Safety and Efficacy of a Candidate rHEV Vaccines

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Candidate vaccine

- Truncated capsid protein (aa 112-607) of Sar 55 strain of HEV (genotype 1)
- Produced w/ BVES in Sf-9 cells
- Purified by column chromatography
- 20 µg protein adsorbed to 0.5 mg alum (0.5 mL of saline)
- Pilot lot of vaccine
  - Protected non-human primates [1]
  - Phase I dose range study in adults (USA) selected 20 µg dose [2]
  - Phase II study confirmed safety, immunogenicity in adults in Nepal [3]

1. Tsarev, *Vaccine* 1997
2. Safary, *Intervirology* 2001
3. Scott, Shrestha, unpublished data

Rationale for the study

- Primary objective → To evaluate the efficacy of the HEV candidate vaccine among healthy adults in Nepal
- Why Nepal?
  - Hepatitis E → public health research priority [4]
  - Documented disease epidemiology
  - Medical infrastructure is in place to monitor the safety of subjects
- Expected outcomes:
  - Proof of concept
  - Further assessment of candidate vaccine's safety
  - Information regarding anti-rHEV as a correlate of protection
  - Information regarding true burden of disease (from active surveillance)

4. *Labrique AB, Epidemiol Rev.* 1999.

Study design

- Population: healthy men and non-pregnant women, from Nepalese Army units in Kathmandu
  - Initial screening for anti-rHEV Ig < 2.5 WHO U/mL (presumed susceptible to hepatitis E)
- Randomized (1:1), double-blind
  - Vaccine (0, 1, 6 months)
  - Placebo (0.5 mg alum in saline; same schedule)
- Active surveillance for hepatitis E for ~ 2 years
- Reactogenicity and immunogenicity evaluated in a random subset
- Safety evaluated in all (spontaneous adverse events during 30 days after any dose and Serious Adverse Events during the entire study)

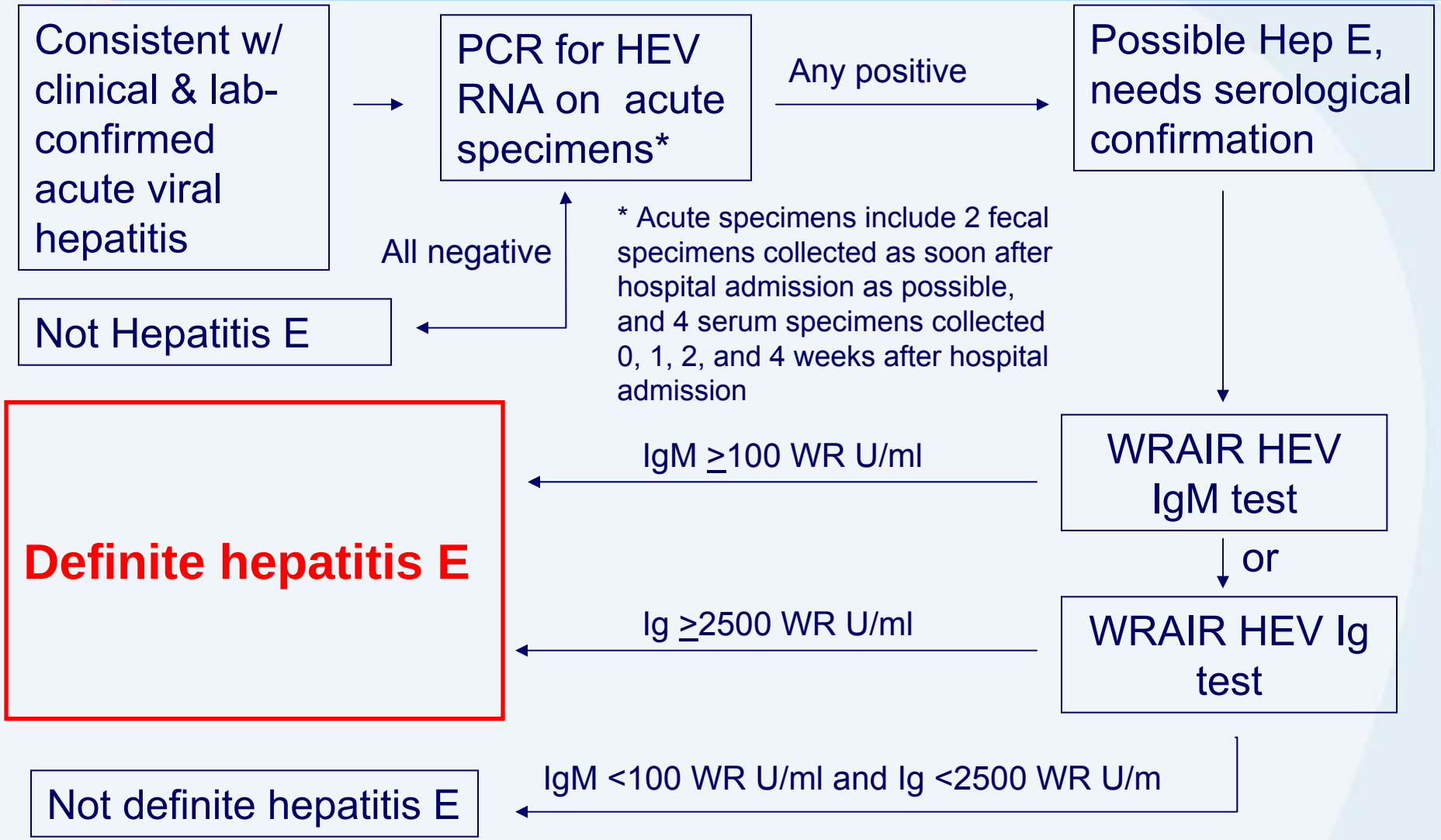
Clinical case definition: acute viral hepatitis

