Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) for Infant Meningococcal Vaccines

Methods for GRADE: Infant Meningococcal Vaccines

Two meningococcal vaccines, MenACWY-D and Hib-MenCY-TT, were licensed for use in infants in April 2011 and June 2012, respectively. Evidence of benefits, harms, values and preferences, and cost-effectiveness were reviewed in accordance with GRADE methods[1]. The primary policy question was "Should meningococcal vaccines be administered routinely to all infants for prevention of meningococcal disease?". The evidence for these two meningococcal vaccines were evaluated to answer these specific questions: "Should the meningococcal vaccine MenACWY-D be administered to all infants at 9 and 12 months of age for prevention of meningococcal disease?" and "Should the meningococcal vaccine Hib-MenCY-TT be administered routinely to all infants at 2, 4, 6, and 12 months of age for prevention of meningococcal disease?".

The benefits outcomes considered for each vaccine included short-term vaccine efficacy (1 month after vaccination) and long-term efficacy (1, 3 and 5 years after vaccination, if data available). The harms outcomes considered for each vaccine included occurrence of serious adverse events (SAE) after vaccination and interference with other co-administered vaccines. Data from four unpublished observational studies (Obs) and 1 unpublished RCT were reviewed for MenACWY-D; data from nine randomized controlled trials (RCT) were reviewed for Hib-MenCY-TT[2-10]. The evidence type for each outcome was derived through a review of study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations (Tables 1 and 2).

Evidence Type 1: Randomized controlled trials, or overwhelming evidence from observational studies. Evidence Type 2: Randomized controlled trials with important limitations, or exceptionally strong evidence from observational studies. Evidence Type 3: Observational studies. Evidence Type 4: Clinical experience and observations, observational studies, or randomized controlled trials with notable limitations.[1]

Tables for GRADE: Infant Meningococcal Vaccines

Table 1. MenACWY-D vaccine for routine use in infants: Evidence Type of Benefits and Harms

Outcome	Design (# studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other (Publication Bias)	Evidence Type
Benefits							
Short-term efficacy	Obs (3)	No serious*	No serious	No serious	No serious	No serious	**3**
Long-term efficacy (3 yr)	Obs (1)	No serious*	No serious	No serious	No serious	No serious	**3**
Harms							
Serious Adverse Events	Obs (3)	Yes (-1)*	No serious	No serious	No serious	No serious	**4**
Serious Adverse Events	RCT (1)	Yes (-1)*	No serious	No serious	Yes (-1)†	No serious	**3**
Interference with Coadministered Vaccines	RCT (1)	No serious*	No serious	No serious	No serious	No serious	**1**

*Large proportion of subject withdrawal or no information about subject withdrawal, single-blind or no blinding †Sample size <300, high upper confidence interval

MenACWY-D Summary: Vaccine is immunogenic in the short-term and safe. Low meningococcal disease burden lowers overall benefits of routine use in infants.
Benefits Evidence Type: 3
Harms Evidence Type: 3
Overall Evidence Type: 3

Table 2. Hib-MenCY-TT vaccine for routine use in infants: Evidence Type of Benefits and Harms

Outcome	Design (# studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other (Publication Bias)	Evidence Type
Benefits							
Short-term efficacy* (infant series)	RCT (5)	No serious**	No serious	No serious	No serious	No serious	**1**
Short-term efficacy* (full series)	RCT (4)	No serious**†	No serious	No serious	No serious	No serious	**1**
Long-term efficacy*	RCT (1)		NA (only 1 study per group)				
(1 yr)		No serious**		No serious	No serious	No serious	**1**
(3 yr)		No serious**		No serious	Yes (-1)***	No serious	**2**
(5 yr)		No serious**		No serious	Yes (-1)***	No serious	**2**
Harms							
Serious Adverse Events	RCT (5)	Yes (-1)**†	No serious	No serious	No serious	No serious	**2**
Interference with Coadministered Vaccines	RCT (2)	No serious**	No serious	No serious	No serious	No serious	**1**

*Efficacy of both the Hib and MenCY components of the vaccine were evaluated **Single-blind or no blinding; †One study with large proportion of subject withdrawal; ***Sample size <300, lower limit of Confidence Interval shows only small difference

HibMenCY-TT Summary: 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 of routine use in infants for protection against meningococcal serogroups C and Y.
Benefits Evidence Type: 2

Harms Evidence Type: 2
Overall Evidence Type: 2

In June 2011, the Advisory Committee on Immunization Practices (ACIP) voted to recommend vaccination against meningococcal disease with MenACWY-D for children aged 9 through 23 months of age at increased risk for meningococcal disease[11]. In October 2012 the ACIP voted to recommend vaccination against meningococcal serogroups C and Y with HibMenCY-TT for children aged 6 weeks through 18 months at increased risk for meningococcal disease[12]. Increased risk infants and toddlers include those with persistent complement pathway deficiencies or anatomic or functional asplenia, those living in communities with a meningococcal disease outbreak for which vaccination is recommended, and those traveling to or residing in areas with hyperendemic or epidemic meningococcal disease. A third meningococcal vaccine, MenACWY-CRM, was licensed for use in infants in August 2013.

