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Infant and Maternal Risk Factors for Diarrhea-Associated Infant Mortality in the United States, 2005-2006

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Abstract

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By Jason Mehal

BACKGROUND: Diarrhea-associated illness and mortality continue to affect children in the United States, especially infants. Diarrheal mortality had fallen in the 30 years prior to 1985 and had remained consistent for several years. Despite identification of risk factors for diarrhea-associated mortality and the recent addition of a rotavirus vaccine to the national routine immunization program, morbidity has remained high in recent years while the number of deaths due to diarrhea has increased.

METHODS: The 2005 and 2006 United States Linked Birth/Infant Death datasets were used to select infant deaths records listing a diarrhea-associated *International Classification of Diseases, Tenth Revision* (ICD-10) code as a cause of death anywhere on the death certificate. Selected records were restricted to singleton infants with birth weight >500 and ≤8000 grams. Infant mortality rates (IMRs) were calculated overall and by sex, race, Hispanic origin, birth weight, age at death, and region. A retrospective case-control study was used to identify potential infant and maternal risk factors for diarrheal mortality.

RESULTS: The overall IMR was 6.9 deaths per 100,000 live births (95% CI: 6.1-7.8) and was higher among males than among females. Black infants, those with low birth weight (<1500g and <2500g), and non-Hispanic infants experienced the highest mortality rates. Multivariable analysis identified male sex and low 5-minute Apgar score as significant risk factors for diarrheal mortality. There were also significant interaction terms. Among infants with low birth weight, older maternal age led to a higher chance of death, and among infants with normal birth weight, younger maternal age led to higher chance of death. Diarrhea-associated deaths were more likely to black infants than were survivors, regardless of marital status.

CONCLUSIONS: The number of diarrhea-associated deaths continues to increase in recent years, despite previous identification of infant and maternal risk factors for diarrheal mortality. Social risk factors influence diarrheal death more among normal birth weight infants while biological risk factors influence death more among low birth weight infants. With the high percentage of infants dying after 6 weeks, the minimum age of vaccination, timely vaccination could help to reduce the diarrheal mortality among infants in the United States.

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1. Introduction

Gastroenteritis (diarrhea-associated illness) is considered one of the leading causes of morbidity and mortality worldwide, especially among children. Many pathogens cause diarrheal illness; only one, rotavirus, has a vaccination. Rotavirus vaccination has been shown to reduce diarrhea-associated mortality, but in the United States deaths from diarrhea have increased in recent years while morbidity has remained high. The purpose of this study is to evaluate diarrhea-associated deaths among infants in the United States and to identify risk factors for diarrhea mortality.

1.1. Prevention/Immunization

Access to uncontaminated water and food is the most effective prevention against diarrhea among children (Knox 2004), but this can be difficult to achieve in many low-income settings. Additionally, sanitary practices such as careful hand washing limit the spread of infection (Knox 2004). The only pathogen associated with diarrhea for which there is a vaccination is rotavirus (Parashar, Hummelman, Bresee, Miller, & Glass, 2003). The first rotavirus vaccination was released in the United States in 1999. Within one year of its release, however, it was discontinued because it was estimated to cause intussusception in one out of every 12,000 vaccinated infants (Parashar, et al., 2003; Tate, Cortese, et al., 2011). Intussusception occurs when a segment of the intestine folds back into another part of the intestine (Bines, Patel, & Parashar, 2009). If left untreated, the blood supply of the bowel can be reduced causing ischemia and even perforation; these complications may be fatal. In 2006, a new pentavalent rotavirus vaccination (RV5; RotaTeq, Merck and Co.) was released in the United States which has not been shown to

be associated with cases of intussusception (Knox 2004; Tate, 2011 #98). Recommendations by the Advisory Committee on Immunization Practices (ACIP) in 2006 included oral vaccination to all infants at 2, 4, and 6 months of age (Knox 2004). In 2008, a monovalent vaccination was added to the recommendations by ACIP (RV1; Rotatrix, GSK Biologicals) (Tate, Cortese, et al., 2011). RV1 is only administered twice: at 2 and 4 months of age. After the introduction of this vaccination program, the number of rotavirus cases dropped considerably; there was an 86% decrease in the number of positive rotavirus tests from the prevaccine era to the 2009-2010 rotavirus season (Tate, Mutuc, et al., 2011). The vaccination program even changed the onset and magnitude of the rotavirus season; the 2007-2008 rotavirus season was delayed 15 weeks with the proportion of rotavirus-positive tests decreasing by 60% (Tate, et al., 2009).

1.2. Biology - Signs/Symptoms

Gastroenteritis involves the presence of diarrhea, with or without vomiting (Knox 2004). Diarrhea describes stools that are loose and/or watery; three or more loose or watery stools per day meets a common case definition for diarrhea (King, Glass, Bresee, & Duggan, 2003). Total fluid volume lost through diarrhea can range from 5 to 200mL/kg body weight per day (World Health Organization, 2005). Other symptoms can include malaise, fever, and severe abdominal pain, although the latter two are more commonly seen with inflammatory diarrhea (Knox 2004). Gastroenteritis can be caused by a variety of pathogens; it can be viral, bacterial, or parasitic. Common causes of viral gastroenteritis can include Norwalk virus, adenovirus, and rotavirus, which the majority of research on gastroenteritis has been dedicated to. Bacterial gastroenteritis can be

caused by cholera, *salmonella*, *shigella*, *E. Coli*, *C. dificile*, as well as other food poisonings and bacteria. Amebiasis, as well as other protozoal intestinal diseases, are the main causes of parasitic gastroenteritis.

1.3. Diagnosis

A child presenting with diarrhea should be evaluated for bloody or persistent diarrhea, malnutrition, and dehydration (World Health Organization, 2005). Malnutrition can be assessed by examining the shoulders, arms, thighs, and buttocks for evidence of muscle wasting, also called marasmus (World Health Organization, 2005). Additionally, weight-for-age and weight-for-height guidelines can be used to evaluate degree of malnutrition; these are percentages of United States National Center for Health Statistics median values (World Health Organization, 2005). If a child is in the 60-75th percentile of weight-for-age or the 70-80th percentile of weight-for-height, the child is considered as having moderate malnutrition; for a child below the 60th percentile of weight-for-age or below the 70th percentile of weight-for-height, malnutrition is considered severe (World Health Organization, 2005). In order to assess dehydration, health professionals examine a patient's condition (alert, restless, or lethargic), eyes (normal or sunken), and thirst (drinks normally, eagerly, or poorly) in addition to performing a skin pinch test to evaluate the speed at which the skin returns to normal (World Health Organization, 2005). Children who show some signs of dehydration should be evaluated to determine the fluid deficit; a fluid deficit of 5-10% indicates some dehydration, and a deficit >10% indicates severe dehydration (World Health Organization, 2005).

