# Hepatitis E Vaccine Clinical Experience

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# Hepatitis E in Nepal

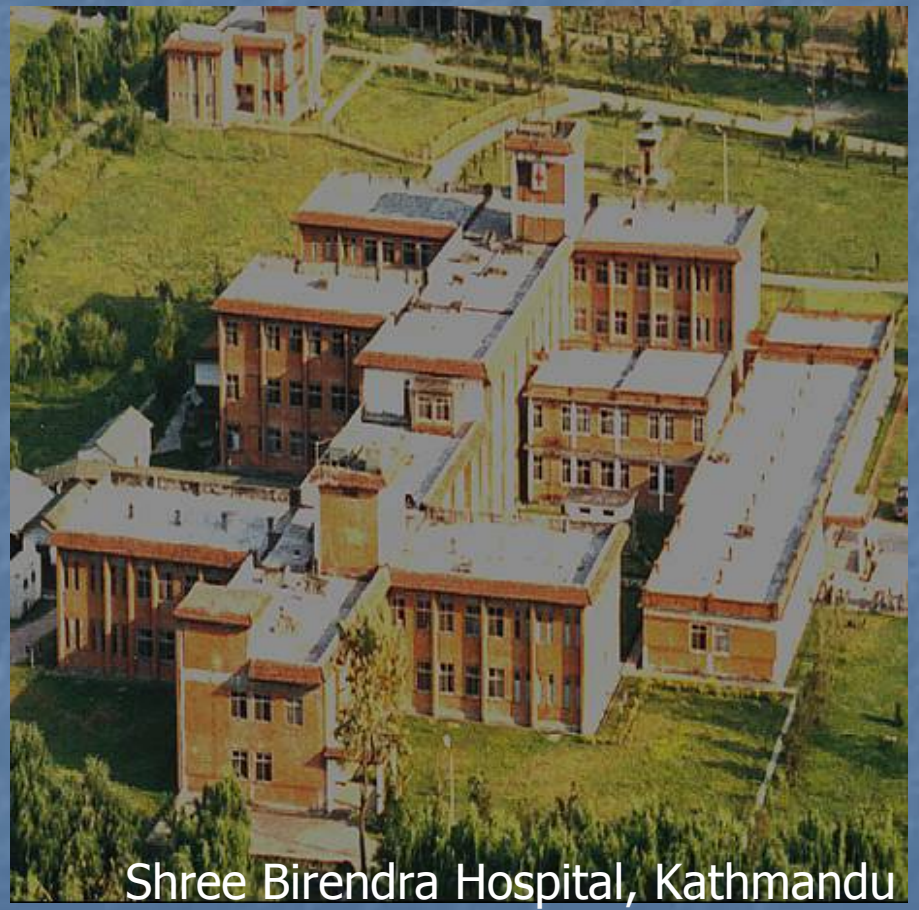
# Hepatitis E in Nepal

- Most common type of acute viral hepatitis
- Occurs in annual rainy season outbreaks
- Responsible for fulminant hepatitis, especially in pregnant women
- Causes sporadic and epidemic disease
- Surveillance in military = 2% AR/yr in Kathmandu Valley
  - Major health problem for soldiers

# Study site & population

- Active duty Nepal Army members
- Male or female of age ≥18 years
- Consenting to participate

| SEX | 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 |


Shree Birendra Hospital, Kathmandu

# Surveillance for disease

- Military personnel were enrolled from 45 Nepalese Army units
  - Active F/U every other week by a unit health worker
  - Clinic and hospital-based surveillance daily
- Suspected cases were evaluated with clinical labs (ALT, bilirubin, with QC by research team)
  - If acute hepatitis suspected, 4 serum specimens (D0, 7, 14, 28) and 2 stool specimens (D0, 3) were collected
  - These were shipped bi-weekly to Bangkok for serologic and RT-PCR testing
- All medically significant illness → hospitalization
  - These events were reported as Serious Adverse Events

