Grading of Recommendations Assessment, Development, and Evaluation (GRADE): Toddler MenACWY-D Vaccine

Elizabeth Briere, MD, MPH

Advisory Committee for Immunization Practices

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Outline

- **GRADE process for toddler meningococcal vaccine, MenACWY-D**
  - Study question
  - Quality of disease burden data
  - Assessment of evidence for outcomes (benefits and harms)
  - Overall evidence type

STUDY QUESTION

Initial study question

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

Study question for today's presentation

- **Should MenACWY-D be administered to all 9 and 12 month olds for prevention of meningococcal disease?**

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QUALITY OF MENINGOCOCCAL DISEASE BURDEN DATA

What is the quality of our data on Meningococcal Disease Burden?

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

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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

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Quality of Meningococcal Disease Incidence Data: Sources

- **Active Bacterial Core surveillance (ABCs)**
  - Population-based active surveillance in 10 sites
  - Limited to culture confirmed cases
  - Observed cases used to estimate incidence in the United States
- **National Notifiable Diseases Surveillance System (NNDSS)**
  - Passive reporting by all US states/territories
  - Includes all cases (confirmed, probable, and suspect)
  - Can include PCR or latex data (as probable case)
  - Limited serogroup information
- **Not independent surveillance systems**

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Representativeness: Similar distribution of cases in NNDSS and ABCs, 1993-2009

Characteristic for cases < 1 year of age	NNDSS*	ABCs (projected to U.S. population)*
<1 year of age	4644	4141
Female	1948	1583
White	2816	3435
Black	557	588
Other	199	118

Unable to compare NNDSS and ABCs by serogroup due to missing data in NNDSS

*Total number for 1993-2009

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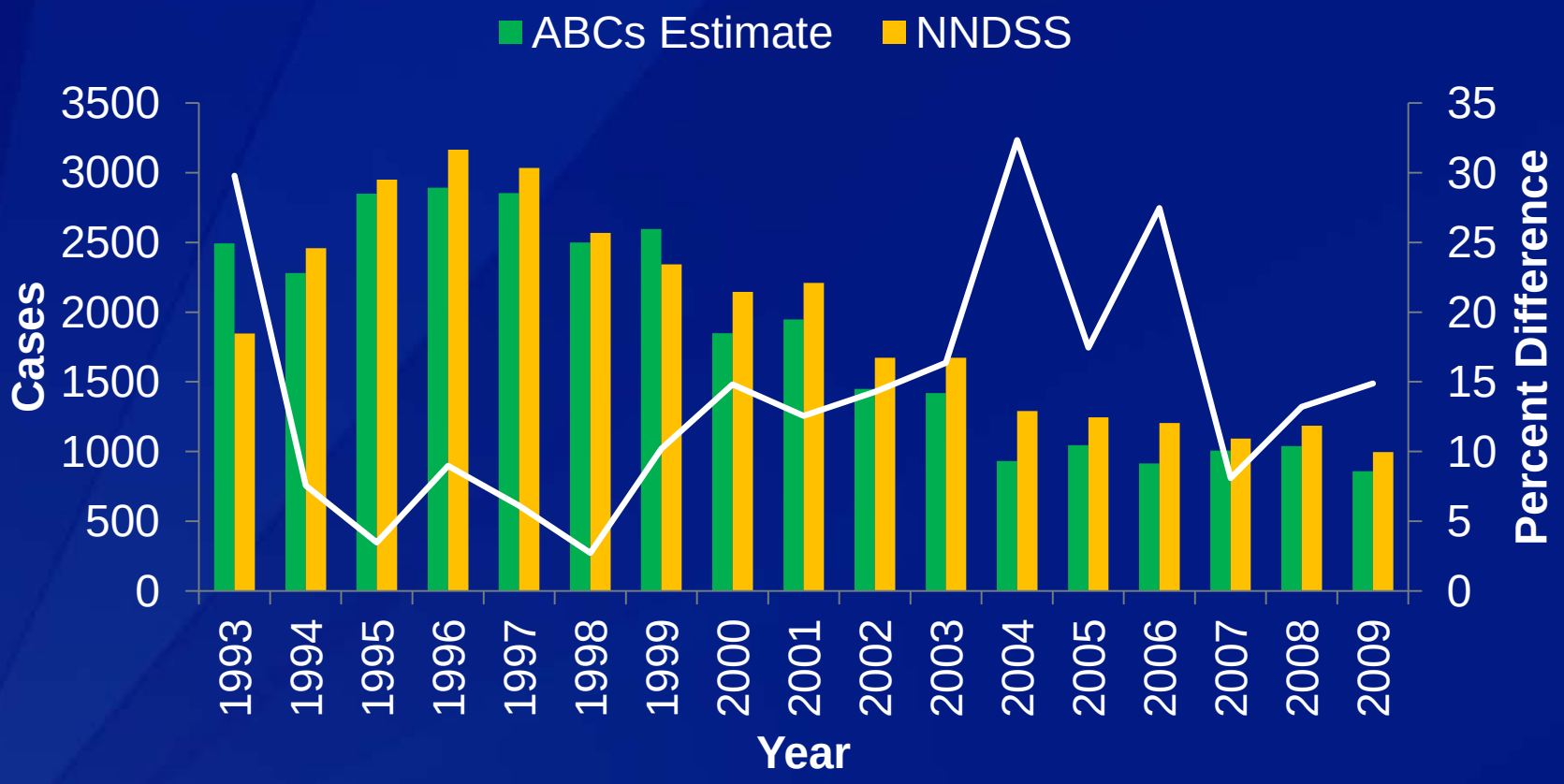
Accuracy:
ABCs may underestimate U.S. burden of meningococcal disease by 15-20%



