Strategies for Surveillance of Pediatric Hemolytic Uremic Syndrome: Foodborne Diseases Active Surveillance Network (FoodNet), 2000–2007

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Background. Postdiarrheal hemolytic uremic syndrome (HUS) is the most common cause of acute kidney failure among US children. The Foodborne Diseases Active Surveillance Network (FoodNet) conducts population-based surveillance of pediatric HUS to measure the incidence of disease and to validate surveillance trends in associated Shiga toxin–producing *Escherichia coli* (STEC) O157 infection.

Methods. We report the incidence of pediatric HUS, which is defined as HUS in children <18 years. We compare the results from provider-based surveillance and hospital discharge data review and examine the impact of different case definitions on the findings of the surveillance system.

Results. During 2000–2007, 627 pediatric HUS cases were reported. Fifty-two percent of cases were classified as confirmed (diarrhea, anemia, microangiopathic changes, low platelet count, and acute renal impairment). The average annual crude incidence rate for all reported cases of pediatric HUS was 0.78 per 100 000 children <18 years. Regardless of the case definition used, the year-to-year pattern of incidence appeared similar. More cases were captured by provider-based surveillance (76%) than by hospital discharge data review (68%); only 49% were identified by both methods.

Conclusions. The overall incidence of pediatric HUS was affected by key characteristics of the surveillance system, including the method of ascertainment and the case definitions. However, year-to-year patterns were similar for all methods examined, suggesting that several approaches to HUS surveillance can be used to track trends.

Hemolytic uremic syndrome (HUS) is a severe sequela of Shiga toxin–producing *Escherichia coli* (STEC) O157 infection characterized by hemolytic anemia, thrombocytopenia, and kidney failure. More than 90% of HUS cases follow a diarrheal illness and most are attributable to STEC O157 infection [1]. HUS is the most common cause of acute renal failure among US children <5 years of age [2, 3]; of the estimated 93 000 domestically acquired STEC O157 infections in the United States each year [4], approximately 6% will develop HUS [2]. The mortality rate is approximately 5% [2]. HUS may result in major long-term complications, including chronic renal failure, neurologic dysfunction, and hypertension [5]. Providing appropriate supportive care in a timely manner improves outcomes [6].

Surveillance for HUS provides a way to monitor trends in STEC O157 infections, can help to assess which strains of STEC are associated with severe outcomes, and can evaluate whether improvements in

medical care are leading to less frequent development of HUS in children infected with STEC. For example, trends in STEC O157 infections can be influenced by changes in diagnostic practices. By providing a stable marker of STEC incidence, HUS surveillance can be used to determine the effectiveness of preventive measures. HUS surveillance is complicated by the lack of a single diagnostic test and the need for multiple data elements to validate each reported case. The significance of HUS as a public health issue was reflected in the Healthy People 2010 goal to reduce the incidence of postdiarrheal HUS among children <5 years of age by 50% (to 0.9 cases per 100 000) [7]. The Foodborne Diseases Active Surveillance Network (FoodNet) conducts active surveillance for HUS in children <18 years using 2 complementary case ascertainment methods. We compare the finding of these 2 methods of case ascertainment and the impact of different case definitions on surveillance data from 2000 to 2007.

METHODS

FoodNet is a collaborative program among the Centers for Disease Control and Prevention, 10 participating state health departments, the US Department of Agriculture's Food Safety and Inspection Service, and the US Food and Drug Administration. FoodNet began in 1996 with 5 sites (California, Connecticut, Georgia, Minnesota, and Oregon) and by 2004 had grown to 10 sites (with the addition of Colorado, Maryland, New Mexico, New York, and Tennessee). FoodNet sites conduct active, population-based surveillance for pediatric HUS (HUS in children <18 years of age) among residents of the FoodNet catchment areas. Until 2007, cases of HUS without a history of diarrhea preceding the illness were also included in surveillance. Cases of thrombotic thrombocytopenic purpura (TTP) were also included because TTP diagnosed after a diarrheal illness is usually caused by infection with STEC O157 or another STEC, and thus likely represents HUS [8].

