2008 Outbreak of Salmonella Saintpaul Infections Associated with Raw Produce


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ABSTRACT

BACKGROUND

Raw produce is an increasingly recognized vehicle for salmonellosis. We investigated a nationwide outbreak that occurred in the United States in 2008.

METHODS

We defined a case as diarrhea in a person with laboratory-confirmed infection with the outbreak strain of Salmonella enterica serotype Saintpaul. Epidemiologic, traceback, and environmental studies were conducted.

RESULTS

Among the 1500 case subjects, 21% were hospitalized, and 2 died. In three case-control studies of cases not linked to restaurant clusters, illness was significantly associated with eating raw tomatoes (matched odds ratio, 5.6; 95% confidence interval [CI], 1.6 to 30.3); eating at a Mexican-style restaurant (matched odds ratio, 4.6; 95% CI, 2.1 to ∞) and eating pico de gallo salsa (matched odds ratio, 4.0; 95% CI, 1.5 to 17.8), corn tortillas (matched odds ratio, 2.3; 95% CI, 1.2 to 5.0), or salsa (matched odds ratio, 2.1; 95% CI, 1.1 to 3.9); and having a raw jalapeño pepper in the household (matched odds ratio, 2.9; 95% CI, 1.2 to 7.6). In nine analyses of clusters associated with restaurants or events, jalapeño peppers were implicated in all three clusters with implicated ingredients, and jalapeño or serrano peppers were an ingredient in an implicated item in the other three clusters. Raw tomatoes were an ingredient in an implicated item in three clusters. The outbreak strain was identified in jalapeño peppers collected in Texas and in agricultural water and serrano peppers on a Mexican farm. Tomato traceback did not converge on a source.

CONCLUSIONS

Although an epidemiologic association with raw tomatoes was identified early in this investigation, subsequent epidemiologic and microbiologic evidence implicated jalapeño and serrano peppers. This outbreak highlights the importance of preventing raw-produce contamination.
Salmonella is a leading bacterial cause of gastroenteritis in the United States, and the incidence has changed little in the past decade. Produce that is eaten raw is an increasingly recognized vehicle for transmission of pathogens, including salmonella species.

On May 22, 2008, the New Mexico Department of Health notified the Centers for Disease Control and Prevention (CDC) about 19 cases of salmonella infection in May. All seven isolates with completed serotyping were Salmonella enterica serotype Saintpaul. Four of the tested isolates had indistinguishable patterns on pulsed-field gel electrophoresis (PFGE). On May 23, the CDC’s staff at PulseNet (a national molecular-subtyping network) identified three additional isolates with the same PFGE pattern from Colorado and Texas. In 2007, only 40 human Saintpaul isolates were submitted to PulseNet. This report describes the nationwide investigation of what became a large foodborne outbreak in the United States.

Methods

Outbreak Identification and Case Finding

Clinical laboratories send salmonella strains from ill persons to state public health laboratories for serotyping and PFGE subtyping with the use of standardized methods. State public health laboratories routinely submit PFGE patterns to PulseNet. We defined a case as laboratory-confirmed infection with the Saintpaul serotype of S. enterica with PFGE XbaI pattern JN6X01.0048 (the outbreak strain) from April 1, 2008, through September 4, 2008. For all studies, we defined diarrhea as at least three loose stools in a 24-hour period.

Epidemiologic Studies of Cases Not Linked to Restaurant Clusters

We initially interviewed case subjects in Texas and New Mexico to generate hypotheses about the source of infections. Three case–control studies were conducted to assess exposures among case subjects that were not linked to restaurants or other common events. Exposures were ascertained by means of interviews, which focused on the week preceding the illness (for case subjects) or the week preceding the interview (for control subjects). All study participants provided oral consent.

Study 1

In May 2008, the departments of health in New Mexico and Texas, the Navajo Nation, the Indian Health Service, and the CDC conducted a case–control study. To generate hypotheses, case subjects were interviewed with the use of a detailed questionnaire about consumption of numerous food items, including red bell peppers, green bell peppers, and other peppers. The subsequent case–control study included all food items that were reported as having been consumed by more than 50% of case subjects in these interviews, in addition to avocado and guacamole. For this study, case subjects had an illness that met the case definition and a reported onset of diarrhea on or after May 1. Control subjects without diarrhea were matched with case subjects according to age group and neighborhood. (For details, see the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Study 2

In June 2008, because of the growing scope of the outbreak and the concern that other food vehicles might be involved, the CDC and state and local health departments in 29 states conducted a multistate case–control study to further investigate possible sources. Data were collected on patterns of eating at Mexican-style restaurants and consumption of produce, including freshly made salsa, raw jalapeño and other hot peppers, raw cilantro, raw tomatoes, and 17 other items. Case subjects had an illness that met the case definition and reported an onset of diarrhea on or after June 1. Control subjects without diarrhea were matched with case subjects according to age group and neighborhood.

