White Paper on Applied Epidemiology

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Executive Summary

Protecting the safety of the food supply from farm to table is a multi-layered task that requires an ongoing effort to identify and control potential hazards. A strong system of public health surveillance for foodborne diseases is critical for maintaining HACCP-based food safety systems. Routine public health surveillance conducted by state and local health departments forms the basis for this system. In addition, FoodNet, the Active Surveillance Network for Foodborne Diseases, was developed to provide a more accurate estimate of the burden and source of foodborne diseases needed by FSIS to evaluate the public health impact of HACCP in meat and poultry slaughter and processing plants. Both FoodNet and PulseNet represent the growing awareness that applied epidemiologic methods are critical to maintaining the safety of our food supply.

Although USDA regulatory actions have traditionally been based on detecting the presence of adulterants in food samples, this is not always possible or timely in outbreak situations. However, because an outbreak implies a common source, it is often possible to identify that source using epidemiologic methods. The theoretical advantages of epidemiology have also been demonstrated in practice. During many outbreak investigations, epidemiology has been shown to be more sensitive and timely than microbiological testing to identify contaminated food vehicles in outbreak settings.

The use of epidemiology in outbreak settings, and the relationships between epidemiologic analyses and microbiologic testing of food products can be demonstrated through reviews of outbreaks published in the medical literature and in national surveillance databases. Among outbreaks with a confirmed bacterial etiology reported to CDC from 1993-1997, food testing was conducted during the course of almost one-half of outbreak investigations. When epidemiologic results were used to guide testing, the agent was isolated from food four times as often as when no specific food item could be implicated.

The vast majority of USDA recalls are driven by results of microbiological testing rather than by identification of products associated with human illness. Although hazard does not equal risk, these findings suggest that outbreak investigations are not being conducted quickly enough, or are failing to provide the sufficiently specific source information needed to remove contaminated products that are still in the marketplace.

The use of epidemiology is well established as a regulatory tool in settings where no agent can be identified (such as for eosinophilia-myalgia syndrome due to consumption of L-tryptophan) and in settings where the agent can not be readily isolated from food (such as for hepatitis A virus).

There is no fundamental reason why a different standard should be applied to outbreak situations caused by bacterial agents that can be isolated from food. For example, Schwan's ice cream was epidemiologically implicated as the source of a nationwide outbreak of *Salmonella* serotype Enteritidis infections based on results of a case-control study conducted in less than 3 days. The product was recalled 10 days before SE was isolated from officially obtained ice cream samples. The rapid recall of Schwan's ice cream serves as a model for the regulatory application of epidemiology.

Improving the safety of our food supply will require a commitment to public health surveillance of foodborne diseases based on the principles of epidemiology. Applying epidemiology to this task will require a similar commitment to increasing:

The sensitivity of outbreak detection
The specificity of outbreak investigation,
with respect both to case-definitions and exposure sources
The speed with which outbreaks are investigated

In the wake of recent terrorist attacks on the US and the threat of an attack on the food supply, the need to quickly respond to foodborne outbreaks has only increased.

Introduction

Protecting the safety of the food supply from farm to table is a multi-layered task that requires an ongoing effort to identify potential hazards, to identify points at which those hazards can be prevented or controlled, and to systematically monitor those control points. This concept of hazard analysis and critical control points (HACCP) has been adopted as a framework for the regulation of the sea food industry by the U.S. Food and Drug Administration (FDA) and for the regulation of the meat and poultry industries by the U.S. Department of Agriculture, Food Safety and Inspection Service (FSIS) (1).

For **HACCP** to be an effective basis for food safety, a strong system of public health surveillance for foodborne diseases must function to identify new hazards and to provide critical feedback on the performance of the HACCP system (2). For example, in 1982 *Escherichia coli* O157:H7 was first identified as a cause of bloody diarrhea as the result of outbreaks associated with hamburgers sold by a fast-food chain (3). A massive outbreak of *E. coli* O157:H7 in 1993 was also associated with fast-food hamburgers (4). This outbreak caused over 500 cases and resulted in four deaths. It directly led to *E. coli* O157:H7 being considered an adulterant in raw ground beef, and to the overhaul of the FSIS regulation of the beef and poultry slaughter and processing industries. *E. coli* O157:H7 was a new hazard identified by food borne disease surveillance that has transformed our entire food safety system through a National Food Safety Initiative.

The Food Safety Initiative led to major changes in the way FSIS regulates the slaughter and processing of meat and poultry and has led to major investments in the public health surveillance system for foodborne diseases (5). Routine public health surveillance has been strengthened in recent years through federal grants to enhance epidemiologic and laboratory capacity in state health departments. The most visible expression of this investment has been the development of the Active Surveillance Network for Foodborne Diseases (FoodNet) and the National Molecular Subtyping Network for Foodborne Diseases (PulseNet) (6,7). **FoodNet** was established by the Centers for Disease Prevention and Control (CDC), FSIS, FDA, and state participants in CDC's Emerging Infections Program. The purpose of FoodNet was to more accurately determine the burden of foodborne diseases in the United States and to determine what proportion of important foodborne pathogens, such as *E. coli* O157:H7, were caused by specific foods, such as ground beef (6). This information was needed by FSIS to establish a baseline incidence of foodborne diseases that were caused by meat and poultry products. FoodNet also monitors changes in the occurrence of these diseases as a way of measuring the public health impact of HACCP in meat and poultry slaughter and processing. **PulseNet** was established to "fingerprint" individual strains of *E. coli* O157:H7 and other foodborne pathogens and to provide a rapid means for communicating information about potential outbreaks (7). Beyond the immediate functions of

FoodNet and PulseNet, both represent the growing awareness that applied epidemiologic methods are critical to maintaining the safety of our food supply.

Food safety regulations are intended to prevent the distribution and consumption of foods that could cause illness or injury to the consumer. Foreign objects such as shards of metal or glass, unlabeled allergens such as milk, egg, or nut proteins, and pathogenic microorganisms in ready-to-eat foods are all considered **adulterants** and are subject to regulatory action leading to withdrawal from the marketplace (8). Regulatory actions against adulterated products have traditionally required detection of the adulterant in the product, and the scope of the action has been limited to a specific "lot" or production run.

Detection of *E. coli* O157:H7 in ground beef, or *Listeria monocytogenes* in ready-to-eat meat products will result in the product's removal from the marketplace. Concern over foodborne outbreaks caused by these organisms has led to increased microbiological surveillance of finished meat products by FSIS at the point of manufacture (*E. coli* O157:H7 and *Listeria monocytogenes)* and at retail (*E. coli* O157:H7). Over the past several years, such testing has resulted in numerous product recalls and the removal of potentially contaminated food products from human consumption (9,10).

