FoodNet Estimate of the Burden of Illness Caused by Nontyphoidal Salmonella Infections in the United States

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To determine the burden of Salmonella infections in the United States, Foodborne Diseases Active Surveillance Network (FoodNet) investigators conducted population-based active surveillance for culture-confirmed Salmonella infections during 1996–1999 at FoodNet laboratories. In addition, all clinical microbiology FoodNet laboratories were surveyed to determine their practices for isolating Salmonella. Telephone interviews were also conducted among residents of the FoodNet sites to determine the proportion of persons with diarrheal illness who sought medical care and the proportion who submitted stool specimens for bacterial culture. Using our model, we estimated that there were 1.4 million nontyphoidal Salmonella infections in the United States, resulting in 168,000 physician office visits per year during 1996–1999. Including both culture-confirmed infections and those not confirmed by culture, we estimated that Salmonella infections resulted in 15,000 hospitalizations and 400 deaths annually. These estimates indicate that salmonellosis presents a major ongoing burden to public health.

Salmonellosis is an important public health problem in the United States. Estimates of the annual number of nontyphoidal Salmonella infections have ranged from 800,000 to 4,000,000 [1–4]: results of a recent study by the Centers for Disease Control and Prevention (CDC; Atlanta, GA) that was based in part on preliminary data from the Foodborne Diseases Active Surveillance Network (FoodNet), indicated that ~1,400,000 cases of salmonellosis occur annually [5]. Although most infections cause mild-to-moderate self-limited illness, serious disease resulting in death does occur. Outbreaks of nontyphoidal Salmonella infections and sporadic illness have been associated with a variety of causes, particularly foods of animal origin (e.g., beef, poultry, eggs, and dairy products)—also implicated are fruits and vegetables that have been contaminated with animal manure and contact with animals, including reptiles [6–14]. The costs associated with salmonellosis, including the costs of medical care and lost productivity, may approach several billion dollars annually [15]. In recent years, new strains of Salmonella, including multidrug-resistant Salmonella serotype Typhimurium definitive type 104 and Salmonella serotype Enteritidis phage type 4 have emerged in the United States and have increased in prevalence [16–18].

Surveillance for culture-confirmed Salmonella infections is important for monitoring incidence trends and detecting outbreaks of disease [5]. National public
health laboratory–based reporting for *Salmonella* infections was established in 1962 by the CDC, in collaboration with the Council of State and Territorial Epidemiologists and the Association of Public Health Laboratories. Although most culture-confirmed cases are reported to health officials, this surveillance system unavoidably underestimates the actual number of *Salmonella* infections as a result of surveillance artifacts. First, a person infected with *Salmonella* must develop symptoms that are severe enough for him or her to seek medical care. Second, the physician must request and collect a specimen from the patient and forward it to a microbiology laboratory for bacterial culture. Third, the laboratory must test the specimen appropriately for *Salmonella* using a sensitive method and, if *Salmonella* is identified, forward this isolate to a state public health laboratory for serotyping. Fourth, the state laboratory, in turn, must report the serotype result to CDC. Although ~30,000–40,000 culture-confirmed cases of nontyphoidal *Salmonella* are reported to CDC each year through the national surveillance system, these cases have been estimated to represent only 1%–5% of the actual number of nontyphoidal *Salmonella* infections that occur [2].

FoodNet was established in 1995 as part of CDC’s Emerging Infections Program [19–21]. FoodNet began as a collaborative study among CDC; the state health departments in California, Connecticut, Georgia, Minnesota, and Oregon; the US Department of Agriculture (USDA) Food Safety Inspection Service; and the US Food and Drug Administration Center for Food Safety and Applied Nutrition. A principal objective of FoodNet is to determine and monitor more precisely the burden of foodborne illnesses, including salmonellosis, through population-based active surveillance and related studies. More precise estimates of the burden of nontyphoidal *Salmonella* infections in the United States will allow public health officials to measure the benefits of foodborne disease–control programs and public health interventions more accurately. For example, the goal of the USDA Hazard Analysis Critical Control Point (HACCP) rule is to prevent human infections by reducing the prevalence of *Salmonella* on meat and poultry in the retail setting [22]. All slaughter plants in the United States with ≥500 employees implemented a HACCP plan by January 1998; these plants accounted for 75% of meat and poultry production. The implementation of HACCP plans in smaller plants followed. By monitoring the burden of human nontyphoidal *Salmonella* infections over time, FoodNet will be used to document the effectiveness of HACCP in reducing the number of cases of foodborne disease in the United States each year. For the present study, we used data from FoodNet population-based active surveillance and related surveys to estimate the actual number of nontyphoidal *Salmonella* infections and resultant physician office visits, hospitalizations, and deaths that occurred annually in the United States during 1996–1999.

