Clinical Trials of a Recombinant Hepatitis E Vaccine

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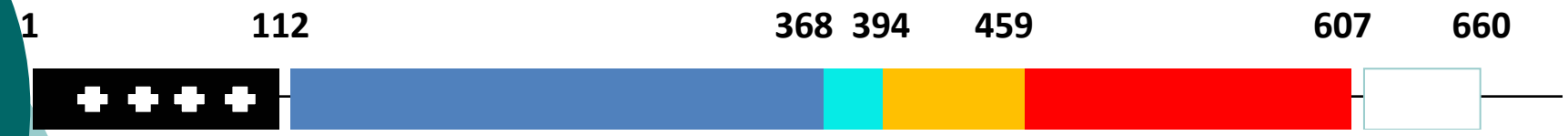
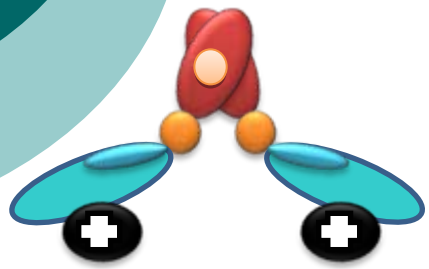
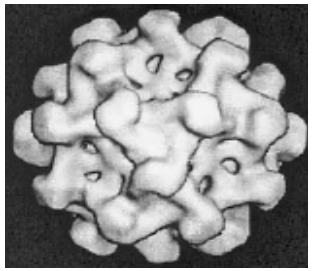
Topics:

- **Development of the candidate recombinant hepatitis E vaccine(p239)**
- **Phase I/II clinical trial**
- **Phase III clinical trial**

Recombinant HEV Structural Proteins







Xing et al Virol 1999

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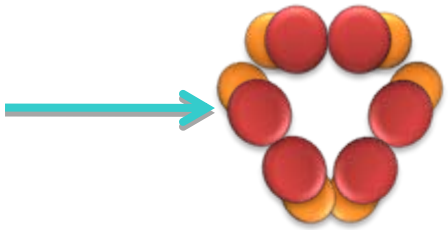
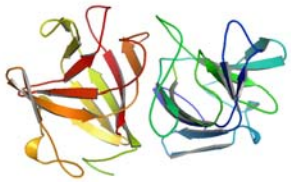
pE2





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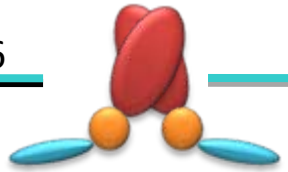

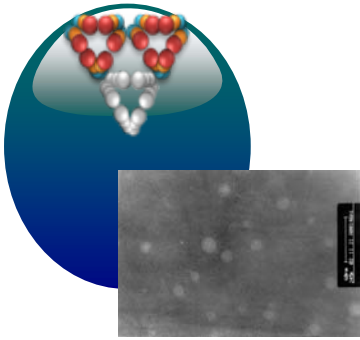

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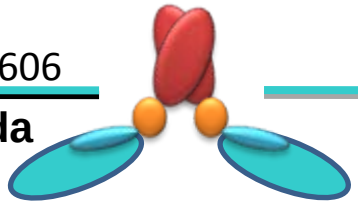
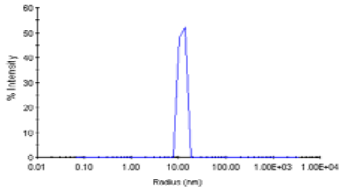
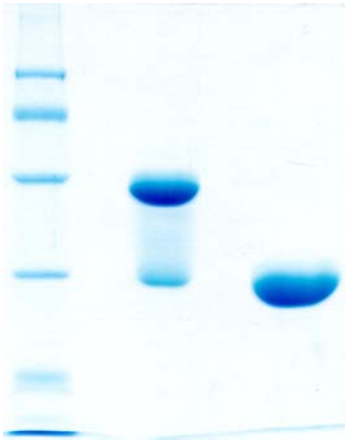


