

# Hemolytic Uremic Syndrome and Death in Persons with *Escherichia coli* O157:H7 Infection, Foodborne Diseases Active Surveillance Network Sites, 2000–2006

L. Hannah Gould,<sup>1,a</sup> Linda Demma,<sup>1</sup> Timothy F. Jones,<sup>3</sup> Sharon Hurd,<sup>4</sup> Duc J. Vugia,<sup>5</sup> Kirk Smith,<sup>6</sup> Beletshachew Shiferaw,<sup>7</sup> Suzanne Segler,<sup>2</sup> Amanda Palmer,<sup>8</sup> Shelley Zansky,<sup>9</sup> Patricia M. Griffin<sup>1</sup>, and the Emerging Infections Program FoodNet Working Group

<sup>1</sup>Enteric Diseases Epidemiology Branch, National Center for Zoonotic, Vector-Borne, and Enteric Diseases, Centers for Disease Control and Prevention, and <sup>2</sup>Georgia Emerging Infections Program, Atlanta, Georgia; <sup>3</sup>Tennessee Department of Health, Nashville; <sup>4</sup>Connecticut Emerging Infections Program, New Haven; <sup>5</sup>California Department of Public Health, Richmond; <sup>6</sup>Minnesota Department of Health, St. Paul; <sup>7</sup>Oregon Department of Human Services, Portland; <sup>8</sup>Maryland Department of Health and Mental Hygiene, Baltimore; and <sup>9</sup>New York State Department of Health, Albany

**Background.** Hemolytic uremic syndrome (HUS) is a life-threatening illness usually caused by infection with Shiga toxin–producing *Escherichia coli* O157 (STEC O157). We evaluated the age-specific rate of HUS and death among persons with STEC O157 infection and the risk factors associated with developing HUS.

**Methods.** STEC O157 infections and HUS cases were reported from 8 sites participating in the Foodborne Diseases Active Surveillance Network during 2000–2006. For each case of STEC O157 infection and HUS, demographic and clinical outcomes were reported. The proportion of STEC O157 infections resulting in HUS was determined.

**Results.** A total of 3464 STEC O157 infections were ascertained; 218 persons (6.3%) developed HUS. The highest proportion of HUS cases (15.3%) occurred among children aged <5 years. Death occurred in 0.6% of all patients with STEC O157 infection and in 4.6% of those with HUS. With or without HUS, persons aged ≥60 years had the highest rate of death due to STEC O157 infection. Twelve (3.1%) of 390 persons aged ≥60 years died, including 5 (33.3%) of 15 persons with HUS and 7 (1.9%) of 375 without. Among children aged <5 years, death occurred in 4 (3.0%) of those with HUS and 2 (0.3%) of those without.

**Conclusions.** Young children and females had an increased risk of HUS after STEC O157 infection. With or without HUS, elderly persons had the highest proportion of deaths associated with STEC O157 infection. These data support recommendations for aggressive supportive care of young children and the elderly early during illness due to STEC O157.

Shiga toxin–producing *Escherichia coli* O157 (STEC O157) infection is the leading cause of hemolytic uremic syndrome (HUS) in the United States. HUS is a life-threatening illness characterized by hemolytic ane-

mia, thrombocytopenia, and renal insufficiency, and it is the most common cause of acute renal failure among children in the United States [1]. Except for supportive care and dialysis, no specific treatment exists for STEC O157 infection and HUS.

Several studies have explored risk factors for developing HUS among persons with STEC O157 infection. Most studies [2–4], but not all [5], have shown young children (age, <5 years) to be at the highest risk of developing HUS, although these studies have largely focused on the development of HUS in children, and few analyses have included adults. To our knowledge, the mortality rate for STEC O157 infection and for

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<sup>a</sup> Present affiliation: Malaria Branch, National Center for Zoonotic, Vector-Borne, and Enteric Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia.