Study 3

In July 2008, the departments of health in New Mexico and Arizona, the Navajo Nation, the Indian Health Service, and the CDC conducted a household-based case–control study to collect information through personal interviews about possible sources of infection and preparation of food. Data were collected about how cilantro, jalapeño peppers, serrano peppers, and tomatoes were brought into, stored, prepared, and consumed in the home. A case household was defined as one with a case subject who had an illness that met the case definition and reported an onset of diarrhea on or after June 1. Case subjects...
residing in the household and the household’s primary food preparer were interviewed. Control households were those without a member who was ill with diarrhea, matched with case households according to neighborhood.

Texas Case Survey
In mid-July 2008, epidemiologists at the Texas Department of State Health Services interviewed 75 case subjects who had had an onset of illness between May 1 and June 7, because these subjects had not been specifically questioned about the consumption of hot peppers early in the outbreak. The questionnaire asked about consumption of raw jalapeño and serrano peppers, raw tomatoes, and other food items.

INVESTIGATION OF CLUSTERS LINKED TO RESTAURANTS OR EVENTS
A restaurant or event cluster was defined as a single location or event in which at least two persons with the outbreak strain became ill within 7 days after their meal date and had meal dates within 10 days of one another. To identify ingredients and sources for implicated food items in clusters, nine epidemiologic studies were conducted. For all studies, a case subject was defined as a person with diarrhea who had eaten at the implicated restaurant in the week before the onset of illness. Confirmed cases were defined as cases with culture confirmation of the outbreak strain or a salmonella strain for which the PFGE pattern was not determined. Some studies also included probable cases, which were defined as cases without culture confirmation of salmonella infection. Control subjects were defined as meal companions or restaurant patrons identified by means of credit-card receipts who had eaten at the restaurant during the same time window but did not have diarrhea. Structured questionnaires that were based on the restaurant menu were administered. Recipes for menu items were collected to allow for ingredient-level analyses.

ENVIRONMENTAL AND TRACEBACK INVESTIGATIONS
State and local health and agricultural departments, the Food and Drug Administration (FDA), and the CDC conducted traceback investigations of the distribution pathway for implicated food items associated with several ill persons and restaurant clusters. Environmental assessments were conducted as part of the restaurant-cluster investigations to determine whether food handlers were ill before the onset of illness in patrons and to identify practices in food preparation, handling, and storage. The FDA collected food samples and conducted environmental investigations along the distribution chain, including at distribution centers, packing facilities, and farms, to determine possible sources of contamination.

STATISTICAL ANALYSIS
Data were entered into a database, and statistical analyses were conducted with the use of SAS software, version 9.1 (SAS Institute). Odds ratios and 95% confidence intervals were calculated, and logistic-regression analyses were conducted. Among the many sub-studies, these regression analyses were variously done with data treated as both unmatched and matched, with and without adjustment for variables, with and without imputed values for missing data, and with and without recoding for response sensitivity. Information was continually reevaluated for evidence of a common causal pathway or pathways, and the process of statistical analysis was exploratory in character.

RESULTS

DESCRIPTION OF THE OUTBREAK
We identified 1500 case subjects who were infected with the outbreak strain of the salmonella Saintpaul serotype in 43 states, the District of Columbia, and Canada. The states with the highest incidence rates were New Mexico (58.4 cases per 1 million population) and Texas (24.5 per 1 million population) (Fig. 1). Illnesses began between April 16 and August 26 and peaked between mid-May and mid-June (Fig. 2). Of the case subjects, 21% were hospitalized, and infection may have contributed to two deaths (Table 1).

INVESTIGATION OF CASES NOT LINKED TO RESTAURANT CLUSTERS
Of the 19 case subjects who were interviewed with the hypothesis-generating questionnaire, more than 50% reported consuming raw tomatoes, eggs, ice cream, potatoes, milk, tortillas, cold breakfast cereal, raw onions, salsa, ground beef, chicken, and lettuce. The food most commonly identified was raw tomatoes, reported by 16 subjects (84%); 5 (26%) reported eating “other peppers” (i.e. other than red or green bell peppers).
Study 1 included 51 case subjects and 106 matched control subjects (Table 2). On univariate analysis, illness was significantly associated with eating raw tomatoes (reported by 88% of case subjects vs. 64% of control subjects; matched odds ratio, 6.7; 95% confidence interval [CI], 1.9 to 36.0) and with eating tortillas (matched odds ratio, 2.8; 95% CI, 1.0 to 10.0). After adjustment for the consumption of tortillas, illness remained significantly associated with eating raw tomatoes (matched odds ratio, 5.6; 95% CI, 1.6 to 30.3). Illness was not significantly associated with eating salsa (matched odds ratio, 1.7; 95% CI, 0.8 to 3.8), guacamole (matched odds ratio, 1.6; 95% CI, 0.7 to 3.5), or any other food item. The consumption of hot peppers was not assessed because only 26% of case subjects reported eating other peppers in hypothesis-generating interviews.

