Composition, safety, immunogenicity and efficacy of the licensed hepatitis E vaccine

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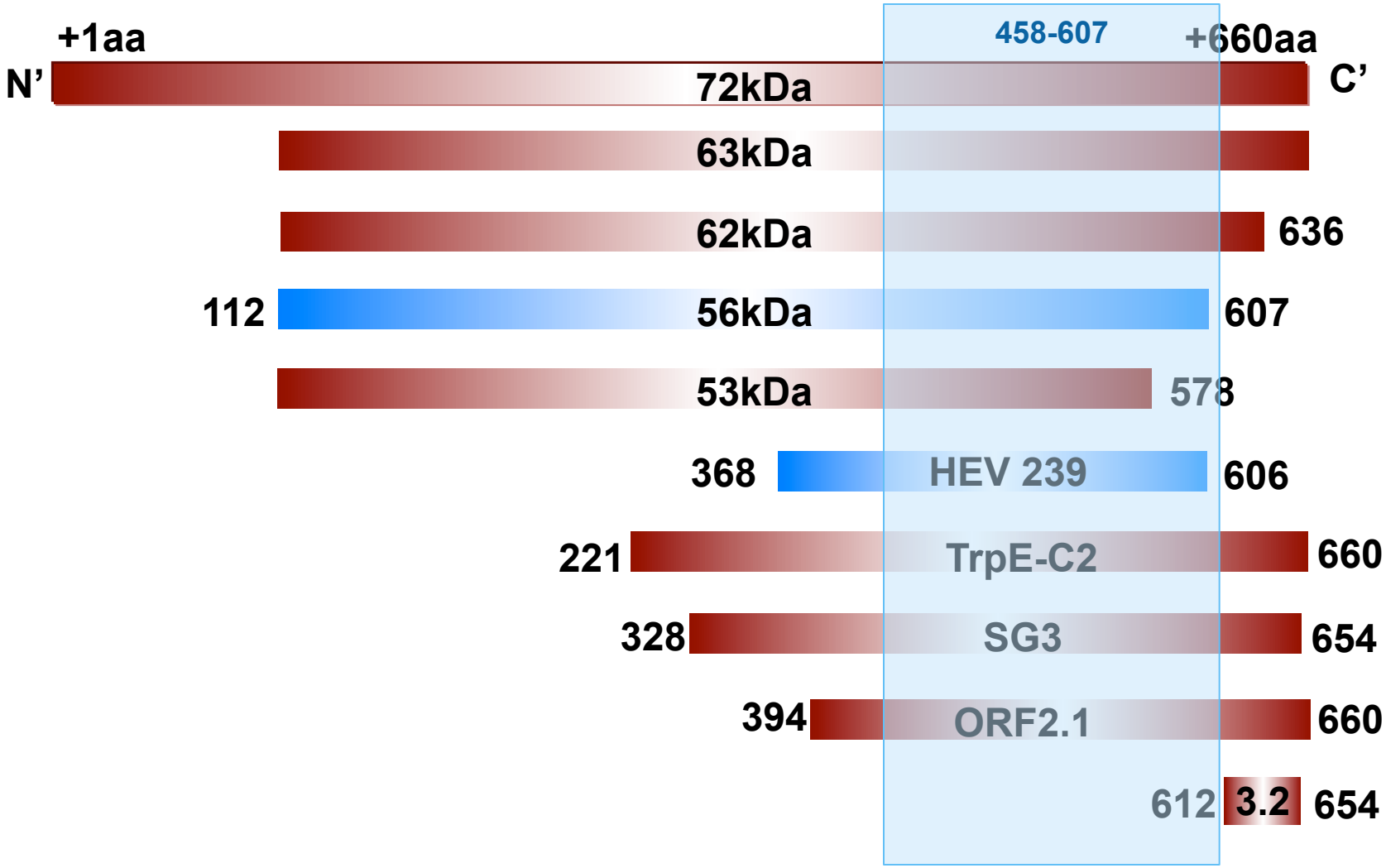
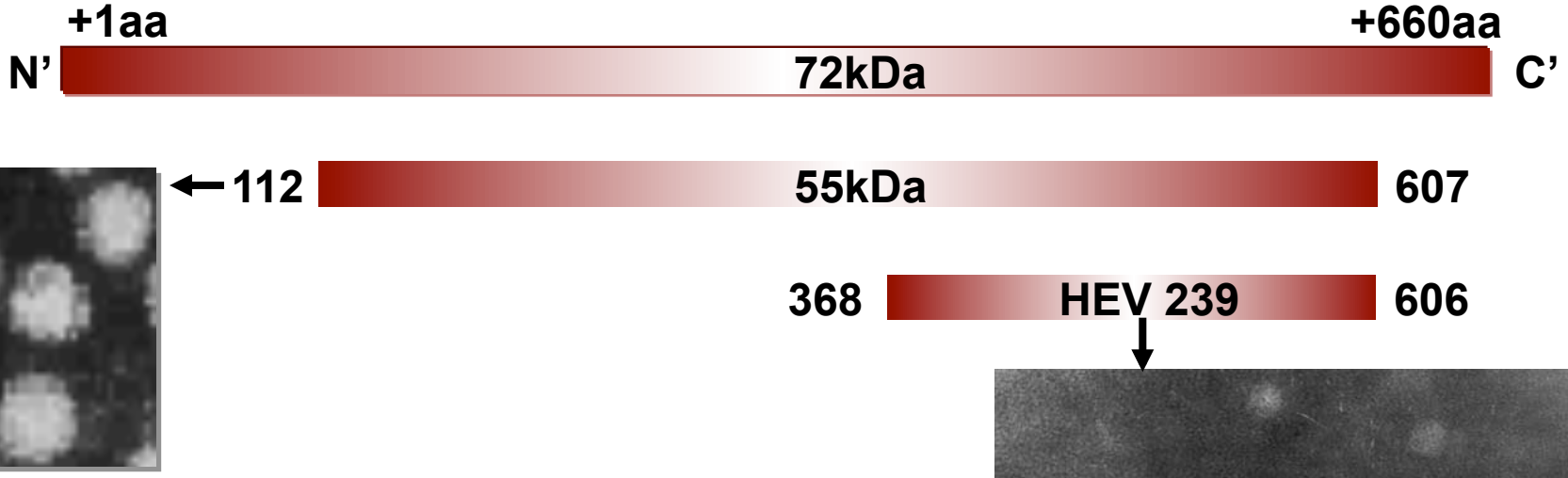
Outline of presentation