*NNDSS includes all case statuses (confirmed, probable, suspect, unknown)

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Accuracy and Applicability of Meningococcal Disease Incidence Data

- **Accuracy**
  - Outbreaks outside of ABCs may not be captured
  - Outbreak cases rarely increase overall disease incidence
    - outbreak cases make up 2-3% of total cases
- **Applicability**
  - Captures meningococcal disease incidence in toddlers
  - Limitations in assessment of serogroup-specific epidemiology using NNDSS data

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Quality of Meningococcal Disease Morbidity and Mortality Data

- **Challenging to measure**
  - Use a combination of data sources (ABCs, published manuscripts)

Published data:

- **Representativeness**
  - Studies often have small numbers, hospital-based
- **Accuracy**
  - Estimates of CFR range from 2-10%*
  - Estimates of long-term sequelae range from <5-50%*
- **Applicability**
  - All-cause bacterial meningitis, limited analysis by age group/serogroup

*Bedford et al., BMJ 2001, 323: 533-7;Chandran et al., PIDJ 2011, 30:3-6.; Erickson and De Wals. CID 1998, 26:1159-64; Kaplan et al., Pediatrics 2006, 118(4):e979-84 ;1993-2009 ABCs data

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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

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OUTCOMES (BENEFITS AND HARMS) EVIDENCE

Study question for today's presentation

- **Should MenACWY-D be administered to all 9 and 12 month olds for prevention of meningococcal disease?**

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Rank outcomes

Outcome	Ranking
1. Short-term efficacy (one month after vaccination)	**Important**
2. Long-term efficacy (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**

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Final outcomes to GRADE

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

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Toddler MenACWY-D: Evidence for Outcomes

	Outcome	Evidence Type (# of studies) for MenACWY-D
Benefits	Short-term efficacy 1 month after 2 dose toddler series	Observational (3)
	Long-term efficacy 1 year 3 year	None Observational (1)
Harms	Serious adverse events	Observational (3), Randomized Controlled Trial (1)
	Interference with co-administered vaccines	Randomized Controlled Trial (1)

- 5 studies in total: 4 observational, 1 Randomized Controlled Trial
- None published

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Evidence of Benefits: Short and Long-term Efficacy

- **Due to relatively low incidence of meningococcal disease, pre-licensure clinical effectiveness studies of meningococcal vaccines are 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

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Evidence of Benefits: Toddler MenACWY-D Efficacy

- **Protective hSBA titers ≥1:8 present for serogroups A, C, Y, and W-135**
  - 82-100% 1 month after vaccination with 2 doses*
  - 13-46% 3 years after vaccination with 2 doses*

- **A booster dose at age 6 years would likely be needed to protect children until the 11-12 year-old vaccination**

*Johnson, D.R. Menactra Infant Indication, ACIP June 22, 2011

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Evidence of Harms: Toddler MenACWY-D Serious Adverse Events

