

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Shrestha MP, Scott RM, Joshi DM, et al. Safety and efficacy of a recombinant hepatitis E vaccine. *N Engl J Med* 2007;356:895-903.

CLASSIFICATION OF HEPATITIS CASES

Overall, 111 (19 in the vaccine group and 92 in the placebo group) suspected acute hepatitis cases were recorded. Among those 111 suspected cases, 87 (9 in the vaccine group and 78 in the placebo group) were classified as virologically and serologically confirmed definite hepatitis E cases and 24 (10 in the vaccine group and 14 in the placebo group) were classified as not hepatitis E cases (Table S1). Of the 24 not hepatitis E cases, 4 were reported by the investigators as adverse events with a diagnosis of hepatitis E. But on review of those 4 cases (see footnote to Table S1), the DSMB concluded none met the case definition of hepatitis E; in 2 cases, there was no laboratory evidence of acute liver injury, and in 2 other cases, no acute illness evaluation was performed.

Table S1 Number of suspected, definite, probable and not confirmed HEV cases during surveillance (total vaccinated cohort)

HEV disease status	Onset	Placebo	Vaccine	Total
Any suspected acute hepatitis (all cases)	Before dose 1	0	1	1
	Within 14 days after dose 1	1	3	4
	Between 14 days after dose 1 and dose 2	5	2	7
	Within 14 days after dose 2	0	0	0
	Between 14 days after dose 2 and dose 3	7	4	11
	Within 14 days after dose 3	1	0	1
	From 14 days after dose 3	78	9	87
	Total	92	19	111
Definite hepatitis E cases	Before dose 1	0	0	0
	Within 14 days after dose 1	1	3	4
	Between 14 days after dose 1 and dose 2	3	2	5
	Within 14 days after dose 2	0	0	0
	Between 14 days after dose 2 and dose 3	7	1	8
	Within 14 days after dose 3	1	0	1
	From 14 days after dose 3	66	3	69
	Total	78	9	87
Probable hepatitis E cases	Total	0	0	0
Not confirmed hepatitis E cases	Before dose 1	0	1	1
	Within 14 days after dose 1	0	0	0
	Between 14 days after dose 1 and dose 2	2 ¹	0	2
	Within 14 days after dose 2	0	0	0
	Between 14 days after dose 2 and dose 3	0	3	3
	Within 14 days after dose 3	0	0	0
	From 14 days after dose 3	12 ²	6 ³	18
	Total	14	10	24

¹ Subjects 2359 and 2567 are “not hepatitis E”. They were acute HEV infection with viremia but no confirmed liver injury.

² Subject 2421 had illness (start date 17JUL2003, end date 25AUG2003) with jaundice, but was not evaluated for clinical hepatitis. A serum specimen collected 01DEC2003 had ALT 29.1 U/L, HEV RT-PCR negative, rHEV IgM 49 WR U/ml and rHEV Ig 852 WR U/ml, results consistent with past HEV infection. The DSMB classified this event “not hepatitis E”.

³ Subject 2860 had illness (start date JAN2003, end date MAR2003) with jaundice, but was not evaluated for clinical hepatitis. A serum specimen collected 20OCT2003 had ALT 18.0 U/L, HEV RT-PCR negative, rHEV IgM 195.9 WR U/ml and rHEV Ig 560.6 WR U/ml, results consistent with past HEV infection. The DSMB classified this event “not hepatitis E”.

The 111 clinically suspected acute hepatitis E cases were also tested for determination of co-infection. Of them, 8 had serological evidence of recent leptospirosis (of which 7 were also confirmed definite hepatitis E), 4 had serological evidence of recent scrub typhus (all 4 were also confirmed definite hepatitis E), 3 had serologically confirmed hepatitis B (all 3 were also confirmed definite hepatitis E) and 1 had serologically confirmed hepatitis C and definite hepatitis E (Table).

