Epidemiologic Issues in Study Design and Data Analysis Related to FoodNet Activities

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The Foodborne Disease Active Surveillance Network (FoodNet) seeks to determine and to monitor the burden of foodborne diseases in the United States more precisely and to attribute these diseases to specific food vehicles or other exposures. These objectives present statistical and epidemiologic challenges. Estimates of the burden of foodborne diseases should include an estimate of the uncertainty in such calculations. Monitoring the burden of foodborne diseases should account for the expansion of the FoodNet population over time. Attributing foodborne diseases to specific vehicles is facilitated by FoodNet case-control studies of sporadic illness. This article discusses the strengths and limitations of the various studies aimed at addressing these objectives in this supplement. Furthermore, because the FoodNet surveillance areas were not chosen specifically to reflect the demographic composition of the US population, this article also discusses the generalizability of FoodNet results to the US population.

Foodborne diseases cause an estimated 76 million illnesses, 325,000 hospitalizations, and 5000 deaths each year in the United States [1]. To better understand the public health impact of foodborne disease, the Centers for Disease Control and Prevention (CDC; Atlanta, GA), in collaboration with selected state health departments, the US Food and Drug Administration, and the US Department of Agriculture's Food Safety and Inspection Service, established the Foodborne Disease Active Surveillance Network (FoodNet). Key objectives of FoodNet are (1) to determine the burden of foodborne diseases in the United States, (2) to monitor trends in foodborne diseases, and (3) to determine the proportion of foodborne diseases attributable to specific foods.

To meet these objectives, FoodNet personnel conduct active laboratory-based surveillance in the FoodNet surveillance area (also called "FoodNet site") for laboratory-confirmed infections caused by *Campylobacter, Cryptosporidium, Cyclospora, Listeria, Salmonella, Shigella, Vibrio,* and *Yersinia* species and Shiga toxin–producing *Escherichia coli* (including *E. coli* O157). FoodNet personnel contact the >450 clinical laboratories that receive stool, urine, blood, and other specimens obtained from residents of the surveillance area, either weekly or monthly (depending on the size of the clinical laboratory), to ascertain cases of laboratory-confirmed infection with the pathogens under surveillance. In addition, FoodNet personnel audit selected clinical labs to evaluate the completeness of case ascertainment.

FoodNet personnel also survey the general population, physicians, and clinical laboratories in the surveillance area to estimate the prevalence of diarrhea in the general population, the proportion of persons with diarrhea who seek medical care, the frequency with which stool specimens from patients who present with diarrhea are submitted to clinical laboratories, and the frequency with which laboratories test stool and other specimens for the bacterial and parasitic pathogens under surveillance. FoodNet personnel also conduct case-control studies of laboratory-confirmed illness to iden-

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tify food consumption and handling practices that place individuals at increased risk for such infections and to estimate the proportion of such infections attributable to these practices.

The purpose of this article is to describe several complex statistical and epidemiologic issues raised by FoodNet activities and to describe the methods chosen to address these issues. This article will also examine the generalizability of FoodNet data to the entire United States by presenting the results of a demographic comparison of the FoodNet and the US populations.

STATISTICAL AND EPIDEMIOLOGIC ISSUES

Estimating the burden of foodborne infectious disease. FoodNet data are essential for more precise estimates of the morbidity, mortality, and economic burden of foodborne diseases in the United States [1, 2]. Although active FoodNet surveillance ascertains all laboratory-confirmed infections caused by the 7 bacterial and 2 parasitic pathogens, laboratory-confirmed infections are only a fraction of the total number of infections caused by these pathogens that occur in the FoodNet population. For a case of infection to be ascertained by laboratory-based surveillance, several steps are necessary. These steps may be described as a "surveillance pyramid" (figure 1). Many cases are not detected because ill persons do not seek medical care or because specimens are not obtained. Furthermore, clinical laboratories do not perform comprehensive diagnostic tests on all specimens. FoodNet estimates the frequency with which cases of foodborne disease go undetected by conducting studies at each step of the surveillance pyramid. These studies include surveys of the general population and clinical laboratories. Surveys are used to estimate the factor by which to multiply data on ascertained cases at each step of the pyramid to obtain an estimate of the total number of cases in the population. The burden of each disease in the entire population is then estimated by extrapolating the number of laboratory-confirmed infections—the number ascertained through active laboratory-based surveillance, corrected using the various surveillance multipliers—to the general population [1].