Study 2 included 141 case subjects and 281 matched control subjects. After adjustment for sex, Hispanic ethnic background, and age, illness was significantly associated with eating at Mexican-style restaurants (matched odds ratio, 4.6; 95% CI, 2.1 to ∞) and with eating pico de gallo (a type of salsa typically composed of tomatoes, onions, hot peppers, and other ingredients) (matched odds ratio, 4.0; 95% CI, 1.5 to 17.8), corn tortillas (matched odds ratio, 2.3; 95% CI, 1.2 to 5.0), and freshly prepared salsa (matched odds ratio, 2.1; 95% CI, 1.1 to 3.9) (Table 2). Illness was not independently associated with the consumption of tomatoes, jalapeño peppers, cilantro, avocados, fresh or bottled salsa, or onions, all of which were significantly associated on univariate analysis.

Study 3 included 41 households with case...
subjects and 107 households with matched control subjects. On univariate analysis, illness was significantly associated with having a raw jalapeño pepper in the home (matched odds ratio, 2.9; 95% CI, 1.2 to 7.6), and illness had a borderline association with having a raw serrano pepper in the home (matched odds ratio, 3.0; 95% CI, 0.9 to 9.6) (Table 2). Illness was not significantly associated with the presence of tomatoes, cilantro, or other food items in the home or with reported consumption of raw jalapeño peppers, raw serrano peppers, raw tomatoes, or other food items.

In the Texas survey of 75 case subjects whose illnesses began on or before June 7, 64 (85%) reported consuming raw tomatoes, 29 (39%) jalapeño peppers, 6 (8%) serrano peppers, 39 (52%) fresh salsa, 26 (35%) pico de gallo, and 27 (36%) guacamole.

INVESTIGATION OF CLUSTERS LINKED TO RESTAURANTS OR EVENTS

State and local health departments in 14 states and the District of Columbia reported 37 clusters of illness associated with either restaurants or events (Fig. 3 in the Supplementary Appendix). Of the 37 clusters, 35 were associated with restaurants, 1 with a mobile Mexican-style food vendor, and 1 with a privately catered event. Of the 35 restaurant-associated clusters, 30 (86%) involved Mexican-style restaurants. The median number of laboratory-confirmed cases for all 37 clusters was 4 (range, 2 to 47); 27 (73%) had 8 or fewer laboratory-confirmed cases.

Analytical studies of nine clusters were conducted, including eight involving Mexican-style restaurants (Table 3). A food item was implicated in six clusters. The items that had a significant association with illness were salsa (in
three clusters), guacamole (in two clusters), and a raw jalapeño pepper garnish (in one cluster). In all three clusters in which a single ingredient was significantly implicated, the ingredient was jalapeño peppers; hot peppers were an ingredient in an implicated item in three additional clusters (jalapeño peppers in one cluster and serrano peppers in two clusters). Raw tomatoes were an ingredient in an item associated with illness in three clusters, including one in which red, round tomatoes were specifically implicated.

**ENVIRONMENTAL AND TRACEBACK INVESTIGATIONS**

Environmental assessments conducted as part of the epidemiologic investigations of nine restaurant clusters did not identify recent diarrheal illness among food handlers. A total of 12 tracebacks of raw Roma and red, round tomatoes were completed: 8 tracebacks from 7 sporadic cases and 4 tracebacks from restaurant clusters. These tracebacks did not converge on any one geographic location, grower, or supplier. All tomato tracebacks included sources from Mexico, Florida, or both. Environmental investigations were conducted at five farms or packing firms in Mexico and three in Florida. Only one firm was packing tomatoes in Mexico at the time of the investigation, and all farms in Mexico and Florida had finished harvesting. The FDA analyses of approximately 183 domestic and imported tomato samples and 113 environmental swabs from tomato operations in Florida and Mexico did not identify salmonella.

Tracebacks to farms from 13 restaurant clusters were completed for jalapeño peppers from five states, including 3 restaurants (cluster D, consisting of two restaurant locations, and cluster G) in which jalapeño peppers were implicated. All 13 tracebacks led to distributors in Texas and Mexico that received jalapeño peppers from Farm A, which grew tomatoes in addition to jalapeño and serrano peppers, harvested all three crops between late April and late July and was an indirect supplier to the packing facility. Farm B supplied the same packing facility both through direct shipments and also indirectly through distributors. Farm B, located approximately 100 miles from Farm A, was this packing facility’s main pepper supplier. Agricultural water samples from Farm A yielded salmonella but not the outbreak strain. The FDA did not collect tomatoes at Farm A. The outbreak strain was isolated from a jalapeño pepper sample obtained from a produce importer in Texas that received jalapeño peppers from a packing facility in Nuevo Leon, Mexico. The traceback from the packing facility was complex, with commingling of products and a network of interrelated distribution points.

The FDA investigated two farms in Mexico (Farm A and Farm B) that supplied peppers to the packing facility (Fig. 2). Traceback records identified other farms that also supplied the facility during this period. Farm A, which grew Roma tomatoes in addition to jalapeño and serrano peppers, harvested all three crops between late April and late July and was an indirect supplier to the packing facility. Farm B supplied the same packing facility both through direct shipments and also indirectly through distributors. Farm B, located approximately 100 miles from Farm A, was this packing facility’s main pepper supplier. Agricultural water samples from Farm A yielded salmonella but not the outbreak strain. The FDA did not collect tomatoes at Farm A. The outbreak strain was isolated from two environmental samples, agricultural water, and serrano peppers on Farm B, which grew jalapeño peppers and serrano peppers, but not tomatoes, and harvested produce from mid-April to mid-June. The Colorado Department of Public Health and Environment isolated the outbreak strain from a jalapeño pepper collected from the home of a case subject in Colorado and traced this pepper from the grocery store where it had been purchased to another distributor in Texas. The source of these jalapeño peppers was not determined.