Case Finding
Cases of HUS among residents of the FoodNet catchment area were ascertained in 2 ways. First, FoodNet personnel routinely contacted an established network of pediatric nephrologists and hospital infection control practitioners to identify patients with a physician diagnosis of HUS (provider-based surveillance). Second, FoodNet sites conducted periodic reviews of hospital discharge data (HDD) to supplement case finding. HDD review was implemented in 2004 and was conducted retrospectively to identify HUS cases occurring since 2000 that may have been missed by the first method. All FoodNet sites conducted HDD reviews, with the exception of

New Mexico. Possible cases were identified from hospital records by *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes: 283.1 (hemolytic uremic syndrome); 584.X, 283.X, and 287.X (acute renal failure with hemolytic anemia and thrombocytopenia); and 446.6 and 008.X, or 446.6 and 009.X (TTP with diarrhea caused by *E. coli* or an unknown pathogen) [9]. FoodNet personnel obtained lists of patients with the specified *ICD-9-CM* codes after annual hospital discharge data were available at each hospital within their site. Medical record reviews were performed for all possible cases that were not previously reported through provider-based surveillance.

A standard case report form was used to collect information for all persons with HUS, including demographics (age, race, sex), dates of hospitalization, month of specimen collection, antimicrobial use, results of laboratory tests for STEC and other pathogens, outcome, date of HUS diagnosis, and date of entry into the FoodNet surveillance system.

Case Definitions
We classified cases as confirmed, probable, and suspected. Confirmed cases met all of the following 5 criteria: (1) diarrhea with onset in the 3 weeks before HUS or TTP diagnosis; (2) anemia [10, 11]; (3) microangiopathic changes consistent with hemolysis on peripheral blood smear (eg, schistocytes or helmet cells); (4) platelet count <150 000 platelets/mL; and (5) acute renal impairment (age ≤12 years: creatinine ≥1 mg/dL; age ≥13: creatinine ≥1.5 mg/dL) [12]. Cases that met all criteria except documented microangiopathic changes were considered probable cases. All other illnesses diagnosed by a physician as HUS were considered suspected cases.

Analysis
We calculated crude incidence rates per 100 000 persons, overall and by site and age, from 2000 to 2007, using population estimates from the US Census Bureau [13]. We summarized the crude incidence rate by case definition and method of ascertainment (provider-based surveillance, HDD review, or both). Cases were excluded from analyses by method of ascertainment in instances where the method of ascertainment was not recorded. We calculated the time that elapsed between the date of HUS diagnosis and the date the case was entered into FoodNet HUS surveillance. We calculated season by the month of HUS diagnosis, where June–August was classified as summer, September–November was classified as fall, December–February was classified as winter, and March–May was classified as spring. We summarized the proportion of patient demographics, illness severity, and laboratory findings for each case definition and method of ascertainment. We used a χ^2 test to determine if there was

a significant difference of at least $P < .05$ among the case definition and the method of ascertainment for each characteristic. The analysis was conducted using SAS software version 9.1.3 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 627 physician-diagnosed pediatric HUS cases were reported to the FoodNet HUS surveillance system during 2000–2007. An average of 78 cases was reported each year (range, 54–110). Most cases (66%; 416) were in children <5 years old; of these, 64% were in children <2 years old. Fifty-six percent (350) were female. The overall incidence rate was 0.78 per 100 000 children. Incidence was highest in children <5 years old (1.9 per 100 000 persons). The highest incidence rates were in Oregon (1.3), Minnesota (1.1), and Tennessee (1.0); the lowest rates were in Georgia and Maryland (0.4).

Of all reported cases, 326 (52%) were classified as confirmed, 53 (8%) as probable, and 248 (40%) as suspected (Table 1). Confirmed, probable, and suspected cases were reported every year. The proportion of cases classified as confirmed in each site ranged from 40% to 67%, the proportion of cases classified as probable ranged from 3% to 30%, and the proportion classified as suspected ranged from 29% to 49%. Among the 248 suspected cases, evidence of microangiopathic changes was the criterion most commonly not met or missing (50% not met, 5% missing), followed by evidence of renal injury, (37% not met, 9% missing), or anemia (31% not met, 8% missing). Sixty-nine (28%) suspected cases did not report diarrhea in the 3 weeks before HUS diagnosis and an additional 5 were missing information on this criterion. Among suspected cases, there were 176 (71%) with 1 criterion not met or missing, 49 (20%) with 2 criteria not met or missing, 2 (8%) with 3 criteria not met or missing, and 3 (1%) with 4 criteria not met or missing.