1.4. Treatment

Dehydration causes many of the deaths associated with diarrhea (World Health Organization, 2005); thus, the most important treatments for diarrhea include rehydration, or prevention of dehydration, and early refeeding (Knox 2004). Children who experience severe dehydration (fluid deficit >10% of body weight) should be hospitalized. When dehydration is not severe, oral rehydration therapy (ORT) is the recommended treatment (Knox 2004) and can effectively treat diarrhea of any etiology in more than 90% of cases (World Health Organization, 2005). Oral rehydration solution (ORS) consists of a mixture of glucose and oral rehydration salts dissolved into a water to form a solution (World Health Organization, 2005). The purpose of this solution is to replace the water and electrolytes lost in the feces, and it can be absorbed in the small intestine, even in the presence of diarrhea. Vomiting can significantly complicate rehydration, and children who experience vomiting should be given small but frequent doses of rehydration solution to prevent further vomiting (Knox 2004). Antidiarrheal and antiemetic medications have not been shown to reduce the amount of diarrhea and are also associated with a high likelihood of side effects; for these reasons, these medications should not be used to treat children <5 years of age (Knox 2004, World Health Organization, 2005).

In addition to dehydration, malnutrition can also be worsened by diarrhea (World Health Organization, 2005). Malnourished children are more at risk for death from diarrheal illnesses, but refeeding during the illness can help to prevent further decline of nutritional status in these children (World Health Organization, 2005). Recent studies have shown that diet supplementation with zinc reduces the disease burden of diarrhea in

children; current recommendations include administration of 10-20 mg zinc per day for 10 to 14 days to children suffering from diarrhea.

1.5. Epidemiology

Diarrhea-associated illness is considered one of the leading causes of morbidity and mortality worldwide, especially among children (Kosek, Bern, & Guerrant, 2003; Wardlaw, Salama, Brocklehurst, Chopra, & Mason, 2010; World Health Organization., 1999). In 2010, diarrhea was responsible for an estimated 15% of all deaths to children <5 years of age worldwide (World Health Organization., 2011) causing an estimated 1.3 million deaths in 2008 (Black, et al., 2010). Although diarrhea-associated mortality dropped significantly between 1955-2000, morbidity remained high over the same time period (Kosek, et al., 2003).

In developing countries, an estimated 1.4 billion cases of diarrhea occur each year among children <5 years of age; about one-third (475 million) occur among infants (children <1 year) (Parashar, et al., 2003). Although the majority of diarrhea cases occur in developing countries, industrialized nations also experience a considerable burden from diarrhea. Recent estimates suggest that there are approximately 136,000 diarrhea-associated hospitalizations among children <5 years of age in the United States and that one in 26 US children will be hospitalized with diarrhea-associated illness during the first 5 years of life (Fischer, et al., 2007). The number of diarrhea-associated deaths each year among children 1 – 59 months of age in the United States decreased over the period 1968-1985, but remained around 300 deaths per year from 1985 to the end of the study in 1991 (Kilgore, Holman, Clarke, & Glass, 1995). During 1992-1998 and 2005-2007,

however, the number of diarrhea-associated deaths among children one-59 months of age in the United States increased to an average of 393 deaths per year (*CDC unpublished data*).

Infants experience the highest morbidity and mortality from diarrhea-associated illness (Kilgore, et al., 1995; Kosek, et al., 2003; Snyder & Merson, 1982); 84% of the diarrhea-associated deaths among US children aged 1 - 59 months between 1992-1998 and 2005-2007 occurred among infants (*CDC unpublished data)*. The number of infant deaths due to diarrhea decreased from 1112 deaths in 1968 to 240 deaths in 1985, but remained steady until the study's end in 1991 (Kilgore, et al., 1995), when there were 257 reported diarrhea-associated deaths among US infants (Parashar, Kilgore, et al., 1998). The diarrhea-associated infant mortality rate (IMR) decreased from 1968 (31.0 deaths per 100,000 live births) to 1991 (6.4 deaths per 100,000 live births) (Kilgore, et al., 1995).

Rotavirus is the most common cause of severe acute diarrhea among children in the United States (Parashar, Holman, Clarke, Bresee, & Glass, 1998). In 2006, the Advisory Committee on Immunization Practices recommended rotavirus vaccination of all U.S. infants 6 weeks of age and older (Curns, et al., 2010). Before the addition of the vaccine to the routine immunization program, rotavirus was responsible for almost 17% of diarrhea cases and caused an estimated 27,000 hospitalizations, and as many as 40 deaths each year among children <5 years of age in the United States (Parashar, Holman, et al., 1998).

1.6. Risk Factors

A 1998 study by Parashar et al examined the effect of social factors on diarrheal mortality in 1991 among US infants with birth weight <1500g (VLBW) and those with birth weight ≥1500g (LNBW). In this study, low 1-minute Apgar score, black maternal race, and lesser maternal education were found to be associated with higher diarrheal mortality among LNBW infants while, among VLBW infants, only low 1-minute Apgar score and black maternal race were found to be associated with higher diarrheal mortality (Parashar, Kilgore, et al., 1998).

2. Methods

2.1. Epidemiological Methods

The National Center for Health Statistics (NCHS) is a division within the Centers of Disease Control and Prevention (CDC) and United States Department of Health and Human Services (HHS) which provides health-related statistics to improve the health of the American people. Data from the United States Linked Birth/Infant Death public use data file for 2005 and 2006 from NCHS were analyzed (National Center for Health Statistics, 2008, 2009). The Linked Birth/Infant Death data provides information on a variety of maternal and infant characteristics of children <1 year of age who died in a given year. Each death certificate is linked to its corresponding birth certificate. This linkage allows the analysis of how factors present at birth affect death in infants.