Reprints or correspondence: Dr L. Hannah Gould, Enteric Diseases Epidemiology Branch, 1600 Clifton Rd NE, MS F-22, Atlanta GA, 30333 (lgould@cdc.gov).

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STEC O157-associated HUS has not been reported by age group. Population-based studies that include adults are needed.

The Foodborne Diseases Active Surveillance Network (FoodNet) is a collaborative project among the Centers for Disease Control and Prevention, participating state health departments, the US Department of Agriculture, and the US Food and Drug Administration, with a catchment area in 2006 of ~45 million persons. We reviewed active, population-based surveillance for STEC O157 infection and active, provider-based surveillance for HUS to determine the proportion of persons with STEC O157 infection who developed HUS, to explore demographic risk factors for development of HUS, and to assess mortality rates by age.

## METHODS

**Surveillance.** During the period 2000–2006, FoodNet conducted active laboratory-based surveillance for STEC O157 infections in Connecticut, Georgia, Maryland, Minnesota, Oregon, and Tennessee, and selected counties in California and New York. FoodNet personnel routinely contacted all clinical laboratories (>500) serving the FoodNet sites to ascertain all cases of STEC O157 infection among residents. A report form that collected information on demographic characteristics (eg, age or gender) and clinical outcomes (eg, hospitalization or death  $\leq 7$  days after specimen collection) was completed for each infection.

HUS is a reportable condition in all FoodNet sites; cases involving pediatric patients (age, <18 years) and adults are routinely ascertained through passive surveillance. To enhance case finding, FoodNet also conducted active, provider-based surveillance for clinically diagnosed postdiarrheal pediatric HUS cases. FoodNet personnel routinely contacted all pediatric nephrologists practicing in the FoodNet sites at least monthly to ascertain cases. In California, Georgia, Minnesota, and New York, infection control practitioners were also routinely contacted to report pediatric and adult cases. To confirm complete case ascertainment, hospital discharge data from 2000–2006 were reviewed to ascertain cases using *International Classification of Diseases, Ninth Revision*, codes 283.11 (hemolytic uremic syndrome); 584.X, 283.X, and 287.X (acute renal failure, acquired hemolytic anemia, and purpura/other hemorrhagic conditions); 446.6 (thrombotic thrombocytopenic purpura); 008.X (diarrhea caused by *E. coli*); and 009.X (infectious colitis enteritis and gastroenteritis or diarrhea of presumed infectious origin). All possible HUS cases were validated by medical record review. A case report form was completed for each case by contacting the patient's physician and by medical record review. For cases identified by hospital discharge data review, this form might have been completed several years after a patient's illness. A report form that collected information on demographic characteristics (eg, age or gender) and clinical outcomes (eg, hos-

pitalization or death at time of hospital discharge) was completed for each case.

**Case definitions.** A case of STEC O157 infection was defined as the isolation from a stool specimen of a resident of a FoodNet site of *E. coli* O157 which had the H7 antigen, produced Shiga toxin, or had a gene that codes for Shiga toxin production.

Persons with physician-diagnosed postdiarrheal HUS or thrombotic thrombocytopenic purpura were considered to be confirmed cases if they met the following criteria: diarrhea with onset in the 21 days before the diagnosis of HUS or thrombotic thrombocytopenic purpura; anemia [6]; platelet count, <150,000 platelets/mm<sup>3</sup>; acute renal impairment (serum creatinine level of  $\geq 1.0$  mg/dL in patients aged <13 years or creatinine level of  $\geq 1.5$  mg/dL in patients aged  $\geq 13$  years), and microangiopathic changes consistent with hemolysis on peripheral blood smear (eg, schistocytes, burr, or helmet cells) [7]. Persons were considered to be probable cases if they met all of the above criteria except that microangiopathic changes were not documented. Both confirmed and probable cases were included in the analysis. Only cases of HUS in persons who met the case definition for STEC O157 infection were included in this analysis.