We compared the crude incidence rates by year for confirmed cases, confirmed and probable cases, and confirmed, probable, and suspected cases (Figure 1A). Regardless of the case definition used, the year-to-year pattern of incidence appeared similar. When both confirmed and probable cases were included, the annual incidence rate was an average of 16% (range, <1%–32%) higher than the rate when only confirmed cases were used. However, the annual incidence rate when all cases (confirmed, probable, and suspected) were included was an average of 92% (range, 81%–119%) higher than the rate calculated with only confirmed cases. Inclusion of both probable and suspected cases did not change the rank order of incidence among sites or in children <5 years.

Two FoodNet sites (Connecticut and Minnesota) had state restrictions to medical record access that limited their ability to conduct HDD review, and therefore, 123 (20%) cases were excluded from our comparison of ascertainment methods. Among the 504 cases for which a method of ascertainment was verified, 76% were captured by provider-based surveillance and 68% were captured by HDD review (Figure 2). Two hundred forty-nine (49%) were identified independently by both provider-based surveillance and HDD review, 136 (27%) were found only by provider-based surveillance, and 96 (19%) were found only by HDD review (Figure 2). An additional 23 cases were found by other means (ie, during an outbreak or during routine STEC surveillance). The proportion of cases identified by provider-based surveillance that were confirmed or probable (55%) was slightly higher than the proportion identified by HDD review (49%), but this difference was not statistically significant (Table 1). At 4 sites (Colorado, Georgia, Maryland, and New York), provider-based surveillance identified a disproportionately greater number of confirmed and probable cases, while in one (Oregon), HDD review identified more cases (Figure 3). The percentage of cases found by both methods ranged from 19% in

Table 1. Number and Proportion of Hemolytic Uremic Syndrome Cases by Method of Ascertainment and Case Definition, FoodNet, 2000–2007

	Method of Ascertainment			
	Provider-Based	Hospital Discharge Data Review	Other or Unknown[a]	All Cases
Case definition				
Confirmed	210 (55)	168 (49)	82 (56)	326 (52)
Probable	36 (9)	29 (8)	14 (10)	53 (8)
Suspected	139 (36)	148 (43)	50 (34)	248 (40)
Total	385	345	146	627

All data are presented as no. (%).