**MATERIALS AND METHODS**

**Active surveillance.** To determine the number of *Salmonella* infections at the 5 original FoodNet surveillance areas (also called “FoodNet sites”), investigators conducted population-based active surveillance for culture-confirmed cases at the 264 microbiology laboratories that receive stool specimens for bacterial culture from residents of the FoodNet surveillance areas. These laboratories include both hospital-based and independent laboratories that are located within the FoodNet catchment areas and several large independent laboratories that are located outside the catchment areas. In 1996, FoodNet catchment areas included Minnesota, Oregon, and selected counties in California (San Francisco and Alameda), Connecticut (Hartford and New Haven), and Georgia (Clayton, Cobb, DeKalb, Douglas, Fulton, Gwinnett, Newton, and Rockdale); the surveillance population, based on 1996 postcensus estimates, was 14,281,096 persons (5.4% of the 1996 US population). In 1997, counties in Georgia (Barrow, Bartow, Carroll, Cherokee, Coweta, Fayette, Forsyth, Henry, Paulding, Pickens, Spalding, and Walton) and Connecticut (Fairfield) were added; the surveillance population, based on 1997 postcensus estimates, was 16,110,250 persons (6.0% of the 1997 US population). In 1998, all counties in Connecticut were included in surveillance; the population, based on 1998 postcensus estimates, increased to 17,173,617 persons. In 1999, the population in the FoodNet sites was 17,393,149 persons, according to 1999 postcensus estimates.

FoodNet investigators conduct frequent audits of laboratory records to ensure complete case ascertainment. Case-report forms are completed for any isolation of *Salmonella* from any specimen source (except urine) that occurs ≥30 days after the previous isolation of *Salmonella*. We excluded cases of *Salmonella* that had been isolated from urine from our analysis, because FoodNet surveillance did not routinely monitor the isolation of *Salmonella* from urine during 1996–1998; the case definition was changed in 1999 to include all sources, including urine. Information collected by FoodNet surveillance included serotype (or serogroup if untyped); specimen source (stool, blood, or other); patient’s age, sex, county of residence, and hospitalization history; and whether the patient died or survived. Beginning in the summer of 1996, additional information, including the patient’s symptoms, was collected from persons who were enrolled in a 12 month case-control study of culture-confirmed *Salmonella* serogroup B and D infections.

**Laboratory practice.** In 1997, to determine laboratory practices for the testing of stool specimens, FoodNet investigators conducted comprehensive surveys of the supervisors of microbiology laboratories located in FoodNet areas and those of the largest independent laboratories outside FoodNet areas that processed specimens from area residents. All surveys were conducted in person or by telephone by interviewers using a
standardized questionnaire. The information collected included the type of laboratory (hospital-based or independent laboratory), the laboratory’s policy for testing for pathogens under FoodNet surveillance (tested for routinely, tested for only on physician request, or not tested for/sent out), the number of specimens tested for pathogens under FoodNet surveillance in 1996, and the methods used to isolate these pathogens. In addition, we reviewed the medical literature to develop an estimate of the sensitivity of stool-culture methods in the United States.