To derive the estimate of the burden of foodborne disease in the general population, certain assumptions are made. One assumption is that our active surveillance results in the comprehensive ascertainment of laboratory-confirmed infection among residents of the FoodNet surveillance area. This assumption is supported by the results of frequent audits, which have demonstrated that active surveillance ascertains >95% of laboratory-confirmed infections. Clinical laboratories in the FoodNet sites have been identified through various means including state licensing lists, FoodNet physician surveys that ask physicians where they send specimens, and outbreak investigations. It is likely that the list of FoodNet clinical laboratories geographically located in the FoodNet sites is comprehensive. It is possible, however, that a resident of the catchment area may become ill, seek medical care, and submit a specimen but that the specimen may be sent to a clinical laboratory that is geographically outside the FoodNet surveillance area. We have attempted to ascertain such cases by contacting the large reference diagnostic laboratories that are likely to receive specimens from residents of the FoodNet sites; such cases currently account for approximately one-fifth of cases ascertained by FoodNet. Clinical laboratories outside the surveillance area that have been identified as having received specimens from FoodNet residents are then added to the list of >450 laboratories that are routinely contacted by FoodNet surveillance officers.

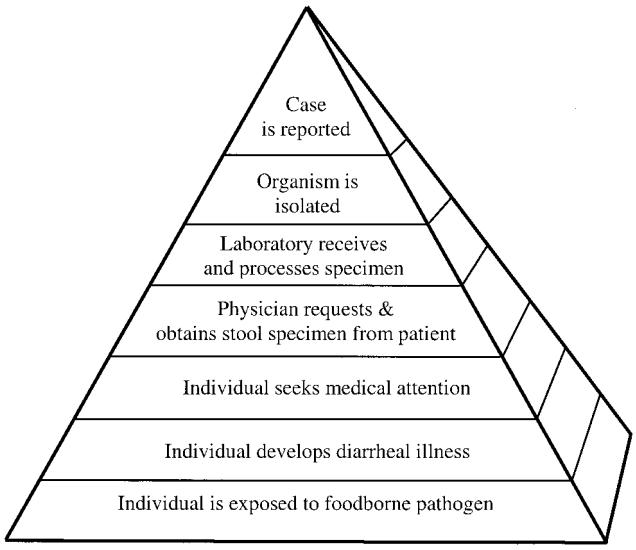

Figure 1. The "burden of illness pyramid" used by FoodNet to assess the burden of foodborne disease in the United States.

The epidemiological method used to estimate the burden of illness in the general population combines data from active surveillance with several cross-sectional studies conducted at various stages of the surveillance pyramid. This design does not allow for the direct measurement of some study factors. For example, we can estimate stool submission and laboratory culturing practices (via the FoodNet Population Survey [3] and FoodNet Laboratory Survey [4], respectively), but we are unable to directly determine the number of stool specimens tested for a specific pathogen. One way to derive such a measurement directly would require the FoodNet surveys to be linked by patient identifier so that, for each ill individual, it could be determined whether or not that person sought care, had a specimen submitted to a clinical laboratory, what the specimen was tested for at the clinical laboratory, and the outcome of the laboratory test. Linking of the isolates by patient identifier would create a cohort study design but would be impractical,

given concerns about patient confidentiality and the size of the population under surveillance. FoodNet researchers are exploring small-scale cohort studies, such as in health maintenance organizations, as a means of validating the estimates derived from FoodNet studies.

As with all surveys, estimates derived from the FoodNet Population Survey and the FoodNet Laboratory Survey are subject to uncertainty. When results from these surveys are combined, this uncertainty is compounded in the overall estimate of burden for each disease. A traditional worst-case/best-case scenario modeling of this process, which only includes the minimum, most likely, and maximum values for each estimate, does not appropriately capture uncertainty. This approach only examines 3 scenarios, 2 of which (worst-case and best-case) are not likely to occur, and is likely to result in wide confidence limits.

We have explored different methods for describing the statistical uncertainty in the overall estimate of burden. In this issue of *Clinical Infectious Diseases*, we used Monte Carlo simulation to quantify uncertainty in 2 studies: the burden of salmonellosis by Voetsch and colleagues [5] and the burden of campylobacteriosis by Samuel and colleagues [6]. This technique incorporates the uncertainty associated with each burden pyramid input data value by use of a probability distribution instead of individual point estimates. Input data values are repeatedly sampled from each probability distribution to produce multiple scenarios. An estimated burden is calculated for each sampled scenario, resulting in a distribution of burden estimates. This distribution reflects the probability that each scenario could occur and has an expected, or typical, value (which serves as the point estimate) and a standard deviation that tells the likely size of the uncertainty.