- **Jaundice** or **illness for at least 3 days** comprised of **at least 3 symptoms**:
  - fatigue, loss of appetite, abdominal discomfort, right upper quadrant pain, nausea, vomiting

AND

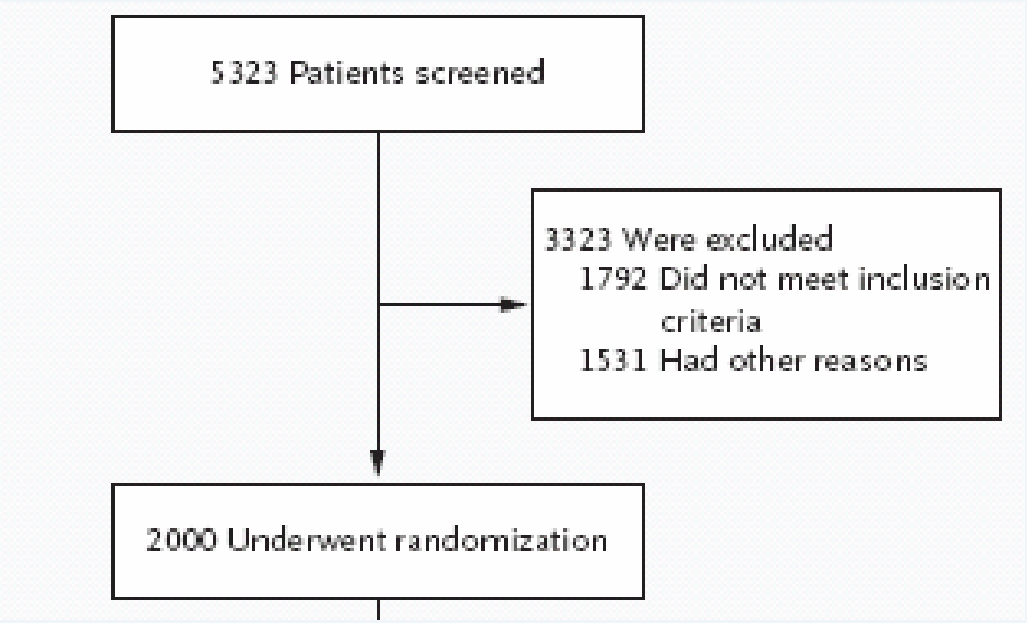
- Peak **ALT > 2.5 times** the upper limit of normal or peak **total bilirubin > 2 mg/dl**