**Table 1. Characteristics of Case Subjects with Confirmed Salmonella enterica Serotype Saintpaul Infections in 2008.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case subjects interviewed for one or more epidemiologic studies — no./total no. (%)†</td>
<td>704/1500 (47)</td>
</tr>
<tr>
<td>Age — yr</td>
<td>Median 31</td>
</tr>
<tr>
<td></td>
<td>Range &lt;1 to 99</td>
</tr>
<tr>
<td>Female sex — no./total no. (%)</td>
<td>733/1478 (50)</td>
</tr>
<tr>
<td>Hospitalization — no./total no. (%)</td>
<td>308/1500 (21)</td>
</tr>
<tr>
<td>Race or ethnic group — no./total no. (%)‡</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>680/889 (76)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>263/938 (28)</td>
</tr>
<tr>
<td>Black</td>
<td>25/889 (3)</td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>106/889 (12)</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>17/889 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>61/889 (7)</td>
</tr>
</tbody>
</table>

† The median time from illness onset until ill persons were reached for an interview was 21 days; 90% were interviewed within 34 days.
‡ Race or ethnic group was self-reported. The number of patients who responded to the question about ethnic group was higher than the number who responded to the question about race.
Multiple public advisories were issued recommending that consumers avoid eating implicated produce items. These included an advisory on June 3, limited to New Mexico and Texas, recommending that consumers avoid eating certain types of tomatoes; this advisory was issued nationwide on June 7. A nationwide advisory concerning jalapeño peppers on July 9 was followed by a warning on July 30 not to eat peppers grown or packed in Mexico (Fig. 4 in the Supplementary Appendix).

**Table 2. Odds Ratios for Selected Food and Other Exposures in Three Case–Control Studies of* Salmonella enterica Serotype Saintpaul Infections Not Linked to Restaurant Clusters in 2008.**

<table>
<thead>
<tr>
<th>Study and Exposure</th>
<th>Case Subjects Exposed</th>
<th>Control Subjects Exposed</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw tomato</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With adjustment†</td>
<td>42/48 (88)</td>
<td>67/104 (64)</td>
<td>5.6 (1.6–30.3)</td>
</tr>
<tr>
<td>Without adjustment</td>
<td>42/48 (88)</td>
<td>67/104 (64)</td>
<td>6.7 (1.9–36.0)</td>
</tr>
<tr>
<td>Tortilla</td>
<td>39/47 (83)</td>
<td>69/104 (66)</td>
<td>2.8 (1.0–10.0)</td>
</tr>
<tr>
<td>Salsa‡</td>
<td>27/48 (56)</td>
<td>47/104 (45)</td>
<td>1.7 (0.8–3.8)</td>
</tr>
<tr>
<td>Guacamole‡</td>
<td>16/50 (32)</td>
<td>26/103 (25)</td>
<td>1.6 (0.7–3.5)</td>
</tr>
<tr>
<td><strong>Study 2§</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating at Mexican-style restaurant</td>
<td>68/138 (49)</td>
<td>64/278 (23)</td>
<td>4.6 (2.1–8.0)</td>
</tr>
<tr>
<td>Pico de gallo</td>
<td>35/127 (28)</td>
<td>26/257 (10)</td>
<td>4.0 (1.5–17.8)</td>
</tr>
<tr>
<td>Corn tortilla</td>
<td>51/126 (40)</td>
<td>67/251 (27)</td>
<td>2.3 (1.2–5.0)</td>
</tr>
<tr>
<td>Salsa</td>
<td>60/130 (46)</td>
<td>73/245 (30)</td>
<td>2.1 (1.1–3.9)</td>
</tr>
<tr>
<td><strong>Study 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jalapeño pepper</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In home</td>
<td>26/41 (63)</td>
<td>42/107 (39)</td>
<td>2.9 (1.2–7.6)</td>
</tr>
<tr>
<td>Consumed, with adjustment for sex and age‡</td>
<td>19/41 (46)</td>
<td>35/107 (33)</td>
<td>1.7 (0.6–5.0)</td>
</tr>
<tr>
<td>Serrano pepper</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In home‡</td>
<td>9/41 (22)</td>
<td>9/107 (8)</td>
<td>3.0 (0.9–9.6)</td>
</tr>
<tr>
<td>Consumed, with adjustment for sex and age‡</td>
<td>4/41 (10)</td>
<td>7/107 (7)</td>
<td>0.5 (0.1–3.1)</td>
</tr>
<tr>
<td>Raw tomato in home‡</td>
<td>19/41 (46)</td>
<td>38/107 (36)</td>
<td>1.6 (0.6–4.9)</td>
</tr>
</tbody>
</table>

* Study 1, the first multistate study, was conducted from May 26 to June 4 in Arizona, New Mexico, the Navajo Nation, and Texas. Study 2, the second multistate study, was conducted from June 26 to July 3 in 29 states: Arizona, California, Colorado, Connecticut, Georgia, Illinois, Indiana, Kansas, Kentucky, Maine, Maryland, Massachusetts, Michigan, Missouri, Nevada, New Mexico, New York, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, Tennessee, Texas, Vermont, Virginia, Washington, West Virginia, and Wisconsin. Study 3, a household-based study, was conducted from July 11 to July 25 in Arizona, New Mexico, and the Navajo Nation.