Population survey. To determine the incidence of diarrheal illness in the study population, the proportion of those with a diarrheal illness who sought medical care, and the proportion who provided a stool specimen for culture, we conducted a telephone survey from 1 July 1996 through 30 June 1997 of randomly selected respondents living in the FoodNet catchment areas [23]. A single contractor conducted interviews in English using a method similar to the CDC’s Behavioral Risk Factor Surveillance System [24, 25]. If a child aged <16 years was randomly selected from a household, a parent was interviewed as a proxy for the child. A diarrheal episode was defined as ≥3 loose stools or bowel movements during any 24-h period. In the analysis, a diarrheal illness was defined as a diarrheal episode that lasted for >1 day or that resulted in significant impairment of daily activities. We used the Council of American Survey Research Organizations (CASRO) formula to calculate response rates [26]. We also calculated a modification of the CASRO response rate, the “upper bound,” which included only refusals, terminations, and completed interviews [26]. We then analyzed the data, using Software for Survey Design and Analysis (version 7.5; RTI) to adjust for the complex sampling design [27, 28].

Burden of illness. We first multiplied the annual FoodNet Salmonella incidence for each year from 1996 through 1999 by the postcensus population estimates for the United States during that year, to estimate the number of culture-confirmed cases in the United States, adjusted for age. We then averaged these 4 totals to account for year-to-year variation. Next, we estimated the 4 surveillance artifacts (care seeking, stool submission, laboratory testing, and culture-method sensitivity) using data from the laboratory practices survey and the population survey. The “multiplier” for these surveillance artifacts was the product of the inverse of these proportions [2, 29]. To increase precision, we calculated separate multipliers for patients with bloody diarrhea and those with nonbloody diarrhea. We then applied these multipliers to the average estimated number of culture-confirmed cases in the United States. To estimate the number of persons who were hospitalized and the number of persons who died, we first multiplied the estimated number of culture-confirmed cases in the United States by the hospitalization and death rates among persons with culture-confirmed cases ascertained by FoodNet. To account for cases not confirmed by culture, we doubled the number of estimated hospitalizations and deaths [4, 5].

To estimate the range of potential estimates, we conducted a sensitivity analysis using a Monte Carlo simulation (@Risk software; Palisades). The range of estimates in the sensitivity model was based on a triangular distribution in which we used the point estimate for the mean value as well as the minimum and maximum values for (1) the proportion of Salmonella infections that resulted in bloody (30%–70%) and nonbloody (30%–70%) diarrhea, (2) the proportion of infected persons who sought care for bloody (10%–30%) and nonbloody (5%–15%) diarrhea, (3) the proportion of physicians who had cultures performed for cases of bloody (70%–100%) and nonbloody (10%–30%) diarrhea, and (4) the sensitivity of stool culture methods (70%–90%).

RESULTS

Active surveillance, 1996–1999. From 1996 through 1999, 8868 culture-confirmed Salmonella infections were ascertained in FoodNet. After we excluded 114 cases of Salmonella serotype Typhi infection, 55 cases of S. Paratyphi B infection, 29 cases of S. Paratyphi A infection, and 1 case of S. Paratyphi C infection, 8669 cases remained for the present analysis. The specimen sources for the 8669 cases of nontyphoidal Salmonella included 8094 isolates (93.4%) from stool, 462 isolates (5.3%) from normally sterile sites including blood, 69 isolates (0.8%) from other nonsterile sites (including abscesses and sputum), and 44 isolates (0.5%) from an unknown specimen source. Among the 843 persons with Salmonella serogroup B or D infections who were interviewed, 424 (50.3%) had bloody diarrhea. The mean annual incidence rate for the 4 years was 13.4 cases/100,000 population. The incidence did not vary significantly by state or by year. The highest mean incidence reported was in Connecticut (16.0 cases/100,000 population), and the lowest was in Oregon (10.3 cases/100,000 population). Average age-specific incidence rates were highest among infants (117 cases/100,000 population) and children aged 1 to <6 years (34 cases/100,000 population). Of 8355 patients whose status was known at the time of specimen collection, 1711 (20%) were hospitalized for a total of 9963 days; the median length of hospitalization was 3 days. Among patients who were aged ≥60 years, 397 (46%) were hospitalized. Among patients who had Salmonella isolated from a normally sterile site, 329 (73%) were hospitalized. There were 42 reported deaths, for a reported case-fatality rate of 0.6%. Of those persons who died, 27 (64%) had Salmonella isolated from a normally sterile site. The median age of those who died was 62 years (range, 6 months–94 years).