**Analysis.** Data from FoodNet surveillance for STEC O157 were linked to data from the HUS surveillance system to determine the proportion of patients with STEC O157 infection who developed HUS. Cases were analyzed for proportion and incidence by age group, FoodNet site, HUS status, and for proportions hospitalized and died. Age group categories (<5, 5–9, 10–17, 18–59, and  $\geq 60$  years) were created to examine the risk of HUS and death in young children, older children, adults, and elderly persons. The Wilcoxon Rank-sum test was used to assess the differences in age and length of hospital stay between STEC O157-infected patients with and without HUS. Differences in categorical variables were examined using the Fisher exact test or the  $\chi^2$  test. A stepwise logistic regression model was used to examine factors associated with HUS. Factors significant at the .10 level, including state, age (<5 vs  $\geq 5$  years), and sex, were entered into the model. Variables remained in the model if the *P* value from its residual  $\chi^2$  test was <.05. The 2-sided *P* value was reported. A separate model was also used to assess factors associated with HUS in adults (age,  $\geq 18$  years). All statistical analyses were performed with SAS software, version 9.1 (SAS Institute).

## RESULTS

**Cases of STEC O157 infection.** During 2000–2006, a total of 3464 culture-confirmed cases of STEC O157 infection were ascertained. Of those, 1854 (54%) were in females. The median age of patients was 15 years: 25% were aged <5 years, 15% were aged 5–9 years, 16% were aged 10–17 years, 32% were

aged 18–59 years, and 11% were aged  $\geq 60$  years. The average incidence was 1.5 cases per 100,000 persons, but the incidence of STEC O157 infection varied by site and age group (Table 1). In every site, the highest incidence was among children aged  $< 5$  years, with a mean incidence in this group of 5.6 cases per 100,000 persons, ranging from 1.4 cases per 100,000 persons in Georgia to 11.5 cases per 100,000 persons in Oregon. Among children aged  $< 5$  years, the incidence was highest among children aged 1 year (6.9 cases per 100,000 persons) and lowest among children aged  $< 1$  year (1.8 cases per 100,000 persons).

Of the 3464 persons with STEC O57 infection, 1449 (42%) were hospitalized (36% of those aged  $< 5$  years, 38% of those aged 5–9 years, 38% of those aged 10–17 years, 42% of those aged 18–59 years, and 66% of those aged  $\geq 60$  years). Persons aged  $< 18$  years were the least likely to be hospitalized ( $P = .004$ ) while persons aged  $\geq 60$  years old were most likely to be hospitalized ( $P < .001$ ).

**STEC O157 infections that resulted in HUS.** Of the 3464 STEC O157 cases ascertained, 218 (6.3%) had HUS, including 159 confirmed and 59 probable cases. Persons with confirmed or probable HUS were similar with respect to sex (61.0% and 67.8% female, respectively;  $P = .36$ ) and age (median 3 and 4 years, respectively;  $P = .61$ ). In most sites,  $< 30\%$  of cases were classified as probable, with the exception of Minnesota and Tennessee where 39.0% and 51.7%, respectively, were classified as probable. Of the 217 HUS cases with information on mode of ascertainment, 194 (89.4%) cases were ascertained through active surveillance, 11 (5.1%) were ascertained through hospital discharge data review only, and 12 (5.5%) were ascertained through another means; confirmed and probable cases did not differ with regards to mode of ascertainment. Confirmed and probable cases were grouped for further analyses.

The proportion of patients with STEC O157 infection and HUS varied by site, from 4.9% in New York to 9.4% in Tennessee. By age group, the percentage was 15.3% among patients aged  $< 5$  years, 7.9% among those aged 5–9 years, 3.4% among those aged 10–17 years, 1.2% among those aged 18–59 years,

and 3.8% among those aged  $\geq 60$  years (Figure 1). The incidence of HUS was 0.28 cases per 100,000 persons aged  $< 18$  years and 0.85 cases per 100,000 children aged  $< 5$  years. Among children  $< 5$  years old, the incidence of HUS was highest in children aged 1 year (1.24 cases per 100,000 children) and lowest in children  $< 1$  year old (0.09 cases per 100,000 children).

