Outbreak of Hepatitis E in Urban Bangladesh Resulting in Maternal and Perinatal Mortality

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Background. Hepatitis E virus (HEV) causes outbreaks of jaundice associated with maternal mortality. Four deaths among pregnant women with jaundice occurred in an urban community near Dhaka, Bangladesh, in late 2008 and were reported to authorities in January 2009. We investigated the etiology and risk factors for jaundice and death.

Methods. Field workers identified suspected cases, defined as acute onset of yellow eyes or skin, through house-to-house visits. A subset of persons with suspected HEV was tested for immunoglobulin M (IgM) antibodies to HEV to confirm infection. We used logistic regression analysis to identify risk factors for HEV disease and for death. We estimated the increased risk of perinatal mortality associated with jaundice during pregnancy.

Results. We identified 4751 suspected HEV cases during August 2008–January 2009, including 17 deaths. IgM antibodies to HEV were identified in 56 of 73 (77%) case-patients tested who were neighbors of the case-patients who died. HEV disease was significantly associated with drinking municipally supplied water. Death among persons with HEV disease was significantly associated with being female and taking paracetamol (acetaminophen). Among women who were pregnant, miscarriage and perinatal mortality was 2.7 times higher (95% confidence interval, 1.2–6.1) in pregnancies complicated by jaundice.

Conclusions. This outbreak of HEV was likely caused by sewage contamination of the municipal water system. Longer-term efforts to improve access to safe water and license HEV vaccines are needed. However, securing resources and support for intervention will rely on convincing data about the endemic burden of HEV disease, particularly its role in maternal and perinatal mortality.

Keywords. Bangladesh; hepatitis E; outbreak; pregnancy; safe water.

Outbreaks of acute infectious hepatitis have been attributed to hepatitis E virus (HEV) since the 1950s [1]. Large HEV outbreaks reported from Asia and Africa have been associated with fecally contaminated drinking water [2–20]. Although persons with HEV disease usually fully recover, clinical studies report that pregnant women who become infected with HEV, and their newborns, often die [21–26], and this has also been observed during HEV outbreaks [4, 9, 27–30]. There is no surveillance for HEV in Bangladesh, although limited studies suggest that it is the commonest cause of fulminant hepatitis [31].

In late 2008, icddb (International Center for Diarrheal Disease Research, Bangladesh) began a maternal health project called “Manoshi” in low-income urban areas. In January 2009, a researcher with this project noted that 4 pregnant women in an urban community called East Arichpur, approximately 15 km north of Dhaka, died following acute onset of jaundice during November and December 2008, suggesting HEV infection [32]. A collaborative team from the Institute of...
Epidemiology, Disease Control and Research, the Ministry of Health and Family Welfare, Government of Bangladesh, and icddr,b investigated with the goals of determining the etiology and size of the outbreak, community perceptions about the cause of the outbreak, and risk factors for illness and death (Supplementary Appendix 1).

METHODS

Case Finding
From 12 January through 23 February 2009, we visited every household in East Arichpur and every fifth household in West Arichpur to record the number of households and residents, their demographics, and the number of suspected cases of HEV, defined as a person with new onset of illness with either yellow eyes or skin occurring during August 2008–January 2009. We used suspected HEV cases to calculate attack rates, mortality rates, and case fatality; we multiplied the number of cases identified in West Arichpur by 5 to estimate the total number of suspected cases. We inquired about all recent deaths during household surveys and investigated all deaths to determine if they had illness with jaundice. Family members were enrolled as proxy respondents for persons who died.

Determining the Etiology of the Outbreak
We invited suspected HEV cases living in the same housing compounds as deceased suspected HEV cases to provide a 5-mL blood specimen for testing. Blood specimens were stored on ice and transported to icddr,b where they were tested for immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies to hepatitis E and hepatitis A viruses (MP Bio, Singapore).