Laboratory practices. All 264 clinical microbiology laboratories surveyed reported that they routinely test all stool
Table 1. FoodNet symptom-specific multipliers used to determine the burden of salmonellosis in the United States, 1996–1999.

<table>
<thead>
<tr>
<th>Surveillance step</th>
<th>Symptom-specific multipliers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory performs routine test for Salmonella</td>
<td>Patients with bloody diarrhea (50.3% of respondents)</td>
</tr>
<tr>
<td>Laboratory identifies Salmonella</td>
<td>1.0</td>
</tr>
<tr>
<td>Physician obtains a stool specimen for bacterial culture</td>
<td>1.4</td>
</tr>
<tr>
<td>Patient seeks medical care</td>
<td>6.8</td>
</tr>
<tr>
<td>Overall</td>
<td>9.8</td>
</tr>
</tbody>
</table>

NOTE. The multiplier for each surveillance step is the inverse of the proportion responding positively. For example, 18.2% of respondents to the FoodNet population survey with nonbloody diarrhea provided a stool specimen for bacterial culture; therefore, the multiplier for this step is 5.5 (1/0.182). The overall multiplier is the product of the multipliers for each surveillance step. Overall multipliers were calculated without rounding at each surveillance step.

specimens received for bacterial culture for Salmonella. Laboratories in these sites estimated testing a total of 231,000 stool specimens (1400 specimens tested/100,000 population) in 1996. This figure, however, may have included stool specimens from persons residing outside the FoodNet catchment areas. Of the specimens they received, 93.1% were from whole stool and 6.9% were from rectal swabs. Two hundred forty-two laboratories (92%) used routine and moderately selective agar media (a combination of eosin–methylene blue or MacConkey with xylose-lysine-desoxycholate [XLD], Hektoen-enteric [HE], or Salmonella-Shigella [SS] agar). The most common combination of plating media was MacConkey and HE (37.3%), followed by MacConkey and XLD (20.2%), and MacConkey, HE, and XLD (9.9%). The remaining 22 laboratories did not use routine media; 7 used a combination of HE and XLD, 2 used HE and SS, 7 used XLD and HE agar, 2 used HE alone, and 4 used XLD alone. Two laboratories routinely used bismuth sulfite, and 1 laboratory used modified semisolid Rappaport-Vassiliadis agar.

Data from our 1997 laboratory survey indicated that most laboratories in the FoodNet areas follow established guidelines for the identification of Salmonella. Stool culture, however, is not 100% sensitive, and variations in specimen collection and specimen transport procedures and laboratory error will further decrease the sensitivity of culture [30]. We therefore estimated that the stool culture method was 70% sensitive for detecting Salmonella in stool specimens from patients with either bloody or nonbloody diarrhea; Chalker and Blaser [2] used the same estimate in 1988.

Population survey. A total of 9003 persons completed interviews; the response rate was 50%, and the upper bound was 71%. After excluding 379 respondents who had chronic diarrhea, we found that 11% of respondents reported having had a diarrheal episode during the 4 weeks preceding their interview. The rate of diarrheal illness was 0.75 illnesses/person/year, which suggests that 12 million episodes of diarrheal illness per year occurred in the FoodNet surveillance areas.

Among those with a diarrheal illness, 12% sought medical care (14.6% of those with bloody diarrhea and 11.6% of those with nonbloody diarrhea). Using these numbers, we estimated that 167,425 persons visited a clinician for the treatment of gastroenteritis annually. Among those who sought medical care, 21% were asked by their physician to provide a stool specimen for culture, and 89% of these complied with this request (100% of those with bloody diarrhea and 18.2% of those with nonbloody diarrhea provided a specimen). Using these numbers, we estimated that 270,815 stool specimens (1660 specimens/100,000 population) were submitted annually by persons residing within the FoodNet areas who had a diarrheal illness.