# Examples of hepatitis E in the study

# Hep E Case (1)
## (Stool samples neg for HEV RNA)

| Sample | Date of sample | ALT | Total bilirubin | HEV PCR | HEV IgM | HEV total Ig | HAV IgM | HBsAg | HBC IgM |
|---|---|---|---|---|---|---|---|---|---|
| bl1 | 21NOV2002 | 3841.0 | 8.16 | POS | 418.2 | 1776.2 | NEG | NEG | NEG |
| st1 | 22NOV2002 | NA | NA | NEG | NA | NA | NA | NA | NA |
| st2 | 23NOV2002 | NA | NA | NEG | NA | NA | NA | NA | NA |
| bl2 | 29NOV2002 | 578.0 | 6.55 | POS | 2527.1 | 2951.6 | NEG | NEG | NEG |
| bl3 | 05DEC2002 | 138.0 | 3.04 | POS | 1744.0 | 2652.4 | NEG | NEG | NEG |
| bl4 | 12DEC2002 | 57.4 | 1.71 | NEG | 1507.3 | 2766.9 | NEG | NEG | NEG |

| Symptoms° | Start date of the disease | End date of the disease |
|---|---|---|
| ABCDEF | 17NOV2002 | 02DEC2002 |

Symptoms:

A = jaundice, B = fatigue, C = anoreixa

D = abdominal discomfort,

E = RUQ abdominal pain, F = nausea

# Hep E Case (2)
## (Serum and stool pos for HEV RNA)

| Sample | Date of sample | ALT | Total bilirubin | HEV PCR | HEV IgM | HEV total Ig | HAV IgM | HBsAg | HBC IgM | HCV IgG |
|---|---|---|---|---|---|---|---|---|---|---|
| bl1 | 01JUL2002 | 4829.0 | 5.43 | POS | 690.6 | 319.7 | NEG | NEG | NEG | NEG |
| st1 | 02JUL2002 | NA | NA | POS | NA | NA | NA | NA | NA | NA |
| st2 | 03JUL2002 | NA | NA | POS | NA | NA | NA | NA | NA | NA |
| bl2 | 08JUL2002 | 483.0 | 2.24 | POS | 721.5 | 536.8 | NEG | NEG | NEG | NEG |
| bl3 | 29JUL2002 | 59.6 | 1.08 | NEG | 207.0 | 1495.8 | NEG | NEG | NEG | NEG |
| bl4 | 05AUG2002 | 45.1 | 0.69 | NEG | 122.3 | 1767.6 | NEG | NEG | NEG | NEG |

| Symptoms° | Start date of the disease | End date of the disease |
|---|---|---|
| ABCFG | 30JUN2002 | 24JUL2002 |

Symptoms:

A = jaundice, B = fatigue, C = anoreixa

F = nausea, G = vomiting

# Hep E Case (3)

## (Later presentation, brief HEV RNA positivity, lower max ALT but intense jaundice)

| Sample | Date of sample | ALT | Total bilirubin | HEV PCR | HEV IgM | HEV total Ig | HAV IgM | HBsAg | HBC IgM | HCV IgG |
|---|---|---|---|---|---|---|---|---|---|---|
| bl1 | 10FEB2003 | 205.4 | 10.18 | POS | 1233.0 | 2676.2 | NEG | NEG | NEG | NEG |
| st1 | 12FEB2003 | NA | NA | POS | NA | NA | NA | NA | NA | NA |
| st2 | 13FEB2003 | NA | NA | POS | NA | NA | NA | NA | NA | NA |
| bl2 | 17FEB2003 | 271.5 | 2.97 | NEG | 731.3 | 17580.0 | NEG | NEG | NEG | NEG |
| bl3 | 24FEB2003 | 114.8 | 1.89 | NEG | 551.3 | 9453.4 | NEG | NEG | NEG | NEG |
| bl4 | 03MAR2003 | 78.8 | 1.73 | NEG | 300.0 | 5945.2 | NEG | NEG | NEG | NEG |

| Symptoms[a] | Start date of the disease | End date of the disease |
|---|---|---|
| ABCDEF | 04FEB2003 | 03MAR2003 |