[a] The method of ascertainment could not be confirmed for 123 cases. Twenty-three cases that were identified through other means (ie, outbreak, routine surveillance for Shige toxin–producing *Escherichia coli*) were also reported.
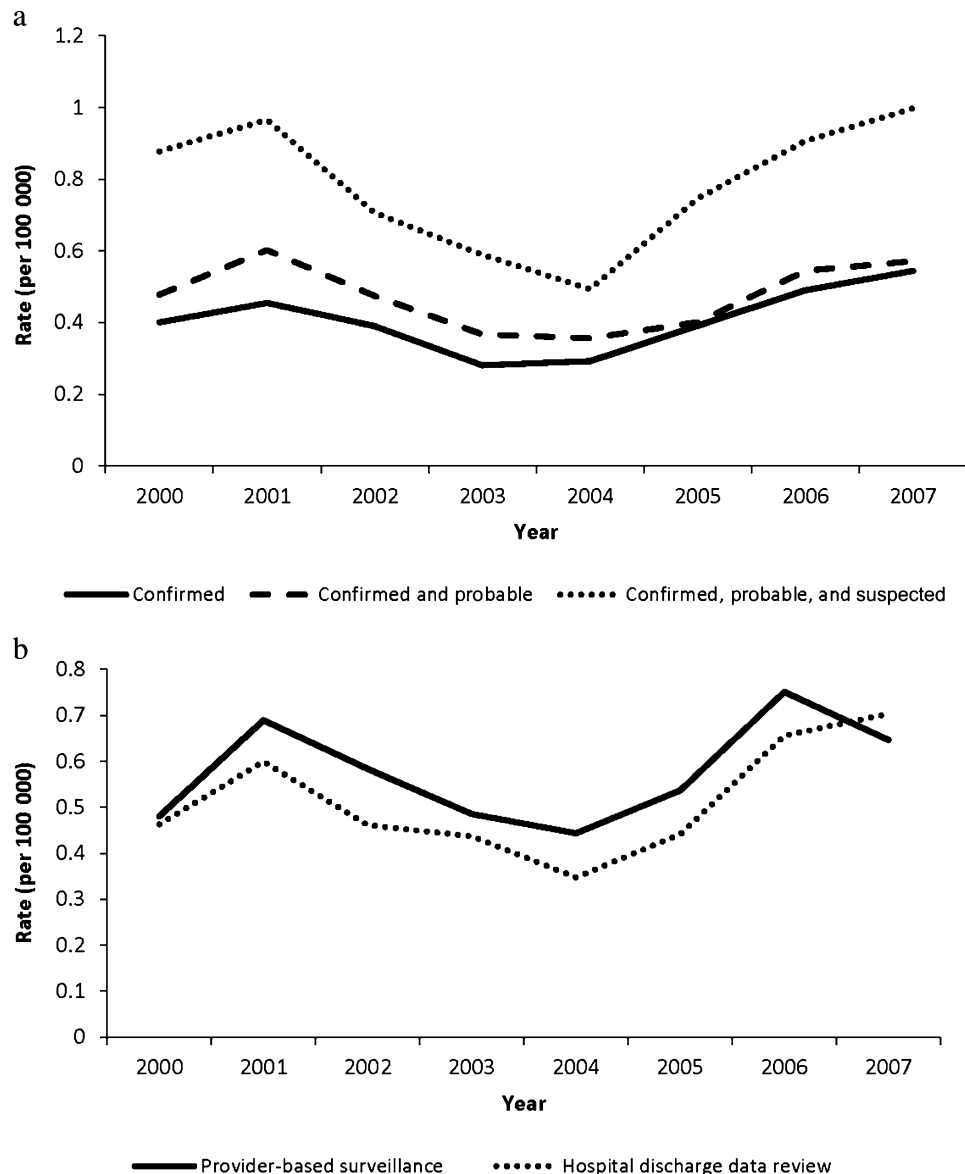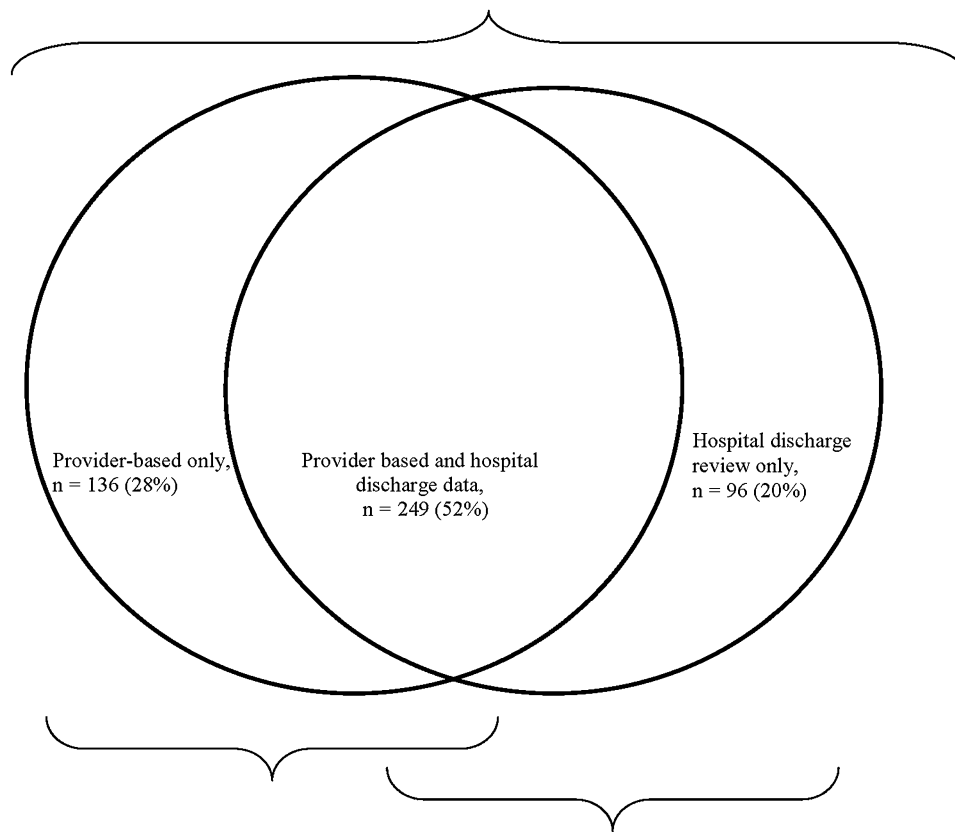
Figure 1. *A*, Comparison of hemolytic uremic syndrome rates in children <18 years old, by year and case definition, FoodNet, 2000–2007. *B*, Comparison of hemolytic uremic syndrome rates in children <18 years old, by year and method of ascertainment, FoodNet, 2000–2007.