A retrospective case-control study was conducted to identify potential risk factors for diarrhea-associated death among selected maternal and infant characteristics. Cases were defined as singleton infants weighing >499 and <8000 grams at birth with diarrhea listed as a cause of death anywhere on the death record. Diarrhea-associated deaths were defined as records listing any of the *International Classification of Diseases, Tenth Revision* (ICD-10) codes found in Table 1 as a cause of death (World Health Organization.; World Health Organization. International Statistical Classification of Diseases and Related Health Problems (ICD-10). 10th ed. Geneva: World Health Organization; 1992.,"). Categories of specified infectious diarrhea were chosen in accordance with previous studies of diarrhea-associated mortality and included viral (A08), bacterial (A00, A02 [excluding A02.2], A03-A05), and parasitic (A06.0-A06.3, A06.8, A06.9). Subgroups of diarrhea of unspecified category included infectious

gastroenteritis and colitis, unspecified (A09) and noninfective gastroenteritis and colitis, unspecified (K52.9). Controls were defined as singleton infants weighing >499 and <8000 grams at birth who survived their first year of life and were randomly selected from the Linked Birth/Infant Death data to obtain a 4:1 ratio of survivors to diarrhea-associated deaths (Ury, 1975). In 2005 and 2006, 1.3% of death records could not be linked to the corresponding birth certificate and were thus excluded from this analysis (National Center for Health Statistics, 2008, 2009).

Selected maternal and infant characteristics were chosen based on findings in the literature and comparability between birth certificate revisions. Some characteristics in the Linked Birth/Infant Death data set are considered by NCHS to be non-comparable between the 1989 and 2003 revisions of the U.S. Standard Certificate of Live Birth, including maternal education, trimester prenatal care began, adequacy of prenatal care, maternal smoking, congenital anomaly, and abnormal newborn condition (Mathews & MacDorman, 2008; National Center for Health Statistics, 2008, 2009). As of January 1, 2005, 38 states used the 1989 revision while 12 states had implemented the 2003 revision (National Center for Health Statistics, 2008); these 12 states included Florida, Idaho, Kansas, Kentucky, Nebraska, New Hampshire, New York, Pennsylvania, South Carolina, Tennessee, Texas, and Washington. The number of states using the 2003 revision increased to 19 as of January 1, 2006, with the addition of California, Delaware, North Dakota, Ohio, South Dakota, Vermont and Wyoming (National Center for Health Statistics, 2009). Including either version of non-comparable variables would exclude a substantial number of infants, so only variables which were comparable between both revisions of the birth certificate were included in the analysis.

2.2. Calculating Confidence Intervals for IMRs

Age at death in weeks was examined overall and by birth weight (<2500g and ≥2500g). Median age at death in weeks for each of the two birth weight groups was statistically compared using the Wilcoxon rank-sum test. Diarrhea-associated infant mortality rates (IMRs), evaluated as the number of deaths per 100,000 live births, and 95% confidence intervals (CIs) were calculated overall and by sex, race (white, black, and other), Hispanic origin, birth weight [(VLBW) (<1500g), moderately low-birth-weight (MLBW) (1500-2499g), low-birth weight (LBW) (<2500g), and normal birth weight (NBW) (≥2500g)], age at death (neonatal, post-neonatal, 1-3 months, and 4-11 months), and region of death (Northeast, Midwest, South, and West) defined using US census guidelines. The "other" race category consists of American Indian/Alaska Native (AI/AN) and Asian/Pacific Islander (A/PI) infants; individually, these characteristics were considered unstable because each had fewer than 20 deaths. Deaths that occur before 28 days of life are considered neonatal deaths; all deaths occurring from 28 days to one year are considered post-neonatal deaths (National Center for Health Statistics, 2008, 2009). Age at death IMRs were calculated as the number of infants who died within a given age range (<1 month, 1-3 months, or 4-11 months) divided by the number of infants who survived at least until the beginning of that specific age range. For characteristics with fewer than 20 deaths, IMRs and CIs were not calculated because of the unreliability associated with such a small numerator. When the number of deaths in the numerator was 100 or more, CIs were calculated assuming the data followed a normal distribution, using the following equations:

$$\text{Lower limit} = \text{IMR} - [1.96 \times (\text{IMR}/\sqrt{\text{B}})]$$

$$\text{Upper limit} = \text{IMR} + [1.96 \times (\text{IMR}/\sqrt{B})]$$

where B=the number of live births. When the number of deaths was greater than 20 but fewer than 100, a Poisson distribution was used to calculate the CI using the following equations:

$$\text{Lower limit}=\text{IMR}*L$$

$$\text{Upper limit}=\text{IMR}*U$$

where L and U are the lower and upper 95% confidence limits, respectively, for the infant mortality rate based on the number of deaths, a Poisson random variable.

2.3. Case-Control Methods

When analyzing events with very low rates (i.e. rare events), it is more effective to use a case-control study than a cohort study. By using a case-control study, you can ensure that you have a sufficient number of cases. In these types of studies, a certain number of cases are selected for analysis; often, controls are selected to obtain a predefined ratio of controls to cases. When analyzing a variable, cases and controls are examined for the presence of an "exposure," and subjects are placed in the corresponding cell in the 2x2 table given below.

	Exposed	Not exposed	
Case	a	b	a+b (fixed)
Control	c	d	c+d (fixed)

In case-control studies, it is more common to use an odds ratio (OR) to describe the effect of a variable rather than using a risk ratio (RR). The OR for a variable is calculated as follows:

$$OR = ad/bc = r$$

where *r* is the result of solving for the odds ratio; the OR is interpreted as: "the odds of exposure among cases are *r* times greater than the odds of exposure among controls." Values of $r > 1$ indicate that presence of the exposure is associated with higher odds of disease while values of $r < 1$ indicate that exposure is associated with lower odds of disease. A value $r = 1$ indicates that the exposure has no apparent effect on odds of disease.

ORs and corresponding 95% CIs are calculated using the logistic procedure in SAS version 9.2. To obtain univariate results, this procedure uses the value of only one infant or maternal risk factor at a time to predict diarrheal death, using the equation

$$\text{logit } pr(y \mid x) = \alpha + \beta_1 x_1$$

where y=1 for cases, y=0 for controls, x=1 if the risk factor being analyzed is present, and x=0 if the risk factor is absent. For categorical variables with $k > 2$ levels, k-1 dummy variables are created, each with its own β coefficient; ORs for these coefficients are computed and interpreted in the same way as mentioned above. The parameters α and β are estimated to be the values which maximize the log-likelihood function:

$$G = -2 \sum [y \log P + (1-y)\log(1-P)]$$

where y=1 for cases, y=0 for controls, and P=the predicted probability of being a case (Breslow & Day, 1980). For each risk factor, there is a unique estimate of the value β and its standard error. To determine the OR between any level of a risk factor and the

reference level for that risk factor, the logistic procedure exponentiates the value of the β coefficient where $OR_{x1=1 \text{ vs. } x1=0} = \exp(\beta_1)$. Along with an estimate of the value of β, the logistic procedure also calculates the standard error (SE) of β. This SE is used to construct a (1- α) % CI for β, where the limits of the CI are calculated by:

$$\text{Lower limit} = \exp[\beta - z_{1-\alpha/2}(SE\ \beta)]$$

$$\text{Upper limit} = \exp[\beta + z_{1-\alpha/2}(SE\ \beta)].$$

Similarly to the univariate case, multivariable logistic regression solves for unknown α and β coefficients by maximizing the log-likelihood function. The difference in this case is that the function now includes *p* β coefficients and risk factors (x_p). This function takes the form:

$$\text{logit } pr(y \mid x) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p$$

where *p* represents the number of predictors in the multivariate model. The OR for each risk factor is computed while controlling for all other variables in the model so that only the β coefficient for the risk factor being analyzed is being exponentiated.