Case definition and diagnostic algorithm



(rule-out probable hepatitis E, i.e. Total Ig ≥1000 WR U/ml)

Outcomes in the screened cohort

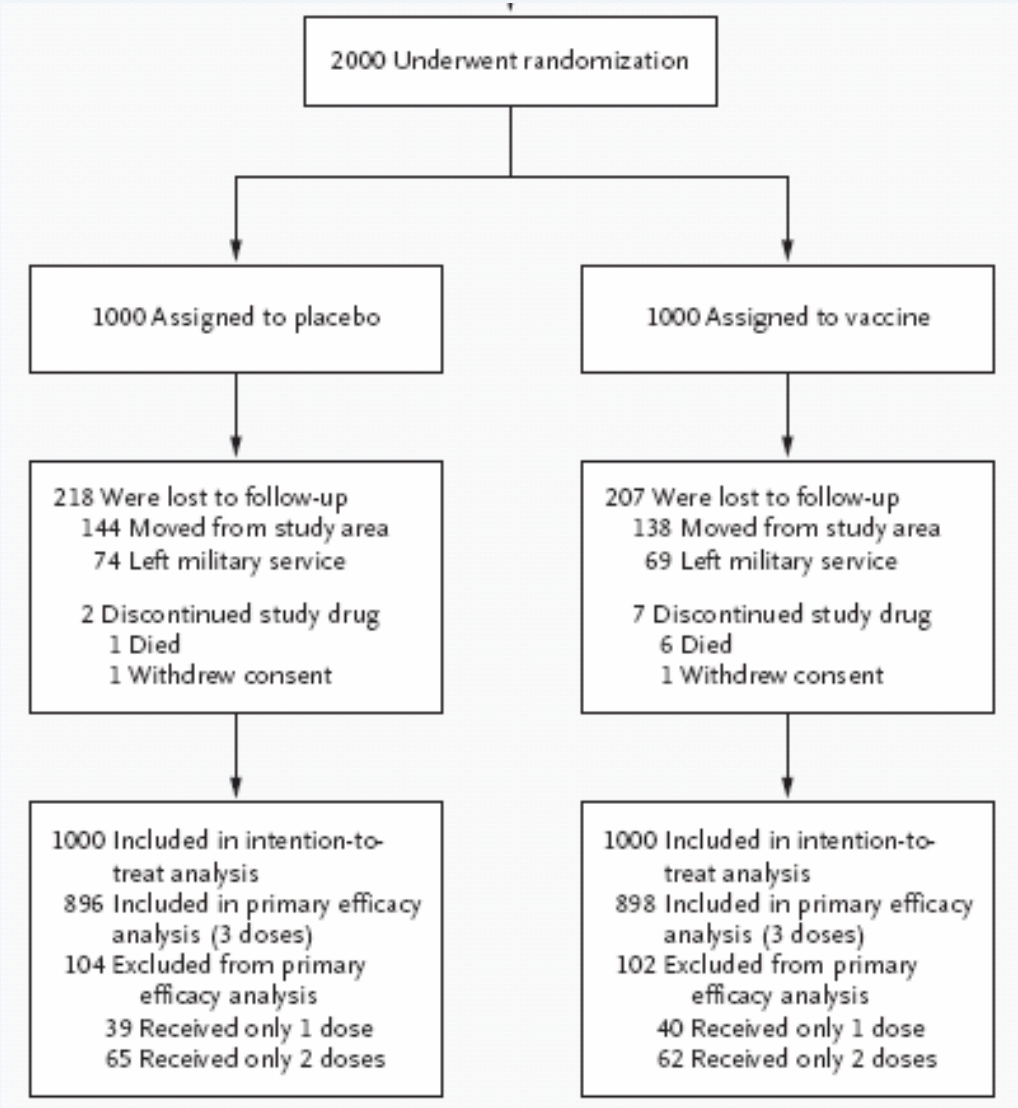


- 66.3% of 5323 screened considered susceptible w/ anti-rHEV Ig <2.5 WHO U/mL
- This population is at high risk if exposed to HEV