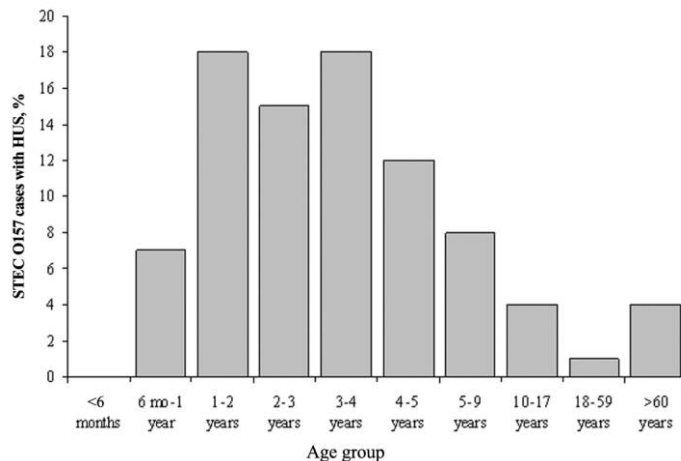
The median age of patients who developed HUS was 4 years (range,  $< 1$  to 87 years), compared with 16 years for those who did not (range,  $< 1$  to 93 years;  $P < .001$  (Table 2). All patients with HUS were hospitalized, compared with 38% of patients without HUS. The median length of hospitalization was 10 days (range, 1–85 days) for persons with HUS. Compared with persons who did not develop HUS, those with HUS were younger, more likely to be female, more likely to be hospitalized, had a longer length of hospital stay, and were more likely to die (Table 2).

In multivariate analysis, age  $< 5$  years and female sex were associated with an increased risk of HUS (odds ratio [OR], 5.37 [95% confidence interval {CI}, 4.04–7.14] and 1.70 [95% CI, 1.27–2.27], respectively). State was also significant ( $P < .01$ ) and was treated as a confounder. When the multivariate analysis was restricted to adults (age,  $\geq 18$  years), both age  $\geq 60$  years and female sex were associated with an increased risk of HUS (OR, 3.18 [95% CI, 1.50–6.77] and 5.26 [95% CI, 1.58–17.53], respectively).

An additional 157 HUS cases without culture confirmation of STEC O157 infection were reported; three persons (1.9%) died. Of these 157 cases, culture for STEC O157 was performed for 135 (86%), but STEC O157 was not isolated. Serologic testing was performed for 63 cases (40.1%); antibodies to STEC O157 were identified in 23 (14.6%). Non-O157 STEC was isolated from 9 patients, and other pathogens were isolated from 8 patients. These patients without culture confirmation of STEC O157 infection were less likely than those with culture confirmation to be female (53% vs 63%). The median age was 4 years in both groups; all of the persons with HUS and without

**Table 1. Incidence of Culture-Confirmed Shiga Toxin–Producing *Escherichia coli* O157 (STEC O157) Infection and Hemolytic Uremic Syndrome (HUS), by Age Group and Foodborne Diseases Active Surveillance Network Site, 2000–2006**

