidence tables for use of MenACWY-D, HibMenCY, and MenACWY-CRM among high risk infants will be added to the ACIP GRADE website

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Thank you

For more information please contact Centers for Disease Control and Prevention

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