- Composition
- Data sources
- Safety data
  - Phase II trial
  - Phase III trial
- Immunogenicity and efficacy data
  - Phase II trial
  - Phase III trial
- Antibody persistence
- Data on specific subgroups (pregnancy, HBsAg positive)

rHEV Proteins as Vaccines in Animal Studies



Hepatitis E Vaccines in Humans



- Expressed in insect cells
- Virus-like particles (VLPs)
- Alum adjuvanted

- Expressed in *E coli*
- 26 nm; HPLC: >500 kDa
- Alum adjuvanted

Tsarev et al. Vaccine 1997; 15: 1834-8.
Li et al. Vaccine 2005: 23: 2893-901.

Vaccine: Composition

- Marketed by Innovax, China as ®

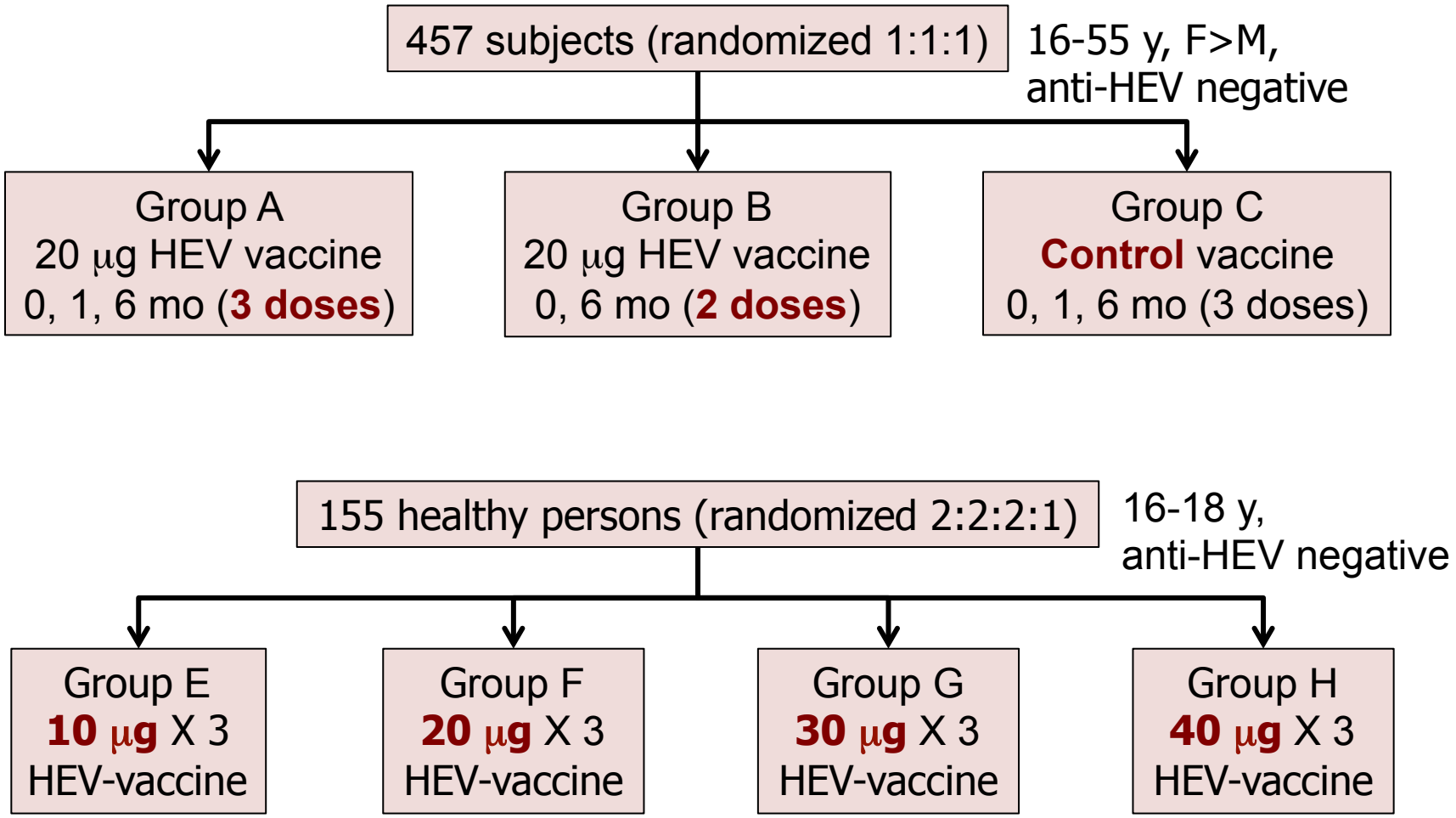
- Purified recombinant HEV antigen: 30 µg
- NaCl, Na_2HPO_4, KH_2PO_4, $AlOH_3$, 25 µg thiomersal
- Pre-filled, single-dose syringes; 0.5 mL white suspension
- Packaging: 13.2 X 3.7 X 2.15 cm ~ 100 cm^3 per dose
- Storage: 2-8°C, out of direct sunlight
- Shelf life: 36 months (stable for 45 months)

Data sources

Phase	***Aim***	***n***	***Reference***
I	Safety	44	Wu *et al*, 2012
IIa	Safety Dose scheduling	457	Zhang *et al*, 2009
IIb	Safety Dose escalation	155	
III	Safety Immunogenicity Efficacy	112,604	Zhu *et al*, 2010
		Inadvertently immunized pregnant women (n=37)	Wu *et al*, 2012
		HBsAg positive persons (n=406)	Wu *et al*, 2013

