

Surveillance at Private Laboratories Identifies Small Outbreaks of Hepatitis E in Urban Bangladesh

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Abstract. Although large outbreaks of hepatitis E are regularly identified in south Asia, the majority of south Asian countries lack surveillance systems for this disease, which has hindered burden of disease estimates and prioritization of resources for prevention. Our study aimed to identify small hepatitis E outbreaks through a sentinel private laboratory in Dhaka, Bangladesh. We identified patients with detectable IgM antibody against hepatitis E virus. We defined a small outbreak as at least two laboratory-confirmed cases or ≥ 2 acute jaundice cases from the sentinel cases' family, neighborhood, or workplace. From November 2008 to November 2009, we identified 29 small outbreaks of hepatitis E from one private laboratory. The median number of cases in each outbreak was three. Cases were identified every month. Eighteen outbreaks occurred among families or neighbors, and 11 in the workplace. Among 103 cases identified as part of outbreaks, 31 (30%) sought care for diagnosis. In Bangladesh, collaboration between government public health surveillance and private laboratories can strengthen capacity for outbreak detection and improve estimates of disease burden.

INTRODUCTION

Hepatitis E is an enterically transmitted viral hepatitis.¹ In south Asia, hepatitis E is usually reported in the literature as large outbreaks involving thousands of cases, such as the 1955–1956 outbreak with 29,000 cases in Delhi, India,² and another with 10,000 cases in Kathmandu, Nepal, during 1973–1974.³ Hepatitis E virus (HEV) infection is endemic in Bangladesh where occasional outbreaks are reported.^{4–6}

Drinking fecally contaminated water has been repeatedly implicated as a risk factor for hepatitis E outbreaks in south Asia, where HEV genotype 1 has been frequently identified in large outbreaks.⁷ In Bangladesh, drinking water is often contaminated by fecal pathogens⁸; hence, many people may be exposed to HEV by drinking contaminated water. During 2008–2009 in Tongi, Bangladesh, 4,751 suspected hepatitis E cases were identified; 17 of these cases died.⁹

Compared with large outbreaks, small clusters in endemic areas are less frequently reported to public health authorities and published in the literature.^{10,11} The Institute of Epidemiology, Disease Control and Research (IEDCR) of the Government of Bangladesh conducts ongoing media screening to identify outbreaks throughout the country. This system, however, might not identify smaller outbreaks of disease or individual cases that do not come to the attention of popular media. An active surveillance in multiple hospitals or a community-based surveillance to detect hepatitis E cases among acute jaundice cases is resource intensive, and laboratory diagnosis of etiology is not available at most public hospitals. As a result, physicians often refer acute jaundice cases to private laboratories to diagnose the etiology of acute jaundice. A surveillance system that incorporates data from private laboratories could offer an additional

method for identifying hepatitis E cases and clusters. An effective hepatitis E vaccine has been developed and is licensed for use in China.¹² A World Health Organization (WHO) position paper on the vaccine noted that global recommendations for use of the vaccine were greatly hindered by a lack of good burden of disease estimates from endemic countries.¹³ The objective of this study was to investigate the frequency and monthly distribution of small hepatitis E outbreaks in Dhaka using data from the private sector, to better describe local hepatitis E epidemiology.

MATERIALS AND METHODS

Study setting and the private laboratory. Dhaka is a rapidly growing megacity with a population of more than 12 million.¹⁴ Popular Diagnostic Center is a private diagnostic laboratory in southwest Dhaka, with three additional branches serving as blood specimen collection centers. Patients seeking care at this laboratory may be self-referred or referred from associated private health-care facilities, or other physicians in Dhaka city. Blood specimens collected from these branches are sent to the main laboratory, which tests around 10 patients per day for anti-HEV IgM antibodies using an assay manufactured by Diagnostic Systems (Saronno, Italy). The diagnostic sensitivity of the assay was 98% and specificity was 95.2%.¹⁵ Laboratory staff diagnose hepatitis E when the sample optical density at 450 nm (S) to cutoff (Co) ratio (S:Co) is > 1.2 . Patients pay US\$10 for the anti-HEV IgM test.

Case enrollment. From November 2008 to November 2009, the study team identified patients with acute jaundice who were referred to Popular Diagnostic Center for anti-HEV IgM testing. For our study, we enrolled cases using a 2-fold higher S:Co (> 2.5) than the usual laboratory value (> 1.2) to reduce false positives.

Sociodemographic data. The study team interviewed all laboratory-confirmed cases in the small outbreaks using a standardized structured questionnaire in the local Bengali language. The team collected demographic information including the highest level of education among family

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members and monthly household expenditure using predefined categories (less than or equal to US\$80, between US\$81 and US\$130, and more than US\$130).

Definition of sentinel case and small outbreaks. Small outbreaks were identified in two ways. First, the study team recorded the “mouza” (smallest administrative unit in Bangladesh) along with the address for all laboratory-confirmed hepatitis E cases identified at the private laboratory. Then, we identified clusters of two or more laboratory-confirmed cases who lived within the same mouza and whose onset of illness occurred within 2 months of any of the other laboratory-confirmed cases were defined as a small outbreak.¹⁶ Residents living in close proximity are likely to share a municipally supplied water source, a well-known source of exposure for hepatitis E infection.^{9,17,18} Though deep tube well water in Dhaka meets WHO drinking-water standards at extraction points, water supplied at the household level through pipelines does not.^{19,20} Water may become contaminated between the extraction point and household taps in the community through leakage in a pipeline. Moreover, water tends to be intermittently supplied from municipality pipes, which increases the likelihood of bacterial contamination.²¹

Second, the study team also visited all laboratory-confirmed case households to detect additional cases occurring nearby among people who did not seek hepatitis diagnostic care at the private laboratory. The team asked laboratory-confirmed cases to identify any family members, neighbors, coworkers, or classmates who had experienced acute onset of yellow eyes or skin, and dark urine (i.e., acute jaundice) in the 2 months preceding the case’s onset of illness or in the 2 months preceding our visit. Additional cases of acute jaundice reported by each laboratory-confirmed case were considered as part of the same outbreak as the laboratory-confirmed case who reported them. The team did not collect blood samples from all household members, including children who came in contact with the index cases or had common source exposure for HEV testing.

Household water quality. The study team interviewed all laboratory-confirmed cases to collect information about drinking water treatment and perceived quality of the municipal supply water during the 2 months before illness onset, including turbidity or alteration of color, odor, and visible undissolved materials like black particles.

The team collected one water sample each from taps in the laboratory-confirmed case households 8–45 days after illness onset to evaluate for fecal contamination.

The study team conducted the hydrogen sulfide (H₂S) test, manufactured by Nongovernmental Organization Forum, Bangladesh, to assess the quality of the municipal supply water used by clustered laboratory-confirmed cases for drinking in the home. In the H₂S test, enteric bacteria reduce sulfur to H₂S, which has a characteristic strong odor and forms a black iron sulfide precipitate in the presence of ferrous iron.²² At 48-hour incubation period of H₂S test, the sensitivity of detecting > 1,000 colony forming units (CFU) of *Escherichia coli* per 100 mL water is 100% (95% exact confidence interval [CI]: 91–100) and 10–99 CFU of *E. coli* per 100 mL water is 73% (95% exact CI: 45–92).²² The study team poured 20 mL of aseptically collected tap water from each case household in bottles containing reagents including ferrous iron and sulfate salts and transported the

samples to icddr,b (formerly, International Center for Diarrheal Diseases Research, Bangladesh) at ambient temperature. The team stored bottles at ambient temperature and observed the presence or absence of clear-to-black color change at 1, 24, and 48 hours. When the bottle content turned black after 24 and/or 48 hours of observation, it was considered to be contaminated with fecal coliform bacteria.

Data analysis. We plotted the temporal distribution of cases occurring as small outbreaks over the study period. Laboratory-confirmed cases not associated with clusters were excluded from the analysis.

Ethical considerations. Adult participants and legal guardians of child participants provided written informed consent for participation in this investigation. Ethical Review Committee of icddr,b reviewed and approved the protocol.

RESULTS

Case and outbreak detection. Through Popular Diagnostic Center, we identified 160 laboratory-confirmed hepatitis E cases. Of these, 31 (19%) laboratory-confirmed cases were part of small outbreaks. We identified laboratory-confirmed cases and associated small outbreaks every month throughout the study period (Figure 1).

Ninety percent (28/31) of the laboratory-confirmed cases reported household expenditures greater than US\$130 per month (Table 1).

We identified 29 small outbreaks of hepatitis E. Among all 29, the median number of cases in each outbreak was three (range: 2–10). Two outbreaks were identified from the Popular Diagnostic Center study logbook records when two laboratory-confirmed hepatitis E cases that lived within the same mouza experienced onset of illness within 2 months of each other for each cluster, hence, outbreaks among neighbors. The remaining 27 outbreaks included 99 cases identified through community visits with a mean of 2.7 additional cases identified per each confirmed case. Eleven outbreaks (44 cases) were identified among neighbors. Five outbreaks occurred among family members (13 total cases). The remaining 11 outbreaks originated in workplaces and dormitories, including eight women living in a dormitory of medical professionals, three physicians from a pediatric hospital, two students from the same class in a public university, and 10 coworkers in a bank (42 total cases). Overall, among 103 cases identified as part of outbreaks, 31 (30%) sought care for diagnosis.

Household water quality. Among 20 laboratory-confirmed cases who were in 18 clusters identified within the same family or neighborhood, 14 (70%) reported turbidity or alteration of the color of the municipal supply water in their homes, 15 (75%) reported an odor in this drinking water, and 14 (70%) reported presence of undissolved material in the household supply water, including black particles, in the 2 months preceding illness onset. Seventeen (85%) reported a film of dirt on top of the water after boiling. Thirteen cases (65%) reported that they usually drank boiled water and seven cases (35%) usually drank unboiled water directly from the supply tap in their home in the 2 months preceding illness onset. All cases reported that supply water was held in a reservoir tank for their apartment building before being supplied to individual households. Eight cases (40%) reported that the reservoir tank had not

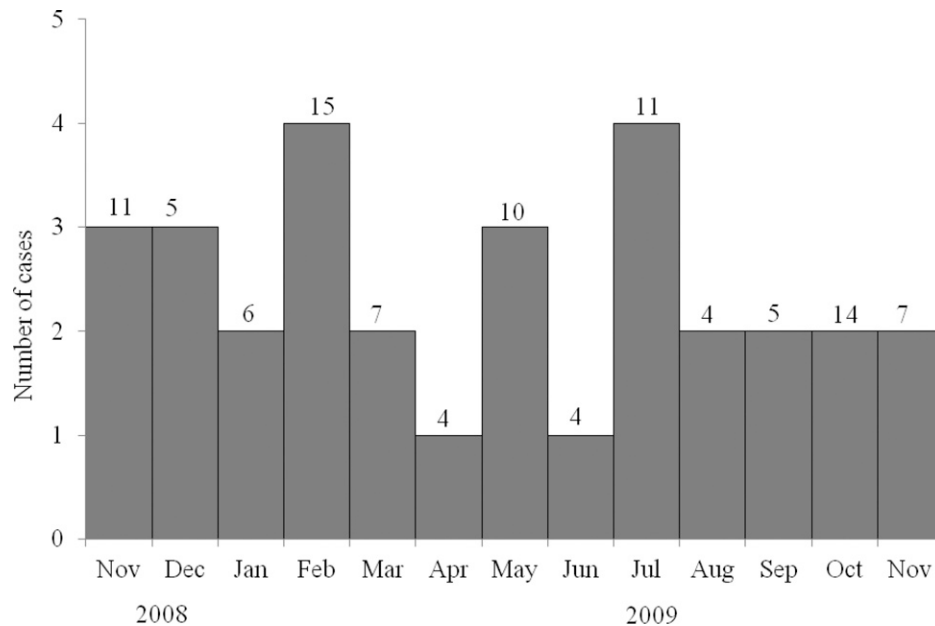


FIGURE 1. Monthly distribution of laboratory-confirmed hepatitis E cases identified from a private diagnostic laboratory by onset of illness, and number of associated acute jaundice cases identified in communities in urban Dhaka, November 2008 to November 2009. The bars indicate the number of laboratory-confirmed cases and the numbers above bars denote associated acute jaundice cases identified with onset between 2 months before the laboratory-confirmed case and the day the laboratory-confirmed cases were investigated.

been cleaned in the 2 months preceding illness onset. Among 20 water samples from the households of the 20 laboratory-confirmed hepatitis E cases, representing 18 clusters in families or neighborhoods, 16 (80%) showed evidence of fecal coliform bacterial contamination.

DISCUSSION

The epidemiology of hepatitis E has been described as having two “faces”; it is typically reported in the literature as either large outbreaks in endemic, low-income countries with inter-epidemic sporadic transmission, or as sporadic cases in high-income countries.²³ The small outbreaks we

identified frequently throughout the year can be described as a new third “face” of hepatitis E epidemiology. The 29 small outbreaks we identified from a single private laboratory suggest that the actual burden of HEV infection in Bangladesh is much greater than the burden described using data from large outbreaks alone, as in the WHO 2010 systematic review of global hepatitis E burden.²⁴

Bangladesh is a country of 160 million people²⁵ with 5,220 private registered diagnostic laboratories.²⁶ HEV infection testing is rare. Our study was conducted from just one diagnostic center and its branches. Accordingly, the number of hepatitis E clusters we detected constitutes a small proportion of the true number of outbreaks occurring countrywide.

TABLE 1

Sociodemographic characteristics of laboratory-confirmed hepatitis E cases of the outbreaks, urban Dhaka, November 2008 to November 2009

Variable	Category	Laboratory-confirmed hepatitis E cases (N = 31) n (%)
Age in years	< 15	1 (3)
	15–39	21 (68)
	≥ 40	9 (29)
Mean age in years (range)		34 (11–61)
Sex	Female	14 (45)
Marital status	Married	19 (61)
	Unmarried	11 (36)
	Widowed	1 (3)
Monthly expenditure of the household (US\$)	≤ 80	2 (7)
	81–130	1 (3)
	> 130	28 (90)
Own	Electric fan	30 (97)
	Television	29 (94)
	Refrigerator	27 (87)
	Private vehicle	11 (36)
Highest level of education obtained among all family members in each family	No schooling (0 years)	0 (0)
	Up to primary (1–5 years)	1 (3)
	Up to secondary (6–10 years)	0 (0)
	Above secondary (≥ 11 years)	30 (97)

Surveillance in collaboration with other private laboratories that offer HEV testing in Bangladesh would likely detect more hepatitis E outbreaks across the country.

However, surveillance at private laboratories also has limitations. Outbreaks occurring in low-income slum areas, where risk of contaminated water may be higher, may still go undetected as the cost of laboratory testing may not be affordable for residents.²⁷ In Bangladesh, patients typically seek care for acute jaundice from informal health-care providers who do not provide laboratory testing.^{9,28} In our study, the majority of laboratory-confirmed hepatitis E cases reported monthly household expenditure above the average monthly household expenditure of Bangladeshi families. Among many acute jaundice cases within each cluster, only a few sought care from health-care facilities and paid for the cost of the test. Despite these limitations, laboratory-based cluster surveillance could be used to monitor trends in disease burden and detect and respond to hepatitis E epidemics. Surveillance data from private laboratories could contribute to detection of hepatitis E, as well as other diseases. The United States has established nationwide electronic laboratory reporting for communicable disease detection across both private and public facilities.²⁹ In The Netherlands, the online electronic laboratory-based surveillance system is being used for detection of outbreaks.³⁰ In contrast to high-income countries, information and communication technologies for data sharing and reporting from private laboratories to central government authorities are not readily available in Bangladesh. However, eHealth and mHealth initiatives have proliferated in the private sector facilitated by widely available mobile phone technology and Internet access.³¹ The government of Bangladesh could enable Internet-based regular reporting from private laboratories to government authorities like IEDCR to enhance their routine surveillance activities. Integrated hepatitis E infection reporting from different private laboratories might be a quick and efficient approach to improve surveillance in this region.

The high percentage of fecally contaminated household water samples suggests a continuing serious threat of waterborne disease in the community, even among residents drinking piped water from municipal systems. Low sensitivity of H₂S test with lower bacterial contamination suggests that we were unable to detect low fecal contamination of household water samples. Therefore, the number of household water samples with fecal contamination could be higher than that we found. Further studies to identify acceptable and affordable strategies to prevent fecal contamination of water, both during supply and at the point of use, are needed and would inform public health interventions for prevention of hepatitis E and other waterborne disease in Dhaka. During 2014, Asian Development Bank began a project to support government of Bangladesh for water supply improvement and World Bank supported the sewerage system improvement in urban Dhaka through resource-intensive infrastructural changes, including establishment of new supply pipe lines throughout the Dhaka City.³² In the long run, successful collaboration between government and international donor organizations might improve the quality of supply water and sanitation, hence control the hepatitis E and other waterborne diseases in Bangladesh.

Our study was limited because the acute jaundice cases identified during community investigations were not laboratory-

confirmed with hepatitis E infection. Therefore, we may have overestimated the number of acute jaundice cases occurring in these outbreaks. Moreover, we may have also missed some cases occurring in the community because we relied upon the laboratory-confirmed case to identify other cases.

Due to lack of HEV testing among children in outbreak households, we are unable to provide any evidence that young children might have asymptomatic infection after exposure but clear their antibody more quickly after their initial infection than adults.

Because we do not know the duration between onset of illness of each acute jaundice cases of a small outbreak in a household, we do not have any evidence whether the HEV transmission was person to person.

A purified recombinant vaccine against HEV was shown to be safe and effective among Chinese adults,¹² and has been available in China since 2012. The WHO strategic advisory group of experts on immunization has suggested that reactive vaccination during hepatitis E outbreaks could be considered to prevent the substantial morbidity and mortality that they can cause.³³ Cluster surveillance could identify opportunities for vaccine intervention to prevent transmission to family members, neighbors, and coworkers in the community. The same report, however, lacked recommendations for use of the vaccine in the general population due to inadequate burden of disease estimates from endemic countries.³³ Improved estimates of disease burden are needed to better inform decisions about hepatitis E prevention in Bangladesh and other endemic countries.

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