† This analysis was adjusted for the consumption of tortillas in the week before the onset of illness.
‡ The consumption of this item was not significantly associated with illness.
§ The analyses listed for study 2 were adjusted for sex, Hispanic ethnic group, and age.

**CONTROL MEASURES**

This outbreak of foodborne disease in the United States was one of the largest salmonella outbreaks ever identified. Because many salmonella illnesses are not confirmed by culture, it is likely that many more occurred than were identified.7 The results of multiple investigations indicate that jalapeño peppers were the major vehicle for transmission, and serrano peppers were also a vehicle. These findings include epidemiologic associations between illness and consumption of...

<table>
<thead>
<tr>
<th>Cluster Identifier</th>
<th>Cluster Location</th>
<th>Date Range of Meals Consumed</th>
<th>Implicated Food and Its Ingredients</th>
<th>Implicated Food in Ingredient-Level Analysis</th>
<th>Case Subjects Exposed</th>
<th>Control Subjects Exposed</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>East Texas</td>
<td>May 4 to June 4</td>
<td>None</td>
<td>None</td>
<td>0/14</td>
<td>0/45</td>
<td>NA</td>
</tr>
<tr>
<td>B</td>
<td>New York City</td>
<td>May 22 to June 5</td>
<td>None</td>
<td>None</td>
<td>0/8</td>
<td>0/55</td>
<td>NA</td>
</tr>
<tr>
<td>C</td>
<td>Central Texas</td>
<td>May 23 to June 9</td>
<td>Red salsa (fresh and canned tomatoes, serrano peppers, cilantro, green onion, salsa spices)†</td>
<td>None</td>
<td>19/20 (95)</td>
<td>24/34 (71)</td>
<td>30.0 (1.6 to 1311.0)‡</td>
</tr>
<tr>
<td>D</td>
<td>North Texas</td>
<td>May 23 to June 12</td>
<td>Salsa (canned tomatoes, jalapeño peppers, dried garlic powder, red pepper flakes, salt)</td>
<td>Jalapeño pepper</td>
<td>21/21 (100)</td>
<td>25/31 (81)</td>
<td>12.8 (1.3 to ∞)§¶</td>
</tr>
<tr>
<td>E</td>
<td>Wichita Falls, TX</td>
<td>May 30 to June 2</td>
<td>Salsa (large tomatoes, jalapeño peppers, dried garlic powder, red pepper flakes, salt)</td>
<td>Jalapeño pepper</td>
<td>45/47 (96)</td>
<td>16/40 (40)</td>
<td>24.7 (3.4 to ∞)§§</td>
</tr>
<tr>
<td>F</td>
<td>Charlotte, NC</td>
<td>June 8 to June 14</td>
<td>Guacamole (Roma tomatoes, serrano peppers, red onions, cilantro, avocados, lime juice, salt)</td>
<td>ND</td>
<td>4/4 (100)</td>
<td>42/113 (37)</td>
<td>8.7 (1.1 to ∞)‡</td>
</tr>
<tr>
<td>G</td>
<td>Roseville, MN</td>
<td>June 13 to June 22</td>
<td>Garnish (jalapeño peppers, red bell peppers)</td>
<td>Jalapeño pepper</td>
<td>17/19 (89)</td>
<td>8/73 (11)</td>
<td>62.0 (12.0 to 321.0)‡</td>
</tr>
<tr>
<td>H</td>
<td>Little Rock, AR</td>
<td>June 14 to June 22</td>
<td>None</td>
<td>None</td>
<td>0/7</td>
<td>0/21</td>
<td>NA</td>
</tr>
<tr>
<td>I</td>
<td>Jefferson County, MO</td>
<td>June 28 to July 2</td>
<td>Guacamole (red round tomatoes, jalapeño peppers, avocados, onions, lettuce, lime juice, cilantro)</td>
<td>None</td>
<td>5/6 (83)</td>
<td>13/44 (30)</td>
<td>11.3 (1.1 to 581.5)¶</td>
</tr>
</tbody>
</table>

* NA denotes not applicable, and ND not done.
† Red salsa was eaten as an appetizer with chips or with other food items.
‡ This odds ratio was calculated by means of multivariable analysis.
§ This matched analysis was adjusted for sex, meal date, and age group (<10 years vs. ≥10 years).
¶ This odds ratio was calculated by means of univariate analysis.
hot peppers, the convergence of tracebacksto a single farm that grew both types of peppers but not tomatoes, and isolation of the outbreak strain from agricultural water and serrano peppers collected on that farm. The consumption of jalapeño peppers was not specifically implicated in either study in which this hypothesis was explicitly tested (studies 2 and 3). However, study 2 implicated foods typically made or consumed with hot peppers, and study 3 implicated the presence of jalapeño peppers in the home. One explanation for the results of study 2 could be that produce items are consumed in small quantities as ingredients of other dishes and might not be recognized or always remembered after several weeks, making the implication of such items more difficult. In study 3, the respondent was often the food preparer, who would be likely to know the ingredients.