Symptoms:

A = jaundice, B = fatigue, C = anoreixa

D = abdominal discomfort,

E = RUQ abdominal pain. F = nausea

# Hep E Case (4)

## (Early presentation, late seroconversion to IgM/Ig, HEV RNA 1st pos marker)

| Sample | Date of sample | ALT | Total bilirubin | HEV PCR | HEV IgM | HEV total Ig | HAV IgM | HBsAg | HBC IgM | HCV IgG |
|---|---|---|---|---|---|---|---|---|---|---|
| bl1 | 26JUN2002 | 642.0 | 1.01 | POS | 12.5 | 9.3 | NEG | NEG | NEG | NEG |
| st1 | 27JUN2002 | NA | NA | NEG | NA | NA | NA | NA | NA | NA |
| st2 | 28JUN2002 | NA | NA | POS | NA | NA | NA | NA | NA | NA |
| bl2 | 02JUL2002 | 1307.0 | 4.26 | POS | 744.0 | 680.9 | NEG | NEG | NEG | NEG |
| bl3 | 09JUL2002 | 160.6 | 1.65 | POS | 690.8 | 1692.2 | NEG | NEG | NEG | NEG |
| bl4 | 17JUL2002 | 39.1 | 1.42 | NEG | 768.6 | 2617.6 | NEG | NEG | NEG | NEG |

| Symptoms° | Start date of the disease | End date of the disease |
|---|---|---|
| ABDE | 23JUN2002 | 17JUL2002 |

Symptoms:

A = jaundice, B = fatigue

D = abdominal discomfort

E = RUQ abdominal pain

# Hep E Case (5)
## (Intense jaundice, longer convalescence)

| Sample | Date of sample | ALT | Total bilirubin | HEV PCR | HEV IgM | HEV total Ig | HAV IgM | HBsAg | HBC IgM | HCV IgG |
|---|---|---|---|---|---|---|---|---|---|---|
| bl1 | 23OCT2002 | 688.0 | 4.63 | POS | 568.4 | 365.2 | NEG | NEG | NEG | NEG |
| st1 | 25OCT2002 | NA | NA | NEG | NA | NA | NA | NA | NA | NA |
| st2 | 26OCT2002 | NA | NA | POS | NA | NA | NA | NA | NA | NA |
| bl2 | 30OCT2002 | 102.9 | 15.72 | POS | 9899.4 | 3826.6 | NEG | NEG | NEG | NEG |
| bl3 | 07NOV2002 | 234.6 | 4.98 | POS | 5393.2 | 2504.1 | NEG | NEG | NEG | NEG |
| bl4 | 14NOV2002 | 99.3 | 2.74 | NEG | 3536.6 | 1885.2 | NEG | NEG | NEG | NEG |

| Symptoms° | Start date of the disease | End date of the disease |
|---|---|---|
| ABCEFG | 18OCT2002 | 03DEC2002 |

Symptoms:

A = jaundice, B = fatigue, C = anoreixa

E = RUQ abdominal pain, F = nausea

G = vomiting

# Hep E Case (6)
## (Viremia persisting 2 weeks after resolution of symptoms)

| Sample | Date of sample | ALT | Total bilirubin | HEV PCR | HEV IgM | HEV total Ig | HAV IgM | HBsAg | HBC IgM | HCV IgG |
|---|---|---|---|---|---|---|---|---|---|---|
| bl1 | 28AUG2002 | 1248.0 | 6.22 | POS | 1274.7 | 442.4 | NEG | NEG | NEG | NEG |
| st1 | 29AUG2002 | NA | NA | POS | NA | NA | NA | NA | NA | NA |
| st2 | 30AUG2002 | NA | NA | NEG | NA | NA | NA | NA | NA | NA |
| bl2 | 04SEP2002 | 295.7 | 1.80 | POS | 669.8 | 413.3 | NEG | NEG | NEG | NEG |
| bl3 | 11SEP2002 | 93.4 | 1.19 | NEG | 527.8 | 496.0 | NEG | NEG | NEG | NEG |
| bl4 | 24SEP2002 | 25.9 | 0.73 | POS | 221.7 | 355.9 | NEG | NEG | NEG | NEG |

| Symptoms° | Start date of the disease | End date of the disease |
|---|---|---|
| ABCF | 23AUG2002 | 10SEP2002 |

Symptoms:

A = jaundice, B = fatigue, C = anoreixa

F = nausea

# Hepatitis E cases:

## Duration, biochemistries

**Duration in days**

| 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 |

**Max ALT (U/L)**

| Parameters | Placebo | Vaccine | Total |
|---|---|---|---|
| N | 78 | 9 | 87 |
| Mean | 1488 | 1799 | 1520 |
| SD | 1134 | 1147 | 1133 |
| Minimum | 156 | 490 | 156 |
| Q1 | 688 | 1040 | 756 |
| Median | 1246 | 1290 | 1248 |
| Q3 | 1868 | 2323 | 1995 |
| Maximum | 4829 | 4214 | 4829 |
| Geo. mean | 1085 | 1504 | 1122 |

**Max Bilirubin (mg/dL)**

| Parameters | Placebo | Vaccine | Total |
|---|---|---|---|
| N | 78 | 9 | 87 |
| 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 |
| Geo. mean | 8.44 | 9.41 | 8.54 |

**No fulminant hepatitis, no deaths**

| Diagnoses of hepatotrophic disease in the Total vaccinated cohort | Placebo | Vaccine | Total |
|---|---|---|---|
| | n | n | n |
| Clinically-suspected hepatitis E | 92 | 19 | 111 |
| Serologically-confirmed hepatitis A (HAV-IgM) | 0 | 0 | 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 & IgM or IgG w. blot) | 3 [9,10] | 1 [11] | 4 |
| Virologically and serologically confirmed hepatitis E | 78 | 9 | 87 |

2 One subject = **Hepatitis E and acute hepatitis B**
3 One subject = **Hepatitis E in a HBV carrier (also possible recent leptospirosis infection)**
4 One subject = **Hepatitis E in a HBV carrier**
5 One subject = **Hepatitis E in an HCV-exposed subject (also possible recent leptospirosis infection)**
6 Four subjects = **Hepatitis E in subjects with possible recent leptospirosis infection**
7 One subject = **Hepatitis E in a subject with possible recent leptospirosis infection**
8 One subject = "not hepatitis E" **(Possible recent leptospirosis infection)**
9 One subject = **Hepatitis E in a subject with possible recent scrub typhus infection**
10 Two subjects = **Hepatitis E in subjects with possible recent scrub typhus infection**
11 One subject = **Hepatitis E in a subject with a possible recent scrub typhus infection**

**Most clinically-suspected acute viral hepatitis was hepatitis E; co-infections with other agents were uncommon**

# "Not hepatitis E" cases

- N = 24
- None had definitive serum markers for :
  - HAV, HBV, HCV
  - Scrub typhus, leptospirosis
- Two cases had HEV infection confirmed by viremia and IgM
  - Both not hepatitis (ALT, bilirubin ≠ case def.)