**Burden of illness.** When we age-standardized the incidence of culture-confirmed infection ascertained by FoodNet to the US population, we estimated that there were 36,242 culture-confirmed Salmonella infections in the United States annually during 1996–1999. Using data from the population and laboratory practices surveys to construct sequential multipliers, we estimated that there were 9.8 cases of Salmonella infection in the community for each culture-confirmed case involving bloody diarrhea and 67.7 cases for each culture-confirmed case involving nonbloody diarrhea (table 1). Overall, we estimated that there were 38.6 cases of Salmonella for each culture-confirmed case. Applying the multipliers to the mean estimated number of culture-confirmed cases, we estimated that there were 1,397,187 cases of Salmonella illness per year in the United States during 1996–1999 and that the incidence was 520 cases/100,000 population (figure 1). The sensitivity model predicted a mean of 1,425,639 cases, with a 90% confidence level of 828,981–2,337,839 cases. Using the hospitalization (20%) and death (0.6%) rates among persons with culture-confirmed cases
and doubling these numbers to account for an equal number of hospitalizations and deaths estimated to have occurred among persons with Salmonella infections that had not been confirmed by culture, we conservatively estimated that Salmonella resulted in 14,860 hospitalizations and 415 deaths annually.

DISCUSSION

Using FoodNet surveillance data from 1996 through 1999 and related surveys, we estimate that, each year in the United States, ~1.4 million persons are infected with nontyphoidal Salmonella, which results in ~15,000 hospitalizations and ~400 deaths. Previous estimates of the burden of Salmonella infection in the United States have been based on a variety of methods, including a meta-analysis of published outbreak reports to calculate surveillance multipliers [1–4]. Such methods yielded estimates of Salmonella infection that ranged from 800,000 to 4 million cases annually, with estimates of 18,000 hospitalizations and 500 deaths. Since the institution of FoodNet, however, we have become able to calculate population-based estimates of the number of Salmonella infections in the United States. These estimates can be used to calculate the morbidity rate, mortality rate, and economic burden imposed by Salmonella and other bacterial enteric infections, as well as to calculate cost-effectiveness ratios for various food-safety interventions.

Our estimated annual number of culture-confirmed cases (36,242), which we derived by age-adjusting and extrapolating FoodNet data to the US population, is similar to that reported through national passive surveillance, despite regional variation for Salmonella serotypes within FoodNet surveillance areas [21] and nationally [31]. The mean number of nontyphoidal Salmonella infections in the United States from 1996 through 1999, as reported by national passive surveillance data, was 32,926, with an associated incidence of 12.3 cases/100,000 population. Furthermore, despite the variation in the prevalence of infection with different Salmonella serotypes among the FoodNet areas, the overall incidence of Salmonella infection among the FoodNet areas was similar, which suggests that the incidence may be relatively homogeneous across the states. These data support the conclusion that national passive surveillance for Salmonella infection is relatively complete and that the incidence of Salmonella infection within the FoodNet areas may reflect the national incidence. After estimating the number of culture-confirmed infections in the United States, we extrapolated, using “multipliers” of surveillance artifacts (care seeking, stool submission, laboratory testing, and culture sensitivity) to estimate the total number of Salmonella infections. Using this method, we estimated that there were 38.6 cases of Salmonella infection for each culture-confirmed case. Using a similar method, Chalker and Blaser [2] calculated a multiplier of 39 to estimate the total number of cases of salmonellosis in the United States, including asymptomatic infections. Mead et al. [5] used a multiplier of 38 that was based on preliminary FoodNet data. In a study of infectious intestinal diseases in England and Wales, researchers estimated that 3.2 cases of salmonellosis occurred for each case reported to national surveillance [32]. Differences in methods used in the 2 countries, in care-seeking behaviors by the 2 populations, in health care delivery, or in the epidemiology of salmonellosis may explain the differences between estimation multipliers used in the United States and those used in England and Wales.