| Site        | Incidence, no. of cases per 100,000 persons, by age |                  |                        |                 |                        |                 |                         |                 |                        |                 |                         |                  |
|-------------|---|------------------|------------------------|-----------------|------------------------|-----------------|-------------------------|-----------------|------------------------|-----------------|-------------------------|------------------|
|             | $< 5$ years   |                  | 5–9 years              |                 | 10–17 years            |                 | 18–59 years             |                 | $\geq 60$ years        |                 | All sites               |                  |
|             | STEC O157<br>(n = 851)                              | HUS<br>(n = 135) | STEC O157<br>(n = 519) | HUS<br>(n = 43) | STEC O157<br>(n = 563) | HUS<br>(n = 23) | STEC O157<br>(n = 1128) | HUS<br>(n = 13) | STEC O157<br>(n = 396) | HUS<br>(n = 15) | STEC O157<br>(n = 3464) | HUS<br>(n = 229) |
| California  | 5.42  | 0.83             | 4.02                   | 0.22            | 1.88                   | 0.00            | 0.36                    | 0.00            | 0.72                   | 0.03            | 1.12                    | 0.07             |
| Connecticut | 3.73  | 1.00             | 3.38                   | 0.25            | 2.86                   | 0.07            | 0.57                    | 0.01            | 1.13                   | 0.07            | 1.31                    | 0.10             |
| Georgia     | 1.42  | 0.26             | 0.91                   | 0.09            | 0.58                   | 0.03            | 0.24                    | 0.00            | 0.15                   | 0.01            | 0.40                    | 0.03             |
| Maryland    | 1.85  | 0.35             | 1.30                   | 0.13            | 0.70                   | 0.00            | 0.29                    | 0.00            | 0.22                   | 0.04            | 0.50                    | 0.04             |
| Minnesota   | 11.12   | 1.36             | 6.40                   | 0.46            | 4.10                   | 0.14            | 1.85                    | 0.02            | 2.39                   | 0.09            | 3.13                    | 0.17             |
| New York    | 5.08  | 0.65             | 3.17                   | 0.20            | 2.49                   | 0.18            | 1.12                    | 0.01            | 0.99                   | 0.00            | 1.60                    | 0.08             |
| Oregon      | 11.53   | 1.45             | 5.82                   | 0.43            | 3.42                   | 0.11            | 1.45                    | 0.02            | 1.85                   | 0.00            | 2.66                    | 0.14             |
| Tennessee   | 4.40  | 0.88             | 2.01                   | 0.28            | 1.09                   | 0.03            | 0.48                    | 0.00            | 0.71                   | 0.06            | 0.95                    | 0.09             |
| Average     | 5.57  | 0.85             | 3.38                   | 0.26            | 2.14                   | 0.07            | 0.80                    | 0.01            | 1.02                   | 0.04            | 1.46                    | 0.09             |



**Figure 1.** Proportion of patients with Shiga toxin–producing *Escherichia coli* O157 (STEC O157) infection with hemolytic uremic syndrome (HUS), by age group, Foodborne Diseases Active Surveillance Network, 2000–2006.

culture confirmation of STEC O157 infection were children aged <18 years.

**STEC O157 infections that resulted in death.** The outcome was known for all persons with HUS and for 3103 (96%) of the 3246 persons without HUS. The 137 persons with an unknown outcome did not differ demographically from the rest of the patients. Twenty-one persons (0.6%) died (Table 3), including 11 (0.4%) of the 3098 persons who did not have HUS and 10 (4.6%) of the 218 persons with HUS. Deaths among persons with HUS occurred a median of 11 days after diarrhea began (range, 8–89 days); information on time to death was not available for persons without HUS.

Of the persons without HUS, mortality was highest among persons aged  $\geq 60$  years (1.9%). Among persons with HUS, the proportion of persons aged  $\geq 60$  years who died (33.3%) was 11-fold higher than the proportion of children aged <5 years who died (3.0%). More than one-half of STEC O157–infected persons aged  $\geq 60$  years who died did not have HUS. The proportion of persons aged  $\geq 60$  years who died increased with age: 3 (1.6%) of 193 persons aged 60–69 years old died, 4 (3.4%) of 118 persons aged 70–79 years died, and 5 (6.3%) of 79 persons aged  $\geq 80$  years died. Among children aged <5 years with HUS, girls were more likely than boys to die (4.0% vs 1.9%), but this difference was not statistically significant. All of the deaths among persons aged  $\geq 60$  years involved women: 5 (38.5%) of 13 women aged  $\geq 60$  years with HUS died, compared with none of 2 men aged  $\geq 60$  years with HUS.