Investigating Water Systems
The outbreak investigation team observed water distribution systems in the area and tested the municipal water supply at the originating pump and at spigots in households of deceased suspected HEV case-patients and tested those for thermotolerant coliforms at icddr,b. Anthropologists trained in outbreak investigation conducted interviews and group discussions with families and neighbors of suspected HEV case-patients who died and asked their opinions about the cause of jaundice in their community.

Case-Control Study for Risk Factors Associated With HEV Disease
During May 2009, we randomly selected 160 households from the East Arichpur household listing who reported a suspected HEV case during case-finding activities. The team visited these households, and if there was no one meeting the suspected HEV case definition who was currently ill with jaundice. The field team collected a blood sample from persons with suspected HEV and asked about their exposures and illness history using a structured questionnaire. Persons with suspected HEV who were ill during May 2009 and had IgM antibodies to HEV in serum were defined as confirmed HEV cases and included as cases in the case-control analysis.

To identify controls, we randomly selected 400 households from our household list and, using a random number table, selected 1 person from each selected household for possible participation. Interviewers made at least 3 attempts to meet with the household members selected as possible controls. We first verified that the person selected had not experienced jaundice in the previous 2 years and then collected a blood sample and exposure history using a structured questionnaire. For the analysis, we defined a control as someone with no history of jaundice during the previous 2 years and no evidence of IgM or IgG antibodies to HEV in their serum.

The sensitivity and specificity of HEV serological tests are suboptimal [33], and asymptomatic infections are common, even in outbreak settings [34]. Therefore, we aimed to improve the positive and negative predictive values of the tests, and thereby reduce misclassification of cases and controls, by selecting only symptomatic laboratory-confirmed cases and asymptomatic laboratory-confirmed controls for the study. Our analysis focused on HEV disease rather than all infections because of concerns about misclassification and the focus on public health burden caused primarily by disease. We compared confirmed HEV cases and controls in terms of their demographics, drinking water supply, and foods consumed using univariate logistic regression. We then built a multivariate logistic regression model to identify risk factors for HEV disease; we used backward stepwise selection and defined the best model as the one with the lowest Akaike information criterion [35]. Exposures were considered statistically significantly associated with HEV disease with a P value <.05 in the multivariate model.

Investigators have suggested the possibility of intra-household transmission of HEV infection, presumably through fecally contaminated hands [36]. To investigate whether HEV might have been transmitted within households through fecally contaminated hands, we compared the proportion of households with a handwashing station with soap between households reporting 1 suspected HEV case and households reporting >1, as this has been shown to be a predictor of hand hygiene behavior in this setting [37].

Outcomes During Pregnancy and Risk of Mortality
A second household survey was completed to estimate the increased risk of perinatal mortality associated with jaundice among women who were pregnant. During 5 March–15 April 2009, we visited every fifth household in East Arichpur and sought to identify all incident pregnancies in these households
from January 2008 through February 2009, the status and outcome of those pregnancies, and whether or not pregnant women experienced jaundice during pregnancy. We compared the proportion of pregnancies ending in miscarriage, stillbirth, or neonatal death between women with and without reported jaundice during their pregnancy.

To identify risk factors for death among persons with suspected HEV disease, we also compared the demographics, environmental exposures, and healthcare-seeking behaviors of persons who died with suspected HEV disease with those who survived HEV disease in East Arichpur using univariate logistic regression.

**Human Subjects Considerations**

All participants provided informed written consent prior to participation in this study, and the government of Bangladesh reviewed and approved the plans for this outbreak investigation.

**RESULTS**

**Description of Arichpur**

Arichpur comprises an area of approximately 1.2 km². Our census identified 29,264 households and 128,926 persons residing there—50,941 residents in East Arichpur and 77,985 in West Arichpur. People frequently lived in compounds where nuclear families shared 1 room and multiple families shared a stove, toilet, and water source.