Voetsch et al. [5] and Samuel et al. [6] both use a method patterned after the risk analysis model developed by Vose [7]. Voetsch and colleagues [5] estimate the burden of salmonellosis, using Monte Carlo simulation with a range of fixed estimates derived from 2 cross-sectional studies. A triangular distribution is ascribed to each input range. Samuel et al. [6] also use Monte Carlo simulation to estimate the burden of campylobacteriosis by ascribing different distributions to the input values on the basis of certain assumptions about the stochastic nature of each input. For example, cases of campylobacteriosis ascertained by FoodNet surveillance are rare events relative to the population size, and it is assumed that the frequency of confirmed cases is a Poisson process. The expected value, or mean, of this distribution is assumed to follow a γ distribution.

To address the objective of reducing the uncertainty in our burden estimates, we are currently investigating the use of advanced sensitivity analysis techniques to determine which model component contributes most to the overall uncertainty in our estimate. Once this is determined, we can investigate how best to manage the uncertainty in that component via changes in future study designs and thereby reduce the uncertainty in the overall burden estimate.

Monitoring foodborne disease trends. A second key objective of FoodNet is to monitor the trends of foodborne diseases over time. In doing so, FoodNet data help in assessing the effectiveness of national food safety interventions such as the Food Safety and Inspection Service's Pathogen Reduction and Hazard Analysis Critical Control Point (PR/HACCP) system and monitoring progress toward our national health objective of reducing the incidence of important foodborne diseases by 50% by 2010 [8]. Monitoring trends in foodborne disease is most efficiently accomplished by focusing surveillance efforts on laboratory-confirmed infections caused by pathogens that are commonly transmitted through contaminated food. Our focus on laboratory-confirmed infection is based on the assumption that surveillance multipliers at each step of the surveillance pyramid remain constant over time. FoodNet attempts to validate that assumption through repeated surveys of the general population and laboratories.

To ascertain laboratory-confirmed cases, FoodNet personnel canvass clinical laboratories using standard case definitions and comparable data collection methods. Despite the use of these standard methods, the incidence of several illnesses caused by the pathogens under surveillance demonstrate marked regional variation. Several of the articles in this issue of *Clinical Infectious Diseases* discuss regional differences in the incidence of laboratory-confirmed infections. Bender and colleagues [9] explored the impact of regional variation in laboratory testing procedures on the regional variation in the incidence of *E. coli* O157 infection. They found that even after controlling for variability in testing practice between sites, the incidence of *E. coli* O157 infection remained elevated in Minnesota and Oregon. Similarly, Ray and colleagues [10] and Samuel and colleagues [6] found regional variation in the incidence of *Yersinia* infections and *Campylobacter* infections, respectively, even after controlling for laboratory testing practices. These studies suggest that regional variation in disease incidence reflects regional differences in exposures, which may include the consumption of contaminated food or other routes of transmission. Additional studies, including a FoodNet retail food study to determine the degree of *Salmonella* and *Campylobacter* contamination in meat and poultry sold in grocery stores, are under way to further explore the impact of regional differences on the observed variation in the incidence of foodborne disease.

An additional issue affecting FoodNet's ability to monitor trends is that the FoodNet population has more than doubled from 1996 to 2001 (from 14.3 million to 33.1 million persons under surveillance). Because of the substantial regional variation observed, the addition of more sites over time can change the collective crude incidence even if no actual change in incidence occurred. Several of the articles in this supplement

describe trends of laboratory-confirmed infections in the FoodNet sites from 1996 to 1999 or 2000 [6, 9–11]. To account for the regional differences in laboratory-confirmed infections and the increased area under surveillance, these articles have limited their assessment of such trends to the original 5-site FoodNet surveillance area. Similarly, FoodNet annual reports before 2001 limited such trend analysis to the original surveillance area [12–16]. Beginning with the annual reports in 2001, we used multivariable Poisson regression models to describe changes in disease incidence over time [17]. The model estimates the effect of time on disease incidence, treating time as a categorical variable. The relative change in incidence rates is estimated using 1996 as the reference year. This multivariable model uses all FoodNet data and includes controls for site-to-site variation and the influence of the changing population base, and will eventually include demographic characteristics such as race, sex, and age.

Attributing proportion of foodborne diseases to specific foods. In addition to estimating disease burden and monitoring disease trends, a key objective of FoodNet is identifying food exposures and food handling practices that place an individual at increased risk for developing foodborne infection and estimating the proportion of disease risk attributable to these exposures.