Early in the outbreak, raw tomatoes were thought to be a vehicle because study 1, conducted by standard methods, yielded a strong association between illness and consumption of raw tomatoes. Tomatoes have been implicated in many salmonella outbreaks.\(^9\)\(^{-11}\) The initial finding that tomatoes were a source was supported by the observation that the number of new cases decreased shortly after the nationwide tomato advisory.

The Texas survey, in which case subjects from early in the outbreak were specifically asked about the consumption of hot peppers and tomatoes, showed a high frequency of tomato consumption, which was similar to the frequency found in study 1, whereas fewer than half of those surveyed reported eating hot peppers. However, tomato traceback did not converge on any one geographic location, supplier, or growing area, and the FDA analyses of tomato samples did not identify salmonella.

The observed epidemiologic association with tomatoes may reflect collinearity between tomatoes and hot peppers, meaning that an association was identified because tomatoes were often eaten with hot peppers. It could also reflect amplified growth of salmonella in food items, such as salsa, containing both tomatoes and contaminated hot peppers. The decline in cases shortly after the nationwide tomato advisory could be explained if avoidance of raw tomatoes indirectly reduced exposure to contaminated hot peppers. The low frequency of reported hot-pepper consumption in the Texas survey could be due to unrecognized exposure to hot peppers as ingredients in other foods.

Salsa and guacamole, both foods typically containing tomatoes and hot peppers, were implicated repeatedly in cluster investigations; these foods may have provided a medium for salmonella growth. Cut or diced tomatoes require prompt refrigeration because of the potential for salmonella growth.\(^12\) However, salsa and guacamole are kept at room temperature for hours in some commercial settings.\(^13\) The addition of both fresh garlic and lime juice to salsas can suppress the growth of salmonella.\(^14\)

On the basis of FDA investigations, pepper contamination probably occurred on the farm. This may not be unusual; a small survey of Mexican farms that grow chile peppers indicated that 6 of 14 irrigation-water samples (43%) and 3 of 5 pepper rinses (60%) yielded salmonella (none of the serotypes were Saintpaul).\(^15\) From 1972 through 1999, only 1.2% of human salmonella isolates that were serotyped at public and private laboratories in Mexico were serotype Saintpaul.\(^16\)

This outbreak investigation highlights the recurring challenges of epidemiologic identification of ingredients in foods that are commonly consumed, rapid identification and investigation of local clusters, the need to continue exploring hypotheses during an ongoing outbreak, and produce tracing in the supply chain. Traceback issues such as commingling, repacking, varying degrees of product documentation throughout the supply chain, difficulty in linking incoming with outgoing shipments to the next level in the distribution chain, and the complexity of the distribution chain continue to hinder product-tracing efforts. Improvements in product-tracing systems and the ability of the systems to work together are needed for more rapid tracing of implicated products through the supply chain in order to maximize public health protection and minimize the economic burden to industry. In addition, an understanding of the mechanisms and ecologies that can lead to contamination of produce on farms and the institution of additional control measures from the source throughout the supply chain are critical for preventing similar outbreaks in the future.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.
REFERENCES


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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

APPENDIX

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Multistate and Nationwide Foodborne Outbreak Investigations

Introduction:

In recent years, large multi-state or nationwide foodborne outbreaks have become more commonly recognized. Improved surveillance systems in the United States are better at identifying outbreaks that would previously have been missed. Changing patterns in global food production have resulted in food being distributed over large distances. This combined with increasing integration and consolidation of agriculture and food production can result in a contaminated food rapidly causing a geographically widespread outbreak.

Public health officials investigate outbreaks to control them, to prevent additional illnesses, and to learn how to prevent similar outbreaks from happening in the future. This supplement explains how the public health community detects, investigates, and controls foodborne disease outbreaks.

Background:

When two or more people get the same illness from the same contaminated food or drink, the event is called a foodborne outbreak. Illnesses that are not part of recognized outbreaks are called "sporadic." Foodborne illnesses are caused by pathogens and toxins or chemicals. More than 250 pathogens and toxins are known to cause foodborne illness, and nearly all of them can cause an outbreak. Many types of foods can become contaminated. Some of the foods that have been...
linked to outbreaks include eggs, fish and shellfish, meat, nuts, poultry, raw (unpasteurized) milk, and raw fruits and vegetables.

