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Estimating the Burden of Acute Gastroenteritis, Foodborne Disease, and Pathogens Commonly Transmitted by Food: An International Review

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The burden of foodborne disease is not well defined in many countries or regions or on a global level. The World Health Organization (WHO), in conjunction with other national public health agencies, is coordinating a number of international activities designed to assist countries in the strengthening of disease surveillance and to determine the burden of acute gastroenteritis. These data can then be used to estimate the following situations: (1) the burden associated with acute gastroenteritis of foodborne origin, (2) the burden caused by specific pathogens commonly transmitted by food, and (3) the burden caused by specific foods or food groups. Many of the scientists collaborating with the WHO on these activities have been involved in quantifying the burden of acute gastroenteritis on a national basis. This article reviews these key national studies and the international efforts that are providing the necessary information and technical resources to derive national, regional, and global burden of disease estimates.

Although a number of countries have conducted studies to determine the burden of foodborne disease, global estimates are lacking. The enormity of the problem is evident, however, from estimates of the incidence of acute gastroenteritis during childhood, for which an important proportion of cases are caused by foodborne pathogens [1]. The globalization of the food supply has presented new challenges for food safety and has contributed to the international public health problem of foodborne disease. To initiate and sustain efforts aimed at preventing foodborne disease at national and international levels, the magnitude of the problem needs to be determined.

Estimations of the burden of foodborne disease are complicated by the fact that very few illnesses can be definitively linked to food. Often these links are only made during outbreak situations. Although acute gastrointestinal diseases are not all foodborne and foodborne diseases do not always result in acute gastroenteritis, food does represent an important vehicle for pathogens causing acute gastroenteritis. Studies determining the burden of acute gastroenteritis provide the basis for estimating the burdens due to food and specific pathogens commonly transmitted by food. This article reviews some of the national and international initiatives providing information and technical resources necessary to derive estimates of national, regional, and global disease burdens. Countries included in this review were invited to participate via international research networks.

Received 25 February 2005; accepted 10 May 2005; electronically published 22 July 2005.

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Clinical Infectious Diseases 2005; 41:698–704

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1058-4838/2005/4105-0018$15.00

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Table 1. Four categories of surveillance systems in relation to the assessment of the burden of foodborne disease.

Variable	Category of surveillance system and definition			
	1	2	3	4
Definition	No formal surveillance	Syndromic surveillance	Laboratory-based surveillance	Integrated food-chain surveillance
Expected outcomes	Nonspecific disease parameters	Nonspecific disease parameters	Etiology-specific, including subtypes	Etiology-specific, including subtypes, greater precision, population-based reservoirs
Contribution of surveillance system to the assessment of burden of foodborne disease	None	Limited	Potentially significant	Significant
External support required to assess the burden of foodborne disease	High	Moderate	Minimal	None
Ability of surveillance system to attribute disease to specific food sources	None	None	Moderate	High
Usefulness of surveillance data for risk analysis	None	Limited	Potentially significant	High, allows validation of models

INTERNATIONAL INITIATIVES

The World Health Organization (WHO) is involved in several initiatives designed to enhance laboratory-based surveillance and to determine the burden of disease in countries and regions lacking such estimates.

WHO Global Salm-Surv. Launched in January 2000, the WHO Global Salm-Surv is an international capacity-building program that strengthens national laboratory-based surveillance and outbreak detection of and response to diseases commonly transmitted by food. It is coordinated by the WHO, the Danish Institute for Food and Veterinary Research, the Centers for Disease Control and Prevention (CDC), Reseau International des Instituts Pasteur, the Public Health Agency of Canada, Animal Sciences Group (The Netherlands), US Food and Drug Administration, Enter-net, and OzFoodNet (Australia) [2]. The core elements include international training courses, an electronic discussion group, a Web site [3], an external quality-assurance system, a country databank of the top 15 annual *Salmonella* serotypes, focused regional and national projects, and reference-testing services. Through 2004, 26 training courses for microbiologists, epidemiologists, and managers have involved ~350 participants from >90 countries. By enhancing laboratory-based surveillance, WHO Global Salm-Surv is helping countries establish a foundation on which to estimate the burden of foodborne disease.

