Grading of Recommendations Assessment, Development, and Evaluation (GRADE): HibMenCY Vaccine

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Outline

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

STUDY QUESTION

Initial study question

- **Should meningococcal vaccines be administered routinely to infants and toddlers for prevention of meningococcal disease?**

Study questions for today's presentation

- Should HibMenCY be administered to all 2, 4, 6, and 12 month olds for prevention of meningococcal disease?
- Can HibMenCY be used for Hib vaccination?

MENINGOCOCCAL DISEASE BURDEN

Low Incidence of Serogroup C, Y, and W135 Disease in Children <5 Years

Age Group	1997-1999 "High Incidence Years"	1993-2009* "Base Case"	2007-2009 "Low Incidence Years"
<5 years	2.60	1.17	0.40
All ages*	0.85	0.47	0.24

Average annual incidence of serogroup C, Y, and W135 meningococcal disease
1993-2009 ABCs data estimated to U.S. population with 18% correction for under reporting
*1993-2005 for adolescents 11-22 years

Evaluation of Meningococcal Disease Burden Data: Overall High Quality Data

Criteria	Incidence	Mortality	Morbidity
Representativeness	Minor	Minor	Minor
Accuracy	Minor	Minor	Minor
Applicability	Minor	Minor	Minor

Considerations for vaccine use: HibMenCY

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 Hib and MenCY (one month after vaccination)	**Important**
2. Long-term efficacy for Hib and MenCY (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 – Hib and MenCY (one month after vaccination)	-US and non-US populations -Proposed US schedule
	2. Long-term efficacy – Hib and MenCY (1, 3, and 5 years after vaccination)	
Harms	3. Occurrence of serious adverse events after vaccination	
	4. Interference with other co-administered vaccines	

HibMenCY: Evidence for Outcomes

	Outcome	Evidence Type (# of studies) for HibMenCY
Benefits	Short-term efficacy: Hib and MenCY 1 month after 3 dose infant series 1 month after full series (infant and toddler dose)	 RCT(5) RCT(4)
	Long-term efficacy: Hib and MenCY 1 year 3 year 5 year	 RCT(1) RCT(1) RCT(1)
Harms	Serious adverse events	RCT(5)
	Interference with co-administered vaccines	RCT(2)

- 9 studies in total: all Randomized Controlled Trials
- 7 published, 1 conference poster, 1 unpublished

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: Correlates of Protection for Hib Disease

- **Anti-PRP titers are accepted as the immunologic correlate of protection for invasive Hib disease**
  - long-term protection correlated with anti-PRP levels ≥ 0.15 ug/ml in unvaccinated populations and ≥ 1.0 ug/ml in vaccinated populations

Kayhty H, Peltola H, Karanko V, Makela PH. The Protective Level of Serum antibodies to the Capsular Polysaccharide of *Haemophilus influenzae* Type b. The Journal of Infectious Diseases 1983;147:1100.

Shapiro ED, Ward JI. The Epidemiology and Prevention of Disease Caused by *Haemophilus influenzae* Type b. Epiemiologic Reviews 1991;13:113-42.

Evidence of Benefits: HibMenCY Efficacy

- **Protective hSBA titers ≥1:8 present for serogroups C and Y**
  - 89-100% (Y) and 96-100% (C) post-dose 3*
  - 95-99% (Y) and 97-99% (C) post-dose 4*
- **Moderate duration of protection 5 yrs post 4th dose****
  - 88% (Y) and 98% (C) one year out
  - 67% (Y) and 81% (C) three years out
  - 69% (Y) and 83% (C) five years out
  - Waning immunity, especially for serogroup Y, indicates vaccine unlikely to provide protection until age 11-12 years
- **Hib portion non-inferior to monovalent Hib vaccine for infant/toddler doses and 1,3,5 years post 4th dose**

*Bryant, K. et al Pediatrics 2011; Marchant, C, et al. PIDJ 2010; Marshall, G. et al PIDJ , May 2010; Nolan, T. et al PIDJ, March 2011

**Miller, JM. Hib-MenCY-TT: Product and Clinical Data Overview, COID, April 17, 2012

Evidence of Harms: HibMenCY Serious Adverse Events

- **Serious adverse events (SAE) reported from time of vaccination through 6-month post-vaccination^**
- **Physician verified**
- **At least 1 SAE reported**
  - 3-14% of study participants who received HibMenCY with concomitant vaccines
  - 2-10% of controls who received monovalent Hib with concomitant vaccines†
- **4 SAE considered related to HibMenCY by non-blinded investigators****
- **Mild local and systemic reactions similar to monovalent Hib vaccine**
- **No deaths considered related to HibMenCY were reported**

^Defined as any medical occurrence that results in death, is life-threatening, requires hospitalization, results in disability/incapacity, is an important medical event. †Difference between intervention and control groups not statistically significant in any of the studies **1 HHE/hypotonia, 3 fever

Evidence of Harms: HibMenCY Interference

- Antibody responses for DTaP-HepB-IPV, MMR, and varicella after co-administration with HibMenCY met criteria for non-inferiority*
- Pneumococcal IgG antibody responses after PCV7 co-administration with HibMenCY met criteria for non-inferiority for all serotypes post-dose 3

*Marshall et al. Human Vaccines, 2011;7(2); 258-64; Marchant et al PIDJ 2010;29(1);48-52; Miller, JM. Hib-MenCY-TT: Product and Clinical Data Overview, COID, April 17, 2012