While these **recalls** may well have prevented some foodborne illnesses, only a small fraction of food products can be tested. In addition, the sensitivity of microbiological testing of finished products is inadequate to prevent the distribution of all potentially contaminated foods. For example, if a product had a 10% rate of contamination, 30 samples would have to be tested to provide more than 95% probability that the contamination would be detected. However, surveys of retail ground beef detect *E. coli* O157:H7 in less than one sample for every 1,000 tested (11). A draft **risk assessment** of the public health impact of *E. coli* O157:H7 in ground beef estimates that the frequency of contaminated cooked ground beef lies between 1 in 36,000 and 1 in 3,300 servings, depending on season (12). Despite these low rates of contamination, CDC estimates that approximately 62,000 foodborne *E. coli* O157:H7 infections occur each year in the US (13).

Because **microbiological surveillance of finished products** cannot prevent the distribution of contaminated foods, **public health surveillance** is needed to rapidly detect, investigate, and identify the source of foodborne disease outbreaks. Removing outbreak-associated foods from the marketplace requires **rapid epidemiologic analysis** to implicate the specific food item. Because an outbreak implies a common source, it is theoretically possible to identify that source using epidemiologic methods. That is, there should always be some quantifiable difference in exposure in an outbreak setting between persons who became ill or infected and those who did not.

In contrast, outbreak-associated foods may not be available at the time of the investigation. Additionally, the level of contamination may be below the detection limits of microbiological testing. Thus, it is not theoretically feasible to microbiologically confirm the source of contamination in every outbreak. Even when it is possible, microbiological confirmation typically requires several days-critical time that could delay a regulatory action and put many more people at risk for foodborne illness.

The changing paradigms for conducting outbreak investigations have been outlined by CDC's Robert Tauxe, M.D.:

Old strategy: Culture all the leftovers
Have to find the pathogen in the food to take action
Assume someone broke the rules
Goal: Assign blame
Treat industry as a perpetrator
Be sure your evidence holds up in court

New strategy: Develop and test hypotheses
Interview ill and well
Look for the difference in exposure between them
Take action on statistics
Goal: Figure out how to prevent it from happening again
Treat industry as a collaborator
Be sure your data are scientifically valid

The old strategy was based on microbiology, the new one on epidemiology. Epidemiologic investigations involve the collection and analysis of information to guide interventions. Thus, the speed of our response to an outbreak should be limited only by the speed at which we can move this critical information. In the wake of recent terrorist attacks on the US and the threat of an attack on the food supply, the need to quickly respond to foodborne outbreaks has greatly increased.

The purpose of this white paper is to review the use of epidemiology in outbreak investigations. In particular, it seeks to explore the use of epidemiologic data as a basis for identifying and eliminating, to the extent possible, the food vehicle of infection.

Epidemiologic Principles and Application to Outbreak Investigations

Definitions. **Epidemiology** is the study of events in populations (14). The most commonly studied events are individual cases or outbreaks of disease. These include cases of infection with specific agents such as *Salmonella*, or the occurrence of illnesses defined by signs and symptoms, such as vomiting and diarrhea. **Outbreaks** are usually defined as the occurrence of more cases of a

given disease than expected in the population over a defined time period. Both the recognition of disease clusters and their comparison to "expected" values imply some ongoing tracking of disease, or surveillance. **Surveillance** is the ongoing collection, analysis, and dissemination of information regarding the occurrence of events, notably diseases, in the population.

Foodborne disease surveillance was initiated on the national level during the early 1900s as a way of tracking the occurrence of outbreaks. During the period before the second world war (WWII), most reported outbreaks of foodborne illness were due to staphylococcal intoxication. These outbreaks tended to involve large group meals and were recognized because a high proportion of persons eating the meal became sick within a few hours later (15). In these settings, outbreak recognition did not require any diagnostic laboratory testing, or anything more than a very qualitative sense that the number of illnesses was unusual.

During the period of economic growth following WWII, food production and distribution systems began to develop in ways that increased the potential for large outbreaks of *Salmonella* infection to occur (16). Recognition of these outbreaks required confirmation of the illness by laboratory testing and a more quantitative sense for the backround rate for the occurrence of *Salmonella* infections. Because the incubation period for *Salmonella* infections commonly exceeded 24 hours, the immediate link between the exposure and illness was broken.

As our awareness of the number and type foodborne illnesses and their clinical and epidemiologic expression expands, it poses novel challenges for our foodborne disease surveillance systems to identify, investigate and control these outbreaks (17,18). Since CDC estimates that 82% of foodborne illnesses are due to infectious agents that have not been identified, epidemiologic methods are critical for the investigation of foodborne outbreaks (13). These methods include the careful description of events, or **descriptive epidemiology**, that forms the basis for public health surveillance systems, and the detailed comparisons of the different rates at which these events occur within groups, known as **analytical epidemiology** (14).

Measures of association. In the context of outbreak investigations, analytical epidemiology involves determining a measure of association between consumption of a specific food item and the occurrence of illness. A simplified representation of the distribution of illness and food consumption histories is displayed in the 2 x 2 table below:

	Ill	**Not ill**	Total
Ate	a	b	a+b
Did not eat	c	d	c+d
Total	a+c	b+d	a+b+c+d

Most foodborne outbreak investigations involve **case-control studies**, in which the measure of association is expressed as an **odds ratio**. This involves comparing the odds of being ill and eating the food item (a/c) to the odds of not being ill and eating the food item (b/d). The odds ratio then becomes (a x d)/ (b x c). To illustrate, a hypothetical set of data are inserted into the table below:

	Ill	Not ill	Total
Ate	8	4	12
Did not eat	2	10	12
Total	10	14	24

In this hypothetical outbreak, there were 10 ill persons (or cases), 8 of whom ate the suspect food item, and 14 not ill persons (or controls), 4 of whom ate the food item. The odds ratio is (8 x 10) / (2 x 4) = 10. Case-control studies are typically conducted when cases can be identified but it is not possible to identify all the individuals who were exposed, or it is not practical to try to interview them all.

In some investigations, controls are selected to have demographic characteristics that match individual cases. Analysis of matched case-control studies is based on the distribution of exposures for complete case-control sets rather than the distribution of exposures for individual cases and controls. This creates some differences in the analysis and interpretation of **matched case-control studies**. For example, in an investigation of *Salmonella enterica* serotype Enteritidis infections in Minnesota during 1994, 10 (65%) of 15 cases reported eating Schwan's ice cream, but only 2 (13%) of 15 controls did (19). Analyzed without matching, the odds ratio was 13. However, there were 10 case-control sets in which the case but not the control ate Schwan's ice cream, and one in which the control but not the case ate Schwan's ice cream. Thus, the matched odds ratio was 10. For most investigations, there should be reasonable agreement between the matched and unmatched estimates of the odds ratio.

The magnitude of the odds ratio is a measure of the strength of the association between exposure and illness. If either all of the cases consumed a contaminated food item, or none of the controls did, the odds ratio would approach infinity and may be reported to be undefined. This occurs because one of the odds introduces a zero into the denominator. For example, in the initial case-control study that implicated a chain of fast-food restaurants as the source of a large multi-state outbreak of *E. coli* O157:H7 infections in 1993, 12 (75%) of 16 cases but no controls reported eating at one of the chain's restaurants during the 10 days before onset of symptoms (4).