In light of the recommendations for routine meningococcal vaccination only for infants who are at increased risk for meningococcal disease, the GRADE tables for MenACWY-D and HibMenCY-TT were updated to evaluate the evidence for vaccine use in increased risk infants. The evidence of benefits, harms, values and preferences, and cost-effectiveness for MenACWY-CRM was also reviewed in accordance with GRADE methods[1]. The evidence for MenACWY-D, Hib-MenCY-TT, and MenACWY-CRM were evaluated to answer the questions: "Should the meningococcal vaccine MenACWY-D be administered to all infants 9 and 12 months of age at increased risk meningococcal disease?" and "Should the meningococcal vaccines Hib-MenCY-TT and MenACWY-D be administered to all infants 2, 4, 6, and 12 months of age at increased risk for meningococcal disease?".

The benefits outcomes considered for each vaccine included short-term vaccine efficacy (1 month after vaccination) and long-term efficacy (1, 3 and 5 years after vaccination, if data available). The harms outcomes considered for each vaccine included occurrence of serious adverse events (SAE) after vaccination and interference with other co-administered vaccines. Data from four unpublished observational studies (Obs) and 1 unpublished RCT were reviewed for MenACWY-D; data from nine randomized controlled trials (RCT) were reviewed for Hib-MenCY-TT[2-10]; data from three published RCT[13-15] and one unpublished RCT were reviewed for MenACWY-CRM. The evidence type for each outcome was derived through a review of study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations (Tables 3,4, and 5).

Evidence Type 1: Randomized controlled trials, or overwhelming evidence from observational studies. Evidence Type 2: Randomized controlled trials with important limitations, or exceptionally strong evidence from observational studies. Evidence Type 3: Observational studies. Evidence Type 4: Clinical experience and observations, observational studies, or randomized controlled trials with notable limitations.[1]

Table 3. MenACWY-D vaccine for routine use in increased risk infants: Evidence Type of Benefits and Harms

Outcome	Design (# studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other (Publication Bias)	Evidence Type
Benefits							
Short-term efficacy	Obs (3)	No serious*	No serious	Yes (-1)**	No serious	No serious	**4**
Long-term efficacy (3 yr)	Obs (1)	No serious*	No serious	Yes (-1)**	No serious	No serious	**4**
Harms							
Serious Adverse Events	Obs (3)	Yes (-1)*	No serious	Yes (-1)**	No serious	No serious	**4**
Serious Adverse Events	RCT (1)	Yes (-1)*	No serious	Yes (-1)**	Yes (-1)†	No serious	**4**
Interference with Coadministered Vaccines	RCT (1)	No serious*	No serious	Yes (-1)**	No serious	No serious	**2**

*Large proportion of subject withdrawal or no information about subject withdrawal, single-blind or no blinding; **Data from healthy infants; †Sample size <300, high upper confidence interval

MenACWY-D Summary: Vaccine is immunogenic in the short-term and safe.
Benefits Evidence Type: 4
Harms Evidence Type: 4
Overall Evidence Type: 4

Table 4. Hib-MenCY-TT vaccine for routine use in increased risk infants: Evidence Type of Benefits and Harms

Outcome	Design (# studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other (Publication Bias)	Evidence Type
Benefits							
Short-term efficacy* (infant series)	RCT (5)	No serious**	No serious	Yes (-1)‡	No serious	No serious	**2**
Short-term efficacy* (full series)	RCT (4)	No serious**†	No serious	Yes (-1)‡	No serious	No serious	**2**
Long-term efficacy*	RCT (1)		NA (only 1 study per group)				
(1 yr)		No serious**		Yes (-1)‡	No serious	No serious	**2**
(3 yr)		No serious**		Yes (-1)‡	Yes (-1)***	No serious	**3**
(5 yr)		No serious**		Yes (-1)‡	Yes (-1)***	No serious	**3**
Harms							
Serious Adverse Events	RCT (5)	Yes (-1)**†	No serious	Yes (-1)‡	No serious	No serious	**3**
Interference with Coadministered Vaccines	RCT (2)	No serious**	No serious	Yes (-1)‡	No serious	No serious	**2**

*Efficacy of both the Hib and MenCY components of the vaccine were evaluated **Single-blind or no blinding; †One study with large proportion of subject withdrawal; ‡Data from healthy infants; ***Sample size <300, lower limit of Confidence Interval shows only small difference

HibMenCY-TT Summary: Vaccine is safe and immunogenic for Hib and MenCY in the short-term and 5 years post-vaccination.
Benefits Evidence Type: 3
Harms Evidence Type: 3
Overall Evidence Type: 3

Table 5. MenACWY-CRM vaccine for routine use in increased risk infants: Evidence Type of Benefits and Harms

Outcome	Design (# studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other (Publication Bias)	Evidence Type
Benefits							
Short-term efficacy* (infant series)	RCT (3)	No serious*	No serious	Yes (-1)†	No serious	No serious	**2**
Short-term efficacy* (full series)	RCT (1) Obs (1)	No serious* No serious*	NA (only 1 study per group) NA (only 1 study per group)	Yes (-1)†	No serious	NA (only 1 study per group) NA (only 1 study per group)	**2** **4**
Long-term efficacy* 28 months	RCT (1)	No serious*	NA (only 1 study per group)	Yes (-1)†	Yes (-1)‡	NA (only 1 study per group)	**3**
Harms							
Serious Adverse Events	RCT (4)	Yes (-1)*	No serious	Yes (-1)†	No serious	No serious	**3**
Interference with Coadministered Vaccines	RCT (3)	No serious*	No serious**	Yes (-1)†	No serious**	No serious	**2**

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

MenACWY-CRM Summary: Vaccine is safe and immunogenic in the short-term. Duration of protection 2 years post-4th dose varies by serogroup.