Colorado to 89% in Oregon. When the crude incidence rates of cases captured by provider-based surveillance and HDD review were compared, the year-to-year pattern appeared similar from 2000 to 2006. In 2007, there was a higher rate among cases captured by HDD review than provider-based surveillance (Figure 1*B*).

Of the 615 reported HUS cases with complete information on dates of illness onset and case ascertainment, the median duration from the date of illness onset to the entry of data into the surveillance system was 2 months. There were 470 (76%) cases entered into the system within 1 year of diagnosis and 535 (85%) within 2 years. Among cases with a verified method

of ascertainment, 79% of those identified by HDD review were entered into the surveillance system within 2 years, compared with 95% of those captured by provider-based surveillance. Most (315, 82%) cases captured by provider-based surveillance were entered into the HUS surveillance system within 6 months of diagnosis.

We compared demographics, illness severity, and laboratory test findings by case definition and method of ascertainment (Table 2). Compared with suspected cases, a higher proportion of confirmed cases were in children <5 years old (71% versus 59%, *P* < .01) and occurred in the summer months (48% versus 33%, *P* < .01). Confirmed cases were

All cases with information on mode of ascertainment, n = 504

| Provider-based only, n = 136 (28%) | Provider based and hospital discharge data, n = 249 (52%) | Hospital discharge review only, n = 96 (20%) |

Figure 2. Venn diagram illustrating the proportion of hemolytic uremic syndrome cases identified through provider-based surveillance and hospital discharge data review, FoodNet, 2000–2007.

also more likely than suspected cases to undergo dialysis (57% versus 34%, $P < .0001$) and to have a stool specimen obtained (97% versus 79%, $P < .0001$) or one cultured for STEC O157 (93% versus 72%, $P = .04$). Cases identified by provider-based surveillance were more likely than those identified by HDD review to occur during the summer months (48% versus 41%, $P = .04$), to have had bloody diarrhea (77% versus 66%, $P < .01$), to have any stool specimen obtained (94% versus 87%, $P < .01$), and to have a stool specimen that was tested for Shiga toxin (40% versus 31%, $P < .01$).

DISCUSSION

The findings of the FoodNet HUS surveillance system were affected by key characteristics of the surveillance system, including the methods for case ascertainment and classification. However, year-to-year patterns were similar for all methods examined, suggesting that although the sensitivity and specificity of the various approaches for HUS surveillance vary, several methods can be used to track trends. For

FoodNet, a central goal of HUS surveillance is to provide accurate information on trends over time to monitor progress toward meeting public health goals. Selection of the optimal surveillance strategy for HUS depends on balancing the best possible sensitivity and positive predictive value with available resources. Because surveillance for syndromes such as HUS is challenging because of the lack of a single diagnostic test, detailed clinical and laboratory information is needed to validate the reported diagnosis. Additionally, the performance characteristics of the case definition will vary based on the level of clinical and laboratory detail that are available. Thus, it is important to evaluate the various factors that affect the findings of the system by using different surveillance methods to find cases.