A closely related tool of analytical epidemiology is the **cohort** study. Retrospective cohort studies are conducted when the entire group with a common exposure can be identified. An example is a wedding reception where a

guest list can be obtained, and individuals interviewed without respect for their illness status. In cohort studies the investigator can directly measure the rate of illness among persons who would have eaten specific food items and compare it to the rate of illness among persons who did not. This **risk ratio** can be directly interpreted as the increased rate of illness among exposed persons, in ways that an odds ratio cannot.

	Ill	Not ill	Total
Ate	8	4	12
Did not eat	2	10	12
Total	10	14	24

The differences between risk ratios and odds ratios can be demonstrated using the previously generated 2 x 2 table above. Eight of 10 cases and 4 of 12 controls had eaten the suspect food item, resulting in an odds ratio of 10. If the 24 subjects were analyzed as a cohort, 8 of 12 persons (66.7%) who ate the food became ill, compared to 2 of 12 persons (16.7%) who did not eat the food item. Thus, the risk ratio (66.7/16.7) = 4. A risk ratio of four implies a four-fold increase in risk associated with the exposure. A ten-fold increase in odds is frequently treated the same way but is not as easily interpreted.

Cohort studies also provide direct estimates of an attack rate for a given exposure or level of exposure. **Attack rates** may help evaluate factors contributing to the occurrence of the outbreak (18). For many bacterial foodborne agents, a high attack rate may imply a high exposure dose. This could suggest prolonged temperature abuse of the product. For example, during an outbreak of shigellosis associated with an airline flight kitchen, 20 (57%) of 35 members of a professional football team who ate contaminated sandwiches became ill (20). However, only 28 (5.5%) of 510 passengers on flights with confirmed shigellosis cases became ill after eating hand-prepared cold food items. Sandwiches served to the football team had spent more than 24 hours in a subtropical climate without refrigeration. High attack rates may also suggest a low infectious dose and uniform contamination. In *Cyclospora* outbreaks associated with raspberries imported from Guatemala, the median attack rate among persons who ate items containing raspberries was 93% (21). Collecting information on the amount of food eaten allows the investigator to estimate a **dose-response** for the foodborne disease by correlating the attack rate with the level of exposure. Dose-response data is critical for use in developing **risk assessments**.

A novel analytical approach that takes advantage of molecular subtyping techniques is the **case-case comparison** study (22). Like a case-control study, the analysis requires establishing a specific case definition based on a PFGE-subtype pattern, or other specific strain characterization. Unlike case-control studies, which use non-ill subjects for comparison with cases, the case-case

comparison study compares outbreak-associated cases with patients infected with unrelated strains of the same pathogen.

For example, during the investigation of a multistate *Listeria monocytogenes* outbreak in 1998, 16 (67%) of 24 patients with listeriosis who had eaten hot dogs had the outbreak strain of *Listeria* (23). In contrast, only two (15%) of 13 patients who had not eaten hot dogs were infected with the outbreak-associated strain. Subsequent tracing of hot dogs by brand name led to the identification of a manufacturing plant in Michigan as the source of the outbreak. Because patients with *Listeria* infections in this investigation were interviewed before their *Listeria* strains were characterized, the study was analyzed as a cohort study. Thus, the investigators reported a risk ratio of 4.3 as the measure of association between eating hot dogs and having the outbreak-associated strain. Had the data been analyzed as a case-control study, the same exposure histories would have produced an odds ratio of 11. Because case-comparison studies do not enumerate the underlying exposed populations or groups, they are conceptually more like case-control than cohort studies.

Measures of variability. Analytical epidemiology also involves determining a measure of the variability, or uncertainty, in the measurement of the point estimate of that association (18). In both case-control studies and cohort studies, the precision of the calculated odds ratios or risk ratios, are measured by the **p-value**, or **95% confidence interval**. It is customary in most studies to consider a p-value < 0.05 as being significant. Similarly, significant associations are expected to have 95% confidence intervals that exclude 1.0. These statistical measures are derived from experimental models where subjects are randomly assigned to exposure categories. In the context of the experimental design, the p-values and 95% confidence intervals measure the likelihood that a given set of results may have been due to the chance assignment of subjects to each exposure category. Thus, as sample sizes increase, the likelihood of results being due to chance allocations decreases, the p-value decreases and the 95% confidence interval narrows. Thus, for any given association, the larger the sample size is, the more likely it is that a statistical association will be observed. The result is that for small studies, even a strong association may not appear significant, while for a very large study, a marginal association may appear to be highly significant.

In observational studies, generally, and in foodborne disease outbreak investigations, specifically, a traditional statistical interpretation of p-values and 95% confidence intervals is not justified on theoretical grounds. Subjects are not randomly assigned to exposure categories, and the distributions of chance assignments are not a theoretical basis for the findings. However, the use of these statistical tests to determine whether the results “may have been due to chance” seems to be justified by empirical evidence. In foodborne outbreak investigations, the **causal pathway** between exposure and illness is usually short and direct. The strength of these associations mitigates strictly theoretical

concerns over the interpretation of statistical tests. Thus, these tests remain useful guides to evaluating whether observed associations are likely to be causal, or may be due to coincidental occurrences (i.e., “chance alone”).

Measurement errors and bias. A concern in epidemiologic analysis is that **measurement errors and bias** can introduce reasons, other than contaminated food, for the findings. The first and most important potential measurement error is in defining case status. As noted above, the causal pathway from contaminated food to illness is usually short and direct. However, detecting that pathway requires that the cases being studied are all part of the outbreak.

In outbreaks at events, such as a banquet or a wedding, the causative agent may not be known at the time of the epidemiologic investigation. In these instances a case may be defined based on a combination of signs, symptoms, and reasonable incubation period following the event. For example, human caliciviruses (Norwalk-like viruses) are the leading cause of foodborne disease outbreaks (13, 24). In outbreaks of foodborne viral gastroenteritis associated with an event, it is reasonable to define a case as an illness with vomiting or diarrhea that occurs within 72 hours of attending the event. This restricts the analysis to illnesses that are likely to be foodborne, without *a priori* establishing specific food exposures as part of the case definition.

In community-wide outbreaks, such as would be indexed by an increase in reported cases of *E. coli* O157:H7 infection, case definitions would not include any reference to possible exposures. In these investigations, the specificity of the case definition would depend on molecular subtyping of the isolates, through a mechanism such as pulsed-field gel electrophoresis (PFGE). The value of PFGE subtyping to increase the sensitivity of surveillance for outbreaks of *E. coli* O157:H7 infection has been widely reported, and serves as one of the justifications for the development of PulseNet. However, the use of PFGE subtyping to increase the specificity of outbreak case definitions may be of even greater importance to outbreak investigations.