**Attack Rates and Etiology**

Eighteen percent (2,273/12,938) of households reported at least 1 suspected HEV case in East Arichpur and 11% (1,920/16,326) in West Arichpur during August 2008–January 2009. The attack rate was 4% overall (4,751/128,926)—5% (2,756/50,941) in East Arichpur and 3% (1,995/77,985) in West Arichpur. Overall, 53% of suspected case-patients were male and 56% were aged 15–34 years (Table 1). Peak incidence of suspected HEV disease occurred during November and December 2008 (Figure 1).

There were 17 deaths among suspected HEV case-patients during the outbreak, and all but 1 occurred in East Arichpur. In addition to the 4 deaths among pregnant women first reported by the Manoshi project, there were 6 additional deaths in women of reproductive age whose pregnancy status was unknown, 5 deaths in adult males, and 2 deaths in neonates born to women with jaundice. The mortality rate for suspected HEV disease in East Arichpur was 3.1 per 10,000 population. The case-fatality ratio overall for suspected HEV disease was 0.4%, and 0.6% in East Arichpur.

We collected illness histories for 90 case-patients—from proxies for 15 suspected HEV cases who died and from 75 surviving suspected HEV cases who were living in the same housing compounds as the case-patients who died. Two neonatal deaths were excluded because their signs and symptoms of illness were more difficult to ascertain. Among these 90 case-patients, the most commonly reported signs and symptoms were yellow eyes (100%), fever (91%), and anorexia (89%) (Table 2). Among the 75 survivors, 73 agreed to provide serum specimens, which were tested for IgM antibodies to HEV and hepatitis A virus (HAV). Fifty-six of 73 (77%) case-patients had IgM antibodies against HEV and 7 (10%) had IgM antibodies against HAV (Table 2).

**Community Perceptions About Jaundice and the Cause of the Outbreak**

Respondents did not believe that jaundice was a serious illness and preferred to seek care from traditional healers rather than allopathic practitioners. Respondents believed that the illness could have resulted from contaminated drinking water and that,

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**Table 1. Age and Sex of Persons With Jaundice in Arichpur, Onset During August 2008–January 2009**

| Age or Sex | East Arichpur (n = 2752) | West Arichpur (n = 1995) | Both Areas (n = 4747) |
|------------|-------------------------|-------------------------|----------------------|
| Median age, y | 22 | 24 | 23 |
| Age group, No. (%) | | | |
| 0–4 y | 127 (5) | 145 (7) | 272 (6) |
| 5–14 y | 422 (15) | 290 (15) | 712 (15) |
| 15–34 y | 1537 (56) | 1110 (57) | 2647 (56) |
| 35–59 y | 613 (23) | 420 (21) | 1033 (22) |
| ≥60 y | 53 (2) | 30 (2) | 83 (2) |
| Male sex, No. (%) | 1394 (51) | 1090 (56) | 2484 (53) |

* a Every fifth household was visited in West Arichpur. The number from the survey was multiplied by 5 to estimate the total number.

* b Age and sex information missing for 3 suspected cases.
ground pump contained no thermotolerant coliforms, the tap-

Although water from city distribution pumps and the under-

underground shallow tube well, and 7 taps located in compounds

pipes ran through open sewers to household taps.

poorly constructed and maintained and many distribution

connections to the main municipal water supply pipes were

shallow tube wells or from taps on their compound connected

to the municipal water supply. The investigation team observed

marking increase in stagnant water in roadways and footpaths.

1 of the 2 main drainage ditches for the community became

source for the entire community through June 2008. In addition,

municipal water pumps that supplied water to the com-

community broke, and the remaining water pump became the water

In the univariate logistic regression, persons with confirmed

HEV disease were significantly more likely than controls to ever find dirty particles in

their home drinking water (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.0–4.3) and to drink sugarcane juice

(OR, 10.0; 95% CI, 4.8–20.6) (Table 3). In addition, persons

with confirmed HEV disease were significantly more likely than controls to have drunk 1–5 glasses of municipal

supply water outside the home each day, and 8.1 (95% CI,

3.1–20.6) (Table 3). In addition, persons

significantly more likely than controls to be

males; work outside the home; drink municipal water outside

the home; and consume sugarcane juice, ice cream, and curd

outside the home (Table 3). In the multivariate logistic regres-

sion model, persons with confirmed HEV disease were signifi-

cantly more likely than controls to find dirty particles in

in their experience, people who regularly boiled their water did

not get sick. They also believed that contact between their feet

and dirty water in the streets and the foul smell they inhaled

from feces in open drains could also be a source of infection.