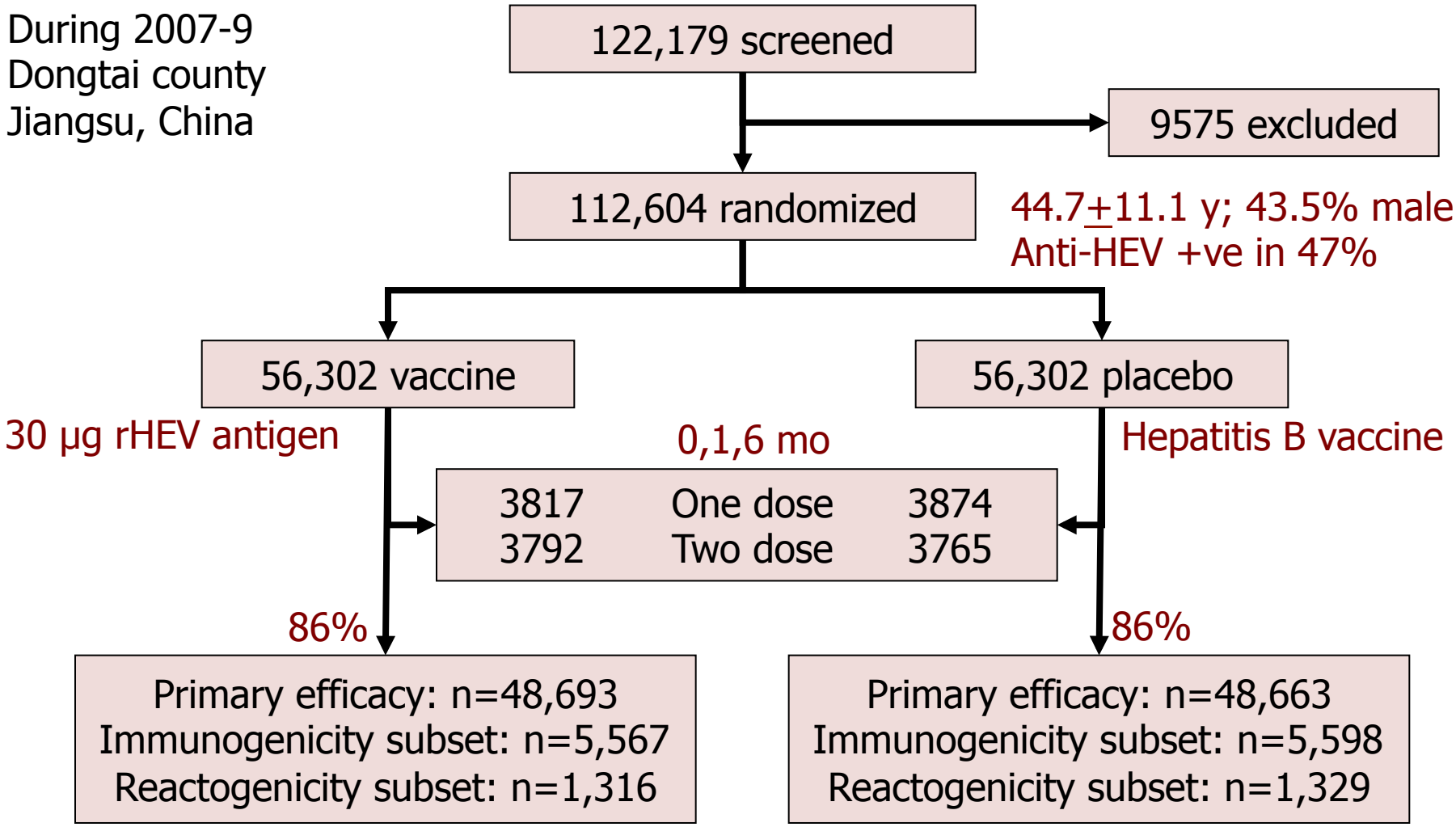
+ unpublished data from the manufacturer

Phase II trials: Design



Zhang et al. Vaccine 2009; 27: 1869-74.

Phase III trial: Design



Zhu et al. Lancet 2010; 376: 895-902.

Extended follow-up data: Design

Hecolin Phase II trial: Safety

- Local adverse events
  - Observed after 5%-8% of doses (20-30 μg)
  - More frequent than with placebo
  - Mostly minor

- No serious local or systemic adverse events

Zhang et al. Vaccine 2009; 27: 1869-74.