This objective is met, in part, by case-control studies of sporadic laboratory-confirmed illness ascertained in the FoodNet surveillance area. The FoodNet surveillance platform gives these case-control studies a particular advantage for studies of sporadic illness. In the case-control studies described in this supplement, FoodNet personnel attempted to enroll all laboratory-confirmed infections ascertained by population-based active surveillance [18–24]. Because all patients with laboratory-confirmed infections occurring in the surveillance area during the study period are ascertained and eligible for the study, FoodNet case-control studies are population-based. In population-based case-control studies, the "base population" (i.e., the population that gave rise to the cases in the study) is defined, and the impact of selection bias is relatively easier to predict than in case-control studies in which the base population is unknown. Furthermore, in epidemiologic terms, population-based case-control studies involve an incidence density sampling design rather than cumulative incidence sampling. In incidence density sampling, direct estimates of disease rate ratios are obtained for the measured exposures. Because the diseases under investigation in the FoodNet population-based case-control studies are rare in all population subgroups, rate ratios closely approximate risk ratios [25, 26]. Along with case exposure percentages, these risk ratio estimates are used to calculate the population-attributable fraction. The population-attributable fraction is defined as the proportion of new cases occurring during a given period in a particular population at risk that was attributable to the effect of one or more exposures. In other words, the population-attributable fraction is the proportion of cases that might not have occurred during the study period if everyone in the population had been unexposed (or had been exposed at reference levels). Because FoodNet case-control studies are population-based, these studies directly estimate the relative risk and population-attributable fraction. An additional important advance in the FoodNet case-control studies is the calculation of precise confidence intervals around the population-attributable fraction. In the 6 FoodNet case-control studies included in this supplement, we computed confidence interval around the point estimates using a "jackknife" procedure to estimate variance. The jackknifing procedure estimates the variance of the estimated population-attributable fraction by using the observed data (rather than statistical assumptions) to approximate the population-attributable fraction distribution [27].

Despite these advantages, FoodNet case-control studies have important limitations. In each investigation, we assess the association of numerous exposure types and attempt to gain a coherent understanding of their combined effect on risk. In common with many such studies, there are limitations on what patients and control subjects remember and can report in an interview. Even an explicit food history may be something of a report of food preferences. The interview format imposes additional constraints.

Another concern related to the conduct and analysis of FoodNet case-control studies is the selection of an appropriate exposure period. The exposure "windows" (i.e., the time periods during which exposures were ascertained for case and control subjects) for the FoodNet case-control studies in this supplement were long: 7 days for most of the exposures in the *Campylobacter* case-control study and 5 days for most exposures in the *Salmonella* case-control studies. The long exposure windows, although useful in determining the proportion of the population exposed (which is used when calculating the population-attributable fraction), pose a potential problem when investigating common exposures. When a long exposure window is used, the likelihood of detecting a difference in exposure between case and control subjects is limited by high exposure frequencies among both case and control subjects [28]. A recent case-control study of sporadic *Salmonella* serotype Enteritidis infection in Denmark found that reducing a 5-day exposure window to 1 day resulted in detection of an increased risk associated with egg consumption, which was a common exposure [29]. Further studies are needed to assess the consequence of using shorter exposure windows in case-control studies of sporadic infection that investigate common exposures.

The case-control study also can identify risk factors that are associated with a lower risk. For example, in the FoodNet case-control study of sporadic *S.* Enteritidis infection by Kimura et

Table 1. Comparison of the demographic characteristics of FoodNet and US populations, 1996.

Characteristic	No. (%) of persons, by population	
	FoodNet	United States
Age in years		
<1	193,549 (1)	4,373,918 (2)
1–4	788,818 (6)	17851953 (6)
5–9	1,011,711 (7)	21,875,539 (8)
10–19	1,984,474 (14)	42,049,510 (15)
20–29	1,970,225 (14)	40,995,792 (14)
30–39	2,518,113 (18)	48,127,144 (17)
40–49	2,242,100 (16)	41,931,055 (14)
50–59	1,343,619 (9)	26,767,325 (9)
⩾60	2,228,487 (16)	45,595,669 (16)
Sex		
Male	7,010,854 (49)	129,810,215 (49)
Female	7,270,242 (51)	135,473,568 (51)
Total	14,281,096 (100)	265,283,783 (100)

al. [23] in this supplement, having a diverse diet (defined as consuming more than the median number of different food items during the exposure period) was found to be protective against infection. This finding suggests that further research is needed to understand the effect of having a diverse diet. A possibly related observation is that, in several FoodNet case-control studies, control subjects were more likely to report higher fruit and vegetable consumption than were case patients during the exposure period. Further research is needed to determine whether eating fruits and vegetables protects against enteric bacterial infection or some other explanation applies.