Quality Control of p239

Product :HEVAC	Mfg. Date: Apr 2003
Batch No: 20030401	Pack size: 0.5 ML

S.No	Tests	Specifications	Result
1	**Fill volume**	**0.5 – 0.6 ml**	Passes
2	**Appearance**	**White turbid liquid**	Whitish turbid liquid
3	**Identity–ELISA**	**Should identify**	Identifies
4	**Al^{+++} content**	**$Al(OH)_3$ 1.4~1.8 mg / ml**	0.56 mg / ml
5	**Thiomersal content**	**39.0 – 67.0 µ g / ml**	50 µ g / ml
6	**pH**	**6.1-7.4**	6.65
7	**Sterility**	**Shall comply**	Passes
8	**Abnormal toxicity**	**Shall comply**	Passes
9	**Bacterial endotoxins**	**Less than 10 EU / 0.5ml**	Passes
10	**Relative potency (ED50)**	**Less than 1.5 µ g**	0.113

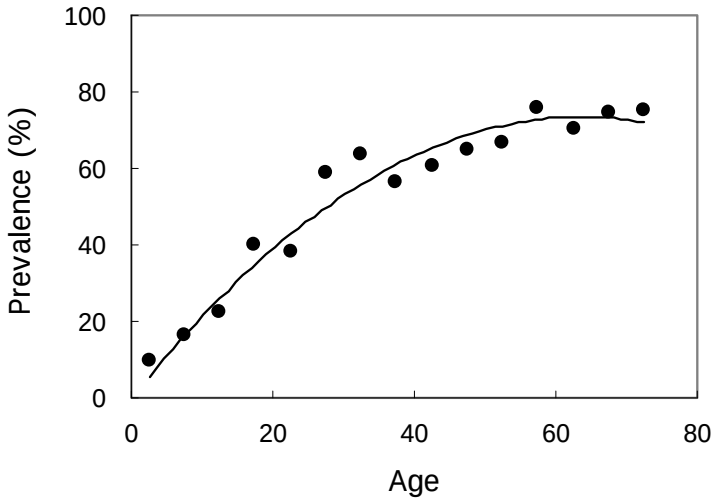


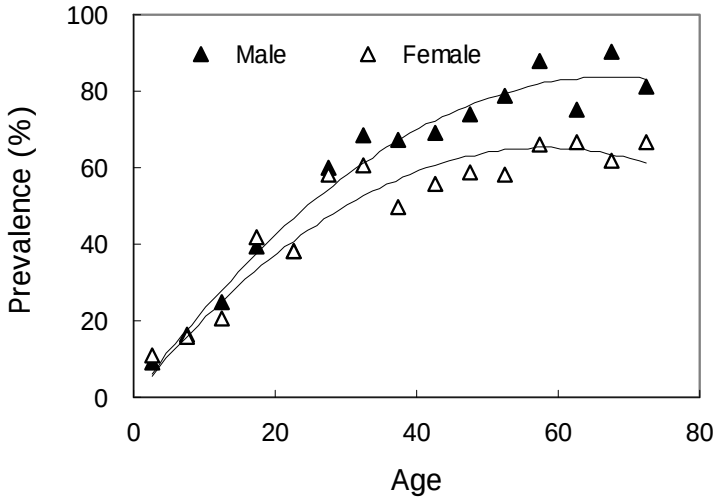


Phase I/II Clinical Trials

Serology in General Population of the Field

地区	n	Prevalence	
		crude	std
LY	1047	58.4	66.1
XA	1037	60.4	59.4
GL	542	57.8	49.4
LC	981	42.2	42.6
TD	377	45.6	38.8
BY	1106	31.1	36.2
LS	1230	21	25.2
LZ	964	43.1	30.4
Total	7284	43.3	43.5
M	3440	45.8	47.1
F	3844	41	39.7