Table S2 Distribution between treatment groups of clinically suspected hepatitis and diagnoses of hepatotropic disease cases occurring during the trial (total vaccinated cohort)

	Placebo group n	Vaccine group n	Total n
Clinically-suspected hepatitis E	92	19	111
Serologically-confirmed hepatitis A (HAV-IgM)	0	0 ¹	0
Serologically-confirmed hepatitis B (HBc-IgM)	1 ²	0	1
Hepatitis B carrier (HBs-Ag positive but HBc-IgM negative)	2 ^{3,4}	0	2
Serologically-detected hepatitis C (HCV-IgG)	1 ⁵	0	1
Serologically-detected leptospirosis (Lepto-MAT and Lepto-IgM)	6 ^{3,5,6}	2 ^{7,8}	8
Serologically detected scrub typhus (IgM by PANBIO test and IgM or IgG western blot)	3 ^{9,10}	1 ¹¹	4
Virologically and serologically confirmed hepatitis E	78	9	87

¹ Subject 1374 is a “not hepatitis E” case and had an equivocal result for HAV-IgM

² Subject 759 is a definite hepatitis E case and had positive tests for HBc-IgM, HBV DNA (by PCR) and anti-HBs but negative tests for anti-HBc and HBsAg (**Hepatitis E and acute hepatitis B**)

³ Subject 509 is a definite hepatitis E case and had a positive test for HBsAg but a negative test for HBc-IgM (**Hepatitis E in a HBV carrier**); he also had a positive lepto-MAT (leptospirosis micro-agglutination test) and a positive test for lepto-IgM results (**Possible recent leptospirosis infection**)

⁴ Subject 1271 is a definite hepatitis E case and had a positive test for HBsAg but a negative test for HBc-IgM (**Hepatitis E in a HBV carrier**)

⁵ Subject 2789 is a definite hepatitis E case and had a positive test for HCV-IgG but a negative test for HCV RNA (by RT-PCR) (**Hepatitis E in an HCV-exposed subject**); he also had a positive lepto-MAT and a positive test for lepto-IgM (**Possible recent leptospirosis infection**)

⁶ Four subjects (127, 337, 1155 and 2343) are definite hepatitis E cases and had positive lepto-MATs and positive tests for lepto-IgM (**Hepatitis E in subjects with possible recent leptospirosis infection**)

⁷ Subject 1544 is a definite hepatitis E case and had a positive lepto-MAT and a positive test for lepto-IgM (**Hepatitis E in a subject with possible recent leptospirosis infection**)

⁸ Subject 1801 is a “not hepatitis E” case but had a positive lepto-MAT and a positive test for lepto-IgM (**Possible recent leptospirosis infection**)

⁹ Subject 2331 is a definite hepatitis E case and had a positive test for scrub typhus IgM (PANBIO test) with a negative IgM western blot but a positive IgG western blot (**Hepatitis E in a subject with possible recent scrub typhus infection**)

¹⁰ Two subjects (1516 and 2164) are definite hepatitis E case and had positive tests for scrub typhus IgM (PANBIO test) with positive IgM but negative IgG western blots (**Hepatitis E in subjects with possible recent scrub typhus infection**)

¹¹ Subject 2126 is a definite hepatitis E case and had a positive scrub typhus IgM (PANBIO test) with a positive IgM western blot but a negative IgG western blot (**Hepatitis E in a subject with a possible recent scrub typhus infection**)

CHARACTERIZATION OF HEPATITIS E CASES

The intensity of illness among the 87 definite hepatitis E cases identified in the total vaccinated cohort was evaluated by tabulating descriptive statistics for three parameters: duration of illness in days; maximum ALT and maximum total bilirubin, considering up to 4 weekly blood specimens collected from the date of the initial clinical evaluation. These parameters, stratified by treatment group, are shown in the tables below.