For each scenario backward elimination was used; this involves fitting the initial multivariate model with all main effects variables significant in the univariate analysis and all interaction terms between these variables. A second model is then fit after removing one variable. The resulting log-likelihood values for each of these models are used to compute a *p*-value using the Likelihood Ratio (LR) test, which indicates the significance of the variable removed from the analysis. In each step of backward elimination, the least significant variable (the variable with the largest *p*-value) is removed; once this occurs, the model that does not contain this variable becomes the full

model for the next step. The process is repeated until all remaining variables are significant.

2.4. Case-Control Application

For the logistic regression analysis, infant characteristics analyzed included sex, live birth order (first, second, and third or more), 5-minute Apgar score (<7 and ≥7), birth weight [low birth weight (LBW) (<2500g) and normal birth weight (NBW) (≥2500g)], and gestational age (<37 and ≥37 weeks). Selected maternal characteristics included race (white, black, and other), Hispanic origin, age (≤19, 20-24, 25-29, and ≥30 years), and marital status (married and unmarried). Maternal race and maternal Hispanic origin as reported on the birth certificate were used to represent infant race and Hispanic origin because they are generally considered to be more reliable than race/ethnicity information of the infant reported on the death certificate (National Center for Health Statistics, 2008, 2009). Five-minute Apgar score was missing for 13% of infants, 94% of whom were from California, which did not report 5-minute Apgar score (National Center for Health Statistics, 2008, 2009). No other variable had >1% missing data.

Because California did not report 5-minute Apgar score, two separate logistic regression models were fit. One model included subjects with 5-minute Apgar score reported, and the second model dropped the variable 5-minute Apgar score so that subjects with missing data for 5-minute Apgar score would not be excluded from the analysis. Univariate analysis for both models was conducted to identify predictor variables to be included in the multivariate models.

Infant and maternal characteristics which were significant in the univariate analysis ($p < 0.10$ or, equivalently, the 90% CI does not include the value 1.0) and interaction terms were used to predict diarrhea-associated death using hierarchically well-formulated multivariate logistic regression modeling. Gestational age was not included in the multivariate model because the measure is unreliable and has a high correlation with birth weight (Kramer, McLean, Boyd, & Usher, 1988). Because it is generally considered more reliable than the Wald test, the Likelihood Ratio (LR) test was used to assess statistical significance (Agresti, 1996; Kleinbaum, 2008; Kleinbaum, Klein, Pryor, & Ebooks Corporation, 2002); interaction terms and predictor variables remained in the multivariate model at $p < 0.05$.

3. Results

During 2005 and 2006, 635 diarrhea-associated deaths among singleton infants weighing >499 and <8000 grams were reported in the Linked Birth/Infant Death dataset. Eighty three percent (n=529) of these deaths were among those with birth weight <2500g. The number of deaths per year increased from 277 in 2005 to 358 in 2006. The mean age at death overall was 12 weeks. The mean age at death in weeks among LBW infants was lower than among NBW infants (11 weeks and 19 weeks, respectively; $p<.0001$). The percentage of infants who died before reaching six weeks of age was twice as high among LBW infants (38%) as among NBW infants (19%) (Figure 1). Ninety five percent (n=604) of diarrheal deaths were of unspecified category; of these deaths, 601 were presumed noninfective (ICD-10 code: K52.9) and 3 were presumed infectious (A09) (Table 1). Three percent (n=19) were of bacterial origin; the most common bacterial codes listed were *C. dificile* (A04.7) (n=11) and *Salmonella* (A02.0, A02.1, A02.8, A02.9) (n=5). Two percent of diarrhea-associated deaths were of viral origin, while there were no deaths classified as parasitic.

3.1 Infant mortality rates

The IMR in 2005 was 6.9 deaths per 100,000 live births (95% CI: 6.1-7.8) and, in 2006, was 8.7 (95% CI: 7.8-9.6). The overall diarrhea-associated IMR was 7.8 (95% CI: 7.2-8.4) (Table 2). This rate was higher among males (9.3 per 100,000; 95% CI: 8.4-10.2) than among females (6.3; 95% CI: 5.5-7.1). Infants with black race (20.9, 95% CI: 18.4-23.5) had a higher IMR than all other race categories. AI/AN and A/PI infant deaths were too few to calculate meaningful IMRs and CIs and were grouped together into “other”

race category. Infants with other race had an IMR of 4.4 (95% CI: 2.8-6.5) while the IMR among white infants was 5.5 (95% CI: 5.0-6.1). The rate among infants with Hispanic origin was 6.7 (95% CI: 5.5-7.8) while among non-Hispanic infants, the rate was 8.2 (95% CI: 7.5-9.0). The rate among infants with LBW was more than 70 times higher than among those with NBW (102.8 per 100,000, 95% CI: 94.1-111.6; and 1.4, 95% CI: 1.1-1.7, respectively); VLBW infants were at an even greater risk of mortality (579.2, 95% CI: 527.4-631.1). The IMR among infants with MLBW was 10.9 (95% CI: 8.0-14.5). Post-neonatal infants were more likely to have a diarrhea-associated death than neonatal infants (7.5 per 100,000, 95% CI: 6.9-8.1; and 0.3, 95% CI: 0.2-0.5, respectively). The IMR among infants 1-3 months of age (5.8, 95% CI: 5.2-6.3) was higher than that for infants 4-11 months of age (1.8, 95% CI: 1.5-2.0).