The size and scope of a foodborne outbreak can vary based on which pathogen or toxin is involved, how much food is contaminated, where in the food production chain contamination occurs, where the food is served, and how many people eat it. Outbreaks can be local, statewide or regional, or nationwide. For example, a local outbreak may occur when a contaminated casserole is served at a church supper and church members become ill. A statewide or regional outbreak may occur when a contaminated batch of ground beef is sold at several locations of a grocery store chain which leads to illnesses in several counties or even in neighboring states. A multistate or nationwide outbreak may occur when contaminated produce from one farm is shipped to grocery stores and/or restaurants in many states or nationwide and causes illness in people in many states.

Public health agencies that identify and investigate foodborne illnesses operate on several levels. Which agency or agencies participate in an investigation depends on the size and scope of the outbreak. Sometimes one agency starts an investigation and then calls on other agencies as more illnesses are reported across county or state lines. Public health officials in just one city or county health department investigate local outbreaks. Typically, the state health department investigates outbreaks that spread across several cities or counties. State health departments often work with the state department of agriculture and with federal food safety agencies. For outbreaks that involve large numbers of people or severe or unusual illness, a state may ask for help from the
Centers for Disease Control and Prevention (CDC). CDC is a non-regulatory agency that focuses on problem identification and source implication. CDC usually leads investigations of widespread, multistate outbreaks—those that affect many states at once. States communicate regularly with one another and with CDC about outbreaks and ongoing investigations.

CDC routinely collaborates with federal food safety agencies, such as the U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA) Food Safety and Inspection Service (FSIS) throughout all phases of an outbreak investigation. FDA and FSIS, by law, oversee U.S. food safety and regulate the food industry with inspection and enforcement. In the case of an outbreak of foodborne illness, the regulatory agencies focus on risk assessment and management, as well as source assessment. They may trace foods to their origins, test foods, assess food safety measures in restaurants and food processing facilities, lead farm investigations, and announce food recalls.

Outbreak investigative teams are usually made up of a variety of professionals, including epidemiologists, microbiologists, environmental health specialists or sanitarians, and regulatory compliance officers and inspectors. The Investigation Team may add other professionals as the investigation proceeds. Additionally, the food industry can play an important role in preventing and responding to outbreaks of foodborne illness.
Investigating Foodborne Outbreaks

A foodborne outbreak investigation goes through several steps. They are described here in order, but in reality, investigations are dynamic and several steps may happen at the same time (Figure 1).

1. Detecting a possible outbreak
2. Defining and finding cases
3. Generating hypotheses about likely sources
4. Testing hypotheses
5. Finding the point of contamination and source of the food
6. Controlling an outbreak
7. Deciding an outbreak is over
Figure 1: Steps in a Foodborne Outbreak Investigation.

**Step 1: Detecting a Possible Outbreak**

Detecting an outbreak is the first step. An outbreak with hundreds of ill persons can be missed if they are spread out over a wide area. One way health officials find outbreaks is through public health surveillance. By gathering reports of illnesses all the time, they know how many illnesses to expect in a given time period in a given area. If a larger number of people than expected appear to have the same illness in a given time period and area, it’s called a cluster. When an
investigation shows that ill persons in a cluster have something in common to explain why they all got the same illness, the group of illnesses is called an outbreak.

Detecting a cluster or possible outbreak of foodborne illnesses can occur in several ways. Informal reports occur when members of a community call the local health department to report a group of suspected food-related illnesses. This might happen if, for example, several people got sick after eating at a group dinner. Formal reporting systems play an important role in outbreak detection. Doctors and microbiologists in each state must report infections that are on a list of notifiable diseases when they diagnose them in patients. This list includes many foodborne illnesses. As public health officials look at disease reports, they may notice that the number of people with a particular illness is higher than expected. Sometimes an astute clinician realizes that he or she is seeing more cases of an illness than would be expected and calls the health department directly to discuss it with them. For some pathogens, like the bacteria Salmonella and E. coli O157, public health laboratories do special tests to help detect clusters that might otherwise be missed. When a doctor suspects that a patient has a foodborne illness, he or she sometimes asks the patient to submit a stool sample (or some other type of sample). The doctor’s office sends the patient’s sample to a clinical laboratory. The clinical laboratory may isolate a certain bacteria and identify it as Salmonella or E. coli O157, for example. The clinical laboratory tells the doctor’s office what the patient has so the doctor can treat the illness, and then sends the bacteria to the state public health laboratory. The state laboratory does further subtyping tests on the bacteria including serotyping and DNA fingerprinting or pulse-field gel electrophoresis (PFGE). Serotyping identifies the specific strain of bacteria based on markers on
the surface of the bacteria. When several strains have the same markers or serotype all at the same time, and there are more with that one serotype than is expected, that’s a sign of a possible outbreak. DNA fingerprinting identifies the bacteria’s specific genetic pattern or DNA fingerprint. Bacteria can have thousands of different patterns. State laboratories report their DNA results to the PulseNet database. Coordinated by CDC, PulseNet is the national molecular subtyping network for foodborne disease surveillance. By looking at the PulseNet database, health officials can identify clusters of illnesses caused by bacteria with the same fingerprint at the same time, even if the ill people are spread across many counties or states. This is especially useful when the number of illnesses in any one county or state is not big enough by itself to point to a possible outbreak. It can take 2 or 3 weeks from the day the person became ill to the day that the results of fingerprinting the bacteria are added to the PulseNet database.