For *E. coli* O157:H7 infections incubation periods may extend from 3-10 days following an exposure. Thus, there is great potential for individuals to forget critical exposures. This reduces the likelihood of detecting the source of the outbreak. If cases of *E. coli* O157:H7 infection that are not part of the outbreak are included in the analysis, the likelihood of identifying the source is further reduced. For example, in Minnesota an outbreak of *E. coli* O157:H7 infections caused by contaminated ground beef sold through a popular chain of grocery stores occurred in November, 2000 (25). The outbreak was detected because seven *E. coli* O157:H7 isolates with a particular PFGE subtype pattern were identified over a 2-day period. A case-control study and additional case finding activities were initiated. Cases were defined as illnesses associated with that particular PFGE pattern. Within 3 days, results of the case-control study demonstrated a significant association with ground beef from the grocery store

chain. Eight (89%) of nine cases and five (31%) of 16 controls reported eating ground beef from the implicated grocery store chain (matched odds ratio = 10, p=0.04). A recall was initiated. Subsequent microbiological testing confirmed the presence of the outbreak-associated strain in the implicated meat, and at the meat processing plant that supplied the grocery store chain. However, had the case-control study included all cases of *E. coli* O157:H7 infection reported during the outbreak period, there would have been a "suggestive" but not "statistically significant" association with ground beef from the grocery store chain, and it would have made subsequent interventions much more difficult to implement.

Two related concerns of epidemiologic studies are **losses to follow-up** and bias in **subject sampling**. In many investigations that start from a base of reported cases, it is not possible to contact the case due to inadequate or incorrect identifying information, the patient may lack a telephone, the patient may not speak English, or because the patient refuses to be interviewed. If the apparent outbreak is small, these losses to follow-up may preclude any meaningful analyses. There is also the concern that the patients who are lost to follow-up may differ from the remaining cases in some meaningful way that could affect their exposure. For example, a non-English speaking minority community may have traditional cultural practices related to foodhandling that increase their risk. For example, an outbreak of trichinosis occurred among southeast Asian immigrants who obtained a pig, privately slaughtered it, and served the undercooked meat at a community gathering.

Similarly, bias in subject sampling could affect the outcome of an investigation. Matching is frequently done to control against bias that could be introduced with the differential inclusion of cases and controls by age, gender and area of residence. For example, in an outbreak of *Salmonella* serotype Agona infections associated with a toasted oats cereal, children were more likely than household controls to have eaten the cereal (26). In this outbreak, matching was done on the basis of the household but not on the age of the case. The investigators chose to use household controls in order to get results more rapidly than would have been possible had they tried to recruit age-matched community controls. An initial matched odds ratio of 22 had an associated p-value of 0.003. After adjusting for age, the p-value diminished to just under 0.05. The implicated cereal was recalled based on the results of the epidemiologic investigation. However, the epidemiological study design chosen to increase the speed of the investigation almost undermined the key finding, which would have delayed public health intervention to remove the contaminated cereal from the marketplace. Ultimately, the cereal was confirmed to be the source of the outbreak through microbiological testing.

Bias in subject sampling is a great concern when cases may be defined in terms of a specific exposure that precludes analysis of the exposure. For example, if a particular fast food restaurant is suspected to be a source for *E. coli* O157:H7 infections, and cases, but not controls are identified based on a history of eating

at the restaurant, the analysis would be biased towards finding an association regardless of whether the hamburgers were actually contaminated. This association may be entirely spurious, because of the flawed design.

Other types of bias include recall bias, detection bias and interviewer bias. **Recall bias** may occur when cases who have thought about what may have caused their illness may recall more potential exposures than would controls who had no comparable stimulus to their memory. **Detection bias** may occur because some cases are more likely to be detected than others. For example, patients who present at a physician's office with bloody diarrhea are more likely to be cultured for *E. coli* O157:H7 than are patients with diarrhea that is not bloody (27). This detection bias makes it difficult to describe the clinical spectrum of *E. coli* O157:H7 infections based on results of routine surveillance. Fortunately, there is no evidence that the occurrence of bloody diarrhea is in any way related to the source of exposure. Thus, this detection bias would not affect the results of an outbreak investigation. If the exposures being evaluated were more likely to lead to detection of the agent, such as might occur with foreign travel and enterotoxigenic *E. coli*, it would be necessary to account for the likely effect of the bias.

A final source of bias that must be accounted for is **interviewer bias**. The presumptions of the interviewer about the source of the outbreak can greatly influence the degree of probing that may occur to identify the suspected exposure. This is a particular concern for agents that have been strongly associated with specific foods, such as *E. coli* O157:H7 and ground beef or *Salmonella* Enteritidis and eggs. If interviewers probe cases very hard to ascertain these potential exposures, but do not similarly probe controls, spurious associations that might appear highly significant can be developed. Such an outcome would have the doubly bad result of missing the actual vehicle, and undermining the credibility of the public health system when the actual source was finally identified. Interviewer training and use of formal written scripts and questionnaires can limit this bias.

Taken to an extreme, interviewer bias can lead to an **exposure assessment bias**, where only previously identified vehicles are assessed. Because of the strong associations between outbreaks of *E. coli* O157:H7 and ground beef, it is understandable that public health officials would seek to establish or rule out a ground beef source for an outbreak. However, assessing only ground beef exposures would preclude identifying other possible sources, such as water, apple cider, lettuce, and alfalfa sprouts, all of which have been implicated as vehicles in outbreaks. Limiting future outbreak investigations to this expanded group of vehicles would similarly restrict our ability to monitor and understand the changing epidemiology of *E. coli* O157:H7 infections.

Confounding occurs when a variable that is not the source of the outbreak is associated both with the occurrence of the disease and exposure to the actual

source. A classic example was an outbreak of hepatitis A infection at a country club in Minnesota (28). Illnesses were associated with eating hot dogs served at the club. A complete investigation identified the source as an infected foodhandler who had contaminated relish that was served on the hot dogs.

A primary concern for foodborne disease outbreak investigations is that the outbreak may conclude with the identification of the confounding variable rather than the actual source. This appears to have happened early in the course of the investigation of *Cyclospora* outbreaks during 1996. State health officials identified the source as strawberries from California and issued an advisory for Texas consumers to avoid them (29). Strawberries had been included in desserts that were implicated at two separate banquets. However, it was ultimately demonstrated that Guatemalan raspberries were also served in these desserts (21). When the full scope of the outbreak nationwide became apparent, California strawberries were exonerated, at the cost of millions of dollars to the industry and an even greater reluctance on the part of food producers and regulatory officials to accept epidemiologic data implicating specific food products as the cause of outbreaks.

Various measures to assess the impact of bias on outbreak investigation results have been proposed, and many are raised during litigation in the few outbreaks that proceed to the courts. In particular, **sensitivity analyses** can be performed to model the interaction and impact of many potential biases and measurement errors simultaneously. However, the demands of the investigation to rapidly identify the likely source do not usually coincide with the demands of formal sensitivity analyses. In most foodborne outbreak investigations, the need for rapid public health interventions and the short causal pathways between exposure and illness preclude the need for detailed sensitivity analyses. Although these investigations may appear to short circuit formal epidemiologic practices, the reliability of epidemiologic methods to rapidly identify contaminated food vehicles has been repeatedly demonstrated.