WHO Sentinel Sites Project. In March 2002, the WHO convened a consultation in Leipzig, Germany, to discuss the feasibility of establishing sentinel sites to determine the burden of foodborne disease in regions lacking estimates. The meeting defined 4 categories of surveillance systems on the basis of each system's ability to generate information on foodborne disease (table 1) and recommended using countries with category 3 or category 4 surveillance systems for burden studies [3]. Jordan was selected as the first sentinel site for this project. A survey administered to clinical laboratories assessed routine laboratory practices and determined the number of specimens submitted and the number of laboratory-confirmed cases of infection with *Salmonella*, *Shigella*, and *Brucella* species. A population survey administered via face-to-face interviews collected data on the number of persons with diarrhea or persistent fever, the number of persons seeking medical care, and the number of persons submitting stool specimens and blood samples for analysis. With data generated from these sources, multipliers were calculated to determine the burden of these pathogens. In addition, a prospective health facility–based study was conducted to determine the proportion of pathogens commonly transmitted by food among patients seeking care in sentinel health care facilities to validate the burden estimates derived from the population and laboratory surveys. The Jordan study serves as a model for future sentinel sites.

International collaboration on enteric diseases: the "burden of illness studies." In response to worldwide interest in studies that estimate the burden of acute gastroenteritis and foodborne disease, an international meeting, hosted by the CDC and chaired by the WHO, was held in Atlanta, Georgia, in 2004 with representatives from 16 countries. The main result of this meeting was the establishment of an international collaboration with the following aims: (1) to foster communication between researchers via a list-server, conference calls, and an annual face-to-face meeting; (2) to create a forum for sharing infor-

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mation about the design, implementation, and analysis of studies on the burden of illness; (3) to provide advice to countries wishing to conduct burden of illness studies; and (4) to contribute to global foodborne disease burden estimates. Currently, >30 countries participate in the collaboration. One of the accomplishments of this group has been the publication of a study that compares the prevalence of acute gastroenteritis in Australia, Canada, Ireland, and the United States with a standardized case definition [4].

NATIONAL INITIATIVES

England, The Netherlands, and the United States [5–9] were among the first countries to embark on specific studies to understand the burden of diseases commonly transmitted by food. Following this first generation of studies, a number of other countries, including Australia, Canada, and Ireland, launched similar studies [10–12]. These studies can be categorized by 2 general designs: (1) prospective cohort studies with community and etiologic components, and (2) cross-sectional surveys with or without supporting targeted studies.

Although prospective cohort studies are relatively expensive and complex, they have the advantage of providing community incidence rates that are pathogen-specific. Enhanced laboratory testing increases the proportion of cases with a laboratory-confirmed diagnosis and provides an opportunity to screen for pathogens not usually included in routine surveillance. In cross-sectional surveys, investigators ascertain the prevalence of self-reported acute gastroenteritis among persons in the community during a set period of time (e.g., 1 month). The advantage of this design is its relative simplicity and lower cost, making it easily repeatable in different populations or for varying time periods. The 6 countries reviewed highlight the different approaches taken to determine the burden of acute gastroenteritis (table 2). Some countries have also calculated estimates of burdens due to specific pathogens commonly transmitted by food and/or have calculated the proportion of acute gastroenteritis transmitted by food or food groups.

England. A collaborative population-based study was conducted in England between 1993 and 1996 [5, 6]. Two of its principal objectives were as follows: (1) to estimate the number and etiology of cases of acute gastroenteritis in the population and the number of patients presenting to general practitioners who routinely send stool specimens for laboratory examination, and (2) to compare the number and etiology of cases with findings from the national laboratory reporting surveillance system.