TABLE S3 Descriptive statistics for duration (in days) of hepatitis E (Definite cases, total vaccinated cohort)

Group	N	Mean	SD	Min	Q1	Median	Q3	Max
Placebo	78	32.53	14.56	8.00	23.00	29.00	39.00	82.00
Vaccine	9	30.33	8.41	18.00	26.00	30.00	39.00	42.00
Total	87	32.30	14.03	8.00	23.00	29.00	39.00	82.00

N = number of subjects with definite hepatitis E
SD = standard deviation

TABLE S4 Descriptive statistics for maximum ALT (Definite cases, total vaccinated cohort)

Characteristic	Parameters	Placebo	Vaccine	Total
ALT	N	78	9	87
	Missing	0	0	0
	Mean	1487.57	1799.39	1519.83
	SD	1134.12	1147.18	1132.77
	Minimum	156.00	490.00	156.00
	Q1	688.00	1040.00	756.00
	Median	1245.50	1290.00	1248.00
	Q3	1868.00	2323.00	1995.00
	Maximum	4829.00	4214.00	4829.00
	Geometric mean	1085.17	1503.79	1122.42

N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter

TABLE S5 Descriptive statistics for maximum total bilirubin (Definite cases, total vaccinated cohort)

Characteristic	Parameters or Categories	Placebo	Vaccine	Total
Bilirubin	N	78	9	87
	Missing	0	0	0
	Mean	10.36	10.35	10.36
	SD	6.13	5.14	6.01
	Minimum	0.62	5.00	0.62
	Q1	6.22	7.56	6.61
	Median	8.98	8.00	8.95
	Q3	13.11	10.90	13.11
	Maximum	31.40	19.62	31.40
	Geometric mean	8.44	9.41	8.54

N = number of subjects

n = number of subjects in a given category

Value = value of the considered parameter

DIAGNOSES FOR “NOT HEPATITIS E” CASES

The Data Safety Monitoring Board reviewed all data available for each suspected hepatitis case and classified each as Definite Hepatitis E, Probable Hepatitis E, Not Hepatitis E, according to case definitions specified in the study protocol. Table S6 shown on the next page summarizes data for the 24 “not hepatitis E” cases. In no case, was a definite cause of liver injury or jaundice established by testing for serum markers related to HAV, HBV, HCV, scrub typhus, or leptospirosis.

Table S6 Summary data for “not hepatitis E” cases

Subj no.	Max ALT	Max T-bili	HAV IgM	HBV (IgM and/or HBsA)g	HCV Ig	Lepto-spirosis serology	Scrub typhus serology	Illness start date	Illness end date	Duration of illness (days)	Diagnosis
0086	23.0	2.90	neg x4	neg x4	neg x4	MAT neg	IgM neg x4	15-Sep-01	2-Oct-01	17	Jaundice, cause unknown
0475	31.8	4.76	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	19-Sep-02	8-Oct-02	19	Jaundice, cause unknown
0663	179.5	0.46	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	7-May-02	31-May-02	24	Liver injury, cause unknown
1047	135.3	1.01	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	3-Sep-02	24-Sep-02	21	Liver injury, cause unknown
1240	56.5	2.74	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	31-Jan-03	17-Feb-03	17	Jaundice, cause unknown
1374	189.0	4.00	neg x2	neg x4	neg x4	IgM neg x4	IgM neg x4	17-Jul-01	20-Aug-01	34	Jaundice and liver injury, cause unknown
1402	90.6	5.71	neg x2	neg x2	neg x2	IgM neg x2	IgM neg x2	31-May-02	10-Oct-02	132	Jaundice and liver injury, cause unknown
1556	33.7	2.74	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	19-Jul-02	29-Jul-02	10	Jaundice, cause unknown
1801	48.3	4.30	neg x2	neg x2	neg x2	MAT pos	IgM neg x2	15-Jan-02	27-Nov-02	316	Incomplete sampling; jaundice, possible recent leptospirosis
1910	73.3	13.82	neg x4	neg x4	neg x4	MAT neg	IgM neg x4	18-Jun-03	21-Jul-03	33	Jaundice, cause unknown
2020	32.8	2.75	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	27-Jul-02	2-Sep-02	37	Jaundice, cause unknown
2078	42.8	3.79	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	22-May-02	16-Jul-02	55	Jaundice, cause unknown
2082	48.2	2.12	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	23-Jun-02	9-Sep-02	78	Jaundice, cause unknown
2314	43.2	2.67	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	29-Oct-02	4-Dec-02	36	Jaundice, cause unknown