Hepatitis E case ascertainment was adequate. Results confirm that hepatitis E is the major cause of acute viral hepatitis among adults in Nepal

# Safety outcomes

# Occurrence of Adverse Events

| Spontaneous report of any adverse event | Vaccine | Placebo |
|---|---|---|
| Reactogenicity subset (N=200) | 28.0% | 27.0% |
| Grade 3 (prevents daily activities) | 3.3% | 3.0% |
| Total cohort minus reacto subset (N=1800) | 25.2% | 24.9% |

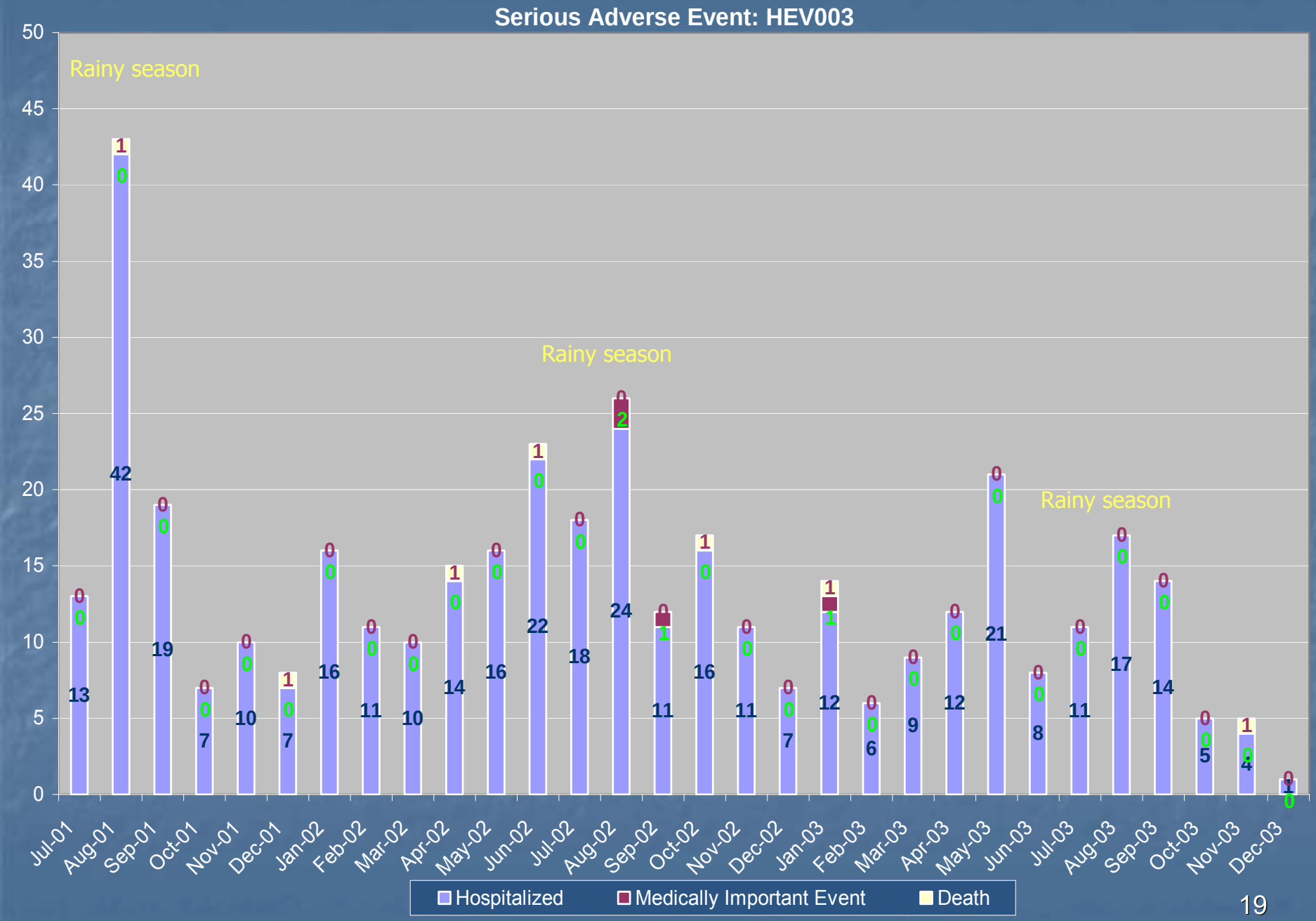
| Serious adverse events (excluding hep E) | Vaccine | Placebo |
|---|---|---|
| Reactogenicity subset (N=200) | 13.5% | 13.7% |
| Infections | 73/135 events | 73/137 events |