Considerations for vaccine use: HibMenCY

Key Factors	Comments
Balance between benefits and harms	**Vaccine is safe and immunogenic for Hib and MenCY in the short-term and 5 years post-vaccination. Low meningococcal disease burden lowers overall benefits for MenCY components.**
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 – HibMenCY

- **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

HibMenCY 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) (5 RCT)	No serious*						
Short-term efficacy (full series) (4 RCT)	No serious*†						
Long-term efficacy (1 yr) (1 RCT) (3 yr) (1 RCT) (5 yr) (1 RCT)	No serious*						
Serious Adverse Events (5 RCT)	Yes*†						
Coadmin Vaccines (2 RCT)	No serious*						

*Single-blind or no blinding; †One study with large % withdrawal

HibMenCY Evidence Table

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Short-term efficacy (full series) (4 RCT)	No serious*†	No serious	No serious		No serious		
Long-term efficacy **(1 yr) (1 RCT)** **(3 yr) (1 RCT)** **(5 yr) (1 RCT)**	 No serious* No serious* No serious*	NA (only 1 study per group)	 No serious No serious No serious		 No serious No serious No serious		
Serious Adverse Events (5 RCT)	Yes*†	No serious	No serious		No serious		
Coadmin Vaccines (2 RCT)	No serious*	No serious	No serious		No serious		

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Coadmin Vaccines (2 RCT)	No serious*	No serious	No serious	No serious	No serious		

*Single-blind or no blinding; †One study with large % withdrawal; **Sample size <300, lower limit of CI shows only small difference

HibMenCY Evidence Table

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Short-term efficacy (infant series) (5 RCT)	No serious*	No serious	No serious	No serious	No serious	1	2
Short-term efficacy (full series) (4 RCT)	No serious*†	No serious	No serious	No serious	No serious	1	
Long-term efficacy (1 yr) (1 RCT) (3 yr) (1 RCT) (5 yr) (1 RCT)	 No serious* No serious* No serious*	NA (only 1 study per group)	 No serious No serious No serious	 No serious Serious** Serious**	 No serious No serious No serious	 1 2 2	
Serious Adverse Events (5 RCT)	Yes*†	No serious	No serious	No serious	No serious	2	2
Coadmin Vaccines (2 RCT)	No serious*	No serious	No serious	No serious	No serious	1	

*Single-blind or no blinding; †One study with large % withdrawal; **Sample size <300, lower limit of CI shows only small difference

Considerations for vaccine use: HibMenCY

Key Factors	Comments
Balance between benefits and harms	**Vaccine is safe and immunogenic for Hib and MenCY in the short-term and 5 years post-vaccination. Low meningococcal disease burden lowers overall benefits for MenCY components.**
Evidence type for benefits and harms	**Benefits: Evidence Type: 2** **Harms: Evidence Type: 2** **Overall Evidence Type: 2**
Values and preferences	
Economic analysis	

VALUES AND PREFERENCES

Capturing Values and Preferences for Infant/Toddler Meningococcal Vaccines

- **Public Engagement Community Meetings (2011)**
  - 4 meetings (Concord, Seattle, Chicago, Denver)
  - 277 participants
  - Included presentations on disease/epidemiology, group discussions, polling questions
- **Provider Survey (2009)**
  - Surveyed physicians in existing sentinel networks (VPCI) recruited from random samples of AAP and AAFP
  - Pediatricians: 357 participated
  - Family practitioners: 248 participated

Working Group Interpretation: Public Engagement

- Issues raised (safety, access, affordability, equity, choice to vaccinate or not) were same as those considered during WG meetings

- Meetings were not representative of the public but provided valuable feedback on how to communicate vaccine issues to the public

Working Group Interpretation: Provider Survey

- **Providers would use meningococcal vaccines if recommended by ACIP, AAP, and AAFP for routine use**
  - If recommended for routine use: 80% of pediatricians and 72% of family practitioners would use
  - If not recommended for routine use: 19% of pediatricians and 17% of family practitioners would use

Courtesy of Alison Kempe

Working Group Values and Preferences

Considerations for vaccine use: HibMenCY

Key Factors	Comments
Balance between benefits and harms	Vaccine is safe and immunogenic for Hib and MenCY in the short-term and 5 years post-vaccination. Low meningococcal disease burden lowers overall benefits for MenCY components.
Evidence type for benefits and harms	Benefits: Evidence Type: 2 Harms: Evidence Type: 2 Overall Evidence Type: 2
Values and preferences	**Public issues consistent with those of the WG; providers rely on the ACIP and provider organizations for vaccine recommendations**
Economic analysis	

ECONOMIC ANALYSIS

HibMenCY has high cost per QALY even at low vaccine price

Cost per dose for 4-dose series	Estimated annual program cost for 4-dose series*	Cost per QALY saved*
$30	$564 million	$647,000

*Using 1993-2007 data

Summary

Key Factors	Comments
Balance between benefits and harms	Vaccine is safe and immunogenic for Hib and MenCY in the short-term and 5 years post-vaccination. Low meningococcal disease burden lowers overall benefits for MenCY components.
Evidence type for benefits and harms	Benefits: Evidence Type: 2 Harms: Evidence Type: 2 Overall Evidence Type: 2
Values and preferences	Public issues consistent with those of the WG; providers rely on the ACIP and provider organizations for vaccine recommendations
Economic analysis	Vaccinating infants with meningococcal vaccine has a high cost per QALY even at low vaccine price

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Thank you

For more information please contact Centers for Disease Control and Prevention
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