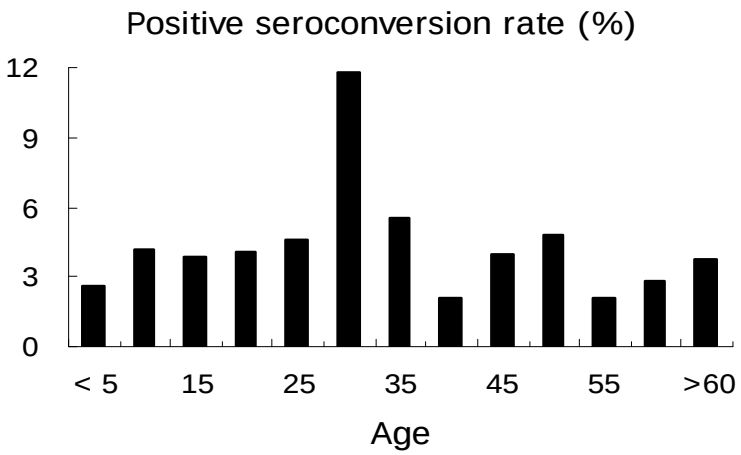


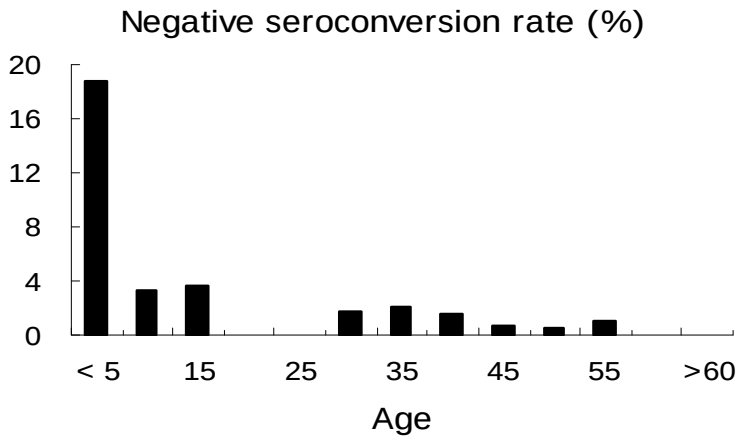


Li RC，et al. *Emerg Infect Dis* 2006,12:1682-8

One-Year Follow-Up Serology

Area	n	Anti-HEV%		Positive conversion % (n)	Negative conversion % (n)
		2003	2004		
LY	738	62.2	78.2	17.9 (50)*	2.0 (9)
XA	533	63.6	65	3.1 (6)	0.3 (1)
GL	340	58.2	59.4	4.2 (6)	3.0 (6)
LC	455	44.4	44.9	2.0 (5)	1.5 (3)
TD	166	48.2	46.9	1.2 (1)	2.5 (2)
BY	657	30.6	31.8	1.8 (8)	0.5 (1)
LS	542	19.4	20.1	0.7 (3)	0.0 (0)
T	3431	46.2	49.1	4.3 (79)	1.4 (22)
M	1597	48.5	52.1	5.0 (41)	1.4 (11)
F	1834	44.1	46.5	3.7 (38)	1.4 (11)





