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

Emily S. Gurley,[1] M. Jahangir Hossain,[1] Repon C. Paul,[1] Hossain M. S. Sazzad,[1] M. Saiful Islam,[1] Shahana Parveen,[1] Labib I. Faruque,[1] Mushtuq Husain,[2] Khorshed Ara,[2] Yasmin Jahan,[2] Mahmudur Rahman,[2] and Stephen P. Luby[1,3]

[1]icddr,b (International Center for Diarrhoeal Disease Research, Bangladesh), and [2] Ministry of Health and Family Welfare, Institute of Epidemiology, Disease Control and Research, Dhaka, Bangladesh; and [3]Global Disease Detection Branch, Division of Global Health Protection, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia

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, icddr,b (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

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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 residing there, they visited the next closest household until they identified someone 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 intrahousehold 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 (2273/12 938) of households reported at least 1 suspected HEV case in East Arichpur and 11% (1920/16 326) in West Arichpur during August 2008–January 2009. The attack rate was 4% overall (4751/128 926)—5% (2756/50 941) in East Arichpur and 3% (1995/77 985) 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,
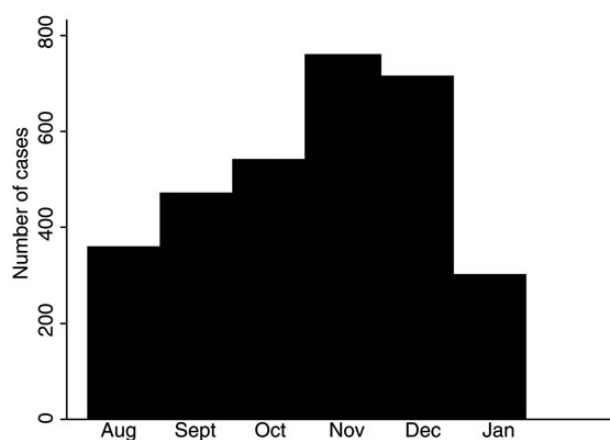
Table 1. Age and Sex of Persons With Jaundice in Arichpur, Onset During August 2008–January 2009

Age or Sex	East Arichpur (n = 2752)	West Arichpur (n = 1995)[a]	Both Areas (n = 4747)[b]
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.

Figure 1. Number of new jaundice cases in Arichpur by month during August 2008–January 2009 based on a community survey. Although cases occurred before and after these dates, we conducted only 1 survey; therefore, dates of onset for those incident cases are missing.

Table 2. Clinical Presentation of Fatal Cases of Suspected Hepatitis E Virus (HEV) and Their Family and Neighbors Who Were Suspect HEV Cases and Serologic Evidence of HEV and Hepatitis A Virus Infections Among Survivors

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.

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 community 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 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.

Case-Control Study for Exposures Associated With Illness

We enrolled 159 suspected case-patients; 61 (38%) had IgM antibodies 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 regression model, 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 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 continuing 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

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 (.8–2.7)	
Ever found dirty particles in drinking water at home	29 (48)	87 (38)	1.5 (.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.

* $P < .05$.

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 4. Exposures Associated With Increased Odds of Death Using Univariate Logistic Regression, East Arichpur, 2008–2009[a]

Exposures	Deaths (n = 13)[b], No. (%)	Survivors (n = 61), No. (%)	Unadjusted OR (95% CI)
Visited an allopathic provider	12 (92)	20 (33)	24.6 (4.9–122.7)[d]
Visited homeopathic provider	1 (8)	4 (7)	1.2 (.12–11.3)
Visited herbal healer	3 (23)	36 (59)	0.2 (.06–.8)[d]
Visited spiritual healer	4 (31)	26 (42)	0.6 (.17–2.15)
Female sex	9 (69)	18 (30)	5.3 (1.3–26.4)[d]
Currently married	12 (92)	34 (56)	9.5 (1.6–57.8)[d]
Work outside the home	7 (54)	51 (84)	0.2 (.07–.78)[d]
Monthly household expenditure >US $85	5 (38)	27 (44)	0.8 (.2–2.7)
Drank municipal supply water at home	12 (92)	40 (66)	6.3 (.9–41.9)
Consumed sugarcane juice from street vendor in past mo	4 (31)	42 (69)	0.2 (.04–.8)[d]
Took paracetamol during illness[c]	4 (40)	7 (12)	5.1 (1.3–20.8)[d]

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Among suspected hepatitis E virus (HEV) case-patients who died (excluding 2 neonates) and surviving HEV case-patients.

[b] The family of 1 case-patient who died left the community and was not available for interview.

[c] Families of 3 case-patients who died were unable to recall if the patient had taken paracetamol, so only 10 deaths were included in this analysis.

[d] $P < .05$.

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 acute liver failure 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.

Drinking from the municipal supply water outside the home was highly associated with HEV disease in a dose-response manner. Drinking sugarcane juice was also associated with HEV disease, likely reflecting another route of exposure to municipal water. Sugarcane stalks are kept in buckets of water by street vendors and pressed by a machine to harvest the "juice" for each customer; sometimes it is also served with ice made with municipal water. Drinking municipal water at home was not associated with disease, but could have represented the baseline "dose" of contaminated water for cases exposed to municipal water outside the home. Although the main municipal supply water pumps showed no evidence of fecal contamination, the water taps all had thermotolerant coliform counts above those recommended by the World Health Organization (0 per 100 mL; available at: http://www.who.int/water_sanitation_health/dwq/2edvol3a.pdf, Accessed 8 June 2014), suggesting that drinking water becomes contaminated through poorly maintained water distribution systems. It is unlikely that this water contamination was a newly emerging problem for this community. Rather, it highlights the ongoing risk for waterborne disease. Working outside the home and drinking sugarcane juice from a street vendor were protective for death. The most likely explanation for this is that males were more likely to have these exposures, but mortality risk was higher for females. There was no evidence from our investigation that direct person-to-person transmission played a major role during this outbreak.

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 exposures associated with disease in our case-control study may have identified transmission routes related to endemic rather than epidemic transmission.

HEV is preventable through provision of clean drinking water; although effective vaccines have been developed, none are currently sold internationally [42, 43]. Interventions to prevent HEV in the low-income countries where HEV is endemic will require redistribution of scarce health resources, which is unlikely to materialize unless better data on the true burden 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 copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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