Causal inference. **Koch's postulates** were originally proposed in the 1800s as a basis for determining that a microbe was the cause of a disease (14). These postulates formed a useful tool to explore the relationships between the expanding worlds of microbiology and medicine. However, as broader ranges of infectious organisms were identified, Koch's postulates served to restrain the ability to demonstrate a causal link between agent and disease. Koch's postulates have been modified on occasion to accommodate viruses and other classes of infectious agents. However, all revisions embody the principle that the presence of the organism should be detectable by laboratory testing to confirm the infection.

The reliance on microbiological testing to satisfy Koch's postulates appears to be a historical reason for basing most food regulatory activities on the results of microbiological testing. In addition, laboratory tests can be standardized, and the

results are objective. However, microbial culture is not always sensitive, foods may not be available for testing and CDC estimates that 82% of foodborne illnesses are caused by agents that have not been identified (13). For all these reasons, alternate tests of causation are needed.

Observational criteria for causation have been proposed. These include:

1. Temporal sequence of exposure preceding the illness,
2. Consistency of findings across independent studies,
3. Strength of the association,
4. Biological gradient of response
5. Specificity of effect
6. Biological plausibility

Epidemiologic investigations of foodborne outbreaks can meet most of these criteria, but not all may be appropriate. For example consistency of findings cannot be demonstrated during the course of a single outbreak investigation. However, consistency of findings across many outbreak investigations led to the identification of Guatemalan raspberries as the cause of widespread outbreaks of *Cyclospora* infections in 1996, even though the biological plausibility of widespread foodborne transmission of *Cyclospora* had not been previously established (21).

The most important epidemiological element to most foodborne outbreaks is the occurrence of a single disease caused by a single agent. The implication of having one disease caused by one agent is that the source should be identifiable by the pattern of relationships between specific exposures and illness. It is this short causal pathway that makes epidemiologic methods powerful and rapid investigative tools.

The other implication of this feature is that the two most important parts of an epidemiologic investigation are creating a specific case definition, and specifically defining sources of exposure. Molecular subtyping techniques such as PFGE have greatly enhanced the **specificity of case-definitions** in outbreaks of *E. coli* O157:H7 and *Salmonella* infections. **Specifically defining exposure sources** remains the task of the epidemiologists, environmental health specialists, and other public health personnel conducting the investigation. Unfortunately, many investigators defer from obtaining specific source information until they can restrict their investigation to one or a handful of sources. In doing so they run the risk of delaying the investigation, or missing the source altogether.

For example, in the outbreak of *Listeria* associated with hot dogs and deli meats, the initial interviews did not include information about brands or sources (23). Once an initial association was found with consumption of hot dogs, cases had to be re-interviewed to determine the source of the hot dogs. It took 11 more days to identify the likely source of the outbreak, and 8 days beyond that before a recall was initiated. In contrast, a recall of Schwan's ice cream was initiated

within 3 days of the initiation of a case-control study because investigators collected detailed information on brand and source of all the food items consumed by both cases and controls in the investigation. However, had they chosen to collect such detailed source information only after a food group (such as ice cream) was associated with illness, the source would not have been identified. Ice cream consumption was common among both cases (87%) and controls (67%) (matched odds ratio 2.5, p=0.2).

Methods of outbreak detection. Outbreaks of foodborne disease are detected by two primary means (18). Many **outbreaks** are **associated with an event or an establishment**. In these situations, members of the exposed groups become ill, talk about it among themselves and associate the illness with the event. These outbreaks typically involve high attack rates and may be caused by a wide range of pathogens. In many of these outbreaks, public health officials may be notified before anyone has seen a physician.

The second type of outbreak is recognized when a cluster of cases are identified through **pathogen-specific surveillance**. These outbreaks are restricted to agents that are commonly diagnosed by clinical laboratories and reported to public health officials. Many outbreaks of *E. coli* O157:H7, *Salmonella,* and even *Listeria* infections are detected this way. Although the agent is confirmed, there is usually no indication of likely sources of exposure.

In some situations, outbreaks associated with events may also be detected by laboratory surveillance. For example, in 1997, during the second consecutive year that outbreaks of *Cyclospora* infections in the US were associated with Guatemalan raspberries, eight outbreaks were identified in California (30). Only three were reported to the local health department by patients (two instances) or physician (one instance) before results of laboratory testing confirmed the diagnosis in index patients. The other five were identified only because of enhanced laboratory-based surveillance, even though laboratory testing of patient specimens was initiated because of concern about a foodborne outbreak.

The outbreak setting usually determines the reasons for investigating the outbreak and the components of the outbreak investigation. For example, if an outbreak of unknown etiology occurs at a banquet, the investigation must seek to identify the agent as well as the likely source. Thus, detailed information on signs and symptoms must be rapidly obtained together with specific histories of food consumption. In addition, clinical specimens would be obtained to confirm the agent and allow for molecular subtyping.

In outbreaks identified through pathogen-specific surveillance, molecular subtyping of isolates should be performed if not already available, case-finding activities should be conducted to determine the scope of the outbreak, and detailed exposure histories covering the potential incubation period should be collected from cases and community controls (31).

For all foodborne outbreak investigations, **telephone interviews** of both cases and controls should be made by dedicated groups of trained interviewers. When conducted in centralized locations, interviews can be rapidly added to outbreak databases to speed analysis. This can shift the time scale of outbreak investigations from days and weeks to hours and days. In food service and food processing establishments, on site, personal interviews of workers, by local environmental health or regulatory personnel, may be conducted concurrently with the larger epidemiologic investigation. This division of labor provides an efficient basis for conducting an outbreak investigation, allows for feedback between epidemiologists and environmental health specialists and minimizes potential delays resulting from moving investigators to the location of the outbreak (18).

In many outbreak settings, potentially contaminated food items have been disposed of before the investigation is conducted. When food items are available from establishments or individual households, the feasibility of collecting the sample and the reasonableness of testing them must be evaluated. In general, there is a low-likelihood of finding the agent in a convenience sample of available foods. Given the high cost of **testing food samples**, this practice should be discouraged. If however, potentially contaminated foods are available, it may be reasonable to collect them and store them until the results of the epidemiologic investigation can identify the likely source. If this is among the food samples collected, testing the sample may provide microbiological confirmation of the epidemiologic results. It is not reasonable to collect and test food samples as an alternative to conducting an epidemiologic investigation.