Hecolin Phase III trial: Safety results

Type of event	Reactogenicity subset			Non-reactogenicity subset		
	Vaccine	Placebo	P	Vaccine	Placebo	P
Solicited local adverse events within 72 h						
Local AE	13.5%	7.1%	<0.0001	2.8%	1.9%	<0.0001
Local AE ≥ gr 3	0.2%	0%	ns	0.1%	0.05%	<0.0001
Pain	10.3%	5.5%	<0.0001	2.1%	1.4%	<0.0001
Pain ≥ gr 3	0	0	ns	0	0	ns
Swelling	2.3%	0.6%	<0.0001			
Swelling ≥ gr 3	0.2%	0.0%	ns			
Solicited systemic adverse events within 72 h						
Systemic AE	20.3%	19.8%	ns	1.9%	1.9%	ns
Systemic AE ≥ gr 3	0.5%	0.3%	ns	0.2%	0.2%	ns

… … only local pain and swelling were more common in the vaccinees

Hecolin Phase III trial: Serious AEs and deaths

	Vaccine (n=56302)	**Placebo** (n=56302)	**p**
Serious adverse events within 30 days of each dose			
All	248 (0.4%)	245 (0.4%)	ns
Hospital admissions	238 (0.4%)	233 (0.4%)	ns
Deaths	10 (0.0%)	12 (0.0%)	ns
Serious adverse events during other periods			
All	1423 (2.5%)	1430 (2.5%)	ns
Hospital admissions	1328 (2.4%)	1336 (2.4%)	ns
Deaths	95 (0.0%)	94 (0.2%)	ns

… … no increase in serious adverse events or deaths in vaccinees

Phase III trial: Extended follow-up (Mortality)

Unpublished data:
Unpublished data: Unpublished data (confidential)

Phase II trial: Immunogenicity

Vaccination		Serum IgG anti-HEV level (U/ml)				
Group	Dose	No.	+ (%)	Range	GM	95% CI
1. Dose schedule						
A	3 × 20 μg	128	100	1.6–106.2	15.9	13.8–18.2
B	2 × 20 μg	109	98	<0.03–97.4	8.6[b]	6.5–11.3
C	3 × 5 μg Ctrl	131	8	nd	nd	nd
2. Dosage escalation						
E	3 × 10 μg	40	100	0.9–51.0	10.1[c]	7.6–13.3
F	3 × 20 μg	44	100	5.3–56.7	15.9	13.6–18.5
G	3 × 30 μg	38	100	5.4–63.9	18.4	15.5–21.9
H	3 × 40 μg	19	100	18.4–126.4	23.4	16.0–33.8

… led to selection of 30 μg X 3 dose (0-1-6 mo) schedule

Zhang et al. Vaccine 2009; 27: 1869-74.