Cohorts of individuals drawn from 70 general practices were recruited, and stool specimens were obtained and examined for bacteria, viruses, and parasites. Data from these practices were also used to determine presentation and reporting rates. It was estimated that 20% of the population of England experienced acute gastroenteritis each year (9.4 million cases) and that the most common etiologic agents were norovirus (606,700 cases), *Campylobacter* species (422,200 cases), rotavirus (344,600 cases), and nontyphoidal *Salmonella* species (106,800 cases). Data from this study were used in conjunction with data from national surveillance and special studies to estimate trends in the burden and etiology of foodborne illnesses [13]. Investigators estimated that domestically acquired foodborne illnesses resulted in 2.9 million cases in 1992 and 1.3 million cases in 2000. *Campylobacter* infection accounted for the most use of health services, and salmonellosis caused the most deaths. More recently, the Communicable Disease Surveillance Centre of the Health Protection Agency developed a model to examine the burden and risk of domestically acquired foodborne disease associated with different food types [14]. Outbreaks traced to a single source of food were classified into broad food groups, and the percentage of outbreaks caused by each type of food was calculated for each pathogen. This information was combined with pathogen-specific estimates to produce pathogen-specific burdens according to food type. Food consumption data were used to derive food-specific risks. It was estimated that consumption of contaminated chicken meat and eggs accounted for nearly one-half of all hospitalizations and nearly one-third of all cases and deaths caused by indigenous foodborne diseases.

The Netherlands. Two key studies of acute gastroenteritis have been conducted in The Netherlands: a general-practitioner–based study and a community-based study [7, 8]. The objectives of both studies were as follows: (1) to estimate the overall incidence and the rate of consultation with general practitioners for acute gastroenteritis, (2) to identify the pathogens responsible for illnesses, (3) to assess the factors associated with presentation to a general practitioner, and (3) to identify risk factors for acute gastroenteritis caused by specific pathogens.

In the nationally representative general practitioner–based study, ~60 practitioners reported the number of consultations for acute gastroenteritis that occurred each week. Approximately 75% of the general practitioners also participated in a case-control study, in which patients seeking consultation and age-matched control subjects were invited to complete a questionnaire and submit stool samples. An age-stratified random sample of patients identified from the registers of the same general practitioner network was selected for a community-based cohort study. For 2 consecutive 6-month periods, cohorts reported symptoms of acute gastroenteritis on a weekly basis. Individuals who developed symptoms according to the case definition and matched control subjects also participated in a case-control component (requiring participants to provide stool samples, complete a questionnaire, and maintain a medical diary). The standardized community-incidence of acute gastroenteritis for The Netherlands was 283 cases per 1000

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Table 2. Characteristics of key studies of the community burden of acute gastroenteritis.

