GRADE Table 03a. Duration of protection against hepatitis E virus infection following primary immunization with hepatitis E vaccine in immunocompetent individuals

Population : Immunocompetent individuals (>16 years)
Intervention : Hepatitis E vaccination (Hecolin®)
Comparison : Non-hepatitis E vaccination
Outcome : Infection with hepatitis E virus

What is the scientific evidence of the continuous duration of protection against infection with hepatitis E virus following primary immunization with hepatitis E vaccine (versus control) in immunocompetent individuals?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		3/ RCT[1, 2]	4
	Factors decreasing confidence	Limitation in study design	Serious[3]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[4]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			Evidence supports a limited degree of confidence in the estimate of effect on health outcome.
	Conclusion			Evidence supports a limited degree of confidence in the estimate of the effect that primary immunization with hepatitis E vaccine provides a sustained level of protection against hepatitis E infection for up to 4.5 years following immunization. No data is available on the long-term protection beyond this time period with this vaccine.

[1] A phase IIa randomized controlled trial (RCT) by Zhang et al. 2009 (1) with 457 study subjects reported a significant difference in hepatitis E episodes after receipt of 3 doses of Hepatitis E vaccine within the 12 months study period. A phase III RCT (Zhu et al. 2010 (3)) including 122.179 subjects reported a significant difference in incidence ($p<0.0001$) of hepatitis E between placebo and vaccine group within the follow-up period of 19 months. The significant difference for a reduced risk of infection after vaccination (RR= 0.15, 95% Ci 0.3-0.83) was confirmed within a 24-month post-vaccination follow-up of 12 409 subjects from the Zhang et al 2013 (2) RCT. The estimated vaccine efficacy was 79.2% (95%CI 67.7-86.6) over the 2 year study period.

[2] An extended follow up of the vaccinated and unvaccinated groups in the phase III RCT, showed at the end of 54 months, a sustained level of antibodies (in 87% of those who received 3 doses of vaccine) and sustained protection against hepatitis E with protective efficacy of 93.3% (95% CI, 78.6-97.9%) in per protocol analysis i.e. those who received 3 doses of the vaccine (Zhang et al. 2015).

[3] Allocation concealment not clearly stated in the trials

[4] Downgrade because published long term study measures protection against disease i.e. tests for infection only after appearance of symptoms and persistence of antibodies, but does not directly measure for possibility of asymptomatic infection.

Reference List[1-4]

1. Zhang J, Liu CB, Li RC, et al. Randomized-controlled phase II clinical trial of a bacterially expressed recombinant hepatitis E vaccine. Vaccine 2009;27(12):1869-1874.

2. Zhang J, Zhang XF, Zhou C, et al. Protection against hepatitis E virus infection by naturally acquired and vaccine-induced immunity. Clin Microbiol Infect 2014:20:O397-405.

3. Zhu FC, Zhang J, Zhang XF, et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. Lancet 2010;376:895-902.

4. Zhang J, Zhang XF, Huang SJ, et al. Long term efficacy of a hepatitis E vaccine. N Engl J Med 2015;372:914-22.