## DISCUSSION

In this population-based study of STEC O157 infection, we found that young children and females had the highest risk of HUS following STEC O157 infection. Elderly persons had the highest rate of death associated with STEC O157 infection, with

or without HUS. These data support recommendations for aggressive supportive care of young children and elderly persons early during illness due to STEC O157.

To our knowledge, this is the first population-based study of demographic risk factors associated with developing HUS following STEC O157 infection conducted in the United States. The strengths of this study are that it included patients with both sporadic and outbreak-associated STEC O157 infections and that both children and adults were included. Because FoodNet provides a geographically diverse, active surveillance network for both culture-confirmed STEC O157 infections and clinically diagnosed HUS, this study provided an analysis of demographic risk factors for HUS that exceeds the scope of previous studies, most of which included only small sample sizes, were conducted during outbreaks, or focused on children.

Children aged <5 years had the highest rates of HUS following STEC O157 infection, confirming findings of smaller studies, most of which involved only children [2–4, 8–10]. This study also found a statistically significant association between female sex and the risk of developing HUS after STEC O157 infection. Although many studies have found no such association [4, 5, 10], we are aware of 3 other analyses in which female patients were more likely than male patients to develop HUS [8, 11, 12], although this was not confirmed by an extension of one of them [2]. Another study found that girls were more likely than boys to develop hemolytic anemia [13].

The high risk of death among elderly individuals is consistent with findings from previous studies [14, 15], but this is (to our knowledge) the first study to compare the magnitude of this risk across age groups. Persons aged  $\geq 60$  years were more likely to be hospitalized than were those in any other age group, and the proportion of persons aged  $\geq 60$  years with HUS who died was 10-fold higher than for all other age groups, providing

**Table 2. Comparison of Patients with Shiga Toxin–Producing *Escherichia coli* O157 Infection With and Without Hemolytic Uremic Syndrome (HUS)**

| Characteristic                                   | Persons with HUS | Persons without HUS | P <sup>a</sup> |
|--|------------------|---------------------|----------------|
| Age, median years (range)                        | 4 (<1 to 87)     | 16 (<1 to 93)       | <.001          |
| Age, <5 years                                    | 130/218 (59)     | 721/3239 (22)       | <.001          |
| Female sex                                       | 137/218 (63)     | 1717/3240 (53)      | .002           |
| Hospitalization                                  | 218/218 (100)    | 1238/3246 (38)      | <.001          |
| Duration of hospitalization, median days (range) | 10 (1–85)        | 3 (1–55)            | <.001          |
| Death  | 10/218 (5)       | 11/3109 (0.4)       | <.001          |

**NOTE.** Data are no. of patients with characteristic/no. with data available (%), unless otherwise indicated.

<sup>a</sup> The Wilcoxon rank-sum test was used to test for differences in median age and duration of hospitalization between persons with HUS and those without; the  $\chi^2$  test was used for the remaining variables.

quantitative data on the excess risk of death in the elderly population. More than one-half of deaths among persons aged  $\geq 60$  years were in those without HUS, underscoring the severity of STEC O157 infection in this age group. Early hospitalization and aggressive supportive care of elderly persons with this infection are essential.

Our finding that the incidence of STEC O157 infection differed by state has been noted before [16, 17]. The incidence of HUS cases also varied by state; overall, the states with the highest incidence of STEC O157 infection were those with the highest incidence of HUS, and vice versa. In addition to differences in surveillance and case ascertainment methods among FoodNet sites, STEC O157 infection appears to be more common in northern than southern US states [16]. Variations in laboratory testing may also contribute to geographic differences, and many cases of STEC O157 infection may not be detected. Cases of STEC O157 infection may be missed because persons did not seek care, because they did not submit a stool specimen, or because the clinical laboratory did not test the stool specimen for STEC O157. In 2000, only 57% of clinical laboratories in FoodNet sites routinely tested all stool specimens for STEC O157, and the proportion varied by site [18]. It has been estimated that >50% of the interstate variability in STEC O157 incidence in the FoodNet sites can be accounted for by differences in physician practices and laboratory culturing practices [17].