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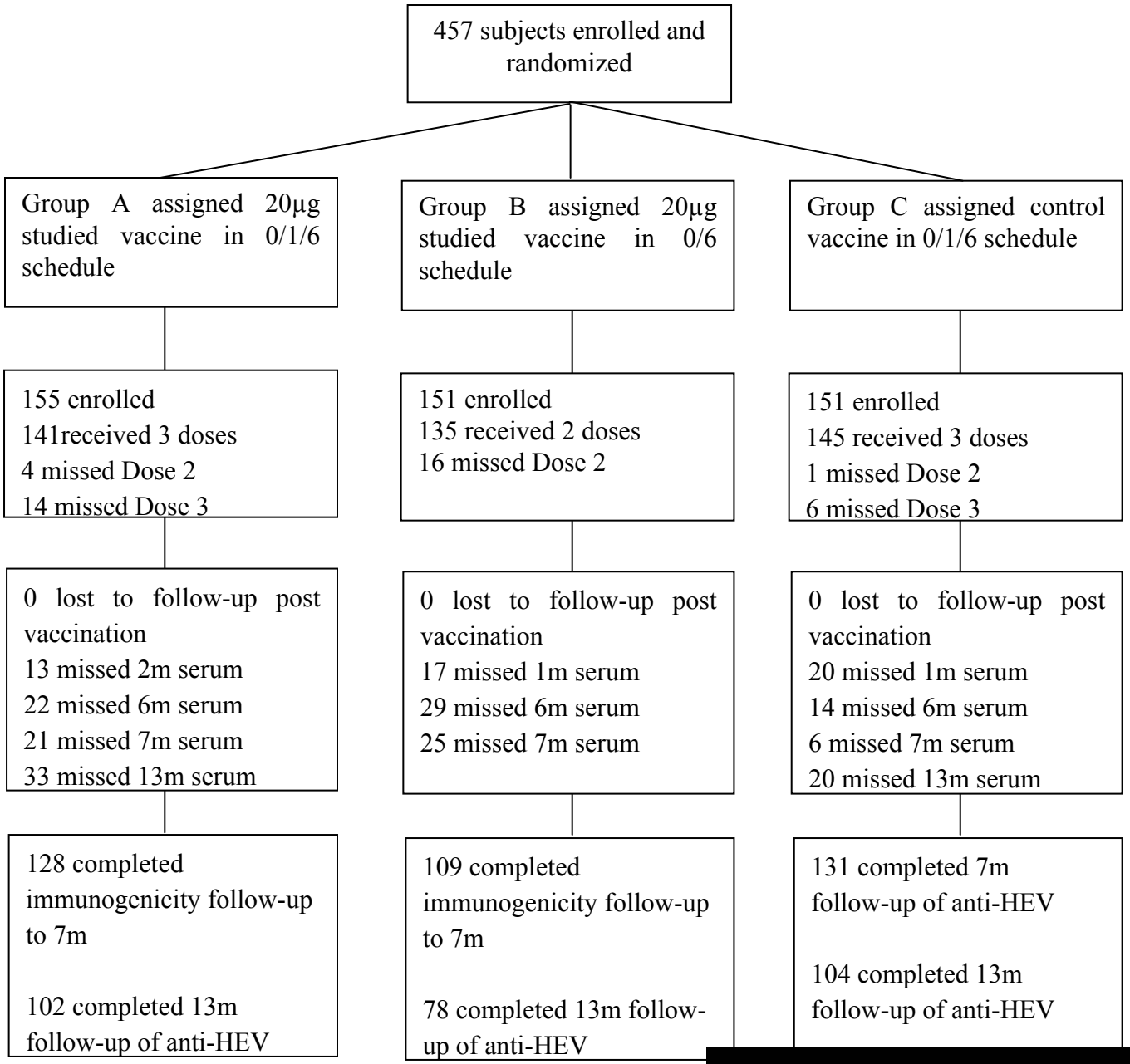
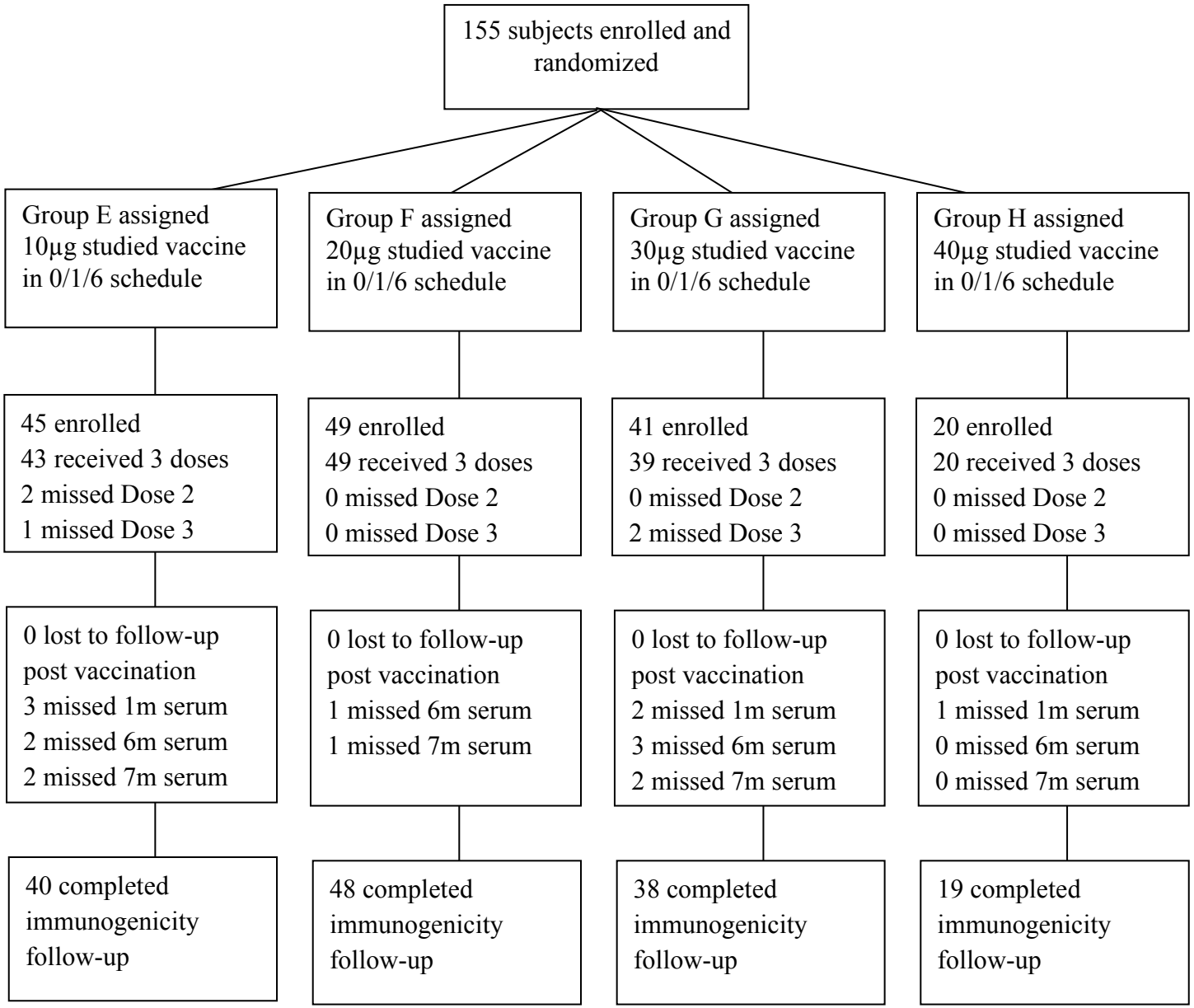
Progression through the dose scheduling study of the HEV 239 vaccine