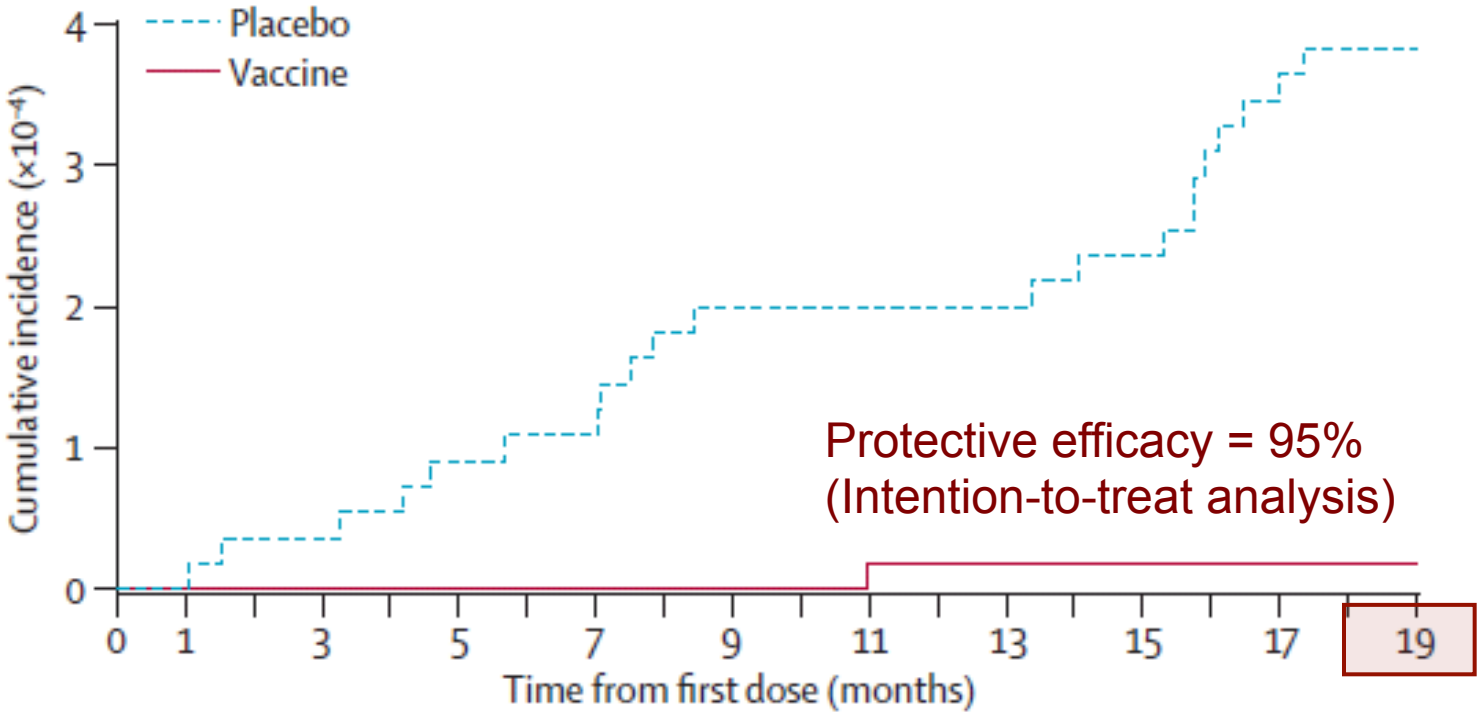
Phase II trial: Efficacy

(Protection against subclinical infection)

Group (dose)		N	Person-mo (A)	Episodes (B)	Incidence (B/A)	Efficacy
During vaccination						
C	Control	131	786	11	1.40	-
B	2 X 20 μg	109	545	10	1.83	-
A	3 X 20 μg	128	512	1	0.20	**86% (18-99)**
After vaccination						
C	Control	104	624	9	1.44	-
B	2 X 20 μg	78	468	1	0.21	**85% (10-99)**
A	3 X 20 μg	102	612	1	0.16	**89% (31-100)**

Zhang et al. Vaccine 2009; 27: 1869-74.

Phase III trial: Efficacy



Protective efficacy = 95%
(Intention-to-treat analysis)

Number at risk											
Placebo	54973	54964	54942	54917	54885	54852	54794	54761	54716	54679	54661
Vaccine	54986	54979	54957	54925	54899	54868	54813	54790	54758	54728	54709
Cumulative number of participants with hepatitis E											
Placebo	0	0	2	5	6	11	11	11	13	19	21
Vaccine	0	0	0	0	0	0	0	1	1	1	1

Zhu et al. Lancet 2010; 376: 895-902.

Phase III trial: Efficacy after 1 or 2 doses

- Efficacy after two doses

– Number of hepatitis E cases after the second dose but before the third dose
  – Placebo: 5/54,973 (20,197 person-years) vs
  – Vaccine: 0/54,986 (20,202 person-years)
  – Efficacy: 100.0% (95% CI = 9.1-100.0%)

– Efficacy: 100.0% (95% CI = 9.1-100.0%)

Phase III trial: Extended follow-up data on efficacy

Phase III trial: Extended follow-up data on efficacy

Extended follow-up data: Antibody persistence

Unpublished data from Innovax (confidential)

Hepatitis E vaccine: Safety in pregnancy

Characteristic	Vaccine group	Placebo group
phase III trial	31,791	31,737
immunized (n)	37	31
3	1	3
Number of doses administered	53	46
Number with elective abortion	19/37	14/31
Number with delivery	18	17

Wu et al. Hepatology 2012; 55: 2038.