Age of randomized cohort

Gender	N	Mean age	SD	Min	Max
F	8	29.6	10.07	20	47
M	1992	25.2	6.23	18	62
Total	2000	25.2	6.25	18	62

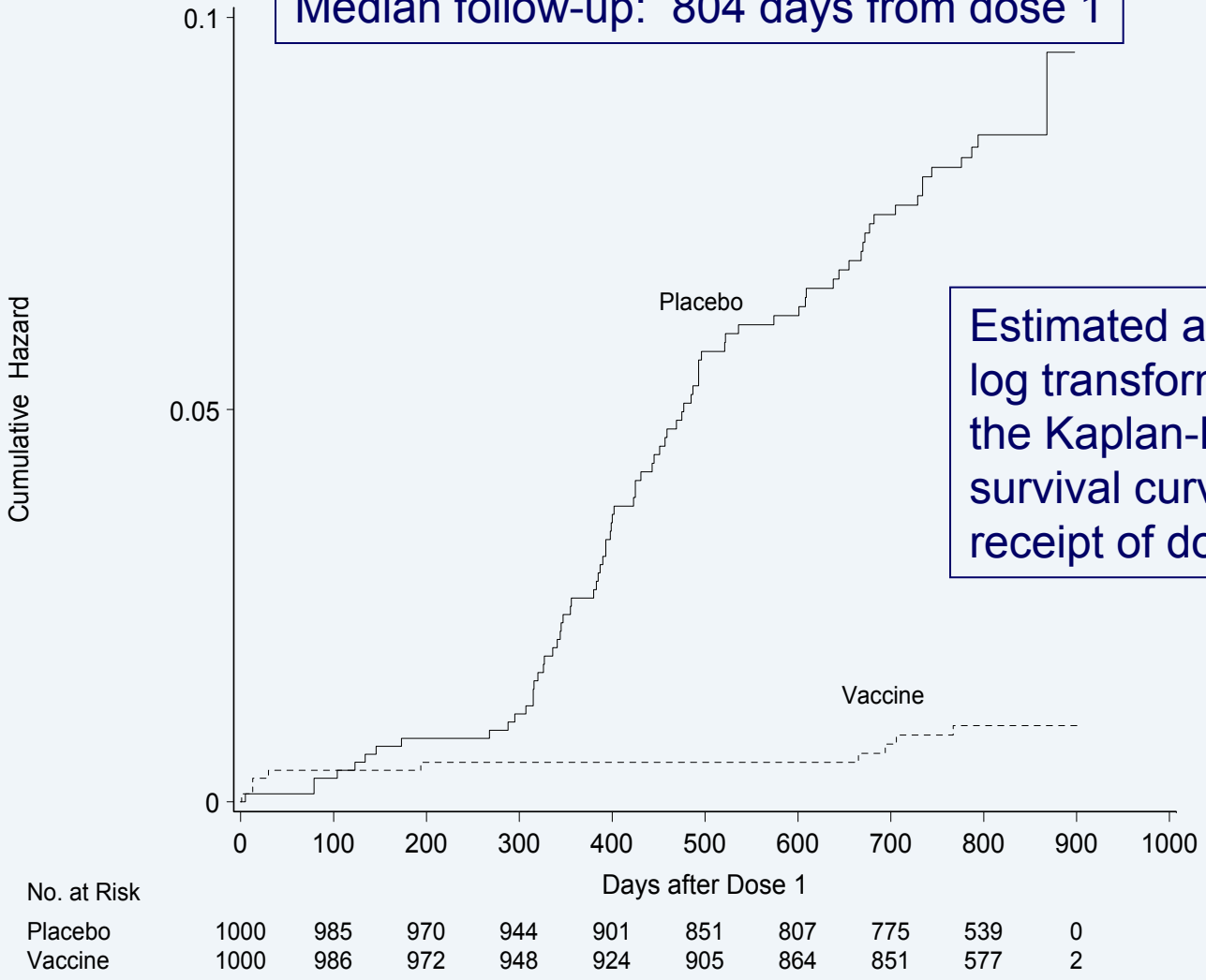
Outcomes in the randomized cohort



- Equal loss to follow-up
- 90% in per-protocol efficacy analysis
  - Exclusion only for incomplete vaccination
- DSMB reviewed 111 episodes of acute hepatitis
  - 87 had hepatitis E
  - 24 not hepatitis E