- **Serious adverse events (SAE) reported from time of vaccination through 6-month post-vaccination^**
- **Physician verified**
- **At least 1 SAE reported**
  - 3.1-5.4% of study participants who received MenACWY-D alone or with concomitant vaccines
  - 1.6-3.6% of controls who received 1 or more childhood vaccines without MenACWY-D*†
- **4 SAE considered related to MenACWY-D by non-blinded investigators****
- **No deaths reported**

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

*Menactra package insert 30 Nov 2011 v0.11

†Difference between intervention and control groups not statistically significant

**IDDM, respiratory distress, 2 febrile seizures

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Evidence of Harms: Toddler MenACWY-D Interference

- **Antibody responses for measles, mumps, rubella, varicella, and Hib after co-administration with MenACWY-D met criteria for non-inferiority***
- **Pneumococcal IgG antibody responses after PCV7 co-administration with MenACWY-D did not meet criteria for non-inferiority for serotypes 4, 6B, and 18C***
  - Detectable functional antibody present, but did not meet non-inferiority for IgG GMC ratio criteria
  - Clinical relevance unclear

*Menactra package insert 30 Nov 2011 v0.11

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Considerations for vaccine use: Toddler MenACWY-D

Key Factors	Comments
Balance between benefits and harms	**Vaccine is immunogenic in the short-term and safe. Low disease burden lowers overall benefits.**
Evidence type for benefits and harms	

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GRADE criteria

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

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Algorithm for determining final evidence type

Study design	Initial evidence Type	Criteria for moving down*	Criteria for moving up*^	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.

Risk of Bias

- **Randomized Controlled Trial**
  - allocation sequence generation and concealment,
  - blinding
  - losses-to-follow-up, adherence to intention to treat principle
  - selective outcome reporting
- **Observational**
  - representativeness of exposed group
  - selection of non-exposed group
  - ascertainment of exposure
  - comparability of cohorts
  - blinding, losses-to-follow-up

Risk of Bias – Toddler MenACWY-D

- **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

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Toddler MenACWY-D Evidence Table

Outcome (# and Study design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other (Publication Bias)	Evidence Type	Overall Evidence Type
Short-term efficacy (3 Obs)	No serious*						
Long-term efficacy (3 yr) (1 Obs)	No serious*						
Serious Adverse Events (3 Obs)	Yes*						
Serious Adverse Events (1 RCT)	Yes*						
Coadmin Vaccines (1 RCT)	No serious*						

*Single-blind or no blinding

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Toddler MenACWY-D Evidence Table

Outcome (# and Study design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other (Publication Bias)	Evidence Type	Overall Evidence Type
Short-term efficacy (3 Obs)	No serious*	No serious	No serious**				
Long-term efficacy (3 yr) (1 Obs)	No serious*	No serious	No serious**				
Serious Adverse Events (3 Obs)	Yes*	No serious	No serious				
Serious Adverse Events (1 RCT)	Yes*	No serious	No serious				
Coadmin Vaccines (1 RCT)	No serious*	No serious	No serious				

*Single-blind or no blinding
**hSBA titers used as correlate of protection

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Toddler MenACWY-D Evidence Table

Outcome (# and Study design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other (Publication Bias)	Evidence Type	Overall Evidence Type
Short-term efficacy (3 Obs)	No serious*	No serious	No serious**	No serious	No serious	3	3
Long-term efficacy (3 yr) (1 Obs)	No serious*	No serious	No serious**	No serious	No serious	3	
Serious Adverse Events (3 Obs)	Yes*	No serious	No serious	No serious	No serious	4	3
Serious Adverse Events (1 RCT)	Yes*	No serious	No serious	Yes†	No serious	3	
Coadmin Vaccines (1 RCT)	No serious*	No serious	No serious	No serious	No serious	1	

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*Single-blind or no blinding **hSBA titers used as correlate of protection
†Sample size <300, wide confidence interval

Considerations for vaccine use: Toddler MenACWY-D

Key Factors	Comments
Balance between benefits and harms	Vaccine is immunogenic in the short-term and safe. Low disease burden lowers overall benefits.
Evidence type for benefits and harms	**Benefits: Evidence Type: 3** **Harms: Evidence Type: 3** **Overall Evidence Type: 3**

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Thank you!

For more information please contact Centers for Disease Control and Prevention
1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: www.cdc.gov