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Subj no.	Max ALT	Max T-bili	HAV IgM	HBV (IgM and/or HBsA)g	HCV Ig	Leptospiroserology	Scrub typhus serology	Illness start date	Illness end date	Duration of illness (days)	Diagnosis
2359	101.8	1.60	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	Unk Aug 01	26-Sep-02	≤57	Not hepatitis; HEV infection confirmed by viremia and IgM
2421	Unk	Unk	neg x1	neg x1	neg x1	IgM neg x1	IgM neg x1	17-Jul-03	25-Aug-03	39	No timely sampling (6 mos convalescent specimen only); hepatitis not confirmed
2475	92.4	2.39	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	6-May-02	1-Jun-02	26	Jaundice, cause unknown
2483	44.2	2.66	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	3-Jul-02	13-Jul-02	10	Jaundice, cause unknown
2489	253.8	2.66	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	24-Jul-03	25-Sep-03	63	Jaundice and liver injury, cause unknown
2567	46.7	1.44	neg x1	neg x1	neg x1	IgM neg x1	IgM neg x1	10-Sep-03	8-Oct-03	28	No timely sampling (6 week convalescent specimen only); hepatitis not confirmed; hepatitis E infection confirmed by viremia and IgM
2647	10.9	2.27	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	10-Oct-02	20-Oct-02	10	Jaundice, cause unknown
2860	Unk	Unk	neg x1	neg x1	neg x1	IgM neg x1	IgM neg x1	Unk Jan 03	Unk Mar 03	≤90	No timely sampling (10mos convalescent specimen only); hepatitis not confirmed
2907	98.8	2.22	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	10-Aug-02	21-Aug-02	11	Jaundice, cause unknown
2944	27.3	2.11	neg x4	neg x4	neg x4	IgM neg x4	IgM neg x4	25-Aug-02	2-Sep-02	8	Jaundice, cause unknown

VACINE EFFICACY

The impact of potential covariates (age, pre-vaccination anti-rHEV antibody concentration) on vaccine efficacy was an *a priori* analysis; data from the Clinical Study Report are presented below.

Table S7 Attack rate of hepatitis E by covariates and overall (total cohort for analysis of efficacy after dose 3)

	Attack Rates								2-sided exact p-value	VE	95% C.I
	Vaccine				Placebo						
	N	n	AR	95% CI	N	n	AR	95% CI			
Age : <25 Years	556	1	0.2	0.0,1.0	561	45	8.0	5.9, 10.6	<0.001	97.8	83.8,99.7
Age : ≥25 Years	342	2	0.6	0.1,2.1	335	21	6.3	3.9,9.4	<0.001	90.7	60.5,97.8
PVT : ≤10 WR U/mL	847	3	0.4	0.1,1.0	845	66	7.8	6.1,9.8	<0.001	95.5	85.6,98.6
PVT : >10 WR U/mL	51	0	0.0	0.0,7.0	51	0	0.0	0.0,7.0	NA	NA	NA
Overall	898	3	0.3	0.1,1.0	896	66	7.4	5.7,9.3	<0.001	95.5	85.6,98.6

N = number of subjects; n = number of subjects with hepatitis E

AR =Attack rate = n / N

PVT=Pre-Vaccination Concentration

AR = Attack Rate (%) = n x 100 / N

AR 95%CI = 95% Confidence interval on attack rates estimated using the exact method for binomial variables

2-sided exact p-value = 2-sided p-value from Fisher's exact test to compare the attack rates

VE= Vaccine Efficacy (%) = $1 - \frac{AR_{Vaccine}}{AR_{Placebo}}$ = 1-Relative risk

VE 95% CI = 95% Confidence interval on vaccine efficacy based on the Mantel-Haenszel 95% CI on relative risk

NA = Not Applicable

The impact of covariates on vaccine efficacy was also determined using logistic regression. Age and pre-vaccination anti-rHEV concentrations had no impact on vaccine efficacy, estimated as 95.8% with or without adjustment.