3.2 Risk factors associated with diarrhea death

A univariate analysis was performed to identify the association between select maternal and infant characteristics and diarrhea-associated death. Infant characteristics univariately associated with diarrheal death included male sex, live birth order (first and third or more), low 5-minute Apgar score, and low birth weight (Table 3). Significant maternal characteristics included black race, non-Hispanic origin, young age, and unmarried status. Infants who died from diarrhea were more likely to have LBW (OR: 74.7, 95% CI: 57.4-97.2) and a 5-minute Apgar score <7 (OR: 48.4, 95% CI: 30.1-77.8) than infants who survived their first year of life. Infants who died from diarrhea were also more likely to be male (OR: 1.4, 95% CI: 1.2-1.7) and have unmarried mothers (OR: 2.3, 95% CI: 1.9-2.7) than infants who survived their first year of life. Deaths were also more

likely to occur among infants born first and those born third or later (OR: 1.5, 95% CI: 1.2-1.9; and OR: 1.3, 95% CI: 1.0-1.7). Among infant diarrheal deaths, mothers were more likely to be younger when compared to a reference group of 25-29 years of age (≤19 years OR: 2.1, 95% CI: 1.6-2.8; 20-24 years OR: 1.3, 95% CI: 1.1-1.7). Mothers were no more likely to be ≥30 than 25-29 (OR: 1.0, 95% CI: (0.8-1.3). Infants who died from diarrhea were more likely to be of black race than white (OR: 3.9, 95% CI: 3.2-4.8), but no significant difference was seen between infants of white race or other race (OR: 0.7, 95% CI: 0.5-1.1). Similar results were seen when the univariate analysis was restricted to infants with reported 5-minute Apgar score.

All infant and maternal characteristics that were significantly associated with diarrheal death in the univariate analysis were then used to predict diarrhea death using multivariable logistic regression modeling. Among infants with a reported 5-minute Apgar score, multivariate analysis identified sex (male vs. female OR: 1.5, 95% CI: 1.1-2.0) and 5-minute Apgar score (<7 vs. ≥7 OR: 14.1, 95% CI 7.3-27.5) as significant predictors for diarrhea death (Table 4). Significant interactions were present between birth weight and maternal age and between maternal marital status and race. Among infants with LBW, higher maternal age (≥30) was more strongly associated with diarrheal death than younger maternal age (≥30 years OR (95% CI): 2.0 (1.2-3.5); 20-24 years OR (95% CI): 1.4 (0.8-2.5); and ≤19 years OR (95% CI): 1.3 (0.7-2.6). Among infants with NBW, however, lower maternal age (≤19 and 20-24) was most strongly associated with diarrheal death than higher maternal age (≥30 years OR (95% CI): 1.6 (0.8-3.3); 20-24 years OR (95% CI): 2.7 (1.4-5.2); and ≤19 years OR (95% CI): 3.4 (1.6-7.3). Among married mothers, other race led to decreased odds of infant diarrheal death (other vs.

black OR: 0.3, 95% CI: 0.1-0.8), but among unmarried mothers, other race resulted in higher odds of diarrheal death (other vs. black OR: 4.6, 95% CI: 1.9-11.5). Among unmarried mothers, black race was associated with diarrheal death (OR: 2.1, 95% CI: 1.4-3.2) while among married mothers, black race was not significantly associated with diarrheal death (OR: 1.7, 95% CI: 0.9-3.3).

In the second model, which did not include 5-minute Apgar score, the significant main effect characteristic was live birth order (third or more vs. second OR: 1.6, 95% CI: 1.1-2.3; first vs. second OR: 1.0, 95% CI: 0.7-1.3). Significant interactions remained between birth weight and maternal age, between maternal marital status and race, and between sex and maternal Hispanic origin. Among female infants, maternal Hispanic origin resulted in statistically similar odds of diarrheal death (Hispanic vs. non-Hispanic OR: 0.7, 95% CI: 0.4-1.2), while among male infants, maternal Hispanic origin resulted in increased odds of diarrheal death (Hispanic vs. non-Hispanic OR: 1.7, 95% CI: 1.1-2.6). Among infants with LBW, maternal age ≥30 years was significantly associated with diarrheal death (OR: 2.1, 95% CI: 1.3-3.5) while age 20-24 years (OR: 1.6, 95% CI: 0.9-2.6) and ≤19 years (OR: 1.6, 95% CI: 0.9-2.9) were not associated with diarrheal death. The opposite results were seen among infants with NBW; maternal age ≥30 years was not associated with diarrheal death (OR: 1.0, 95% CI: 0.5-1.9) while age 20-24 years (OR: 2.0, 95% CI: 1.2-3.6) and ≤19 years (OR: 2.7, 95% CI: 1.3-5.3) were significantly associated with diarrheal death. Among infants with married mothers, black race led to higher odds of diarrheal death (OR: 2.1, 95% CI: 1.2-3.9) while other race led to lower odds (OR: 0.2, 95% CI: 0.1-0.5). Black race remained similarly associated with diarrheal

death among infants with unmarried mothers (OR: 1.5, 95% CI: 1.5-3.4), but the association of other race changed drastically (OR: 5.1, 95% CI: 2.2-11.5).

4. Discussion

Mortality due to diarrhea-associated illness continues to affect infants in the United States; the highest rates are seen in infants with low-birth-weight, particularly in infants with very-low-birth-weight. Many other infant and maternal characteristics were also found to be associated with higher diarrheal mortality including sex, 5-minute Apgar score, race, maternal age, and maternal marital status. When Apgar score was not included in the model, Hispanic origin and birth order were associated with increased odds of diarrheal death as well. The relationships between some of these variables were complex, with interaction present between birth weight and maternal age, between maternal marital status and race, and between sex and Hispanic origin. These findings are consistent with analyses from previous studies which evaluate risk factors for diarrhea-associated death. Despite the identification of significant variables in earlier studies, diarrheal deaths among US infants and children have shown increases in recent years.

In 2005, the number of diarrhea-associated infant deaths reported (n=277) increased slightly compared to numbers reported by Kilgore, et al. (1995) from 1985-1991, but the IMR 6.9 deaths per 100,000 live births (95% CI: 6.1-7.8) was similar to those seen in earlier years (1991 IMR: 6.4). In 2006, however, the number of deaths increased further to 358, and the IMR increased to 8.7 (7.8-9.6). Annual infant mortality due to diarrhea has not been evaluated since the studies by Kilgore, et al. (1995) and Parahsar, et al. (1998), for which the most recent study year was 1991. Although no trends can be definitively assessed due to the lack of data since 1991, the number of diarrhea-associated deaths among infants and the IMR both appear to be increasing.

Birth weight was the single most important factor in predicting diarrhea-associated death. LBW infants are more biologically fragile and tend to have more health problems than NBW infants. For this reason, LBW infants are generally less affected by social factors and more affected by biological factors than NBW infants. Evidence of the fragility of LBW infants can also be seen in the fact that these infants died at younger ages than those who were of NBW. Among infants with LBW, those with older maternal age (≥30 years) were at an increased risk of diarrhea-associated death; among infants with NBW, however, those with lower maternal age (≤19 and 20-24) were at a higher risk. It is unknown why this particular association exists. Maternal age was a more important factor for mortality in the NBW group than in the LBW group; this is presumably due to the assumption that infants in the low-birth-weight group are dying as a result of their biological fragility rather than other social factors which may also affect mortality. Despite gestational age being a very significant predictor in the univariate analysis, its unreliability and correlation with birth weight prohibited its inclusion in the multivariate analysis.