Last, the issue of population immunity and patient susceptibility to infection is an ongoing challenge to identifying an association between exposures and infection in case-control studies, including the FoodNet case-control studies of sporadic illness. If a relatively common infection conveys durable immunity, an important segment of the population may be immune and, therefore, not susceptible to infection. This may be the case for *Campylobacter* infection. As reported by Samuel and colleagues [6], an estimated 1.4 million *Campylobacter* infections occur each year. It is known that some immunity exists after *Campylobacter* infection [30]. If such immunity is both present and protective, it would make demonstration of an association between exposures and increased risk of infection more difficult. If a recurrent exposure to a risky food ultimately results in immunity, some control subjects might be frequent, but immune, consumers of food contaminated with *Campylobacter* species. Studies are needed to determine whether such factors contribute to the findings of several FoodNet case-control studies that have suggested that exposure to certain foods (e.g., chicken) eaten inside the home is associated with low risk of infection, whereas exposure to these same foods eaten outside the home (e.g., in restaurants) is associated with increased risk of infection.

Generalizability of FoodNet data. State health departments that participate in FoodNet were selected on the basis of the strength of their proposal to conduct population-based surveillance and to achieve geographic diversity. These proposals were received from state health departments after the publication of a Request for Proposals in the US Federal Register. FoodNet sites were not chosen to be representative of the US population. It was anticipated, however, that the inclusion of multiple sites comprising 5%–10% of the US population would allow estimates to mirror national trends. A demographic comparison of the FoodNet and US populations in 1996 suggests that the 2 populations had similar age and sex distributions (table 1). However, the racial/ethnic distributions of the 2 populations differed. Asians were overrepresented in the FoodNet population: 6% of the population was Asian, compared with 4% of the US population. Hispanics were underrepresented in the FoodNet population: 6% of the population was Hispanic, compared with 12% of the United States population. The 1996 FoodNet surveillance area consisted of 135 counties. County-level comparison of the FoodNet and US populations indicated a lower population density in the FoodNet counties (a median of 31 persons per square mile, compared with a median for the Unites States of 41 persons per square mile). The FoodNet population also had a smaller percentage of persons living at or below the poverty level (FoodNet, 11%; United States, 14%).

A demographic comparison of the expanded FoodNet population and the US population in 2000 again found little variation in age and sex distributions (table 2). In contrast to the

Table 2. Comparison of the demographic characteristics of the FoodNet and the US populations, 2000.

Characteristic	No. (%) of persons, by population	
	FoodNet	United States
Age in years		
<1	408,356 (1)	3,805,648 (1)
1–9	3,843,172 (13)	35,919,655 (13)
10–19	4,351,338 (14)	40,747,962 (14)
20–29	4,185,016 (14)	38,345,337 (14)
30–39	4,890,414 (16)	43,217,052 (15)
40–49	4,760,988 (16)	42,534,267 (15)
50–59	3,441,646 (11)	31,054,785 (11)
⩾60	4,662,092 (15)	45,797,200 (16)
Sex		
Male	14,973,523 (49)	138,053,563 (49)
Female	15,569,499 (51)	143,368,343 (51)
Total	30,543,022 (100)	281,421,906 (100)

situation in 1996, in 2000 both populations had a similar proportion of Asians (4%). Hispanics, however, remained underrepresented in the FoodNet population; 6% of the population was Hispanic, compared with 12% of the US population. The underrepresentation of Hispanics in FoodNet surveillance, despite the increases in the FoodNet surveillance area, may influence the reported incidences of several foodborne diseases discussed in this supplement. Although these comparisons suggest that the differences between the demographic characteristics of the FoodNet population and the US population are limited, further studies to evaluate the generalizability of FoodNet data to the entire US population would be helpful.

CONCLUSION

FoodNet is an important national disease-surveillance resource that provides unique and timely data to aid in national decision-making about efforts to mitigate the burden of foodborne diseases. The results of the various FoodNet studies can provide valuable information on the burden of foodborne diseases, trends in foodborne disease incidence, and the sources of foodborne diseases. The analysis and interpretation of these studies involve several complex statistical and epidemiological issues. In some instances, further operational research may help define how best to address those issues, and FoodNet offers a platform for conducting such assessments.

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