Zhang et al. *Vaccine* 2009,27:1869-74

Progression through the dosage escalation study of the HEV 239 vaccine



Zhang et al. *Vaccine* 2009,27:1869-74

Reactogenicity of the p239 Hepatitis E Vaccine

Vaccination			Enrollment		% Total (grade 3) AE/Dose		
group	Dose	No.	Age Mean±SD(range)	M/F	doses	Local	Systemic
1. Dose schedule							
A	3×20 μg	155	30.1±12.3(17~55)	0.67	447	8.5 (1.6)	7.6(0)
B	2×20 μg	151	32.8±12.5(17~55)	0.66	286	5.2(0)	4.9(0)
C	3×5μg Ctrl	151	33.6±12.5(16~55)	0.74	446	2.0(0)*	5.6(0)
2. Dosage escalation							
E	3×10 μg	45	18.0±0.62(17~19)	0.36	132	8.3(0)	15.2 (0.8)
F	3×20 μg	49	18.0±0.56(17~19)	0.58	147	6.8(0)	12.9(0)
G	3×30 μg	41	17.9±0.66(17~19)	0.58	121	8.3(0)	9.9(0)
H	3×40 μg	20	17.9±0.45(16~19)	0.67	60	8.3(1.7)	11.7(1.7)

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Imunogenicity of the p239 Hepatitis E Vaccine

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	6.5~11.3
C	3×5μg Ctrl	131	8	nd	nd	nd
2. Dosage escalation						
E	3×10 μg	40	100	0.9~51.0	10.1	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