A limitation of the present study is the non-comparability of several variables between revisions of the birth certificate. For these variables, the format of the questions on the birth certificate differed substantially and precluded the combination of the data. For each of these variables, infants with non-comparable data were assigned a value of "missing" for the respective incompatible birth certificate revision. When performing multivariable logistic regression in SAS, any infant with missing data for any of the variables included in the model are deleted from the analysis, so caution must be taken when selecting which variables to include. Those with high percentages of missing data,

in this case primarily due more to non-comparability than to non-reporting, will substantially limit the number of infants included in the analysis and thus compromise the descriptive value of the results; for these reasons, only variables comparable between birth certificate revisions were included in the analysis. The inability to use these non-comparable items in the multivariate modeling prohibits their possible detection as risk factors for diarrhea-associated death among infants.

Additionally, the non-reporting of 5-minute Apgar score by the state of California necessitated separate models to be run, so the effect of the other infant and maternal characteristics on diarrhea-associated infant death could only be evaluated among infants not born in California or among all infants in the absence of 5-minute Apgar score. In both years of this study, 1.3% of death certificates could not be linked to the corresponding birth certificate and thus are not included in this analysis. Although only a small percentage of records could not be linked, the number of diarrhea-associated deaths and calculated IMRs will likely underestimate the truth.

Rotavirus is the most common pathogen associated with severe acute diarrhea among US children and is responsible for almost 17% of diarrhea cases. Prior to the introduction of its vaccine to the routine immunization program by the ACIP in 2006, rotavirus caused an estimated 20-40 deaths per year among US infants >5 years of age. Recommendations for this vaccine include administration of the first dose to infants at least 6 weeks of age and a completion of the series by 8 months of age. Among LBW infants, 62% of deaths occurred among infants at least 6 weeks of age; this number was 81% among NBW infants. It can be seen from the high percentage of deaths occurring after reaching the minimum vaccination age that timely administration of the rotavirus

vaccine may be an important factor in reducing the rates of diarrheal mortality among US children.

A specific pathogen was listed on the death certificate in only 5% of deaths, and although only .5% of diarrhea-associated deaths (n=3) were coded as rotavirus, the large proportion of deaths coded as unspecified category prevented the accurate measurement of deaths due to rotavirus. With an improvement in the specificity of diagnosing cause of death, the extent to which the prevention of rotavirus through immunization could reduce diarrhea-associated mortality could be better understood.

Understanding the risk factors associated with diarrheal mortality is an important step in developing prevention strategies aimed to reduce mortality rates. Infants with low- and very-low-birth-weights continue to experience the highest mortality rates from diarrhea; many other infant and maternal characteristics also continue to be identified as risk factors for diarrheal mortality. Rotavirus vaccination may substantially lower the risk of death among some of these infants, and its impact on other risk factors for diarrheal mortality should be further investigated.

REFERENCES

Agresti, A. (1996). *An introduction to categorical data analysis*. New York: Wiley.

Bines, J. E., Patel, M., & Parashar, U. (2009). Assessment of postlicensure safety of rotavirus vaccines, with emphasis on intussusception. *J Infect Dis, 200 Suppl 1*, S282-290.

Black, R. E., Cousens, S., Johnson, H. L., Lawn, J. E., Rudan, I., Bassani, D. G., et al. (2010). Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet, 375*(9730), 1969-1987.

Breslow, N. E., & Day, N. E. (1980). Statistical methods in cancer research. Volume I - The analysis of case-control studies. *IARC Sci Publ*(32), 5-338.

Curns, A. T., Steiner, C. A., Barrett, M., Hunter, K., Wilson, E., & Parashar, U. D. (2010). Reduction in acute gastroenteritis hospitalizations among US children after introduction of rotavirus vaccine: analysis of hospital discharge data from 18 US states. *J Infect Dis, 201*(11), 1617-1624.

Fischer, T. K., Viboud, C., Parashar, U., Malek, M., Steiner, C., Glass, R., et al. (2007). Hospitalizations and deaths from diarrhea and rotavirus among children <5 years of age in the United States, 1993-2003. *J Infect Dis, 195*(8), 1117-1125.

Kilgore, P. E., Holman, R. C., Clarke, M. J., & Glass, R. I. (1995). Trends of diarrheal disease--associated mortality in US children, 1968 through 1991. *JAMA, 274*(14), 1143-1148.

King, C. K., Glass, R., Bresee, J. S., & Duggan, C. (2003). Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep, 52*(RR-16), 1-16.

Kleinbaum, D. G. (2008). *Applied regression analysis and other multivariable methods* (4th ed.). Belmont, Calif.: Thomson Brooks/Cole Publishing.

Kleinbaum, D. G., Klein, M., Pryor, E. R., & Ebooks Corporation (2002). Logistic regression a self-learning text, Statistics for biology and healthpp. xiv, 513 p.). Available from http://www.emory.eblib.com/EBLWeb/patron/?target=patron&extendedid=P%5F231363%5F0

Kosek, M., Bern, C., & Guerrant, R. L. (2003). The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bull World Health Organ, 81*(3), 197-204.

Kramer, M. S., McLean, F. H., Boyd, M. E., & Usher, R. H. (1988). The validity of gestational age estimation by menstrual dating in term, preterm, and postterm gestations. *JAMA, 260*(22), 3306-3308.

Mathews, T. J., & MacDorman, M. F. (2008). Infant mortality statistics from the 2005 period linked birth/infant death data set. *Natl Vital Stat Rep, 57*(2), 1-32.

Mathews, T. J., & MacDorman, M. F. (2009). Infant mortality statistics from the 2006 period linked birth/infant death data set. *Natl Vital Stat Rep, 58*(17), 1-31.

National Center for Health Statistics (2008). *Public use data file documentation: 2005 period linked birth/infant death data set*. Hyattsville, MD: National Center for Health Statistics.

National Center for Health Statistics (2009). *Public use data file documentation: 2006 period linked birth/infant death data set*. Hyattsville, MD: National Center for Health Statistics.

Parashar, U. D., Holman, R. C., Clarke, M. J., Bresee, J. S., & Glass, R. I. (1998). Hospitalizations associated with rotavirus diarrhea in the United States, 1993 through 1995: surveillance based on the new ICD-9-CM rotavirus-specific diagnostic code. *J Infect Dis, 177*(1), 13-17.