Although epidemiologic methods can be rapid and powerful instigative tools to identify the source of a foodborne outbreak there are **limitations of epidemiologic investigations**. First, if the illness being investigated is non-specific, such as the occurrence of nausea and abdominal cramping for a period less than 24 hours, it may not be possible to craft a useful case definition.
If the actual vehicle is not included in the interview, it is unlikely to be identified. This underscores the value of ascertaining exposure histories with a combination of open ended and specific questions. In addition, inadequate exposure characterization may prevent any analysis from identifying the source. Recall that ice cream, per se was not associated with *Salmonella* serotype Enteritidis infection during the Schwan's outbreak.

Finally, at many banquets, there is near universal exposure of all attendees to a limited menu of food items. When every one is exposed to the contaminated source, qualitative analyses of food histories will not distinguish cases from controls. This was observed in several restaurants that were part of the international outbreak of shigellosis associated with chopped parsley in 1998 (32). It also obscured the source of an outbreak of *Salmonella* serotype Agona infections associated with a popular savory snack in Israel (33). It was only after

the imported snacks were implicated as the source of outbreaks in England, Wales, and the US that they were also implicated as the source of a widespread outbreak in Israel. Overall, 93% of cases and 88% of controls in Israel had eaten the snacks (34). However, it was demonstrated that cases had eaten twice as many packages of the snack as had the controls. Thus, a quantitative evaluation of the exposure data established a dose-response relationship between exposure and illness.

Review of Available Sources of Information on Results of Epidemiologic Analysis and Microbiologic Testing During the Investigation of Foodborne Outbreaks

In order to evaluate recent trends in the investigation of foodborne outbreaks, several sources of information were reviewed. These included recently published reports in the medical literature, foodborne outbreak databases compiled by the Centers for Disease Control and Prevention, and food recall databases compiled by the Food Safety and Inspection Service of U.S. Department of Agriculture.

Literature Review of Published Outbreaks. The scientific literature on outbreaks published from 1999-2001 was reviewed to explore the relationships between results of epidemiologic analysis and microbiologic testing. Only the most recent literature was reviewed to allow a comparison of current public health practices with current microbiological testing methods (see Appendix).

The following PubMed Search Terms were used to identify published reports:

"food" AND "outbreak"
"Salmonella" and "outbreak"
"E. coli" and "outbreak"
"virus" and "outbreak" and "food"

All searches were limited to the English language and articles about humans. References published from 1999 – 2001 were selected for review. Outbreaks inside the United States, as well as other countries, were included.

Four pieces of information were compiled for each published account of an outbreak:

Agent
Vehicle
Whether the vehicle was epidemiologically implicated
Whether the agent recovered (through laboratory testing) from the vehicle

Fifity-four outbreak reports were reviewed. In 51(94%) outbreaks the vehicle was implicated by epidemiologic investigation. In 27 (50%) outbreaks the agent was recovered from the vehicle (Table 1). *Salmonella*, *E. coli*, and Norwalk-like viruses comprised 44 (78%) of the outbreaks reviewed. Of these, the agent was recovered from the vehicle in 24 (54%).

Table 1. Recovery of Agent from Vehicle, by Agent

	Agent Recovered		
Agent	**Yes**	**No**	**Total**
Bacteria	22 (56%)	17 (44%)	39
Salmonella	14 (67%)	7 (33%)	21
E. coli	6 (50%)	6 (50%)	12
Campylobacter	0	2	2
Listeria	2	0	2
Clostridium	0	1	1
Yersinia	0	1	1
Virus	4 (31%)	9 (69%)	13
NLV	4 (44%)	5 (56%)	9
Hepatitis A	0	3	3
Rotavirus	0	1	1
Parasite	0	1	1
Cyclospora	0	1	1
Chemical	1	0	1
Total	27 (50%)	27 (50%)	54

Although information on microbiological testing was available, it was frequently difficult to find out when the testing was done. This made it difficult to determine what actions were taken, if any, based solely on epidemiological data as opposed to laboratory-testing evidence.

Review of National Foodborne Outbreak Databases, 1993-1997. CDC maintains a national database of foodborne disease outbreaks reported by state and local public health agencies (35). The most recently compiled and published data cover outbreaks reported from 1993-1997 (N=3,257 outbreaks). During this time period, a vehicle was identified for 1,133 outbreaks (35% of all reported outbreaks). Among outbreaks with a vehicle identified, the agent was isolated from the implicated food item in 302 outbreaks (27% of outbreaks with a confirmed vehicle). However, food items were not tested or the information was not available in 575 (51%) outbreaks.

The etiology was reported as unknown in 2,172 (67%) outbreaks. Among 1,053 outbreaks with a known etiology, 449 (43%) were caused by *Salmonella*, and 95 (9%) were caused by *E. coli* O157:H7.

A vehicle was identified in 220 *Salmonella* outbreaks (49% of all reported *Salmonella* outbreaks). Among these, *Salmonella* was isolated from the implicated food in 90 outbreaks (41% of outbreaks with a confirmed vehicle).

Similarly, a vehicle was identified in 51 *E. coli* O157:H7 outbreaks (54% of all reported *E. coli* O157:H7 outbreaks). Among these, *E. coli* O157:H7 was isolated from the implicated food in 20 outbreaks (39% of *E. c*oli O157:H7 outbreaks with a confirmed vehicle).

In addition to outbreaks for which a vehicle was epidemiologically implicated, a food sample tested positive for a known foodborne pathogen in 30 (1.4%) of 2,092 outbreaks in which the vehicle was unknown. Test results (both positive and negative) were reported for 461 (22%) of these outbreaks. Positive food samples were reported for 16 (4%) of 400 outbreaks with a known etiology, and 14 (0.8%) of 1,692 outbreaks with an unknown etiology. Thus, results of testing in these settings were not adequate to establish the vehicle or the etiology of the outbreak.

E. coli O157:H7 outbreaks reported to CDC, 1998-2000. During 1998-2000, 149 confirmed outbreaks of *E. coli* O157:H7 infections were reported to CDC. Of these, 71 (48%) were likely due to foodborne transmission and in 65 (44%) a food vehicle was identified.

Salmonella Enteritidis outbreaks reported to CDC, 1998-1999. During 1998-1991, 89 outbreaks of *Salmonella* Enteritidis were reported to CDC. All were attributed to foodborne transmission and in 37 (42%) a food vehicle was identified.

Review of USDA Recall Databases 1998-2001. FSIS maintains a database of all items under their jurisdiction that have been recalled. Information on recalls from 1996 until present time (September 2001) is available on their public website.

All of the Class 1 recalls from 1998 to 2001 were reviewed and a spreadsheet created with the following information:

- USDA identification number
- Recall date
- Microbiological agent
- Vehicle (food item)
- How was the problem identified?
- FSIS testing
- Other government agency testing
- Company testing
- Illness

Data from years 1996-1997 was excluded from analysis because less information was available for these years – no information was given on how the problem was identified and many did not have links to press releases.

FSIS files were checked and the spreadsheet updated with information on which recalls were initiated by the occurrence of human illness, how many were based

on epidemiological evidence only, and how many were based on laboratory testing.

