Table IVa. Efficacy of MenA conjugate vaccine.. Does conjugated MC group A-vaccine protect children aged ≥12 months <5 years against invasive meningococcal disease?				
			Rating	Adjustment to level
Quality Assessment	No of Studies/Starting quality level		2 RCTs*	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			Conjugated MC group A-vaccine protects children aged ≥12 months <5 years against meningococcal disease.

*Publication by Sow et al represents two trials

[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; Adrews NR et al 2003*; and *Goldschneider IEC 1969.*

Table IV b. Efficacy of MenA conjugate vaccine. Does conjugated MC group A-vaccine protect children aged ≥5 years against invasive meningococcal disease?				
			Rating	Adjustment to level
Quality Assessment	No of Studies/Starting quality level		3 RCTs*	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			Conjugated MC group A-vaccine protects individuals ≥5 years old against meningococcal disease.

*Publication by Sow et al represents two trials

[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 Ia).

Randomised Controlled Trials on Immunogenicity

A recent RCT by *Sow et al* (2011) in Mali and Gambia included 601 children, 12 to 23 months of age, who were randomly assigned to receive PsA-TT, a quadrivalent polysaccharide reference vaccine (PsACWY), or a control vaccine (*Haemophilus influenzae* type b conjugate vaccine [Hib-TT]). Ten months later, these children underwent another round of randomization within each group to receive a full dose of PsA-TT, a one-fifth dose of PsACWY, or a full dose of Hib-TT, with 589 of the original participants receiving a booster dose. 96.0% of the subjects in the PsA-TT group and 63.7% of those in the PsACWY group had SBA titers that were at least four

times as high as those at baseline. The PsA-TT group had higher antibody titers at week 40 than the PsACWY group and had obvious immunologic memory after receiving a polysaccharide booster vaccine.

The second study by the same authors included 900 African participants 2-29 years of age. Subjects were randomized to receive a single injection of either PsA-TT vaccine (MenAfriVac™) or a licensed meningococcal tetravalent polysaccharide vaccine (ACWY). Baseline titers increased with age. Group A specific IgG ≥ 4-fold rises pre- to post-vaccination in the PsA-TT group were significantly higher than in the PsACWY group in all age groups. Post-vaccination, Group A-specific IgG GMCs were significantly higher in PsA-TT than in PsACWY recipients in all age groups. Also, post-vaccination, the percentage of subjects with MenA IgGELISA concentrations ≥ 2 μg/mL is significantly higher in the PsA-TT than in the PsACWY group (100% vs. 88%).

Kshirsagar et al (2007) conducted a double-blind, randomized, controlled phase I study to assess the safety, immunogenicity, and antibody persistence of the new meningococcal group A conjugate vaccine (PsA-TT) in healthy volunteers aged 18–35 years in India. Of the 74 male subjects enrolled, 24 received the PsA-TT vaccine (Group 1), 25 received the Meningoccoccal Polysaccharide Vaccine A + C™ (Group 2), and 25 received the Tetanus Toxoid Vaccine Adsorbed™ (Group 3). Four weeks post-vaccination, a slightly higher proportion of Group 1 subjects had a four-fold increase in SBA titers compared to Group 2 subjects (83% versus 72%, $p > 0.05$). SBA GMTs in Groups 1 and 2 were higher than in Group 3 ($p < 0.05$). Serogroup A-specific IgG GMCs were significantly higher in Group 1 than in Groups 2 and 3. After 1 year SBA titers were significantly higher in Group 1 than in Group 2. The new PsA-TT vaccine was shown to be safe, immunogenic, and able to elicit persistent functional antibody titers in adults.

References:

1.Sow SO, Okoko BJ, Diallo A, Viviani S, Borrow R, Carlone G, et al. Immunogenicity and safety of a meningococcal A conjugate vaccine in Africans. N Engl J Med. 2011 Jun 16;364(24):2293-304.

2. Kshirsagar, N., N. Mur, U. Thatte, N. Gogtay, S. Viviani, M. P. Preziosi, C. Elie, H. Findlow, G. Carlone, R. Borrow, V. Parulekar, B. Plikaytis, P. Kulkarni, N. Imbault, and F. M. LaForce. "Safety, Immunogenicity, and Antibody Persistence of a New Meningococcal Group A Conjugate Vaccine in Healthy Indian Adults." *Vaccine* 25 Suppl 1 (2007): A101-7.

References on immunologic correlates of protection

Borrow, R., P. Balmer, and E. Miller. "Meningococcal Surrogates of Protection—Serum BactericidalAntibody Activity." *Vaccine* 23, no. 17-18 (2005): 2222-7.

Andrews, N., R. Borrow, and E. Miller. "Validation of Serological Correlate of Protection for Meningococcal C Conjugate Vaccine by Using Efficacy Estimates from Postlicensure Surveillance in England." *Clin Diagn Lab Immunol* 10, no. 5 (2003): 780-6.

Goldschneider, I., E. C. Gotschlich, and M. S. Artenstein. "Human Immunity to the Meningococcus. I. The Role of Humoral Antibodies." *J Exp Med* 129, no. 6 (1969): 1307-26.