Parashar, U. D., Hummelman, E. G., Bresee, J. S., Miller, M. A., & Glass, R. I. (2003). Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis, 9*(5), 565-572.

Parashar, U. D., Kilgore, P. E., Holman, R. C., Clarke, M. J., Bresee, J. S., & Glass, R. I. (1998). Diarrheal mortality in US infants. Influence of birth weight on risk factors for death. *Arch Pediatr Adolesc Med, 152*(1), 47-51.

Snyder, J. D., & Merson, M. H. (1982). The magnitude of the global problem of acute diarrhoeal disease: a review of active surveillance data. *Bull World Health Organ, 60*(4), 605-613.

Tate, J. E., Cortese, M. M., Payne, D. C., Curns, A. T., Yen, C., Esposito, D. H., et al. (2011). Uptake, impact, and effectiveness of rotavirus vaccination in the United States: review of the first 3 years of postlicensure data. *Pediatr Infect Dis J, 30*(1 Suppl), S56-60.

Tate, J. E., Mutuc, J. D., Panozzo, C. A., Payne, D. C., Cortese, M. M., Cortes, J. E., et al. (2011). Sustained decline in rotavirus detections in the United States following the introduction of rotavirus vaccine in 2006. *Pediatr Infect Dis J, 30*(1 Suppl), S30-34.

Tate, J. E., Panozzo, C. A., Payne, D. C., Patel, M. M., Cortese, M. M., Fowlkes, A. L., et al. (2009). Decline and change in seasonality of US rotavirus activity after the introduction of rotavirus vaccine. *Pediatrics, 124*(2), 465-471.

Ury, H. K. (1975). Efficiency of case-control studies with multiple controls per case: continuous or dichotomous data. *Biometrics, 31*(3), 643-649.

Wardlaw, T., Salama, P., Brocklehurst, C., Chopra, M., & Mason, E. (2010). Diarrhoea: why children are still dying and what can be done. *Lancet, 375*(9718), 870-872.

World Health Organization. World Health Organization. International Statistical Classification of Diseases and Related Health Problems (ICD-10). 10th ed. Geneva: World Health Organization; 1992.

World Health Organization. (1999). Making a difference. The World Health Report 1999. *Health Millions, 25*(4), 3-5.

World Health Organization. (2011). *World health statistics 2010*. Geneva: World Health Organization.

World Health Organization. International Statistical Classification of Diseases and Related Health Problems (ICD-10). 10th ed. Geneva: World Health Organization; 1992.

APPENDIX

Table 1. Diarrhea-associated Infant Deaths by International Classification of Diseases, 10th Revision (ICD-10) Code, 2005-2006, United States.

Diagnostic Code	ICD-10 code(s)	Number of deaths
Unspecified Category		
Infectious gastroenteritis and colitis, unspecified	A09	3
Noninfective gastroenteritis and colitis, unspecified	K52.9	601
Specified Infectious Category		
Viral		
Rotavirus	A08.0	3
Adenovirus	A08.2	0
Norwalk Virus	A08.1	0
Other viruses	A08.3, A08.4, A08.5	10
Bacterial*		
Cholera	A00	0
Salmonella	A02.0, A02.1, A02.8, A02.9	5
Shigella	A03	0
Other food poisonings	A05	1
E. Coli	A04.0-A04.4	0
Other unspecified bacteria	A04.5-A04.9 (excl. A04.7)	2

C. dificile	A04.7	11
Parasitic**		
Amebiasis (intestinal)	A06.0-A06.3, A06.8, A06.9	0
Other protozoal (intestinal)	A07.0	0
Total[+]		636

*Excludes typhoid and paratyphoid (A01), localized non-intestinal *Salmonella* infection (A02.2).

**Excludes extra-intestinal amebiasis (A06.4-A06.7).

[+]More than one diagnostic category may be listed on a death record

Table 2. Diarrhea-Associated Deaths and Infant Mortality Rates (IMRs) for Select Characteristics, United States, 2005-2006.[+]

Characteristic	Deaths	Live births	IMR (95% CI)*
Total	635	8108162	7.8 (7.2-8.4)
Sex			
Female	249	3953412	6.3 (5.5-7.1)
Male	386	4154750	9.3 (8.4-10.2)
Race			
White	350	6312742	5.5 (5.0-6.1)
Black	261	1246993	20.9 (18.4-23.5)
Other‡	24	548427	4.4 (2.8-6.5)
AI/AN	7	90133	-
A/PI	17	458294	-
Hispanic origin			
Yes	132	1976066	6.7 (5.5-7.8)
No	501	6074968	8.2 (7.5-9.0)
Birth weight (g)			
≥2500	106	7593729	1.4 (1.1-1.7)
<2500	529	514433	102.8 (94.1-111.6)
<1500	482	83217	579.2 (527.4-631.1)
1500-2499	47	431216	10.9 (8.0-14.5)
Age at death**			
Neonatal mortality	26	8108162	0.3 (0.2-0.5)
Post-neonatal mortality	609	8087005	7.5 (6.9-8.1)
1-3 months of age	467	8087005	5.8 (5.2-6.3)

4-11 months of age	142	8086620	1.8 (1.5-2.0)
Region of death			
Northeast	99	1295239	7.6 (6.2-9.3)
Midwest	119	1724188	6.9 (5.7-8.1)
South	315	3057217	10.3 (9.2-11.4)
West	102	2031518	5.0 (4.0-6.0)

* Infant mortality rate (IMR) expressed as the number of diarrhea-associated deaths per 100,000 live births.

**Mortality rate is calculated by dividing the number of deaths registered among live-born infants in a particular age group by the number of infants who survived at least until the beginning of the age group.

[+]Does not include death records that could not be linked to the corresponding birth certificate (1.3% of records in 2005 and 2006).

‡ Due to unstable numbers (fewer than 20 deaths), IMRs and CIs for AI/AN and A/PI race categories were not calculated; these race categories were combined into an "other" race category.

Table 3. Comparison of Select Infant and Maternal Characteristics between Diarrhea-Associated Infant Deaths and Infant Survivors in the United States, 2005-2006.