We determined rates of care seeking and stool-specimen submission from the population survey. Although these data allowed us to calculate a robust estimate of care seeking, data on stool-specimen submission were sparse. However, data from separate FoodNet surveys yielded remarkably similar estimates of the total number of stool samples submitted: the population...
survey data suggested 270,815 stool specimens, and the laboratory survey respondents reported testing 231,000 stool specimens during 1996. Further studies may determine whether the rate of care seeking and of stool-specimen submission change over time. If the actual proportion of persons with diarrheal illness who seek care or submit a stool specimen decreases, the multiplier and the resulting burden of illness estimate will increase.

We also estimated the rate of laboratory testing and culture-method sensitivity. The 1997 survey of microbiology laboratories in the FoodNet areas showed that all laboratories routinely tested stool specimens submitted for culture for *Salmonella*. This result was validated by that of a national study of 601 microbiology laboratories that showed that 99.3% routinely tested stool specimens for *Salmonella* [33]. However, infections may not be confirmed by culture because of the insensitivity of stool culture; the fewer the organisms in a specimen, the less likely that the culture is going to yield *Salmonella*. Isolation rates for *Salmonella* may also be affected by suboptimal handling of specimens, the selection of culture media, variations in laboratory testing, and receipt of antimicrobial treatment before culture specimens were obtained [34–53]. Considering these factors, we estimate that, although all laboratories routinely culture stool specimens for *Salmonella*, the sensitivity of stool culturing is only 70%. Further studies are needed to confirm this estimate; if the actual sensitivity is higher, our calculations overestimate the burden of illness imposed by *Salmonella*.

Other sources of error in the present study may also have affected the estimates. First, we assumed that persons with diarrheal illness who sought care and provided specimens were as likely to have *Salmonella* isolated from their stool as were those who did not seek care or provide specimens. However, this assumption was based on the premise that physicians were randomly selecting patients for performance of culture instead of using objective criteria, training, and experience to determine which patients were likely to be culture-positive for *Salmonella*. Our model only accounted for one index of severity—bloody diarrhea. Thus, we may have underestimated the proportion of persons infected with *Salmonella* who provided stool specimens for culture and, therefore, we may have overestimated the multiplier for this step. For example, if the rate of *Salmonella* positivity was twice as high among the stool specimens requested by physicians as among those not requested (i.e., if the proportion of true positive samples tested was 36%), our estimate of the number of cases of salmonellosis per year would be reduced to 800,000. Second, we assumed that the rate of care seeking among all those with diarrheal illness was the same for those persons infected with *Salmonella*. However, persons infected with *Salmonella* may have a longer duration of diarrhea or greater severity of other symptoms and thus may be more likely to seek medical care than those with non-*Salmonella* diarrhea. If this were true, our estimate for the multiplier for this step would also be too high. Our estimates of disease burden are most sensitive to variations in the estimates of the percentage of persons missed because of mild disease or lack of stool culture. Third, FoodNet active surveillance, although population based, cannot guarantee complete case ascertainment. For example, stool specimens may be sent to laboratories outside the catchment area, not all of which may have been contacted. Loss of cases because of incomplete ascertainment would increase our estimate. Further studies are needed to evaluate these assumptions. Finally, the 5 FoodNet areas are not an exact mirror of the US population, and the extrapolation of FoodNet data to make national estimates could be affected by the sample of sites. However, because active population-based surveillance was conducted in each of the FoodNet areas, we believe that these data represent the best available information.

We have shown that salmonellosis is a major public health problem in the United States in terms of morbidity and mortality. The reinforcement of traditional disease-control methods and the use of novel interventions are necessary to reduce the burden of these illnesses. Since the recent introduction of the USDA’s HACCP rule, fewer bacteria, including *Salmonella*, have been found on meat and poultry after processing. The irradiation of these products could further reduce the level of bacterial contamination [54]. Control measures that target other sources of *Salmonella*—such as eggs, pet reptiles, alfalfa sprouts, and juice—also play a role in disease prevention [55–57]. Finally, public health education campaigns, such as Fight-BAC, are targeting consumers and food handlers [58]. This broad strategy is necessary to curb the public health threat of foodborne diseases. Continued FoodNet activities are necessary to monitor changes in the burden and epidemiology of salmonellosis in the United States.

**FOODNET WORKING GROUP MEMBERS**

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