Community residents described that during February 2008, 1

of the 2 municipal water pumps that supplied water to the com-

munity broke, and the remaining water pump became the water

source for the entire community through June 2008. In addition,

1 of the 2 main drainage ditches for the community became

clogged and remained blocked for most of 2008, which led to a

marked increase in stagnant water in roadways and footpaths.

Environmental Contamination

Most community residents obtained drinking water from either

shallow tube wells or from taps on their compound connected
to the municipal water supply. The investigation team observed

that connections to the main municipal water supply pipes were

poorly constructed and maintained and many distribution

pipes ran through open sewers to household taps.

Water samples from the 2 municipality distribution pumps, an

underground shallow tube well, and 7 taps located in compounds

where deaths occurred were tested for thermotolerant coliforms. Although water from city distribution pumps and the under-
ground pump contained no thermotolerant coliforms, the tap-

water samples collected from households had 12–12,000 (median,

38) thermotolerant coliform-forming units/100 mL of water.

Case-Control Study for Exposures Associated With Illness

We enrolled 159 suspected case-patients; 61 (38%) had IgM an-
tibodies to HEV in their serum and were used as cases in the analysis. We enrolled 352 persons with no history of jaundice in

the previous 2 years as potential controls; 125 (36%) of these persons had IgM or IgG antibodies to HEV in their serum, and the remaining 227 persons were used as controls.

In the univariate logistic regression, persons with confirmed

HEV disease were significantly more likely than controls to be males; work outside the home; drink municipal water outside

the home; and consume sugarcane juice, ice cream, and curd

outside the home (Table 3). In the multivariate logistic regres-
sion model, persons with confirmed HEV disease were signifi-
cantly more likely than controls to ever find dirty particles in

their home drinking water (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.0–4.3) and to drink sugarcane juice

(OR, 10.0; 95% CI, 4.8–20.6) (Table 3). In addition, persons

with confirmed HEV disease were 4.3 (95% CI, 2.0–9.4) times

more likely than controls to have drunk 1–5 glasses of municipal

supply water outside the home each day, and 8.1 (95% CI,

3.1–21.5) times more likely than controls to have drunk >5 glasses (Table 3).

Households with 1 reported case of jaundice were no more likely to have a handwashing station with soap than those

with >1 case (57% [33/58] vs 38% [6/16]; \( P = .169 \)).

Outcomes During Pregnancy and Exposures Associated

With Mortality

We identified 270 incident pregnancies between August 2008 and

February 2009, among which 21 (8%) women reported

having acute onset of jaundice during the pregnancy. Of these

21 pregnancies complicated by jaundice, 8 (38%) were continu-
ing at the time of interview, 4 (19%) had ended in miscarriage

\( n = 2 \) or stillbirth \( n = 2 \), and 9 (43%) resulted in live births. Of the 9 live births, 2 (22%) resulted in a neonatal death.

Among the 249 pregnancies uncomplicated by jaundice, 126

(51%) were continuing at the time of interview; 23 (9%) had ended in miscarriage or stillbirth, and 99 (40%) ended in live

births; 3 of these neonates died (3%). Pregnancies complicated

by acute onset of jaundice had a 2.7 increased odds (95% CI,

1.2–6.1) for miscarriage, stillbirth, or neonatal death compared

with pregnancies without jaundice.