Characteristic	Deaths, n (%)	Survivors, n (%)	OR (95% CI)[+]
Total	635	2540	--
Sex			
Female	249 (39.2)	1199 (47.2)	Reference
Male	386 (60.8)	1341 (52.8)	1.4 (1.2-1.7)
Race			
White	350 (55.1)	1980 (78.0)	Reference
Black	261 (41.1)	375 (14.8)	3.9 (3.2-4.8)
Other	24 (3.8)	185 (7.2)	0.7 (0.5-1.1)
Hispanic origin			
No	501 (79.2)	1887 (74.8)	Reference
Yes	132 (20.8)	634 (25.2)	0.8 (0.6-1.0)
Maternal age (years)			
≤19	113 (17.8)	260 (10.2)	2.1 (1.6-2.8)
20-24	191 (30.1)	692 (27.2)	1.3 (1.1-1.7)
25-29	147 (23.2)	713 (28.1)	Reference
≥30	184 (29.0)	875 (34.4)	1.0 (0.8-1.3)
Maternal marital status			
Married	255 (40.2)	1540 (60.6)	Reference
Unmarried	380 (59.8)	1000 (39.4)	2.3 (1.9-2.7)

Live birth order			
First	308 (49.0)	1062 (42.1)	1.5 (1.2-1.9)
Second	160 (25.4)	831 (32.9)	Reference
Third or more	161 (25.6)	632 (25.0)	1.3 (1.0-1.7)
5-minute Apgar score*			
<7	173 (30.7)	20 (0.9)	48.4 (30.1-77.8)
≥7	390 (69.3)	2183 (99.1)	Reference
Birth weight (grams)			
<2500	529 (83.3)	159 (6.3)	74.7 (57.4-97.2)
≥2500	106 (16.7)	2381 (93.7)	Reference
Gestational age (weeks)			
<37	536 (85.4)	278 (11.0)	47.1 (36.5-60.7)
≥37	92 (14.6)	2246 (89.0)	Reference

*California did not report data for 5-minute Apgar score

⁺OR indicates odds ratio; CI, confidence interval

Table 4. Summary of Multivariate Logistic Regression Analysis of Select Risk Factors for Diarrhea-Associated Infant Death as Compared with Infant Survivors, with and without 5-minute Apgar Score in the Model, United States, 2005-2006.

	Apgar Score Included in the Model*	Apgar Score not Included in the Model
Characteristic	OR (95%CI)+	OR (95%CI)+
Sex		
Female	Reference	--
Male	1.5 (1.1-2.0)	--
Live birth order		
First	--	1.0 (0.7-1.3)
Second	--	Reference
Third or more	--	1.6 (1.1-2.3)
5-minute Apgar score		
<7	14.1 (7.3-27.5)	--
≥7	Reference	--
Interaction		
Birth weight <2500g		
Maternal age ≤19 years	1.3 (0.7-2.6)	1.6 (0.9-2.9)
Maternal age 20-24 years	1.4 (0.8-2.5)	1.6 (0.9-2.6)
Maternal age 25-29 years	Reference	Reference
Maternal age ≥30 years	2.0 (1.2-3.5)	2.1 (1.3-3.5)

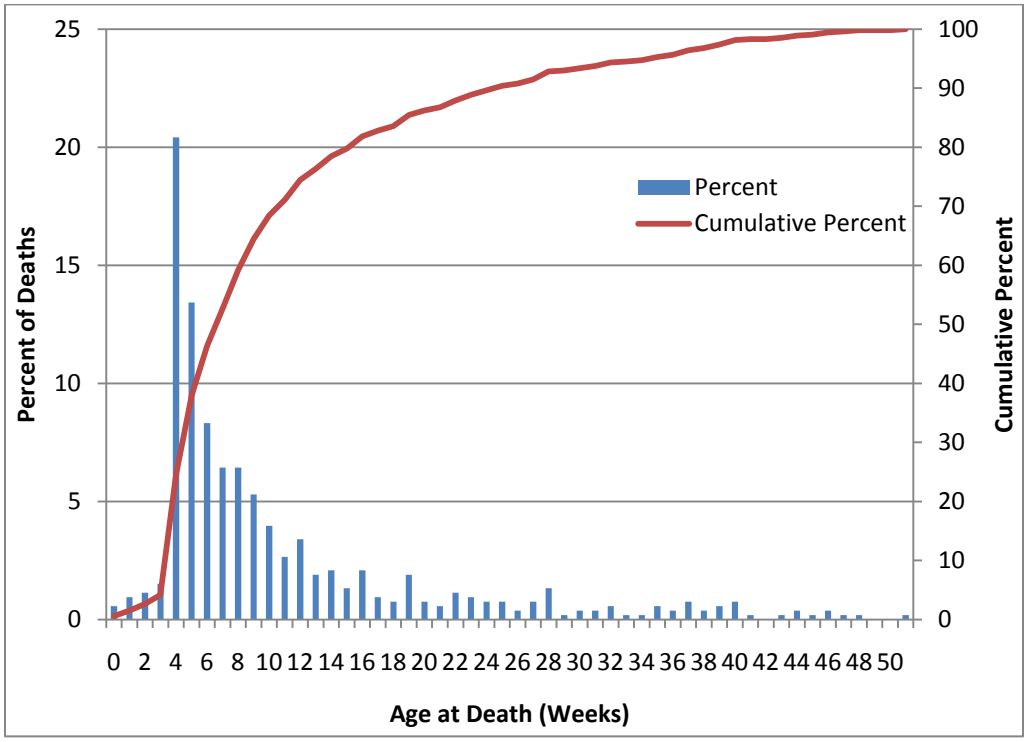
Birth weight ≥2500g		
Maternal age ≤19 years	3.4 (1.6-7.3)	2.7 (1.3-5.3)
Maternal age 20-24 years	2.7 (1.4-5.2)	2.0 (1.2-3.6)
Maternal age 25-29 years	Reference	Reference
Maternal age ≥30 years	1.6 (0.8-3.3)	1.0 (0.5-1.9)
Mother Married		
White Race	Reference	Reference
Black Race	1.7 (0.9-3.3)	2.1 (1.2-3.9)
Other Race	0.3 (0.1-0.8)	0.2 (0.1-0.5)
Mother Unmarried		
White Race	Reference	Reference
Black Race	2.1 (1.4-3.2)	2.3 (1.5-3.4)
Other Race	4.6 (1.9-11.5)	5.1 (2.2-11.5)
Female		
Non-Hispanic origin	--	Reference
Hispanic origin	--	0.7 (0.4-1.2)
Male		
Non-Hispanic origin	--	Reference
Hispanic origin	--	1.7 (1.1-2.6)

*5-minute Apgar score was included in the model; therefore the analysis is restricted to those records that reported Apgar score.

†OR indicates odds ratio; CI, confidence interval

Figure 1. Percent of Diarrhea-associated Deaths by Age at Death in Weeks among LBW Infants (A) and NBW Infants (B) in the United States, 2005 and 2006.

A. LBW Infants



B. NBW Infants