Table VI a. Efficacy of quadrivalent meningococcal conjugate vaccines. Do combined conjugated MC vaccines protect children aged ≥12 months to <5 years against invasive meningococcal disease?				
			Rating	Adjustment to level
Quality Assessment	No of Studies/Starting quality level		1 RCT + 1 observational	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious[1]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect¨	Not applicable	0
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final rating of quality of evidence			3
Summary of Findings	Statement on quality of evidence			We are moderately confident in the estimate of effect on the health outcome.
	Conclusion			Combined conjugated MC vaccines protect against meningococcal disease in children ≥12 months to <5 years of age.

[1]Immunogenicity rather than clinical protection is used as an endpoint. Serum bactericidal activity (SBA) at titres ≥1:4 (tests using human complement, hSBA) or 1:8 (tests using rabbit complement, rSBA) are considered reliable immunologic correlates of protection. References providing the rationale for this conclusion include *Borrow RP et al 2005; Andrews NR et al 2003*; and *Goldschneider IEC 1969.*

Table VI b. Efficacy of quadrivalent meningococcal conjugate vaccines. Do combined conjugated MC vaccines protect individuals aged ≥5 years against invasive meningococcal disease?				
			Rating	Adjustment to level
Quality Assessment	No of Studies/Starting quality level		1 RCT + 1 observational	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious[1]	-1
		Imprecision	None serious	0
		Publication bias	Serious[2]	-1
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final rating of quality of evidence			2
Summary of Findings	Statement on quality of evidence			Our confidence in the estimate of the effect on the health outcome is limited.
	Conclusion			Limited evidence that vaccination with combined conjugated MC vaccines protect individuals aged ≥5years against invasive meningococcal disease..

[1]Immunogenicity rather than clinical protection is used as an endpoint. Serum bactericidal activity (SBA) at titres ≥1:4 (tests using human complement, hSBA) or 1:8 (tests using rabbit complement, rSBA) are considered reliable immunologic correlates of protection. (For references providing the rationale for this conclusion, see Table Va).

[2]Studies conducted by the manufacturer. Internationally published evidence so far limited.

Randomised controlled trials

A study conducted in Canada *(Halperin SA et al 2010)* included healthy children 6-12 months of age. MenACWY-CRM was given IM at 6 and 12 months of age (Group 1) or 12 months of age (Group 2). MenC and MenACWY-CRM were given by intramuscular injection at 12 and 18 months of age (Group 3). In all, 2907 children received the study vaccine. In group 1, vaccination at 6 months resulted in 14%, 88%, 45%, and 27% achieving an hSBA ≥1:8 for serogroups A, C, W, and Y, respectively. After the second dose at 12 months, hSBA ≥8 was achieved by 83%, 100%, 100%, and 100% against serogroups

A, C, W, and Y, respectively. In the group that received MenACWY-CRM at 12 months of age only, the responses against A, C, W, and Y were 60%, 93%, 93%, and 57%, respectively.

In 2009, *Reisinger et al* conducted a phase III trial to compare the safety and immunogenicity of the an investigational quadrivalent meningococcal CRM(197) conjugate vaccine, MenACWY-CRM, to those of the licensed meningococcal conjugate vaccine, Menactra, when administered to healthy adults. 1,359 adults 19 to 55 years of age were randomly assigned to one of four groups (1:1:1:1 ratio) to receive a single dose of one of three lots of MenACWY-CRM (Menveo) or a single dose of Menactra. The percentages of seroresponders were consistently higher in the MenACWY-CRM group than in the Menactra group for serogroups C (67% versus 58%), W-135 (50% versus 41%), and Y (56% versus 40%), while the percentages were similar in the two vaccine groups for serogroup A (67% versus 68%).

Observational trial

In 2011, *Macneil JR et al* based on a simulation approach and actual reports of breakthrough meningococcal disease after vaccination with MenACWYD estimate the expected number of cases in vaccinated persons in the USA. Between 2005 and 2008, 14 breakthrough cases occurred. At a vaccine effectiveness (VE) of 90%, 7 breakthrough cases would be expected (range, 1-17); at VE of 85%, 11 cases (range, 2-30); at VE of 80%, 15 cases (range, 5-28); and at VE of 75%, 18 cases (range, 7-32) would be expected. The probability of the ≥14 observed cases occurring was 2.9% at VE of 90%, 29.3% at VE of 85%, 66.1% at VE of 80%, and 83.0% at VE of 75%. This report suggests that within 3 to 4 years after vaccination MenACWYD effectiveness is 80% to 85%, similar to the VE reported for meningococcal polysaccharide vaccine.

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