Country	Study description (study period)	Sampling method	Sample size	Supporting and/or related studies	Name of study (key collaborators)
Australia	Cross-sectional population-based survey (September 2001–August 2002)	Overall sample was stratified by state (there are 7 states and/or territories in Australia) with households and respondents randomly selected; each respondent gave details about his/her own experience and about gastroenteritis in other household members	6087 Respondents who provided information about 16,400 persons	Laboratory survey and analytic studies conducted to determine the burden of foodborne illnesses	OzFoodNet (Commonwealth Department of Health and Ageing; State and Territory health authorities; the Communicable Disease Network of Australia; the National Centre for Epidemiology and Population Health, Australian National University; Food Standards Australia New Zealand; and the Public Health Laboratory Network)
Canada	Multiple cross-sectional population-based surveys (1999–2004)	Random selection of households and respondents (i.e., family member with the soonest upcoming birthday) located nationally and in selected health regions: health regions were selected to represent urban and rural conditions	17,500 Respondents from 4 selected health regions and 3500 respondents on the national level	Laboratory survey, physicians survey, local health unit survey, and case definition analysis	NSAGI (Public Health Agency of Canada; provincial epidemiologists and laboratory directors; Department of Population Medicine, and the University of Guelph)
England	Prospective cohort study (August 1993–January 1996)	Sampling of cohort from general practitioners' registers stratified randomly by age and sex	9776 Patients enrolled in a cohort	Physician-based studies, nested-case control study; and analytic studies to determine the burden of foodborne illnesses and food-specific risks	IID Study (Public Health Laboratory Service; the Medical Research Council General Practice Research Framework; and the London School of Hygiene and Tropical Medicine)
Ireland	Cross-sectional population-based survey (December 2000–November 2001)	Random telephone dialing in the Republic of Ireland and Northern Ireland and random selection households and respondents (i.e., family member with the soonest upcoming birthday)	9600 Respondents (400 per month in the Republic of Ireland and 400 per month in Northern Ireland)	Physician survey	(Communicable Disease Surveillance Centre-Northern Ireland; the Department of Public Health Medicine and Epidemiology, University College, Dublin; the Department of General Practice, Queen's University, Belfast; the Food Safety Authority of Ireland; the Food Safety Promotion Board; the Food Standards Agency, Northern Ireland; the National Disease Surveillance Centre; and the Irish College of General Practitioners)
The Netherlands	Prospective cohort study (December 1998–December 1999)	Random selection of individuals within representatively selected general practitioners' catchments	4860 Patients enrolled in a cohort (1050 cases developed, microbiology was determined for 713 cases and 684 controls)	Physician-based studies and nested-case control study	General Practitioner Study, SENSOR Study (National Institute of Public Health and the Environment [Department of Infectious Disease Epidemiology; the Research Laboratory for Infectious Diseases; Diagnostic Laboratory for Infectious Diseases; and the Microbiological Laboratory for Health Protection] and The Netherlands Institute of Primary Health Care)
United States	Four multiple cross-sectional population-based surveys (1996–1997, 1998–1999, 2000–2001, and 2002–2003)	Random selection of households and individuals (i.e., family member with the soonest upcoming birthday) in selected counties or states	52,605 Respondents (9003, 12,755, 14,647, and 16,200 respondents from the first, second, third, and fourth surveys, respectively)	Laboratory surveys; active surveillance; case control studies; and analytic studies to determine the burden of foodborne illnesses	FoodNet (Centers for Disease Control and Prevention; 10 Emerging Infections Program sites; the US Department of Agriculture; and the US Food and Drug Administration)

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person-years (4.5 million cases), and the incidence for persons who presented to a general practitioner was 14 cases per 1000 person-years (220,000 cases) [7, 8]. The most common pathogen at the community level was norovirus (11%). In the general practitioner study, rotavirus was most common in patients <5 years of age who sought consultation (17%), and *Campylobacter* infection was most common in patients ⩾5 years of age (12%).

United States. The Foodborne Diseases Active Surveillance Network (FoodNet) was established in 1996 and is the principle foodborne illness component of the CDC's Emerging Infections Program [9]. In 2004, the total population of FoodNet-monitored sites was 43.3 million, or 15% of the US population. The objectives of FoodNet are to determine the burden of foodborne disease and monitor trends over time.

To determine the burden of foodborne disease, FoodNet conducts active surveillance at >450 laboratories [15]. Active surveillance is complemented by surveys that collect data about diagnostic practices from clinical laboratories [16] and physicians [17]. Cross-sectional telephone surveys of the general population have also been conducted to investigate the burden of acute gastroenteritis in the community and to determine the proportion of patients who are seeking care and submitting stool specimens for testing [18]. The rate of acute gastroenteritis was estimated to be 0.72 episodes per person-year, which suggests the existence of 195 million episodes nationally [18].

The burdens associated with specific pathogens and food types have been estimated on the basis of data obtained by FoodNet. The burden of illness due to *Salmonella* species was estimated by calculating the expected number of laboratory-confirmed cases of *Salmonella* infection (based on data obtained by FoodNet's active surveillance) and applying multipliers for bloody and nonbloody diarrhea (based on data obtained by FoodNet's population survey) to adjust for cases not detected by laboratory-based surveillance. It was estimated that each year *Salmonella* infection accounts for 1.4 million cases of illness, 15,000 hospitalizations, and 400 deaths [19]. In a separate study, pathogen-specific estimates of burdens caused by a wide range of bacteria, parasites, and viruses were calculated with data obtained by FoodNet. Multipliers of 20 for bloody diarrhea, 38 for nonbloody diarrhea, and 2 for pathogens causing severe disease were used. This study also estimated the proportion of cases of acute gastroenteritis associated with food on the basis of outbreak data, targeted studies, and expert opinion. It was estimated that 76 million cases of foodborne disease occur each year, of which 82% have unknown etiology [20].