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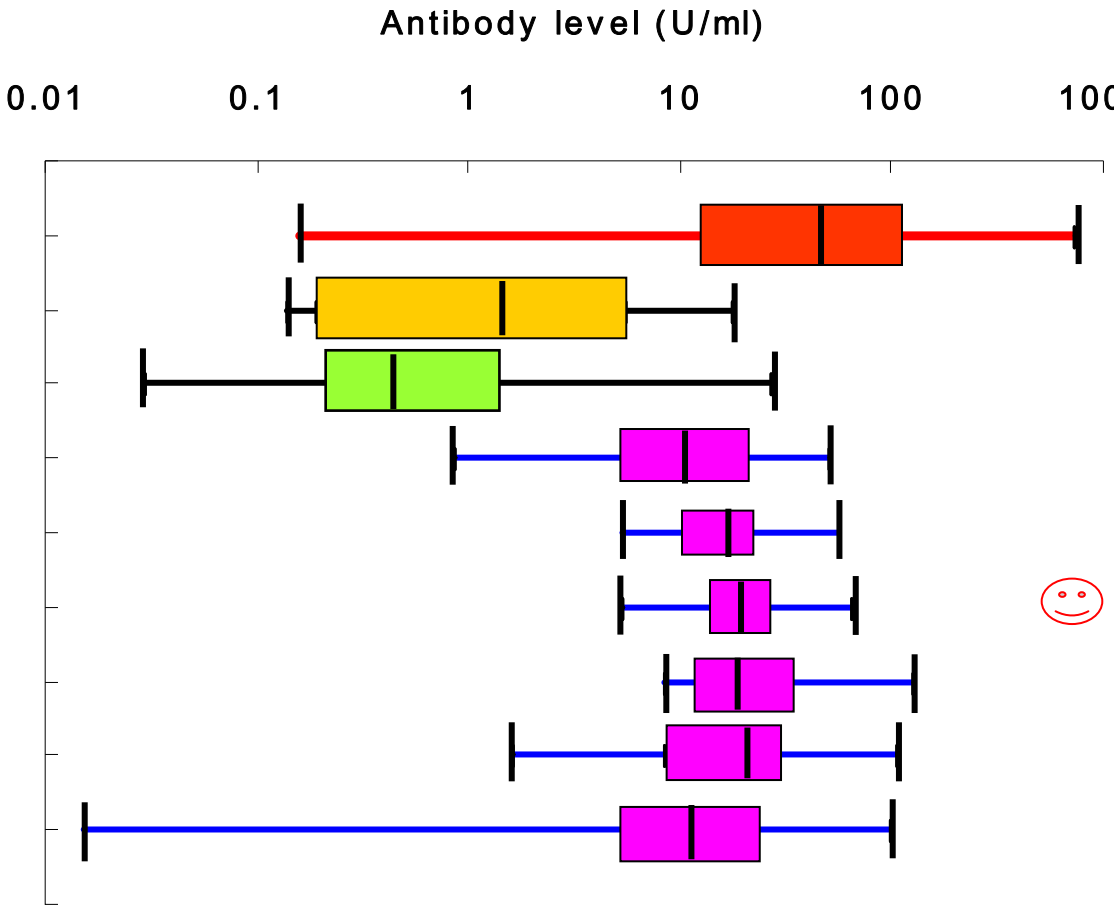
Anti-HEV IgG level



Acute HE (n=114)

Asymptomatic infection (n=10)

General population (n=105)

E. 3×10 μg (n=45)

F. 3×20 μg (n=49)

G. 3×30 μg (n=41)

H. 3×40 μg (n=20)

A. 3×20 μg, 0/1/6m (n=128)

B. 2×20 μg, 0/6m (n=110)

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Occurrence of New Infection

Subjects		Infection Case Identified	
groups	No.	Episodes	Efficacy percent (95%CI)
During vaccination (0m-6m)			
C	131	11	-
B	109	10	-
A	128	1	86.0(18.3 ~ 99.4)
After vaccination (7m-13m)			
C	104	9	-
B	78	1	85.2 (9.8 ~ 99.3)
A	102	1	88.7(31.0 ~ 99.5)

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3. Phase III Clinical Trial

- Primary end-point
  - Efficacy against hepatitis E
  - Safety in large scale population
- Secondary end-point
  - Immunogenicity
  - Antibody persistence

Field for phase III——DT, Jiangsu province

Establishment of Survey System for Acute Hepatitis in DT

- **2006.10~; 8 townships: 310,000 residents**
- **2007.1~; 10 townships: 480,000 residents**

- **Survey point:**
  - Village clinical site
  - Town hospital
  - Country hospital

- **Clinical inclusion standard:**
  - Fatigue or lost appetite ⩾3d

- **Laboratory diagnosis**
  - ALT
  - IgM anti-HEV
  - Elevation of IgG anti-HEV
  - Serum RT-PCR