Cumulative hazard of hepatitis E
(Total vaccinated cohort)

Median follow-up: 804 days from dose 1



Estimated as minus-log transformation of the Kaplan-Meier survival curve from receipt of dose 1

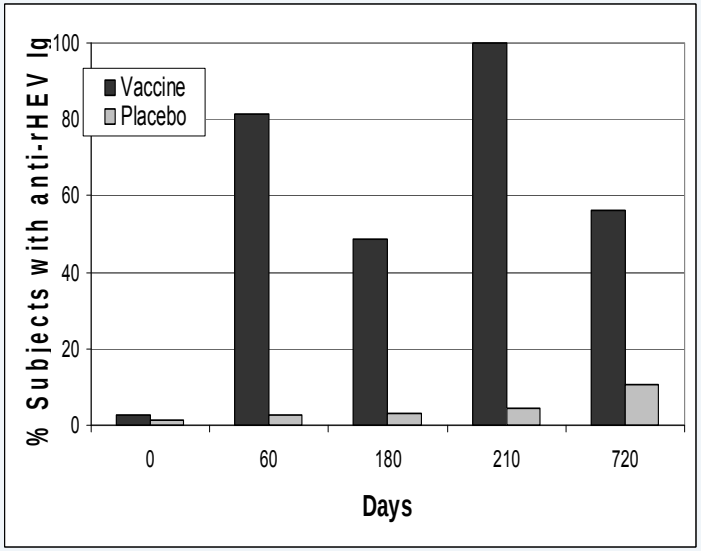
No. at Risk										
Placebo	1000	985	970	944	901	851	807	775	539	0
Vaccine	1000	986	972	948	924	905	864	851	577	2