During this time period there were 184 Class I recalls, 151 (82%) were due to bacterial foodborne pathogens. Of these, 81 (54%) were due to *Listeria monocytogenes*, 56 (37%) were due to *E. coli* O157:H7, 14 (9%) were due to *Salmonella*, and 1 was due to *Clostridium botulinum*.

Recalls were stimulated by human illness in 20 (13%) instances and by the results of microbiological testing in 131 (87%) instances.

In two others recalls in which the agent was unknown, the recall was stimulated by the occurrence of human illness.

Summary of database surveys. A review of these available sources of information on the results of epidemiologic analysis and microbiologic testing revealed several trends. First, a high proportion of outbreaks which were published in the medical literature were due to *Salmonella*, *E. coli*, and Norwalk-like viruses. Reports of these investigations generally included both epidemiologic and microbiologic results. Agents were identified from the implicated vehicle in half of the published outbreaks. This reflects a publication bias for reporting outbreaks that are highly characterized and that report new agents, vehicles or new applications of methods.

Among outbreaks reported to CDC, etiologic agents were only isolated from food vehicles a little more than a quarter of the time. However, food testing was frequently done during the course of outbreak investigations, including in 22% of outbreaks in which a food vehicle could not be epidemiologically implicated. The usefulness of epidemiologic results in guiding microbiologic testing was demonstrated by the following observation. Among 358 outbreaks with a confirmed bacterial etiology for which food test results were reported, a positive result was reported for 205 (73%) of 280 outbreaks in which the vehicle was known, compared to 14 (18%) of 78 outbreaks in which the vehicle was not known. Thus, testing of food samples is more productive when epidemiologic analysis targets the food items to be tested, even for agents that can be readily isolated from foods.

Finally, the vast majority of USDA recalls were driven by results of microbiological testing rather than by identification of products associated with human illness. Regarding foods regulated by USDA, this implies:

1. While keeping some contaminated products from the marketplace, microbiologic testing appears to be identifying sporadic contamination of products at levels below which detectable outbreaks tend to occur. Thus, hazard does not equal risk, and as demonstrated by the *E. coli*

O157:H7 risk assessment, most contaminated products continue to reach the marketplace.

2. In some outbreak settings:

    a. Outbreak investigations are not being conducted quickly enough to remove contaminated products that are still in the marketplace.
    b. Outbreak investigations are failing to provide the sufficiently specific source information that is needed to stimulate a recall.

Selected Outbreaks that Highlight Use of Epidemiology to Guide Public Health Interventions

In addition to the systematic review of published and reported outbreaks, several well-characterized outbreaks highlight the importance of using epidemiology to guide public health interventions.

The first is an example of an outbreak where there was no laboratory data available because no agent was ever identified. In October 1989, physicians in New Mexico and Minnesota reported that three patients with an unusual illness characterized by peripheral eosinophilia and incapacitating muscle pain had all consumed dietary supplements containing tryptophan (36). Case-control studies based on a clinical case definition of eosinophilia myalgia syndrome (EMS) demonstrated a strong association between EMS and consumption of L-tryptophan containing products. In Minnesota, all 12 cases and none of 12 community controls consumed such products (37). Results of these case-control studies combined with surveillance demonstrating the widespread occurrence of serious illnesses, led to the products being withdrawn from the marketplace by FDA.

Follow-up case-control studies identified the source as single manufacturer of tryptophan, located in Japan (38). In addition, specific manufacturing conditions were associated with the implicated products through a detailed analysis of product information collected during the case control study. For example, it was demonstrated that implicated batches of tryptophan were made with a recently modified strain of *Bacillus amyloliquefaciens*, were made with less stringent purification processes, and contained a specific chemical marker detectable by high-performance liquid chromatography. Thus, without ever knowing the actual etiologic agent, the epidemiologic results gave investigators a reasonable understanding of how the outbreak occurred (38).

The use of epidemiology has been accepted as the only approach to investigating outbreaks, such as the one described above, where the agent is unknown. Epidemiologic results have also been generally accepted in outbreaks involving agents, such as hepatitis A virus, that cannot be isolated from

contaminated foods (39). However, even for pathogens that can be readily cultured, such as *Salmonella,* epidemiologic methods offer advantages over microbiologic testing in terms of sensitivity and timeliness.

The outbreak of *Salmonella* Enteritidis infections associated with Schwan's ice cream has been previously discussed. It serves as a useful model for the rapid conduct of an epidemiologic investigation and the initiation of public health interventions based on the results of that investigation. As previously noted, the case-control study ascertained detailed source information about a wide variety of food items. Within 3 days of initiating the case-control study, a product was implicated and a recall was initiated. Ultimately, confirmed or probable cases of salmonellosis associated with this outbreak were reported from 41 states, and the outbreak caused an estimated 224,000 illnesses (19). Of particular importance for this discussion is the fact that while *Salmonella* Enteritidis was isolated from the implicated ice cream, the results of the first official samples collected were not available until 10 days later. Thus, delaying the recall until the microbiologic results were available to "confirm" the source would have left thousands of consumers at risk for a preventable illness.

The results of Schwan's outbreak demonstrate the importance of conducting rapid and thorough epidemiologic investigations to implicate a specific food item or product. When epidemiologic studies are criticized it is usually because inadequate information was collected to identify a specific food item or source. This can lead either to imprecise public health recommendations, or the more damaging situation in which a product is falsely implicated. Unfortunately, both may lead to public challenges of the investigation's findings. The resolutions of such conflicts do not always attract as much attention as the conflicts themselves.

For example, from May through October 1989, a multistate outbreak of *Salmonella* serotype Javiana occurred due to contaminated mozzarella cheese manufactured in Green Bay, WI (40). Results of an initial case-control study in Minnesota implicated cheese products as the likely vehicle. Because the data did not allow for a specific manufacturing source to be identified, the Minnesota Department of Health recommended that consumers avoid eating any cheese produced in Wisconsin unless it was cooked. Unfortunately, this recommendation was made at the start of National Dairy Month, and extensive marketbasket testing of cheese products failed to identify any contaminated cheeses. A second case control study including detailed information on cheese sources for 50 cases and 100 controls. This study implicated both mozzarella cheese made at the Green Bay plant and other shredded cheeses that had been contaminated from the mozzarella. Thus, the results of the first study were corroborated and clarified. Ultimately, the outbreak-associated strain of *Salmonella* Javiana was isolated from the implicated cheese at levels ranging from 0.36 colony forming units (CFU) per 100g to 4.3 CFU per 100g (40).

An example of false conclusions based on inadequate information that has been previously discussed resulted in a Texas public health advisory issued regarding *Cyclospora* infections and strawberries (29). In this situation, local and state public health officials had data that properly implicated dessert items served at two banquets. However, their results could not distinguish between the various ingredients in the dessert. In addition, their recommendations were apparently made without regard for other outbreaks occurring elsewhere that might have helped clarify the potential risk from the strawberries, raspberries, or other ingredients in the dessert, and conflicting information had been obtained about the exact ingredients in the desserts. This outbreak is frequently cited as an example of why epidemiology is not reliable. However, while this example represented a failure of epidemiologic analysis, the cause of the failure was not the nature of epidemiology, but rather the application of epidemiologic methods; specifically, the failure to precisely define the exposure source. In fact, it was the result of epidemiologic investigations from a larger series of outbreaks that definitively demonstrated that Gautemalan raspberries were the actual source of the Texas outbreaks (21).