The magnitude of the incidence rate reported by the FoodNet HUS surveillance system varied by as much as 92% depending on how cases were classified. Although all persons with HUS were identified through a provider network or were found using hospital discharge codes for HUS and related conditions, almost half were classified as suspected
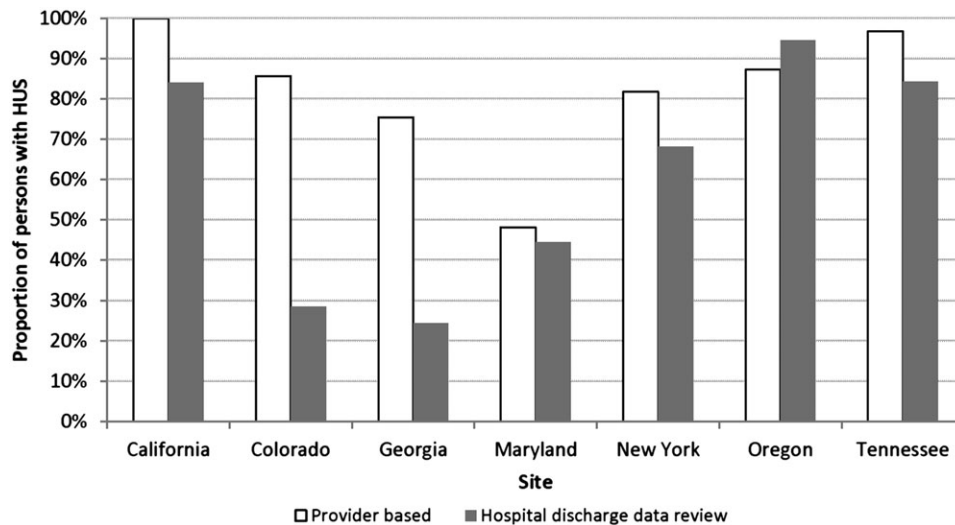
Figure 3. Proportion of confirmed and probable hemolytic uremic syndrome cases ascertained by provider-based surveillance and hospital discharge data review, by site, FoodNet, 2000–2007 (N = 481). Categories are not mutually exclusive—cases could be identified by either or both methods. Percentage of cases identifed by both methods: California, 80%; Colorado, 19%; Georgia, 25%; Maryland, 19%; New York, 82%; Oregon, 89%; Tennessee, 64%. Three FoodNet sites (Connecticut, Minnesota, New Mexico) had state restrictions to medical record access that limited their ability to conduct hospital discharge data review. Abbreviation: HUS, hemolytic uremic syndrome.

using our definitions. However, regardless of the case definition, the interpretation of trends remained the same, suggesting that the system would yield similar incidence patterns independent of ascertainment methods or case definition. The use of a more sensitive, less specific case definition for HUS that did not require laboratory evidence of HUS likely led to the inclusion of some persons without HUS, as well as many with less severe HUS, as evidenced by the considerably lower dialysis requirements of children meeting only the suspected case definition. Conversely, the use of a less sensitive, more specific case definition (confirmed cases only) would likely result in a failure to include some true HUS cases. All case definitions showed similar changes in HUS rates at FoodNet sites over time.

Provider-based surveillance was the more sensitive method of case ascertainment, contributing 28% more cases than HDD review alone. However, using HDD review to supplement active surveillance increased the total number of cases by 19%. In a perfect world, all cases of HUS would be identified by both methods. However, we observed considerable site-to-site variation in the proportion of cases found by each method, illustrating potential gaps in surveillance that require improvement. Using multiple methods of case ascertainment periodically can also help to validate the effectiveness of surveillance.

Cases found by HDD review were less likely to be confirmed than those found by provider-based surveillance. This was likely due, in part, to the use of broad discharge codes to

identify potential HUS cases for surveillance purposes. Because the FoodNet form did not collect information on the specific codes that were used to identify each case, it was not possible to look at the sensitivity of each code by the level of case classification. However, most of the other case characteristics were similar, regardless of the mode of ascertainment, suggesting that either method will capture a similar cross-section of cases. Differences in the proportion of cases where stool was tested for Shiga toxin indicate that providers should be informed about the importance of testing for Shiga toxin.