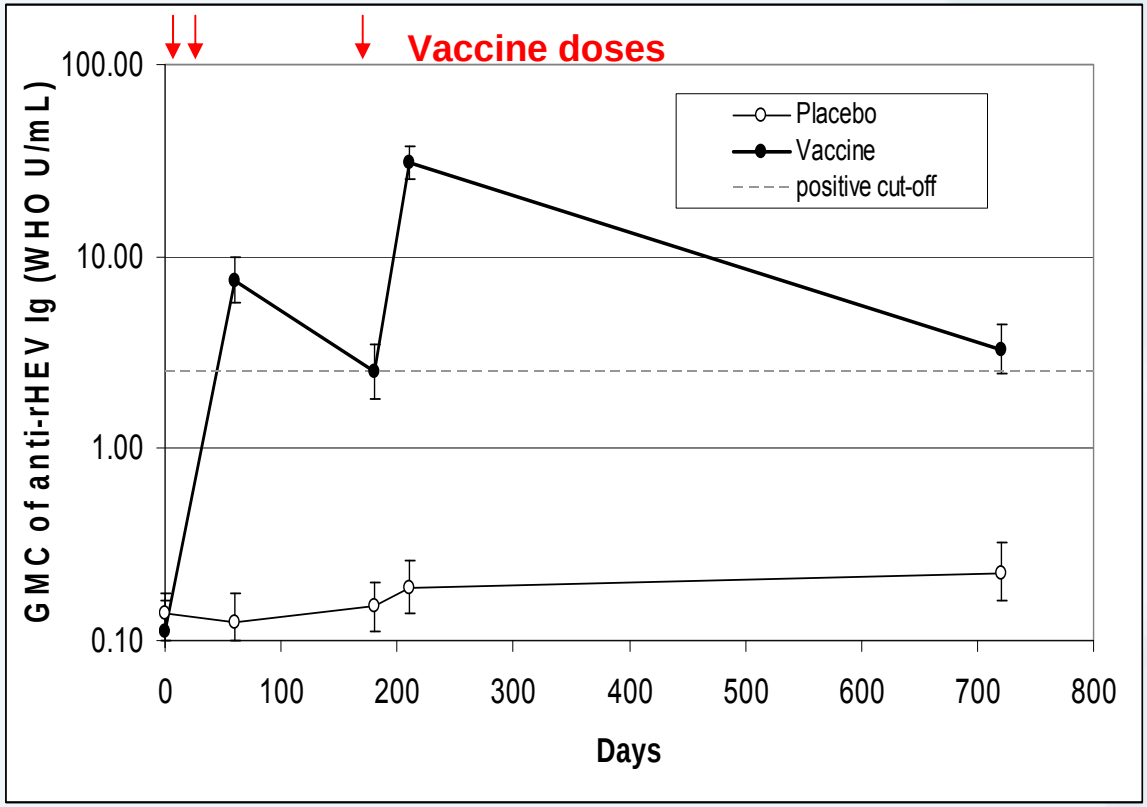
Vaccine efficacy estimates

Period of observation (endpoint category)	Vaccine		Placebo		Vaccine efficacy (95% CI)
	No. of cases	No. in cohort	No. of Cases	No. in cohort	
From 14 days after dose 3 onwards (*a priori* primary endpoint)	3	898	66	896	95.5 (85.6 to 98.6)
From 14 days after dose 2 until dose 3 (*a priori* secondary endpoint)	1	960	7	961	85.7 (-16.0 to 98.2)
From 14 days after dose 2 until 14 days after dose 3 (*a posteriori* secondary endpoint)	1	960	8**	961	87.5 (0.1 to 98.4)
From dose 1 onwards (exploratory endpoint)	9	1,000	78	1,000	88.5 (77.1 to 94.2)

Efficacy estimated as 1-relative risk, with the 95% confidence interval based on the Mantel Haenszel confidence interval for relative risk

Antibody responses





Reactogenicity (Days 0-7 in N=200, any dose)

Symptom	Intensity *	Number and percent reporting indicated finding (95% CI for percent)		p-value **
		Vaccine (N=100)	Placebo (N=100)	
Injection Site				
Pain	Any	82 (73.1, 89.0)	68 (57.9, 77.0)	0.033***
	Grade 3	1 (0, 5.4)	0 (0, 3.6)	1.000
Redness	Any	24 (16.0, 33.6)	19 (11.8, 28.1)	0.491
	Grade 3	0 (0, 3.6)	0 (0, 3.6)	—
Swelling	Any	20 (12.7, 29.2)	17 (10.2, 25.8)	0.716
	Grade 3	0 (0, 3.6)	0 (0, 3.6)	—
Systemic				
Fatigue	Any	43 (33.1, 53.3)	47 (36.9, 57.2)	0.670
	Grade 3	0 (0, 3.6)	0 (0, 3.6)	—
Headache	Any	46 (36.0, 56.3)	46 (36.0, 56.3)	1.000
	Grade 3	0 (0, 3.6)	0 (0, 3.6)	—
Fever	Any	30 (21.2, 40.0)	36 (26.6, 46.2)	0.452
	Grade 3	1 (0, 5.4)	1 (0, 5.4)	1.000

* Grade 3 pain, headache or fatigue prevented normal activities; grade 3 redness or swelling had diameter >50 mm; grade 3 fever was temperature >39.0ºC ** Two-sided Fisher's exact test *** Rate difference: 14.0 % (95% CI , 2.0 to 25.8 %)

Safety

- Vaccine was well-tolerated and no safety signal was identified.

Summary

- This PoC study established the following:
  - rHEV antigen (BVES; aa 112-607; 20 mcg adsorbed to 0.5mg alum) offered 95% protection against hep E on a 3-dose schedule
    - Protection after 2 doses not determined (insufficient AR)
  - Vaccine elicited an immune response in all subjects; but seropositivity by indirect ELISA declined to ~50% at 800 days
    - During period of antibody decline → continuing protection, suggesting protective memory had been established
  - Vaccine was well-tolerated and no safety signal was identified
  - Antibody neg males in Nepal Army (18-62 yrs) were at sustained high risk for hepatitis E, confirming the potential benefit of vaccination vaccine

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