Table S8 Vaccine efficacy against hepatitis E disease cases by covariates and overall (total cohort for analysis of efficacy after dose 3)

	(Vaccine N =898) (Placebo N =896)		
	V.E.	95% CI for V.E.	p-value
Unadjusted	95.8	88.6 - 99.0	<0.001
Adjusted for age	95.8	88.6 - 99.0	<0.001
Adjusted for Pre-Vaccination Concentration	95.8	88.7 - 99.0	<0.001

N = Number of subjects

Unadjusted = logistic regression without covariates

Adjusted for age = logistic regression adjusted by age category (< 25 or ≥ 25 Years)

Adjusted for Pre-Vaccination Concentration = logistic regression adjusted by Pre-Vaccination anti-rHEV Concentration category (≤10 or >10 WR U/mL)

V.E. = Vaccine efficacy obtained from logistic regression

95% CI = 95% confidence interval obtained from logistic regression

P-value = result of comparison of attack rates between groups by Fisher’s exact test (unadjusted) / Mantel Haenszel test (adjusted)

VACCINE SAFETY

Additional tabulated safety data from pre-specified descriptive analyses comparing vaccine and placebo groups in the total vaccinated cohort or named subset, prepared for the Clinical Study Report, are presented below. Adverse events are grouped within MedRA system-organ-class categories. In these adverse event tabulations, hepatitis E cases are censored

Tables S9 presents unsolicited adverse events in the 1,800 subjects who had no extra monitoring to record solicited symptoms after vaccination (total vaccinated cohort minus the reactogenicity subset). Table S10 presents unsolicited adverse events in the 200 subjects who had additional monitoring to record solicited symptoms (reactogenicity subset).

TABLE S9 Percentage of subjects reporting the occurrence of unsolicited symptoms (excluding Hepatitis E) classified by MedDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (total vaccinated cohort minus the reactogenicity subset)

Primary System Organ Class (CODE)	Placebo N = 900				Vaccine N = 900			
	n	%	95% CI		n	%	95% CI	
			LL	UL			LL	UL
At least one symptom	224	24.9	22.1	27.8	227	25.2	22.4	28.2
----- ()	0	0.0	0.0	0.4	1	0.1	0.0	0.6
Blood and lymphatic system disorders (10005329)	0	0.0	0.0	0.4	2	0.2	0.0	0.8
Congenital, familial and genetic disorders (10010331)	0	0.0	0.0	0.4	2	0.2	0.0	0.8
Ear and labyrinth disorders (10013993)	4	0.4	0.1	1.1	0	0.0	0.0	0.4
Eye disorders (10015919)	4	0.4	0.1	1.1	3	0.3	0.1	1.0
Gastrointestinal disorders (10017947)	43	4.8	3.5	6.4	52	5.8	4.3	7.5
General disorders and administration site conditions (10018065)	46	5.1	3.8	6.8	48	5.3	4.0	7.0
Hepatobiliary disorders (10019805)	1	0.1	0.0	0.6	2	0.2	0.0	0.8
Immune system disorders (10021428)	3	0.3	0.1	1.0	3	0.3	0.1	1.0
Infections and infestations (10021881)	84	9.3	7.5	11.4	74	8.2	6.5	10.2
Injury, poisoning and procedural complications (10022117)	11	1.2	0.6	2.2	15	1.7	0.9	2.7
Metabolism and nutrition disorders (10027433)	3	0.3	0.1	1.0	3	0.3	0.1	1.0
Musculoskeletal and connective tissue disorders (10028395)	15	1.7	0.9	2.7	17	1.9	1.1	3.0
Nervous system disorders (10029205)	54	6.0	4.5	7.8	40	4.4	3.2	6.0
Psychiatric disorders (10037175)	2	0.2	0.0	0.8	4	0.4	0.1	1.1
Renal and urinary disorders (10038359)	0	0.0	0.0	0.4	4	0.4	0.1	1.1
Reproductive system and breast disorders (10038604)	1	0.1	0.0	0.6	2	0.2	0.0	0.8
Respiratory, thoracic and mediastinal disorders (10038738)	9	1.0	0.5	1.9	12	1.3	0.7	2.3
Skin and subcutaneous tissue disorders (10040785)	9	1.0	0.5	1.9	12	1.3	0.7	2.3
Surgical and medical procedures (10042613)	3	0.3	0.1	1.0	5	0.6	0.2	1.3