Several factors determine the optimal strategy for HUS surveillance. While provider-based surveillance is timelier than HDD review, extensive resources are necessary to establish and maintain relationships with healthcare providers. Although less timely, HDD review can be a valuable surveillance tool for illnesses that frequently result in hospitalization, are rare, or have severe outcomes [14–16]. HDD review can be done only once annually, although issues of restricted access to medical records can delay the process. In the case of some FoodNet sites, this resulted in delays of >2 years until a case was reported, or not having access to the patient-level clinical data needed to confirm the HUS diagnosis because some sites were only allowed access to aggregate data on HUS cases that were identified through HDD review. These issues might make HDD review prohibitive for other states that are considering strengthening or expanding HUS surveillance.

Table 2. Comparison of Characteristics of Cases of Hemolytic Uremic Syndrome by Case Definition and Method of Case Ascertainment, FoodNet, 2000–2007

Characteristic	Case Definition				Method of Ascertainment		
	Confirmed (n = 326) No. (%)	Probable (n = 53) No. (%)	Suspected (n = 248) No. (%)	P Value	Provider-Based (n = 385) No. (%)	Hospital Discharge Data Review (n = 345) No. (%)	P Value
Median age, years	3	3	4	…	3	3	…
Age <5 years	230 (71)	39 (74)	147 (59)	<.01	276 (72)	237 (69)	.42
Female	175 (54)	33 (62)	142 (57)	.40	223 (58)	195 (57)	.71
June–August (summer)	157 (48)	22 (42)	82 (33)	<.01	185 (48)	140 (41)	.04
Illness severity							
Death	9 (3)	0 (0)	10 (4)	…[c]	10 (3)	8 (2)	.82
Median days hospitalized	12	13	10	…	12	11	…
Bloody diarrhea	253 (78)	48 (91)	137 (55)	.18	297 (77)	229 (66)	<.01
Dialysis	186 (57)	31 (58)	85 (34)	<.01	202 (52)	159 (46)	.09
Laboratory testing							
Stool specimen obtained	315 (97)	51 (96)	197 (79)	<.01	360 (94)	300 (87)	<.01
Stool tested for Shiga toxin[a]	160 (49)	29 (55)	88 (53)	.16	155 (40)	106 (31)	<.01
Stool positive for Shiga toxin[b]	100 (63)	25 (86)	63 (72)	.11	114 (74)	75 (71)	.67
Stool cultured for STEC O157[a]	303 (93)	49 (92)	179 (72)	.04	346 (90)	279 (81)	.08
STEC O157 isolated from stool[b]	162 (53)	32 (65)	110 (61)	.07	212 (61)	155 (56)	.16
Stool cultured for STEC non-O157[a]	40 (12)	2 (4)	12 (5)	…[c]	28 (7)	15 (4)	.16
STEC non-O157 isolated from stool[b]	9 (23)	2 (100)	2 (17)	…[c]	6 (21)	5 (33)	.47
Serum collected	47 (14)	7 (13)	28 (11)	.05	73 (19)	55 (16)	.33
Serum positive for STEC LPS[b]	42 (89)	7 (100)	23 (82)	.20	50 (68)	39 (71)	.56

Abbreviations: LPS, lipopolysaccharide; STEC, Shiga toxin–producing *Escherichia coli*.

[a] Of stools obtained.

[b] Of stools tested/cultured.

[c] Cells too small to conduct a valid statistical test.

Because we limited our analysis only to the surveillance techniques used by the FoodNet surveillance system, our findings might not be comparable to other studies that found cases of HUS using other case definitions [17–21]. Despite the use of 2 surveillance techniques, it is likely that we missed cases and that other surveillance mechanisms could further enhance case finding. At some sites, the majority of cases were identified by only one method, suggesting that there may have been other cases that were missed. Surveillance for HUS is challenging, ideally requiring the use of multiple methods to detect trends over time and ascertain all cases. Health departments should consider available resources and data needs when choosing the optimal surveillance strategy.

Notes

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