Northern Ireland and the Republic of Ireland. Two studies of acute gastroenteritis were conducted in Northern Ireland and the Republic of Ireland between 2000 and 2003. The objectives were to determine the incidence of acute gastroenteritis in the community and to describe physician treatment of patients with acute gastroenteritis.

Between December 2000 and November 2001, a population-based, cross-sectional telephone survey of 9903 people was conducted to determine the incidence of acute gastroenteritis and the health-seeking behaviors of ill persons [12]. The rate of acute gastroenteritis was estimated at 0.60 episodes per person-year, which, if extrapolated to include the total population, amounts to 3.2 million episodes of gastroenteritis each year. During 2002 and 2003, a postal survey was conducted to better understand the management of patients with acute gastroenteritis, and it was completed by 679 general practitioners.

Australia. In late 2000, the Australian Government Department of Health and Ageing established OzFoodNet, a collaboration of foodborne disease epidemiologists, to more accurately determine the burden of foodborne illness in Australia. To achieve this, the National Centre for Epidemiology and Population Health, in collaboration with OzFoodNet, conducted a nationwide community survey to estimate the burden of acute gastroenteritis. They analyzed data from notifiable surveillance, outbreak summaries, community surveys, laboratories, and other sources to estimate the burden of illness of 16 pathogens known to cause acute foodborne gastroenteritis [10].

The number of cases of foodborne illness was estimated for each of the 16 pathogens commonly transmitted by food, and the proportion of all cases of acute gastroenteritis due to foodborne transmission was calculated. Because such estimates have an inherent degree of uncertainty that is caused largely by a paucity of appropriate data about each of the known pathogens, a plausible distribution of data values was used for calculations instead of a single estimate. Wherever possible, real data were used to inform the parameters of the simulated distribution of all elements. The plausible interval estimates are credibility intervals with an interpretation similar to that of credibility intervals in Bayesian inferences. The surveillance and outbreak data were adjusted for under-ascertainment, with information obtained from the community survey and other sources. For each pathogen, the proportion of cases of foodborne acute gastroenteritis was derived for Australia from the literature and a Delphi process. Diseases that were potentially foodborne but did not cause acute gastroenteritis or that were not acquired in Australia were not included in the estimation. It was estimated that 5.4 million cases of foodborne gastroenteritis occur in Australia each year (95% CI, 4.0–6.9 million cases). Annually, foodborne transmission accounts for ~32% (95% CI, 24%–40%) of a total of 17.2 million cases of gastroenteritis (due to all causes) in Australia [10].

Canada. The National Studies on Acute Gastrointestinal Illness were developed in 1999 with the aim of estimating the incidence of acute gastroenteritis and quantifying under-ascertainment at key interfaces in Canada's national surveillance

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program. To address this aim, 4 studies were implemented: population, physician, laboratory, and public health–reporting studies.

The incidence of acute gastroenteritis was ascertained through a telephone survey conducted in 4 health regions and nationally. The rate of acute gastroenteritis was estimated to be 1.3 episodes per person-year [11]. Data obtained by the physician survey, which was administered to general practitioners and pediatricians in the same health regions, demonstrated that 3.4% of patients seen by physicians received diagnoses of acute gastroenteritis each month, of whom 22.3% were asked to submit a specimen for laboratory testing [21]. The laboratory survey was designed to quantify pathogen yields and to examine interlaboratory variation in practices or policies that may influence pathogen yield. In 2000, there were 459,982 stool specimens tested for enteric pathogens, of which 5%, 15%, 8%, and 19% were positive for enteric bacteria (excluding *Clostridium difficile*), *C. difficile*, parasites, and viruses, respectively [22]. The public health reporting study focused on reporting practices at the health-unit level. Based on these studies, it was calculated that each case of acute gastroenteritis reported to the Provincial Health Authority represented between 105 and 1389 community cases, with a mean of 313 cases [23].