Hepatitis E was the most common medically significant illness in the placebo group

The next most common illness overall was enteric fever (2.0% in vaccine group, 2.4% in placebo group

# Serious Adverse Events (SAE)

| Category | | | Total |
|---|---|---|---|
| MEDICINE | *COMMUNICABLE* | *247 (61.3%)* | 297 (73.7%) |
| | *NON COMMUNICABLE* | *50 (12.4%)* | |
| DEATH | | | 7 (1.7%) |
| DERMATOLOGICAL | | | 5 (1.2%) |
| PREGNANCY | | | 2 (0.5%) |
| PSYCHIATRIC | | | 3 (0.7%) |
| READMISSION | | | 14 (3.5%) |
| SURGICAL | | | 72 (17.9%) |
| UNDIAGNOSED | | | 3 (0.7%) |
| Total | | | 403 (100%) |


Serious Adverse Event: HEV003
Rainy season
Rainy season
Rainy season
50
45
40
35
30
25
20
15
10
5
0
Jul-01
Aug-01
Sep-01
Oct-01
Nov-01
Dec-01
Jan-02
Feb-02
Mar-02
Apr-02
May-02
Jun-02
Jul-02
Aug-02
Sep-02
Oct-02
Nov-02
Dec-02
Jan-03
Feb-03
Mar-03
Apr-03
May-03
Jun-03
Jul-03
Aug-03
Sep-03
Oct-03
Nov-03
Dec-03
Hospitalized
Medically Important Event
Death

| Communicable diseases among Serious Adverse Events | | |
|---|---|---|
| **Primary Diagnosis** | Total | % |
| HEPATITIS | 91 | 36.8 |
| ENTERIC INFECTION | 80 | 32.4 |
| RESPIRATORY TRACT INFECTION | 22 | 8.9 |
| VIRAL FEVER | 18 | 7.3 |
| DIARRHOEA | 9 | 3.6 |
| MALARIA | 6 | 2.4 |
| INFESTATION | 4 | 1.6 |
| MUMPS | 3 | 1.2 |
| URINARY TRACT INFECTION | 3 | 1.2 |
| HERPES ZOSTER | 2 | 0.8 |
| LEPTOSPIROSIS | 2 | 0.8 |
| OTITIS MEDIA | 2 | 0.8 |
| CONJUNCTIVITIS | 1 | 0.4 |
| JAPANESE ENCEPHALITIS | 1 | 0.4 |
| MEASLES | 1 | 0.4 |
| RHEUMATIC FEVER | 1 | 0.4 |
| SEXUALLY TRANSMITTED DISEASE | 1 | 0.4 |
| **Total** | 247 | 100.0 |

# Summary

- In Nepal, hepatitis E is the major cause of acute liver disease in adults
- Active surveillance found a 2-fold higher rate of hepatitis E than expected
- Annual disease intensity varies, so multi-year evaluation of vaccine efficacy is useful
- Hepatitis E presents in varied ways
  - RT-PCR (serum) is the preferred diagnostic test
  - Serology can be confirmatory
- In this cohort, hepatitis E was the most common medically significant diagnosis
- Safety monitoring required evaluation of many other infectious illnesses
- Global attention is required for prevention of this disease in order to reduce socio economic burden and maternal-perinatal mortality in endemic region.

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- Final Clinical Study Report: “A phase II, prospective, Randomized, Double-blind, Placebo Controlled, Field Efficacy Trial of a candidate Hepatitis E Vaccine in Nepal”

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