In univariate logistic regression, case-patients who died were

significantly more likely to be female, to be married, to have

municipal water at home, to have visited an allopathic provider,

and to have taken paracetamol (acetaminophen) during their

illness (Table 4). None of the patients who died after taking

paracetamol were pregnant women. Patients who died were

| Characteristics                      | No. (%) |
|--------------------------------------|---------|
| Signs and symptoms (n = 90\(^a\))    |         |
| Yellow eyes                          | 90 (100)|
| Fever                                | 82 (91)|
| Anorexia                             | 80 (89)|
| Weakness                             | 74 (82)|
| Nausea                               | 72 (80)|
| Yellow skin                          | 71 (79)|
| Vomiting                             | 46 (51)|
| Abdominal pain                       | 45 (50)|
| Headache                             | 28 (30)|
| Diarrhea                             | 23 (26)|
| Serology (n = 73\(^b\))              |         |
| HEV IgM positive                     | 56 (77)|
| HAV IgM positive                     | 7 (10)|
| IgM antibodies to both HEV and HAV   | 4 (6)|
| HEV and HAV IgM negative             | 14 (19)|

Abbreviations: HAV, hepatitis A virus; HEV, hepatitis E virus; IgM, immunoglobulin M.

\(^{a}\) Includes 75 spatially matched jaundice cases and 15 adult deaths.

\(^{b}\) Includes 73 survivors who agreed to provide a blood sample.

Signs and symptoms (n = 90) were tested for thermotolerant coliforms. Although water from city distribution pumps and the underground pump contained no thermotolerant coliforms, the tap-water samples collected from households had 12–12,000 (median, 38) thermotolerant coliform-forming units/100 mL of water.
less likely than those who survived to report a history of seeking care from an herbal healer and consuming sugarcane from a street vendor (Table 4).

DISCUSSION

This large outbreak of jaundice (>4000 suspected cases) in a densely populated, low-income, urban community was likely due to HEV, and evidence from this investigation suggests that it was spread through fecal contamination of the municipal water system. Although the highest risk of illness was among men who worked outside the home, most deaths occurred in women with confirmed pregnancies, their neonates, or women of reproductive age whose pregnancy status was unconfirmed; being female was associated with increased odds of death. Numerous clinical case series from India have reported increased severity of HEV disease among pregnant women [24, 25, 38], and the few studies of neonates born to women with HEV show that they frequently die and are infected [24, 26]. Verbal autopsy studies from Bangladesh have shown that approximately 19%–25% of maternal and 7%–13% of neonatal deaths are associated with acute onset of jaundice during pregnancy [39], and estimates of the maternal and neonatal mortality burden from HEV are urgently needed.

Ill persons who took paracetamol, an antipyretic also known as acetaminophen and metabolized by the liver, were significantly more likely to die than those who did not take the drug. We were unable to measure the dose of the drug that patients took, so we cannot comment on how this may have

Table 3. Demographic and Environmental Exposures Associated With Hepatitis E Virus Disease in Univariate and Multivariate Logistic Regression During March 2009