Phase III Clinical Trial

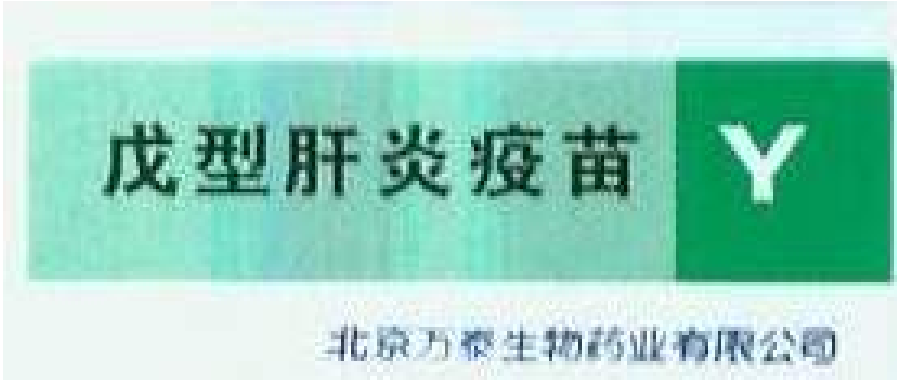
- **Target subjects age: 16-65**
- **IIIa:** To confirm vaccine **immunogenicity & safety** for general population. (Volunteers in phase II clinical study were all HEV seronegative subjects.)
- **IIIb:** To determine **protection efficiency** against hepatitis E over 12 months after completing vaccination course;
- To re-confirm vaccine safety

Sample Size Calculation

- **IIIa. 2x ~1000 subjects per group.**
- **IIIb. 2x ~50,000 subjects per group**
  - α = 0.05; β = 0.8
  - Efficacy: > 80%
  - Incidence rate in control group: 3.5 / 10,000
  - Three doses （complete vaccination）rate: 80%
  - Cannot be followed up: < 15%

Study Design – Blinding & Randomization

- Placebo: commercial HB vaccine
- Blinding: vaccines were labeled with **A/D/K/Y** by manufactory，two for HE vaccine, two for HB vaccine
- Block randomization for vaccine



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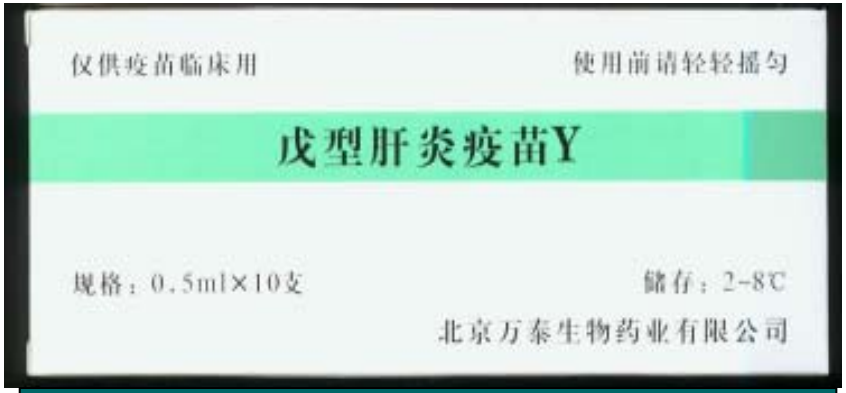

Label on the external package

Publications:

- Zhang J, et al. *Vaccine* 2009,27:1869-1874.
- Wu T, et al. *Intervirology* 2008, 51:322-317.
- He SZ, et al. *J Gen Virol* 2008, 89:245-249.
- Chen YW, et al. *Biomed Environ Sci* 2007, 20:488-494.
- Ge SX, et al. *Biomed Environ Sci* 2007, 20:521-515.
- Luo WX, et al. *FEMS. Immunol Med Microbiol* 2007, 51:18–25.
- Wu T, et al. *Mol Immunol* 2007, 44:3161-3266..
- Zheng YJ, et al. *J Infect Dis* 2006, 193:1643-1649.
- Li RC, et al. *Emerg Infect Dis* 2006, 12:1682-1688..
- Li SW, et al. *J Biol Chem* 2005, 280:3400-3406.
- Zhang J, et al. *Vaccine* 2005, 23: 2881-2892.
- Li SW, et al. *Vaccine* 2005, 23: 2893-2901.
- Xia NS, et al. *Vox Sang* 2004, 86:45-47.
- Zhang J, et al. *J Med Virol* 2003, 71:518-526.
- Wang YC, et al. *J Med Virol* 2003, 67:516-521.
- Zhang JZ, et al. *J Med Virol* 2002, 66:40-48.
- Zhang JZ, et al. *J Med Virol* 2001, 64:125-132.
- Im S, et al. *Vaccine* 2001, 19:3726-3732.