Hepatitis E vaccine: Safety in pregnancy

Table 1. Solicited Adverse Events of Vaccination at Different Time Points During Gestation and in Matched Nonpregnant Controls

	Time of Gestation					
	First Trimester	Second Trimester	Third Trimester	Total	Nonpregnant*	*P*
Vaccine group (n = 37)						
First dose	0/14	0/5	0/2	0/21	3/42	–
Second dose	1/12	0/1	0/6	1/19	1/38	>0.05
Third dose	0/11	0/1	0/1	0/13	0/26	–
Total	1/37	0/7	0/9	1/53	4/106	>0.05
Placebo group (n = 31)						
First dose	1/14	0/2	0/2	1/18	0/36	–
Second dose	0/9	0/3	0/2	0/14	1/28	–
Third dose	0/10	0/1	0/3	0/14	0/28	–
Total	1/33	0/6	0/7	1/46	1/92	>0.05

Data are presented as no. of adverse events/no. of vaccine doses.

*Eligible matching nonpregnant women included those who received three doses of the same vaccine, whose age was within 2 years of the matched pregnant women and residing in the same township as the matched pregnant women. For each pregnant woman, two matched nonpregnant women were randomly selected by SAS from among all those who were eligible.

Wu et al. Hepatology 2012; 55: 2038.

Hecolin: Safety in pregnancy -- Newborns

Characteristic		Vaccine group (n=18)	Placebo group (n=17)
Delivery:	Vaginal Caesarean	7 11	7 10
Gestational age (days)		276.2 ± 67.6	276.6 ± 67.1
Birth weight (g)		3,574 ± 357	3,566 ± 532
Birth length (cm)		50.7 ± 1.3	50.8 ± 1.5

Wu et al. Hepatology 2012; 55: 2038.

Vaccine safety in HBsAg-positive persons

Event type	Vaccine group		Placebo group		P value
	HBsAg +ve	HBsAg -ve	HBsAg +ve	HBsAg -ve	
Reactogenicity subset (N)	95	1,220	116	1,210	
Solicited local AE, 72h					
All	11.6	13.6	4.3	7.4	ns
≥ gr 3	0	0.16	0	0	ns
Solicited systemic AE, 72h					
All	11.1	20.2	11.2	20.7	ns
≥ gr 3	0	0.6	0.9	0.3	ns
Other than the subset (N)	311	5409	308	5396	
Solicited local AE, 72h					
All	1.9	2.0	0.7	1.0	ns
≥ gr 3	0.3	0.2	0	0.1	ns
Solicited systemic AE, 72h					
All	1.3	1.8	1.0	1.7	ns
≥ gr 3	0.3	0.1	0	0.2	ns

Wu et al. Hum Vaccin Immunother 2013;9:2474-9.

AE data are shown as %

Vaccine safety in HBsAg-positive persons

Event type	Vaccine group		Placebo group		P value
	HBsAg +ve	HBsAg -ve	HBsAg +ve	HBsAg -ve	
N	406	6629	424	6606	
Unsolicited AE, 30 days					
All	9.6	10.7	9.4	11.3	ns
≥ gr 3	0.5	1.3	0.7	1.2	ns
Serious AE, 0-31 mo	7.1	5.5	5.9	5.4	ns

AE data are shown as %

Wu et al. Hum Vaccin Immunother 2013;9:2474-9.

Summary

- Safety
  - More frequent local adverse events than a control vaccine
  - No increase in systemic or serious adverse events

- Immunogenicity and efficacy
  - Induces anti-HEV antibodies: 98% after 2 doses and nearly 100% after 3 doses
  - Three doses lead to higher antibody titers
  - Highly protective against hepatitis E disease
  - Protection extends up to 4 years

HEV vaccine: Information gaps

- Data on protection
  - Duration of protection and protective antibody titer
  - Protection against high viral dose
  - Protection against severe disease
- Data on specific population subgroups
  - Persons with liver disease or immunosuppression
  - Pregnant women
  - Children
  - Outbreak settings
- Vaccine target: High-risk groups versus general population
  - Better disease burden data
  - Cost-benefit ratio