| Characteristic                                      | Case-Patients (n = 61), No. (%) | Controls (n = 227), No. (%) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|-----------------------------------------------------|---------------------------------|-----------------------------|-------------------|----------------------|
| Age group, y                                        |                                 |                             |                   |                      |
| <20                                                 | 23 (38)                         | 84 (37)                     | Ref               |                      |
| 20–45                                               | 34 (56)                         | 126 (56)                    | 0.99 (.5–1.8)     |                      |
| >45                                                 | 4 (7)                           | 17 (7)                      | 0.86 (.3–2.8)     |                      |
| Male sex                                            | 43 (70)                         | 93 (41)                     | 3.4 (1.8–6.7)*    |                      |
| Work outside the home                               | 51 (84)                         | 147 (65)                    | 2.7 (1.2–6.5)*    |                      |
| Monthly household expenditure >US $85               | 27 (44)                         | 103 (45)                    | 1.0 (.5–1.8)      |                      |
| Migrated to Dhaka within last 12 mo                 | 4 (7)                           | 38 (17)                     | 0.3 (.1–1.0)*     | 0.3 (.1–1.2)        |
| Drink municipal supply water at home                |                                 |                             |                   |                      |
| No                                                  | 28 (46)                         | 88 (39)                     | Ref               |                      |
| Yes                                                 | 33 (54)                         | 139 (61)                    | 0.8 (.4–1.4)      |                      |
| No. of glasses of municipal supply water consumed per day in the home | | | | |
| 0 glasses                                           | 28 (46)                         | 88 (39%)                    | Ref               |                      |
| 1–5 glasses                                         | 7 (11)                          | 34 (15)                     | 0.6 (.3–1.6)      |                      |
| >5 glasses                                          | 26 (43)                         | 105 (49)                    | 0.8 (.4–1.4)      |                      |
| Ever found odor or bad smell in drinking water at home | 26 (43)                         | 77 (34)                     | 1.4 (1.8–2.7)     |                      |
| Ever found dirty particles in drinking water at home | 29 (48)                         | 87 (38)                     | 1.5 (1.8–2.7)     | 2.1 (1.0–4.3)*      |
| Always boil water at home before drinking           | 8 (13)                          | 30 (13)                     | 0.99 (.4–2.4)     |                      |
| Average No. of glasses of municipal supply water drank outside the home per day | | | | |
| 0 glasses                                           | 19 (31)                         | 159 (70)                    | Ref               | . . .                |
| 1–5 glasses                                         | 26 (43)                         | 47 (21)                     | 4.6 (2.3–9.4)*    | 4.3 (2.0–9.4)*      |
| >5 glasses                                          | 16 (26)                         | 21 (9)                      | 6.4 (2.7–15.0)*   | 8.1 (3.1–21.5)*     |
| Consumed from a street vendor or shop in the past mo |                                 |                             |                   |                      |
| Bottled fruit juice                                 | 26 (43)                         | 79 (35)                     | 1.4 (.7–2.6)      |                      |
| Soft drink                                          | 41 (67)                         | 142 (63)                    | 1.2 (.7–2.4)      |                      |
| Sugarcane juice                                     | 42 (69)                         | 43 (19)                     | 9.5 (4.8–18.7)*   | 10.0 (4.8–20.6)*    |
| Ice cream                                           | 41 (67)                         | 119 (52)                    | 1.9 (1.0–3.6)*    |                      |
| Curd                                                | 28 (46)                         | 67 (30)                     | 2.0 (1.1–3.8)*    | 1.9 (.9–3.9)        |
| Grilled meat kabob                                  | 7 (12)                          | 12 (5)                      | 2.3 (.7–6.7)      |                      |

Abbreviations: CI, confidence interval; OR, odds ratio.
* P < .05.
affected their disease outcome. It is possible that patients who died were more seriously ill and therefore took more medicines than less ill patients, including paracetamol; this is also supported by the association between seeking allopathic care and death. However, a causal association between paracetamol use and death is plausible. Paracetamol poisoning is a leading cause of death in the United States [40], and its use or overuse is a plausible contributor to mortality among patients with HEV infection. A study of patients with acute HAV infections in France demonstrated that patients who developed liver failure were more likely than those who did not to have taken acetaminophen during their illness (80% vs 37%), although the difference was not statistically significant, perhaps due to limited sample size [41]. The possible role of paracetamol use in increasing risk of mortality among patients with HEV deserves further study. Due to the possible added stress to the liver, patients presenting with jaundice should be offered alternative analgesics.

By the time this outbreak was reported, the peak of illness onset had already passed. We were unable to collect specimens from persons who died to diagnose their cause of death; however, family members or neighbors who experienced jaundice at the same time as the deaths had IgM antibodies to HEV, providing strong evidence that the deaths were likely caused by HEV. The late reporting of the outbreak also meant that exposure-related mortality is a characteristic feature of HEV outbreaks [32], of HEV justifying intervention are assembled. Given that maternal mortality is a characteristic feature of HEV outbreaks [32], existing maternal health programs in HEV-endemic countries could be leveraged to measure the burden of HEV on maternal and child health.

### Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.
Notes

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References

1. Labrique AB, Thomas DL, Stoszek SK, Nelson KE. Hepatitis E: an emerging infectious disease. Epidemiol Rev 1999; 21:162–79. 1
2. Rai RR, Nijhawan S, Mathur A, Sharma MP, Udawat HP, Singh N. Seroepidemiology and role of polymerase chain reaction to detect viremia in an epidemic of hepatitis E in western India. Trop Gastroenterol 2008; 29:202–6. 2
3. Sailaja B, Murhekar MV, Hutin YJ, et al. Outbreak of waterborne hepatitis E in Hyderabad, India, 2005. Epidemiol Infect 2009; 137:234–40. 3
4. Bile K, Isse A, Mohamud O, et al. Contrasting roles of rivers and wells as sources of drinking water on attack and fatality rates in a hepatitis E epidemic in Somalia. Am J Trop Med Hyg 1994; 51:466–74. 4
5. Maila HT, Bowyer SM, Swanepoel R. Identification of a new strain of hepatitis E virus from an outbreak in Namibia in 1995. J Gen Virol 2004; 85(pt 1):89–95. 5
6. Escriba JM, Nakone E, Recio C, et al. Hepatitis E, Central African Republic. Emerg Infect Dis 2008; 14:681–3. 6
7. Teshale EH, Howard CM, Grytdal SP, et al. Hepatitis E epidemic, Uganda. Emerg Infect Dis 2010; 16:126–9. 7
8. WHO. Hepatitis E, Chad [in English and French]. Wkly Epidemiol Rec 2004; 79:313. 8
9. Bocca D, Guthmann JP, Klovstad H, et al. High mortality associated with an outbreak of hepatitis E virus among displaced persons in Darfur, Sudan. Clin Infect Dis 2006; 42:1679–84. 9
10. McCarthy MC, He J, Hyams KC, el-Tigani A, Khalid IO, Carl M. Acute hepatitis E infection during the 1988 floods in Khartoum, Sudan. Trans R Soc Trop Med Hyg 1994; 88:177. 10
11. Bili S, Kar SS, Kumar S, Ratho RK, Dhiman RK, Kumar R. Hepatitis E epidemic with bimodal peak in a town of north India. Indian J Public Health 2008; 52:189–93, 199. 11
12. Bandyopadhyay S, Khera AK, Banerjee K, Kar NJ, Sharma RS. An investigation of an outbreak of viral hepatitis in a residential area of Delhi. J Commun Dis 1993; 25:67–70. 12
13. Bryan JP, Iqbal M, Tsarev S, et al. Epidemi of hepatitis E in a military unit in Abbottabad, Pakistan. Am J Trop Med Hyg 2002; 67:662–8. 13
14. Kumar S, Ratho RK, Chawla YK, Chakraborti A. Virological investigation of a hepatitis E epidemic in North India. Singapore Med J 2006; 47:769–73. 14
15. Naik SR, Aggarwal R, Salunke PN, Mehrotra NN. A large waterborne viral hepatitis E epidemic in Kanpur, India. Bull World Health Organ 1992; 70:597–604. 15
16. Neogi DK, Bhattacharya N, De PN, et al. An institutional outbreak of hepatitis E—reported first time from Calcutta city. J Commun Dis 1995; 27:229–33. 16
17. Sharma SP. Hepatitis E and cholera outbreak in Kathmandu. CMAJ 2006; 175:860. 17
18. Ticehurst J, Popkin TJ, Bryan JP, et al. Association of hepatitis E virus with an outbreak of hepatitis in Pakistan: serologic responses and pattern of virus excretion. J Med Virol 1992; 36:84–92. 18
19. Swain SK, Baral P, Hutin YJ, Rao TV, Murhekar M, Gupte MD. A hepatitis E outbreak caused by a temporary interruption in a municipal water treatment system, Baripada, Orissa, India, 2004. Trans R Soc Trop Med Hyg 2010; 104:66–9. 19
20. Martoli HC, Hutin Y, Ramachandran V, Manickam P, Murhekar M, Gupte M. An outbreak of hepatitis E tracked to a spring in the foothills of the Himalayas, India, 2005. Indian J Gastroenterol 2009; 28:99–101. 20
21. Bista BK, Rana A. Acute hepatitis E in pregnancy—study of 16 cases. J Nepal Med Assoc 2006; 45:182–5. 21
22. Hamid SS, Jafri SM, Khan H, Shah H, Abbas Z, Fields H. Fulminant hepatic failure in pregnant women: acute fatty liver or acute viral hepatitis? J Hepatol 1996; 25:20–7. 22
23. Khuroo MS, Kamilli S, Jameel S. Vertical transmission of hepatitis E virus. Lancet 1995; 345:1025–6. 23
24. Patra S, Kumar A, Trivedi SS, Puri M, Sarin SK. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. Ann Intern Med 2007; 147:28–33. 24
25. Rathi U, Bapat M, Rathi P, Abraham P. Effect of liver disease on maternal and fetal outcome—a prospective study. Indian J Gastroenterol 2007; 26:59–63. 25
26. Singh S, Mohanty A, Yosh JY, Deka D, Mohanty S, Panda SK. Mother-to-child transmission of hepatitis E virus infection. Indian J Pediatr 2003; 70:37–9. 26
27. Goumba CM, Yandoko-Nakoune ER, Komas NP. A fatal case of acute hepatitis E among pregnant women, Central African Republic. BMC Res Notes 2010; 3:103. 27
28. Guthmann JP, Klovstad H, Bocca D, et al. A large outbreak of hepatitis E among a displaced population in Darfur, Sudan, 2004: the role of water treatment methods. Clin Infect Dis 2006; 42:1685–91. 28
29. Isaacson M, Frean J, He J, Seriwatana J, Innis BL. An outbreak of hepatitis E in northern Namibia, 1983. Am J Trop Med Hyg 2000; 62:619–25. 29
30. Rab MA, Bile MK, Mubarak MM, et al. Water-borne hepatitis E virus epidemic in Islamabad, Pakistan: a common source outbreak traced to the malfunction of a modern water treatment plant. Am J Trop Med Hyg 1997; 57:151–7. 30
31. Sheikh A, Sugitani M, Kinukawa N, et al. Hepatitis E virus infection in fulminant hepatitis patients and an apparently healthy population in Bangladesh. Am J Med Hyg 2002; 66:721–4. 31
32. Teo CG. Fatal outbreaks of jaundice in pregnancy and the epidemic history of hepatitis E. Epidemiol Infect 2012; 140:767–87. 32
33. Khudyakov Y, Kamilli S. Aetiology, clinical course and outcome of sporadic acute viral hepatitis in pregnancy. J Viral Hepat 2003; 10:61–9. 33
34. Gurley ES, Halder AK, Fields H, et al. Evidence of person-to-person transmission of hepatitis E virus during a large outbreak in northern Uganda. Clin Infect Dis 2010; 50:1006–10. 34
35. Luby SP, Halder AK, Tronchet C, Akhter S, Bhuinya A, Johnston RB, Household characteristics associated with handwashing with soap in rural Bangladesh. Am J Trop Med Hyg 2009; 81:882–7. 35
36. Khuroo MS, Kamilli S. Virology, clinical course and outcome of sporadic acute viral hepatitis in pregnancy. J Viral Hepat 2003; 10:61–9. 36
37. Gurley ES, Halder AK, Stromfield PK, et al. Estimating the burden of maternal and neonatal deaths associated with jaundice in Bangladesh: possible role of hepatitis E infection. Am J Public Health 2012; 102:2248–54. 37
40. Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005; 42:1364–72.

41. Rezende G, Roque-Afonso AM, Samuel D, et al. Viral and clinical factors associated with the fulminant course of hepatitis A infection. Hepatology 2003; 38:613–8.

42. Zhang J, Liu CR, Li RC, et al. Randomized-controlled phase II clinical trial of a bacterially expressed recombinant hepatitis E vaccine. Vaccine 2009; 27:1869–74.

43. 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.