GRADE Table 01a. Efficacy of hepatitis E vaccination in immunocompetent individuals against hepatitis E virus infection

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

What is the scientific evidence of the efficacy of primary immunization with hepatitis E vaccine (versus control) to prevent hepatitis E disease in immunocompetent individuals?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		3/ RCT 1/observational[1]	4
	Factors decreasing confidence	Limitation in study design	Serious[2]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[3, 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 the effect on the health outcome.
	Conclusion			Evidence supports a limited degree of confidence in the estimate of the effect that primary immunization with hepatitis E vaccine decreases the incidence of hepatitis E virus infection significantly compared to a control. A phase II trial estimated that after receipt of 3 vaccine doses, the vaccinated groups had a significantly lower percentage of episodes of subclinical Hepatitis E per person per month (0.21% and 0.16% vs 1.44%)

[1] A phase IIa randomized controlled trial (RCT) by Zhang et al. 2009(2) reported on the occurrence of new Hepatitis E infection among 457 study subjects by assessing IgG anti-Hepatitis E vaccine levels in successive pairs of consecutive serum samples. Within the control group, 20 episodes (17 individuals) of seroconversion and 13 episodes (13 individuals) within the vaccinated group were reported during the study period of 12 months. After receipt of 3 doses of the vaccine, the vaccinated groups had a significantly lower percentage of episodes per person month (0.21% and 0.16% vs 1.44%). Vaccine efficacy was 85.2%(95% CI: 9.8-99.3% using a 2 dose schedule) and 88.7%(95%CI: 31.0-99.5% using a 3 dose schedule). All 33 episodes were subclinical as no study subject revealed a history of hepatitis E during the trial. Zhu et al. 2010 (3) reported only on clinical 23 hepatitis E cases (22 cases in placebo vs 1 case in the vaccine group) within a large phase III RCT including 122.179 subjects corresponding with an estimated vaccine efficacy within the follow-up period of 19 months of 95.5% (95% CI 66.3-99.4%) within an intention to treat analysis that included everybody having received at least one dose (though most received 3 doses)and assessed a significant difference in incidence ($p<0.0001$) of hepatitis E between placebo and vaccine group. No data on protection against subclinical infection is available. 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 RCT of 12 409 subjects from Zhang et al 2013 (4). The estimated vaccine efficacy was 79.2% (95%CI 67.7-86.6) over the 2 year study period. An observational subset of hepatitis b surface antigen positive subjects (Wu et al.2013 (1)) showed no significant difference (98.38% vs. 98.69%, p=.06063) in seroconversion rates to anti-HEV IgG after 3 doses of the vaccine.

[2] Allocation concealment not clearly stated (Zhang et al. 2009 (2)and Zhu et al. 2010 (3)). The vaccine proved to be efficacious against genotype 1 and 4. The phase III trial was conducted in a region where both genotype 1 and 4 co-circulate. No proved protection against genotype 2 and 3.

[3] Only healthy individuals aged 16- 65 were included, no data available on immunization of children and immunocompromised. No downgrading for indirectness, as the determined age group in which the vaccine should be used may vary among settings.

[4] The phase III trial provided no data on efficacy against subclinical infection with hepatitis E virus.

Reference List[1-4]

1. Wu T, Huang SJ, Zhu FC, et al. Immunogenicity and safety of hepatitis E vaccine in healthy hepatitis B surface antigen positive adults. Hum Vaccin Immunother 2013;9:2474-2479.

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

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