Our finding that the rate of hospitalization increased with age—in particular, that children aged <5 years were hospitalized the least frequently—could be because milder cases were disproportionately ascertained in younger age groups. This could occur if physicians are more likely to order STEC O157 tests for children or if laboratories only routinely test for STEC O157 in children, resulting in a bias towards pediatric cases of STEC O157 infection.

Variations in diagnosis of STEC O157 infections also result in many cases of diarrhea-associated HUS being ascertained without documentation of whether STEC O157 was respon-

sible. Although most cases of diarrhea-associated HUS are due to STEC O157 infection, typically only approximately two-thirds are confirmed by culture [7]. Overall, ascertainment of HUS cases is very good, because such patients are usually hospitalized; however, by the time a patient develops HUS, STEC O157 organisms may no longer be shed in the stool, contributing to an underestimation of the number of STEC O157–associated HUS cases. Serologic tests can help establish an etiology of STEC in persons with HUS [19]. Our finding of an additional 157 cases of HUS without culture confirmation of STEC O157, including 23 persons with serologic evidence of STEC O157 infection, supports this finding. Because this analysis included only cases with culture confirmation of STEC infection, we may have underestimated the proportion of persons with STEC O157 infection who developed HUS. In addition, 48 cases of STEC infection in persons with physician-diagnosed postdiarrheal HUS did not meet our case definition for definite or probable HUS, in some cases because of missing information; some of these persons probably truly had HUS (eg, 23 underwent dialysis).

We were unable to directly evaluate some putative predictors of HUS, including antibiotic use, elevated leukocyte count, and

**Table 3. Characteristics of Persons with Shiga Toxin–Producing *Escherichia coli* O157 Infection Who Died, by Age and Hemolytic Uremic Syndrome (HUS) Status**

| Age group        | No. of deaths/no. of persons (%) |                     |               |
|------------------|----------------------------------|---------------------|---------------|
|                  | Persons with HUS                 | Persons without HUS | All           |
| <5 years         | 4/130 (3.0)                      | 2/678 (0.3)         | 6/808 (0.7)   |
| 5–9 years        | 1/41 (2.4)                       | 0/450 (0.0)         | 1/491 (0.2)   |
| 10–17 years      | 0/19 (0.0)                       | 1/525 (0.2)         | 1/544 (0.2)   |
| 18–59 years      | 0/13 (0.0)                       | 1/1075 (0.1)        | 1/1088 (0.1)  |
| >60 years        | 5/15 (33.3)                      | 7/375 (1.9)         | 12/390 (3.1)  |
| All <sup>a</sup> | 10/218 (4.6)                     | 11/3103 (0.4)       | 21/3321 (0.6) |

<sup>a</sup> Information on age was not available for 6 persons without HUS.

Shiga toxin profiles [20], because the surveillance system does not collect these data. In addition, we could not review death certificates to directly attribute the causes of each death. Deaths that occurred outside the follow-up period would not have been reported. Because the surveillance population included only 15% of the US population in selected states, cases captured by this system may not be representative of all cases of STEC O157 infection or HUS in the United States [21]. Lastly, because active surveillance was conducted only for pediatric cases, the HUS surveillance system may have been more likely to detect cases of HUS in children than adults.

More information is needed for physicians to better predict the risk of HUS and death among persons with STEC O157 infection, especially among persons at the extremes of age. These data from FoodNet surveillance provide important evidence that early and aggressive supportive care is needed to prevent HUS and death in young children and elderly persons with STEC O157 infection. Health care providers should have a low threshold for aggressive oversight of patients in these high-risk groups. To diagnose STEC infection, all stool specimens submitted for diagnosis of acute community-acquired diarrhea (*Salmonella*, *Shigella*, and *Campylobacter* species) should be cultured for O157 STEC on selective and differential agar and assayed for non-O157 STEC with tests that detects the Shiga toxins. Clinical laboratories should promptly report positive findings for STEC to the physician and to public health authorities [22].

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