Benefits Evidence Type: 3
Harms Evidence Type: 3
Overall Evidence Type: 3

References

1. Ahmed F, Temte J, Campos-Outcalt D, Schunemann H, ACIP Evidence Based Recommendations Work Group. Methods for developing evidence-based recommendations by the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC). Vaccine 2011;29:9171-6.
2. Bryant KA, Marshall GS, Marchant CD, et al. Immunogenicity and Safety of *H. influenzae* Type b-*N meningitidis* C/Y Conjugate Vaccine in Infants. Pediatrics 2011;127:e1375.
3. Marchant CD, Miller JM, Marshall GS, et al. Randomized Trial to Assess Immunogenicity and Safety of *Haemophilus influenzae* Type B and *Neisseria meningitidis* Serogroups C and Y-Tetanus Toxoid Conjugate Vaccine in Infants. The Pediatric Infectious Diseases Journal 2010;29:48-52.
4. Marshall GS, Marchant CD, Blatter M, et al. Immune Response and One-Year Antibody Persistence after a Fourth Dose of a Novel *Haemophilus influenzae* Type B and *Neisseria Meningitidis* Serogroups C and Y-Tetanus Toxoid Conjugate Vaccine (HibMenCY) at 12 to 15 Months of Age. The Pediatric Infectious Diseases Journal 2010;29:469-71.
5. Marshall GS, Marchant CD, Blatter M, Friedland LR, Aris E, Miller JM. Co-administration of a novel *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine dose not interfere with the immune response to antigens contained in infant vaccines routinely used in the United States. Human Vaccines 2011;7:258-64.
6. Marshall GS, Mesaros N, Aris E, Marchant CD, Blatter M, Miller JM. Persistence of Immunity Three Years after an Investigational *Haemophilus influenzae* type b and *Neisseria meningitidis* Serogroups C and Y Tetanus Toxoid (HibMenCY-TT) Conjugate Vaccine. 45th National Immunization Conference (NIC); March 28-31, 2011; Washington, D.C.
7. Miller JM. Hib-MenCY-TT: Product and Clinical Data Overview. COID; April 17, 2012.
8. Nolan T, Lambert S, Roberton D, et al. A novel combined *Haemophilus influenzae* type b-*Neisseria meningitids* serogroups C and Y-tetanus-toxoid conjugate vaccine is immogenic and induces immune memory when co-administered with DTPa-HBV-IPV and conjugate pneumococcal vaccines in infants. Vaccine 2007;25:8487-99.
9. Nolan T, Richmond P, Marshall H, et al. Immunogenicity and Safety of an Investigational Combined *Haemophilus influenzae* Type B-*Neisseria meningitidis* Serogouprs C and Y-Tetanus Toxoid Conjugate Vaccine. The Pediatric Infectious Diseases Journal 2011;30:190-6.
10. Rinderknecht S, Bryant KA, Nolan T, et al. The safety profile of *Haemophilus influenzae* type b-*Neisseria meningitidis* serogroups C and Y tetanus toxoid conjugate vacine (HibMenCY). Human Vaccines and Immunotherapeutics 2012;8:1-8.
11. CDC. Prevention and Control of Meningococcal Disease: Recommendations of the Advisory Commitee on Immunization Practices (ACIP). MMWR 2013;62.
12. CDC. Infant Meningococcal Vaccination: Advisory Commitee on Immuniation Practices (ACIP) Recommendations and Rationale. MMWR 2013;62:52-4.
13. Klein NP, Reisinger KS, Johnston W, et al. Safety and Immunogenicity of a Novel Quadrivalent Meningococcal CRM-conjugate Vaccine Given Concomitantly with Routine Vaccinations in Infants. Pediatric Infectious Disease Journal 2012;31:64-71.

14. Tregnaghi M, Tregnaghi M, D'Andrea U, Grana MG, Dull P, Bedell L. Imunogenicity of a Quadrivalent MenACWY-CRM Conjugate Vaccine Administered in Various Schedules to Argentinean Infants and Toddlers. 29th ESPID Meeting; June 7-11, 2011; The Hague, The Netherlands.
15. Nolan T, Naz A, Hohenboken M, Bedell L, Odrljin T, Dull P. Safety and Immunogenicity of Meningococcal Quadrivalent Conjugate Vaccine (MenACWY-CRM) Given Concomitantly with Routine Infant and Toddler Vaccines in Infants from 2 Months of Age. IDWeek; October 17-21, 2012; San Diego, CA.