At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)

N = number of subjects with at least one administered dose

n/% = number/percentage of subjects reporting at least once the symptom

95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Data source = Appendix table IICi

TABLE S10 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (reactogenicity subset)

Primary System Organ Class (CODE)	Placebo N = 100				Vaccine N = 100			
	n	%	95% CI		n	%	95% CI	
			LL	UL			LL	UL
At least one symptom	27	27.0	18.6	36.8	28	28.0	19.5	37.9
Blood and lymphatic system disorders (10005329)	0	0.0	0.0	3.6	1	1.0	0.0	5.4
Eye disorders (10015919)	0	0.0	0.0	3.6	1	1.0	0.0	5.4
Gastrointestinal disorders (10017947)	8	8.0	3.5	15.2	6	6.0	2.2	12.6
General disorders and administration site conditions (10018065)	6	6.0	2.2	12.6	8	8.0	3.5	15.2
Hepatobiliary disorders (10019805)	0	0.0	0.0	3.6	1	1.0	0.0	5.4
Immune system disorders (10021428)	1	1.0	0.0	5.4	0	0.0	0.0	3.6
Infections and infestations (10021881)	15	15.0	8.6	23.5	11	11.0	5.6	18.8
Injury, poisoning and procedural complications (10022117)	1	1.0	0.0	5.4	1	1.0	0.0	5.4
Metabolism and nutrition disorders (10027433)	1	1.0	0.0	5.4	0	0.0	0.0	3.6
Musculoskeletal and connective tissue disorders (10028395)	2	2.0	0.2	7.0	1	1.0	0.0	5.4
Nervous system disorders (10029205)	2	2.0	0.2	7.0	6	6.0	2.2	12.6
Renal and urinary disorders (10038359)	0	0.0	0.0	3.6	1	1.0	0.0	5.4
Respiratory, thoracic and mediastinal disorders (10038738)	1	1.0	0.0	5.4	4	4.0	1.1	9.9
Skin and subcutaneous tissue disorders (10040785)	1	1.0	0.0	5.4	1	1.0	0.0	5.4
Surgical and medical procedures (10042613)	0	0.0	0.0	3.6	1	1.0	0.0	5.4

At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)

N = number of subjects with at least one administered dose

n/% = number/percentage of subjects reporting at least once the symptom

95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Data source = Appendix table IICi

For table S10, there were no hepatitis E cases to exclude.

None of the differences between vaccine and placebo with regards to occurrence of any unsolicited adverse event reported during the 30-day follow-up period was statistically significant (P-value <0.05, no adjustment for multiplicity).

Table S11 presents serious adverse events in the total vaccinated cohort, grouped by MedDRA system-organ-class.

Table S11 Percentage of subjects reporting the occurrence of Serious Adverse Events (excluding Hepatitis E) classified by MedDRA Primary System Organ Class, during the entire follow-up period (total vaccinated cohort)