The fact that widespread distribution of contaminated food products can produce a series of related outbreaks adds another dimension to the use of epidemiology. As demonstrated above, identifying imported raspberries the source for a group of outbreaks helped implicate raspberries as the source for other outbreaks. In this example, the cumulative results of a series of related outbreaks transcended the individual outbreak results.

Another example of this occurred in August 1998 (32). Two *Shigella* outbreaks were detected in Minnesota restaurants. Both were initially investigated as independent events. Preliminary interviews with patrons failed to identify any suspicious food items. Ill food workers were identified in both restaurants. Thus, these outbreaks seemed to fit the expected epidemiological picture of foodborne shigellosis. However, results of PFGE subtyping of *Shigella sonnei* isolates from patients and foodworkers demonstrated that the outbreaks were caused by a common outbreak-associated strain that was different from other endemic strains of *Shigella* in Minnesota (32).

This finding led to a re-evaluation of the epidemiologic data looking at ingredients rather than complete menu items. In one restaurant, chopped parsley was associated with illness. In the other, chopped parsley was used on most menu items, and was served to a high proportion of both cases and controls. Ultimately, eight separate outbreaks of shigellosis that occurred during August 1998 were linked by PFGE subtype results and the use of chopped parsley on implicated food items. The source of parsley served in these restaurants was traced to a farm in Mexico. Although no parsley was available for testing, and eating chopped parsley was not independently implicated in each of these eight outbreaks, the consistency of findings by PFGE subtype, parsley source, and parsley use characteristics confirmed that all were part of the larger outbreak.

Thus, the epidemiologic “whole” of this outbreak was greater than the sum of the epidemiologic “parts”.

Summary

The use of epidemiology in the investigation of foodborne disease outbreaks has resulted in the identification and removal of many contaminated foods from the marketplace. It has also identified numerous deficiencies in our food system, that were subsequently addressed to make food safer. Applied epidemiology is the foundation of outbreak investigation and public health intervention. The fundamental role for epidemiology can be justified based on the proposition that in theory, information regarding the relationship between specific exposures and illness should be available for every outbreak setting, while appropriate food samples will not. Epidemiology has been shown to be more sensitive and timely than microbiological testing to identify contaminated food vehicles in outbreak settings. Empirically, it can also be demonstrated that results of epidemiologic investigations form the basis for our current system of foodborne disease surveillance in the US. Thus, the value of good outbreak investigations is demonstrated by the safety of our food supply.

Given these considerations, public health investigations can be improved. Critical questions regarding the speed and specificity of outbreak investigations remain to be addressed. To improve both the quality and speed of outbreak investigations, interviewers need to ascertain detailed information on potential food sources at the start of the investigation. While collecting this information may add several minutes to each interview, it may save several days of re-interviewing cases and controls later. Outbreaks can be investigated faster if the emphasis is placed on moving information rather than people. Centralized groups of trained interviewers can rapidly interview large numbers of cases and controls by telephone during most outbreaks. Data generated from interviews can be rapidly entered into databases and analyses conducted to facilitate co-ordination between the epidemiologists, public health laboratories, and environmental health specialists who may be evaluating specific establishments.

Models for developing such epidemiologic support for local outbreak investigations need to be explored on the national and state levels. Multistate outbreaks are usually investigated independently by local or state health departments, often with co-ordination by CDC. However, central co-ordination does not always address the lack of resources at the state or local level to conduct the investigation. Thus, in the 1998 multistate outbreak of listeriosis, it took over a month to complete a case-control study despite CDC's efforts to co-ordinate the investigation.

The outbreak of listeriosis associated with hot dogs and sandwich meat, and the *Salmonella* Enteritidis outbreak associated with Schwan's ice cream provide interesting comparisons in terms of methods and outcomes. Both were large multistate outbreaks that led to major product recalls. However, one was

investigated primarily by a single state health department. Detailed source information was collected through telephone interviews. A recall was initiated based on a strong and specific epidemiologic association. The other was conducted by several states co-ordinated by CDC. Detailed source information was only collected after consumption of hot dogs was initially implicated. A recall was initiated after epidemiologic information was supported by preliminary microbiological test results of products obtained from cases. Although both investigations ultimately resulted in product recalls, the differences between them, in terms of agents, the length of incubation periods, ease of diagnosis and microbiological culture, and investigation methods used demonstrate the complexities of foodborne disease surveillance.

Public health surveillance for foodborne diseases has demonstrated many successes at applying epidemiology to identify, control, and prevent outbreaks of foodborne disease. Further improving the safety of our food supply will require a strengthened commitment to public health surveillance of foodborne diseases based on the principles of epidemiology. Applying epidemiology to this task will require a similar commitment to increasing:

The sensitivity of outbreak detection
The specificity of outbreak investigation,
with respect both to case-definitions and exposure sources
The speed with which outbreaks are investigated

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-Appendix: Published Outbreaks Reviewed

1. University outbreak of calicivirus infection mistakenly attributed to Shiga toxin-producing Escherichia coli O157:H7--Virginia, 2000. MMWR Morb Mortal Wkly Rep 2001;50(23):489-91.

2. Foodborne outbreak of Group A rotavirus gastroenteritis among college students--District of Columbia, March-April 2000. MMWR Morb Mortal Wkly Rep 2000;49(50):1131-3.

3. Outbreaks of Norwalk-like viral gastroenteritis--Alaska and Wisconsin, 1999. MMWR Morb Mortal Wkly Rep 2000;49(10):207-11.

4. Outbreak of Escherichia coli O157:H7 infection associated with eating fresh cheese curds--Wisconsin, June 1998. MMWR Morb Mortal Wkly Rep 2000;49(40):911-3.

5. Escherichia coli O111:H8 outbreak among teenage campers--Texas, 1999. MMWR Morb Mortal Wkly Rep 2000;49(15):321-4.

6. Aldicarb as a cause of food poisoning--Louisiana, 1998. MMWR Morb Mortal Wkly Rep 1999;48(13):269-71.

7. Outbreak of Salmonella serotype Muenchen infections associated with unpasteurized orange juice--United States and Canada, June 1999. Can Commun Dis Rep 1999;25(19):164-7.

8. Outbreak of Escherichia coli O157:H7 and Campylobacter among attendees of the Washington County Fair-New York, 1999. MMWR Morb Mortal Wkly Rep 1999;48(36):803-5.

9. Norwalk-like viral gastroenteritis in U.S. Army trainees--Texas, 1998. MMWR Morb Mortal Wkly Rep 1999;48(11):225-7.

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