DISCUSSION

By enhancing laboratory-based surveillance and determining the burden of gastroenteritis in regions lacking such estimates, the global initiatives coordinated by the WHO and the national studies described in this article represent important steps toward estimating the global burden of foodborne disease. When national estimates are determined, they must take into account the burden of illness that is not ascertained by routine surveillance. Because many patients with acute gastroenteritis do not visit a health care provider or do not submit a specimen for laboratory testing [5, 6, 23, 24], clinical and laboratory-confirmed diagnoses greatly underestimate the burden of illness in the community. When the burden of acute gastroenteritis is known, food-specific and pathogen-specific estimates can be calculated. The most accurate way to assign burden to a specific pathogen is through prospective cohort studies. Because patient and physician behaviors are influenced by factors related to an infectious agent, the use of multipliers based on a syndrome from a retrospective survey may lead to an underestimation (e.g., noroviruses that cause mild self-limiting illnesses) or overestimation (e.g., rotaviruses that affect young children) of pathogen-specific burdens [5, 6, 24]. In addition, future studies could be enhanced by taking into consideration the role of immunity when deriving pathogen-specific burden estimates.

Estimating the proportion of cases of acute gastroenteritis associated with food requires researchers to combine information from multiple sources and often to rely heavily on expert opinion [20, 25]. The use of a plausible distribution of values, instead of a point estimate, allows researchers to convey the inexact nature of these assessments. Estimating the proportion of cases of acute gastroenteritis associated with food is more challenging in countries without good outbreak data and in developing countries where the role of food as a vector and the spectrum of pathogens causing acute gastroenteritis are not well understood. Improved surveillance and response capacity, both of which are addressed through WHO Global Salm-Surv, are critical to developing these estimates. Studies to better understand the causes of acute gastroenteritis in the high proportion of patients with negative results of stool cultures will avoid the assumption that the proportion of foodborne transmissions is similar among cases of known and unknown etiology and will further improve estimates of foodborne transmission of disease. The impact of dietary differences on foodborne disease estimations also needs to be assessed.

When data obtained from various countries are pooled to derive regional or global estimates, the impact of the study design and existing surveillance systems needs to be considered. Prospective and retrospective studies yield different disease estimates. In the English study, when respondents were surveyed retrospectively, prior to the prospective study, an incidence of 5.5 cases per person-year was calculated, which is nearly 3 times the incidence calculated by the prospective study [5]. This retrospective estimate was similar to previous estimates from retrospective studies conducted in the United Kingdom [26, 27], Australia, Canada, Ireland, and the United States [4]. Conversely, the prospective estimates from The Netherlands study are similar to prospective estimates from the English study [5, 8]. Reasons for the differences have largely been attributed to recall bias or telescoping [5]. However, a more thorough examination of the effect of study design on disease estimates would be beneficial prior to a comparison of data from national studies. Efforts are underway to develop a model case definition for acute gastroenteritis to further facilitate the international comparability of data. The attributes of surveillance systems that generate data used in burden estimates (such as sensitivity, representativeness, and positive predictive value) are also important variables to consider when comparing data between countries and regions.

While researchers continue to improve estimates of the burden of foodborne disease, numerous studies are also attempting to attribute disease to specific food-animal sources. Approaches to attributing disease to food include the use of data from outbreaks [5] and sporadic case-control studies [9]. Molecular source-tracking methods have been used when subtype information is made available from human and non-human sources [28]. With more accurate information about the relative contribution of different foods to the total disease burden and with more precise estimates of the burden of foodborne illness, these

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studies support the overall goal of reducing the socioeconomic burden of essentially preventable diseases.

Acknowledgments

We thank the Centers for Disease Control and Prevention for reviewing and providing comment on this article.

Potential conflicts of interest. All authors: no conflicts.

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