Primary System Organ Class (CODE)	Placebo N = 1000				Vaccine N = 1000			
	n	%	95% CI		n	%	95% CI	
			LL	UL			LL	UL
At least one symptom	137	13.7	11.4	15.7	135	13.5	11.3	15.6
Blood and lymphatic system disorders (10005329)	0	0.0	0.0	0.4	3	0.3	0.1	0.9
Cardiac disorders (10007541)	1	0.1	0.0	0.6	1	0.1	0.0	0.6
Congenital, familial and genetic disorders (10010331)	2	0.2	0.0	0.7	1	0.1	0.0	0.6
Ear and labyrinth disorders (10013993)	0	0.0	0.0	0.4	1	0.1	0.0	0.6
Eye disorders (10015919)	2	0.2	0.0	0.7	1	0.1	0.0	0.6
Gastrointestinal disorders (10017947)	9	0.9	0.4	1.7	9	0.9	0.4	1.7
General disorders and administration site conditions (10018065)	8	0.8	0.3	1.6	6	0.6	0.2	1.3
Hepatobiliary disorders (10019805)	10	1.0	0.5	1.8	8	0.8	0.3	1.6
Infections and infestations (10021881)	73	7.3	5.5	8.7	73	7.3	5.5	8.7
Injury, poisoning and procedural complications (10022117)	18	1.8	1.1	2.8	24	2.4	1.5	3.6
Investigations (10022891)	1	0.1	0.0	0.6	0	0.0	0.0	0.4
Metabolism and nutrition disorders (10027433)	1	0.1	0.0	0.6	0	0.0	0.0	0.4
Musculoskeletal and connective tissue disorders (10028395)	3	0.3	0.1	0.9	7	0.7	0.3	1.4
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	0	0.0	0.0	0.4	1	0.1	0.0	0.6
Nervous system disorders (10029205)	5	0.5	0.2	1.2	3	0.3	0.1	0.9

	Placebo N = 1000				Vaccine N = 1000			
	n	%	95% CI		n	%	95% CI	
LL			UL	LL			UL	
Primary System Organ Class (CODE)								
Pregnancy, puerperium and perinatal conditions (10036585)	1	0.1	0.0	0.6	1	0.1	0.0	0.6
Psychiatric disorders (10037175)	4	0.4	0.1	1.0	5	0.5	0.2	1.2
Renal and urinary disorders (10038359)	1	0.1	0.0	0.6	3	0.3	0.1	0.9
Reproductive system and breast disorders (10038604)	2	0.2	0.0	0.7	2	0.2	0.0	0.7
Respiratory, thoracic and mediastinal disorders (10038738)	5	0.5	0.2	1.2	2	0.2	0.0	0.7
Skin and subcutaneous tissue disorders (10040785)	0	0.0	0.0	0.4	3	0.3	0.1	0.9
Social circumstances (10041244)	1	0.1	0.0	0.6	0	0.0	0.0	0.4
Surgical and medical procedures (10042613)	2	0.2	0.0	0.7	4	0.4	0.1	1.0
Vascular disorders (10047065)	2	0.2	0.0	0.7	3	0.3	0.1	0.9

At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)

N = number of subjects with at least one administered dose

n/% = number/percentage of subjects reporting at least once the symptom

95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Leptospirosis was the only serious adverse event for which vaccine and placebo group incidence rates were statistically different. The incidence rates in the vaccine and placebo groups respectively were 0.2% and 1.2%; the rate difference was -1.0%, in favor of the vaccine group (95% confidence interval -1.91%, -0.32%; P=0.013). As testing for leptospirosis was triggered by a clinical diagnosis of hepatitis, and as hepatitis E accounted for the great majority of all clinical hepatitis, there was less testing in the vaccine group. This case ascertainment bias most likely explains the observed rate difference.

Table S12 lists the 7 deaths observed during the study. The subject with cholangiocarcinoma (bile duct cancer) in retrospect had evidence of disease prior to enrolment

Table S12 Percentage of subjects who died during the study and reporting the occurrence of Serious Adverse Events classified by MedDRA Primary System Organ Class and Preferred Term, during the entire follow-up period (Total vaccinated cohort)

		Placebo N = 1000				Vaccine N = 1000			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom		1	0.1	0.0	0.6	6	0.6	0.2	1.3
General disorders and administration site conditions (10018065)	Accidental death (10063746)	1	0.1	0.0	0.6	0	0.0	0.0	0.4
	Death (10011906)	0	0.0	0.0	0.4	5	0.5	0.2	1.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	Bile duct cancer (10004593)	0	0.0	0.0	0.4	1	0.1	0.0	0.6

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)

N = number of subjects with at least one administered dose

n/% = number/percentage of subjects reporting at least once the symptom

95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit