Estimating the Burden of Maternal and Neonatal Deaths Associated With Jaundice in Bangladesh: Possible Role of Hepatitis E Infection

Emily S. Gurley, PhD, Amal K. Halder, PhD, Peter K. Streatfield, PhD, Hossain M.S. Sazzad, MHE, Tarique M. Nurul Huda, MPH, M. Jahangir Hossain, MSc, and Stephen P. Luby, MD

Objectives. We estimated the population-based incidence of maternal and neonatal mortality associated with hepatitis E virus (HEV) in Bangladesh.

Methods. We analyzed verbal autopsy data from 4 population-based studies in Bangladesh to calculate the maternal and neonatal mortality ratios associated with jaundice during pregnancy. We then reviewed the published literature to estimate the proportion of maternal deaths associated with liver disease during pregnancy that were the result of HEV in hospitals.

Results. We found that 19% to 25% of all maternal deaths and 7% to 13% of all neonatal deaths in Bangladesh were associated with jaundice in pregnant women. In the published literature, 58% of deaths in pregnant women with acute liver disease in hospitals were associated with HEV.

Conclusions. Jaundice is frequently associated with maternal and neonatal deaths in Bangladesh, and the published literature suggests that HEV may cause many of these deaths. HEV is preventable, and studies to estimate the burden of HEV in endemic countries are urgently needed. (*Am J Public Health.* 2012;102: 2248–2254. doi:10.2105/AJPH.2012.300749)

Hepatitis E virus (HEV) infection is endemic in Asia and many parts of Africa, where it is a leading cause of sporadic and epidemic acute hepatitis.[1–3] HEV is primarily transmitted through the fecal–oral route, and outbreaks in endemic areas are typically associated with contaminated drinking water sources.[4–13] Clinically, it is indistinguishable from other causes of acute viral hepatitis, and jaundice, the yellowing of the eyes and skin, is the most common clinical feature.[14] Jaundice is caused by a buildup of bilirubin, a product of dying red blood cells, in the blood. The healthy liver removes bilirubin from the blood, but when the liver's ability to process bilirubin is impaired, the buildup occurs. Additional clinical signs and symptoms include anorexia, malaise, fever, dark urine, vomiting, and stomach pain.[14] Adults are more likely to have HEV disease and antibodies to HEV than are children in endemic areas, which is unexpected given the young ages at which most people are exposed to other enteric pathogens in low-income countries.[15]

In general, fewer than 1% of patients with clinical HEV die, but case fatality ratios among pregnant women have been reported to be as high as 6% to 20%.[12,14,16–18] A high case fatality rate among pregnant women is a characteristic feature of HEV that has not been observed for other etiologies of acute viral hepatitis.[19] Pregnant women whose deaths are associated with HEV typically die of hemorrhage or hepatic neuropathy.[20,21] The few studies that investigated vertical transmission of HEV noted that neonates born to mothers with HEV infections were frequently infected and often died from complications such as prematurity, liver failure, hypothermia, or hypoglycemia.[21–25]

Hepatitis is not considered to be an important cause of maternal or neonatal mortality globally,[26–28] but some data suggest that acute hepatitis might significantly contribute to maternal mortality in HEV endemic countries. A retrospective, community-based study of maternal mortality from southern India reported that 11% of maternal deaths were attributable to infectious hepatitis, resulting in a maternal mortality ratio of 8 per 1000 live births.[29] Another record review of maternal mortality from Ethiopia concluded that 15% of maternal deaths were the result of infectious hepatitis.[30] An autopsy study from India found that the most common cause of maternal deaths at 1 large hospital was acute viral hepatitis, which accounted for 42% of all maternal deaths.[31] Notably, none of these studies provided evidence about the etiology of these hepatitis illnesses, so it is not known if they were caused by HEV. However, given that HEV is a particularly fatal cause of acute hepatitis among pregnant women,[19] the possibility that HEV could meaningfully contribute to maternal mortality in these countries should be considered.

However, to our knowledge, no studies have attempted to quantify the burden of HEV-associated maternal and neonatal mortality. In low-income countries in Asia and Africa where HEV is commonly found,[1–3] population-based estimates of mortality usually come from verbal autopsy studies that use structured questionnaires to interview relatives of the deceased about signs and symptoms of illness before death, and then use coding algorithms to determine cause of death based on the interview data.[32] The verbal autopsy questionnaires include questions about new onset of jaundice before death in pregnant women, or new onset of jaundice in the mother as a complication of pregnancy for neonatal deaths. Thus, data from verbal autopsy studies can be used to calculate population-based estimates of maternal and neonatal mortality associated with jaundice. However, the nature of these data precludes conclusions about deaths from specific infectious etiologies, such as HEV. Hospital-based studies can provide important information about etiologic causes

of maternal and neonatal deaths associated with jaundice that occur in hospital settings of HEV endemic countries. We investigated the possible contribution of HEV to maternal and neonatal mortality by analyzing data from 4 population-based verbal autopsy studies in Bangladesh and comparing these data with the published literature from hospital-based studies of the etiologic causes of jaundice-associated deaths during pregnancy.

METHODS

Four population-based studies of mortality were used for our analysis: the 2001 Bangladesh Maternal Health Services and Mortality Survey; the 2003 to 2005 data from the Matlab Health and Demographic Surveillance System; a study of mortality in children younger than 5 years in urban Dhaka; and mortality data from the Sanitation, Hygiene Education, and Water Supply-Bangladesh (SHEWA-B) project.

The Bangladesh Maternal Health Services and Mortality Survey was a nationally representative survey of 500 000 people conducted in 2001 to identify deaths among women of reproductive age that occurred between 1998 and 2000. Detailed methods of the survey are described elsewhere[33]; in brief, sampled households were asked about deaths in women aged 10 to 49 years that occurred during the previous 3 years, and a detailed verbal autopsy questionnaire was used to collect data on the signs and symptoms experienced by women in the illness episode immediately preceding death.

We analyzed verbal autopsy records for all 928 deaths in women aged 10 to 49 years to determine the proportion of total deaths and the proportion of maternal deaths associated with jaundice. Some hard to reach areas were oversampled, and each maternal death was assigned a cluster sampling weight; we used these weights to calculate the maternal mortality ratio associated with jaundice.[33]

The health and demographic surveillance system in Matlab, Bangladesh, began in 1966 and is the longest running health and demographic surveillance site in the world. Vital events are recorded for a population of approximately 200 000 people, and all deaths have been investigated since 1966.[34] Since 2003, a standardized World Health Organization verbal autopsy questionnaire has been used to systematically collect data on events surrounding deaths. We analyzed data on maternal and neonatal deaths associated with maternal jaundice that occurred from 2003 to 2005. We estimated the maternal morality and neonatal mortality ratios based on the number of live births in Matlab from 2003 to 2005.

During 2007, representative households from catchment areas of 2 pediatric hospitals in urban Dhaka were surveyed to identify all deaths in children aged younger than 5 years occurring in the 5 years before the survey. The details of the survey sampling methods are described elsewhere.[35] In short, 7000 households were visited in the hospital catchment area to identify deaths in children younger than 5 years. For each identified child death, a structured verbal autopsy questionnaire was completed, detailing events of the death; neonatal verbal autopsy questionnaires included questions about symptoms experienced by the mother during pregnancy and birth. We identified 150 neonatal deaths, and we measured the proportion of neonatal deaths associated with maternal jaundice as a pregnancy complication and calculated the neonatal mortality ratio associated with maternal jaundice.

The Sanitation, Hygiene Education, and Water Supply Bangladesh (SHEWA-B) project is an initiative by UNICEF aiming to bring safe water and improved hygiene to 30 million people in Bangladesh. The International Centre for Diarrheal Diseases Research, Bangladesh (ICDDR,B) conducted a baseline survey in 86 000 rural households across Bangladesh and completed verbal autopsy questionnaires for all deaths in children younger than 5 years. We analyzed records for 3339 neonatal deaths to determine the proportion associated with maternal jaundice, and we calculated the neonatal mortality ratio per 1000 live births associated with jaundice during pregnancy.

All 4 of these studies used a standardized verbal autopsy questionnaire, including distinct modules for adult and neonatal deaths. These questionnaires were administered by trained data collectors with at least 12 years of formal education, but without medical training. In maternal verbal autopsy questionnaires, the respondents were asked if the women experienced "jaundice," defined as "yellow eyes," during their final illness. In the neonatal verbal autopsy questionnaire, respondents were asked if the newborn's mother experienced jaundice as a pregnancy complication. Jaundice in the SHEWA-B study was defined as a physician's diagnosis of jaundice as reported by the respondents; all other studies defined jaundice by respondent report of yellow eyes in the mother. Cause of death was assigned either based on physician review in the SHEWA-B, Bangladesh Maternal Health Services and Mortality Survey, and the child mortality survey in Dhaka, or by paramedic review for the Matlab health and demographic surveillance data. We tabulated the assigned cause of death for maternal and neonatal deaths associated with jaundice during pregnancy.

We defined maternal deaths as those that occurred during pregnancy or within 42 days following a birth, stillbirth, or miscarriage. A neonatal death was defined as a death occurring within 28 days of birth.

Although maternal and neonatal deaths associated with jaundice could be suggestive of HEV-related death, there could be other causes of these deaths or other diseases causing jaundice. We summarized data from hospital-based studies to understand what proportion of maternal deaths associated with jaundice during pregnancy was diagnosed with HEV. Using the PubMed search engine, we queried all English language articles that had "pregnancy" and "hepatitis E" in any field. We reviewed all articles returned by the search, as well as relevant studies cited by the articles identified during the PubMed search. We included articles that systematically tested pregnant women with acute jaundice or fulminant hepatic failure for HEV and reported the proportion of all deaths among these women that were HEV-related in known HEV endemic countries. We excluded studies that only screened women with clinical evidence of viral hepatitis, beyond jaundice, because these could provide overestimates.

Three of the verbal autopsy study protocols were reviewed and approved by ICDDR,B's ethical review committee. SHEWA-B was an evaluation of a public health program rather than a research study and was therefore not reviewed by an institutional review board. All respondents interviewed in all studies provided informed consent before participation.

RESULTS

One hundred eighty-six maternal deaths occurred in households sampled in the Bangladesh Maternal Health Services and Mortality Survey, and 35 (19%) women had new onset of jaundice during their pregnancy before their deaths. The weighted maternal mortality ratio associated with jaundice from this survey was 54 per 100 000 live births (Table 1). Of 35 maternal deaths with jaundice, 33 (94%) occurred in rural areas. Twelve women with jaundice died while pregnant, including 7 during the third trimester (58%). Twenty-three women with jaundice died after delivery, and 14 (61%) of these occurred within the first week after delivery. Six (17%) women delivered live babies who survived the first month of life.

From January 1, 2003 to December 31, 2005, the Matlab Demographic and Health Surveillance System identified 33 maternal deaths. Nine (27%) of these 33 women reportedly experienced new onset of jaundice during their pregnancy, resulting in a maternal mortality ratio of 55 per 100 000 live births associated with jaundice (Table 1). Data on the timing of death in relation to pregnancy was not available. None of the women delivered live infants who survived.

There were 524 neonatal deaths identified in Matlab during this same time period. In 69 (13%) of these deaths, respondents reported that the mother had jaundice as a complication of pregnancy, resulting in a neonatal mortality ratio of 4.2 per 1000 live births associated with maternal jaundice (Table 1).

One hundred fifty neonatal deaths were identified from the child mortality study in Dhaka, and 18 (12%) were associated with maternal jaundice. The neonatal mortality ratio associated with maternal jaundice was 2.2 per 1000 live births (Table 1). Of 18 infants, 4 (22%) died on the day of birth and 14 (78%) died within the first week of life.

There were 3339 neonatal deaths identified from the SHEWA-B study, and 2816 verbal autopsy respondents reported that they knew whether or not the mother experienced jaundice during pregnancy. Of these 2816 respondents, 184 (7%) reported that the mother had jaundice as a complication of pregnancy, and that this diagnosis was confirmed by a physician. The neonatal mortality ratio associated with jaundice during pregnancy was 2.4 per 1000 live births (Table 1). Fifty-seven percent (105 of 184 births) died within the first 2 days of life.

We identified 44 maternal deaths associated with jaundice in the National Maternal Health Services and Mortality Survey (n = 35) and from the Matlab surveillance site (n = 9). Twelve of these deaths (27%) were categorized as deaths from hemorrhage, and 9 (20%) were either coded as "other unspecified cause" or were not classified at all (Table 2).

We identified 203 neonatal deaths from 3 verbal autopsy studies (Table 1), and the most commonly coded immediate causes of death were birth asphyxia (43%) and congenital Streptococcus B sepsis (36%); 9% received no code (Table 3). The major underlying causes of death were other prematurity, slow fetal growth or low birth weight (26%), other ill-defined unspecific causes (21%), and neonatal jaundice (12%; Table 3)

The majority of publications we reviewed from hospital-based studies of HEV-related maternal deaths were not appropriate for our analysis because they reported the proportion of women with HEV disease who died rather than the proportion of all maternal deaths associated with jaundice that were diagnosed with HEV. We found only 8 published articles in the English language literature that reported the proportion of maternal deaths caused by HEV in pregnant women with acute jaundice or fulminant hepatic failure. These articles represented 3 countries; 5 were published from India. In total, 659 pregnant women with jaundice were studied; 223 deaths in these women were observed, and 129 (58%) of these deaths were HEV-related (Table 4; Table A, available as a supplement to the online version of this article at http://www.ajph.org).

DISCUSSION

Our data suggested that 19% to 27% of all maternal deaths and 7% to 13% of all neonatal deaths in Bangladesh are associated with jaundice during pregnancy. The maternal

TABLE 1—Number, Proportion, and Estimated Rates of Maternal and Neonatal Deaths Associated With Maternal Jaundice in Bangladesh

	National Maternal Health Services and Maternal Mortality Survey, 2001	Matlab Health and Demographic Surveillance System, 2003–2005	Survey for Deaths in Children Younger Than 5 Years in Urban Dhaka	SHEWA-B, 2003–2005
Maternal deaths, no.	186	33	. . .	. . .
Maternal mortality rate/100 000 live births	322	202		
Maternal deaths associated with jaundice			. . .	. . .
No. (%)	35 (19)	9 (27)	. . .	. . .
Mortality rate/100 000 live births	54	55	. . .	. . .
No. of neonatal deaths	. . .	524	150	3339[a]
Neonatal mortality rate/1000 live births	. . .	32	18	37
Neonatal deaths associated with maternal jaundice				
No. (%)	. . .	69 (13)	18 (12)	184 (7)
Mortality rate/1000 live births	. . .	4.2	2.2	2.4

Note. SHEWA-B = Sanitation, Hygiene Education, and Water Supply Bangladesh.
[a]Of 3339 neonatal deaths, only 2816 were answered "yes" or "no" to the question regarding maternal jaundice during pregnancy, and only these records were used for analysis.

TABLE 2—Causes of Death Assigned to Maternal Verbal Autopsies Associated With Jaundice in Bangladesh

Cause	Bangladesh National Maternal Mortality Survey 2001, No.	Matlab Demographic and Health Surveillance 2003–2005, No.	Total No. (%)
Hemorrhage (antepartum and postpartum)	10	2	12 (27)
Eclampsia	8	0	8 (18)
Anemia	4	1	5 (11)
Not classified	5	0	5 (11)
Other indirect	3	1	4 (9)
Abortion related	1	2	3 (7)
Maternal infectious and parasitic disease complicating pregnancy	0	1	1 (2)
Preexisting hypertension complicating pregnancy	0	1	1 (2)
Other obstetric trauma	0	1	1 (2)
Puerperal sepsis	1	0	1 (2)
Cardiovascular disease	2	0	2 (5)
Respiratory disease	1	0	1 (2)
Total	35	9	44 (100)

mortality ratio associated with jaundice during pregnancy in Bangladesh was 54 to 55 per 100 000 live births, and the neonatal mortality ratio associated with jaundice during pregnancy was 2.2 to 4.2 per 1000 live births. Many diseases could cause jaundice during pregnancy, some of which might have been coincidental and not associated with the death at all.[43] However, our review of hospital-based studies conducted in HEV endemic countries showed that 58% of maternal deaths in women with acute liver disease or fulminant hepatitis were HEV-related. Data from our verbal autopsy analysis, combined with the published literature, suggested that HEV could play an important role in maternal and neonatal deaths in Bangladesh. Prospective, laboratory-based incidence estimates of HEV deaths are urgently needed in HEV endemic countries among pregnant women and their newborns. A useful first step in assessing the burden of mortality could be the development of algorithms to diagnose "possible HEV" from verbal autopsy data in accordance with the published literature and their application in endemic countries.

Other data from this analysis supported the conclusion that many of these deaths might be caused by HEV. First, pregnant women with HEV in hospital-based studies either died because of hemorrhage or hepatic encephalopathy.[20,21] The causes of maternal deaths associated with jaundice in our analysis were consistent with these clinical findings; 27% were attributed to hemorrhage, and 18% were classified as eclampsia, a condition that typically includes seizures or coma. The majority of deaths classified as eclampsia were not medically attended, and deaths associated with neurologic signs and jaundice might be more indicative of HEV than eclampsia. Similarly, the causes of death assigned to neonates were consistent with clinical descriptions of neonates who died because of vertically transmitted HEV, which include premature birth and acute hepatitis.[21,22,25] The most common underlying cause of death assigned for neonates in this study was "other prematurity, low birth weight, or pre term delivery" (26%); 11% died because of underlying unspecified neonatal jaundice. Notably, 20% of maternal deaths and 31% of neonatal deaths associated with jaundice during pregnancy in our analysis were either assigned no code or classified in "other unspecified" categories, suggesting that the disease syndromes did not match well with algorithms used to assign causes of maternal and neonatal deaths. Given that they were associated with sclera icterus during pregnancy, many of these nonspecific diagnoses might represent HEV deaths.

Both maternal and neonatal mortality ratios and the proportion of maternal and neonatal deaths associated with jaundice during pregnancy were consistent across all data sets, suggesting that our estimates of deaths associated with jaundice during pregnancy were reliable. The estimate of 7% of neonatal deaths associated with jaundice during pregnancy from the SHEWA-B study might be lower than that in other studies because of the fact that the physician report was required to diagnose jaundice during this study. Given that many women do not seek care for pregnancy complications,[33] the SHEWA-B data likely underestimated the true incidence of jaundice in these mothers. The highest proportions of deaths associated with jaundice during pregnancy were reported from the Matlab Health and Demographic Surveillance. This represented the smallest sample size of all 4 studies, which could account for the difference in estimates. However, these data were collected through ongoing mortality surveillance efforts, which decreases the period between death and data collection. Therefore, the higher proportion of deaths associated with jaundice in this data set could represent better recollection of signs and symptoms of disease among respondents.

Limitations

Our study findings were limited because they relied upon family report of signs and symptoms, sometimes years after the event occurred. We had no laboratory or even clinical reports for the majority of these deaths. Nonetheless, family report of sclera icterus was likely a reasonable indicator of liver disease. The experience of yellow eyes can be reported by persons without any medical training, and this is a common sign of liver disease. A study conducted in a medical setting assessing sensitivity and specificity of physician diagnosis of sclera icterus in patients with elevated bilirubin concluded that as levels of bilirubin increased, physicians were more likely to report this clinical feature.[44] Family members' report of sclera icterus might not be a sensitive tool for diagnosing liver disease, but might be specific, particularly if the patient experienced severe liver disease. In addition, we relied on published data on maternal deaths associated with HEV disease to interpret our findings, but these data were suboptimal for this purpose

TABLE 3—Causes of Neonatal Death Associated With Maternal Jaundice: the Matlab Health and Demographic Surveillance, 2003–2005, Sanitation, Hygiene Education, and Water Supply Bangladesh, 2003–2008, and the Dhaka Urban Child Health Survey Verbal Autopsy Study, 2007, Bangladesh

Underlying Cause of Death	Immediate Cause of Death				
	No Code, No. or No. (%)	Birth Asphyxia, No. or No. (%)	Streptococcus B Sepsis, No. or No. (%)	Other Immediate Cause[a], No. or No. (%)	Total No. (%)
None	0	0	0	1	1 (0)
Maternal disorders					
Maternal hypertensive disorders	0	3	0	0	3 (1)
Maternal infectious/parasitic disease	0	1	1	1	3 (1)
Labor and delivery complications					
Malpresentation, malposition, disproportion, or breach delivery	0	12	0	0	12 (6)
Other delivery complications[a]	1	8	1	0	10 (5)
Other unspecified complications of labor and delivery	0	17	1	0	17 (8)
Prematurity or low birth weight					
Premature rupture of membranes	0	4	1	0	5 (2)
Neonatal jaundice associated with preterm delivery	0	0	0	1	1 (0)
Other prematurity, slow fetal growth or low birth weight	8	27	11	7	53 (26)
Congenital or neonatal infectious disease					
Congenital pneumonia related to viral agent	1	0	19	1	21 (10)
Neonatal jaundice, unspecified	2	0	20	2	24 (12)
Other congenital infectious diseases	0	0	3	0	4 (2)
Other					
Congenital malformation	6	0	0	0	6 (3)
Other ill-defined unspecified cause	0	16	16	11	43 (21)
Total	18 (9)	88 (43)	73 (36)	24 (12)	203 (100)

[a]Indicates "other" categories defined by the authors: other birth complications were prolapsed cord, birth asphyxia, obstructed labor, compression of the umbilical cord, or unspecified birth injury; and other immediate causes were bacterial sepsis, congenital pneumonia, hypothermia, hypovolemic shock, neonatal jaundice unspecified, suffocation or strangulation, or other unspecified causes.

because they included only women who died in hospital, and deaths from our analysis included many women who did not seek care at hospital or who did seek care but died at home.[33] Many of the studies we reviewed had very small sample sizes, and findings from some of the larger studies were difficult to interpret because some women who might have had jaundice were excluded from the

TABLE 4—Summary of Published Literature From Hepatitis E Virus Endemic Countries on the Proportion of Maternal Deaths Associated With Jaundice or Fulminant Hepatic Failure Diagnosed With Hepatitis E Virus Infection

Study	Year of Publication	Country	Pregnant Women With Acute Viral Hepatitis or Fulminant Hepatic Failure Studied, No.	Women Who Died, No.	Women Who Died From HEV, No.	Deaths From HEV, %
Hossain et al.[36]	2009	Pakistan	35	6	2	33
Bhatia et al.[37]	2008	India	234	134	74	55
Rasheeda et al.[38]	2008	India	115	5	3	60
Rathi et al.[23,a]	2007	India	96	19	4	21
Jilani et al.[39]	2007	India	50	27	25	93
Strand et al.[40]	2003	Angola	20	6	2	33
Beniwal et al.[41]	2003	India	97	24	18	75
Hamid et al.[42]	1996	Pakistan	12	2	1	50
Total			659	223	129	58

Note. HEV = hepatitis E virus. Details on where these data are located in the cited article are included in Table A (available as a supplement to the online version of this article at http://www.ajph.org).
[a]HEV testing was not systematically completed for all women in the study.

analysis,[21] HEV testing was not completed for all women,[23] or a large proportion of maternal deaths went undiagnosed.[37] HEV diagnostics are notoriously imprecise; therefore, the proportion of deaths attributable to HEV reported in the literature might vary according to the diagnostic method used.[45,46]

Conclusions

This article presents evidence on the burden of maternal and neonatal deaths associated with jaundice in Bangladesh and the role that HEV might play in causing these deaths. If future laboratory-based studies confirm the role of HEV in maternal and neonatal mortality, preventing HEV infections could have a significant impact on global maternal and child survival, given that HEV disease is endemic in South Asia, where approximately 40% of worldwide maternal[26,47] and 45% of worldwide neonatal deaths[27] occur each year. HEV could be prevented through provision of safe drinking water, and better burden estimates could also be used to garner the support and political will required to ensure access to safe drinking water to large populations at risk. Effective vaccines have also been developed,[48–50] but licensure and production of vaccine will depend upon a better understanding of population-based estimates of disease and death to assess cost-effectiveness. ■

About the Authors

Emily S. Gurley, Amal K. Halder, Peter K. Streatfield, Hossain M. S. Sazzad, Tarique M. Nurul Huda, M. Jahangir Hossain, and Stephen P. Luby are with the International Centre for Diarrheal Diseases Research, Bangladesh (ICDDR,B), Dhaka, Bangladesh. Steven P. Luby is also with Centers for Disease Control and Prevention (CDC), Atlanta, GA.

Correspondence should be sent to Emily S. Gurley, Centre for Communicable Diseases, ICDDR,B, 68 Shaheed Tajuddin Ahmed Sarani, Mohakhali, Dhaka-1212, Bangaldesh (e-mail: egurley@icddrb.org). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

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Contributors

E. S. Gurley conceptualized the study, conducted the data analyses, searched the published literature, and drafted the first article. A. K. Halder, P. K. Streatfield, H. M. S. Sazzad, and T. M. N. Huda were involved in collecting and analyzing verbal autopsy data and reviewing the article. M. J. Hossain and S. P. Luby assisted with data interpretation and revised the article. All authors approved the final draft of the article.

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Human Participant Protection

All studies used in this analysis, except Sanitation, Hygiene Education, and Water Supply Bangladesh (SHEWA-B), were approved by the institutional review board of the ICDDR,B. SHEWA-B was an evaluation of a public health program rather than a research study and was therefore not reviewed by an institutional review board.

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