**Step 2: Defining and Finding Cases**

Often, the first illnesses that are recognized are only a small part of the total outbreak. Finding more persons who are ill is important to help public health officials understand the size, timing, severity, and possible sources of the outbreak. Health officials develop a case definition to spell out which ill persons will be included as part of the outbreak. Case definitions may include details about: features of the illness, the pathogen or toxin, if known, certain symptoms typical for that pathogen or toxin, time range for when the illnesses occurred, geographic range, such as residency in a state or region, and other criteria, such as DNA fingerprint (if the pathogen is tracked by PulseNet). There might be several case definitions for an outbreak investigation, each with a different purpose. For example, one case definition might be for confirmed illnesses and
another for probable illnesses. The number of illnesses that meet the case definition is called the case count.

Using the case definition, investigators search for more illnesses related to the outbreak. They do this by reviewing regular surveillance reports, reviewing laboratory reports to PulseNet, asking local clinical and laboratory professionals to report cases of the particular illness more quickly, as soon as they suspect the diagnosis, reviewing emergency room records for similar illnesses, surveying groups that may have been exposed, and asking health officials in surrounding areas to watch for illnesses that might be related.

Investigators watch the progression of an outbreak by keeping track of who becomes ill, when they become ill, and where they live. To help keep track of the number of illnesses over time, investigators use a graph called an epidemic curve or epi curve. The epi curve shows the number of illnesses over time. The pattern of the epi curve can help investigators decide if ill persons were exposed to the same source of illness over a short period or if the exposure to the source was over a longer time. Investigators use maps to mark where ill persons live so they can easily see whether and how the outbreak is spreading over an area or community.

**Step 3: Generating Hypotheses About Likely Sources**

Pathogens that cause foodborne illness can also spread by contaminated water or by direct contact with an ill person or direct or indirect contact with an infected animal. When looking for the source of the illness, investigators first need to decide on the likely mode(s) of transmission.
The pathogen causing illness, where ill persons live or how old they are may suggest the mode of transmission, and even a specific source. Hypothesis generation should be thought of as an iterative process in which possible explanations are continually refined or refuted.

When exposure to a food is suspected, the investigators next must consider the large number of foods that may be the source or vehicle of infection. The number of different food items is vast, so the investigation needs to narrow the list to the foods that the ill people actually ate before they got sick, and then further narrow it to the specific foods that many of the ill people remember eating. Health officials interview persons who are ill to find out where and what they ate in the days or weeks before they got sick. These interviews are called “hypothesis-generating interviews.”

The time period they ask about depends on the pathogen’s incubation period—the time it takes to get sick after eating the contaminated food. This varies for different pathogens. Which foods they ask about depends on what investigators already know about the exposure. If several cases have occurred at a restaurant, hotel, or catered event, for instance, interviews will focus on the menu items prepared, served, or sold there. If there is no obvious place of exposure or subcluster of cases identified, investigators may use a standardized questionnaire, also known as a "shotgun" questionnaire.
A shotgun questionnaire may include questions that ask whether a person ate any of a long list of food items, open-ended questions that review each meal a person ate in the days before illness began, and questions about food shopping habits, travel, restaurant dining, and attendance at events where food was served. From the interviews, investigators create a short list of the foods and drinks that many ill persons had in common. Foods that none or very few of the sick people reported eating are considered as less likely to be the source. Investigators then look at other information, such as the results of any food testing, past experience with the suspected pathogen, and the age or ethnicities of ill persons. Based on all the information they gather, the investigators make a hypothesis about the likely source of the outbreak. However, shotgun interviews can only suggest hypotheses that are contained on the questionnaire. This approach may not lead to any refined testable hypothesis. Intensive open-ended interviews can help in this situation.

Coming up with a hypothesis is often challenging and may take time for several reasons. First, interviews of ill persons are highly dependent on their memories. The time from the start of illness to knowing that the ill person was part of an outbreak is typically about 2–3 weeks. Ill persons may not remember in detail what they ate that long ago. Also, when the contaminated food is an ingredient (such as eggs, spices or herbs, or produce in a salsa), the task becomes even harder. People often don’t remember or know the ingredients of the foods they ate. These challenges may prevent a hypothesis from quickly appearing. In some cases, ill persons may be interviewed multiple times as new ideas arise about possible sources. It can sometimes be helpful
to visit someone's home and look at the foods in their pantry and refrigerator, or to get their permission to review the information from their shopper cards.

A useful method for generating hypotheses in large, multistate outbreaks includes rapid and thorough investigation of restaurant clusters; these cluster investigations are critical to identifying specific food vehicles and provide detailed ingredient content and information on sources of food items for traceback investigations. However, delays inherent in the current system of surveillance for and investigation of foodborne disease outbreaks contribute to the time it takes to recognize clusters. The median time from illness onset to submission of the PFGE pattern of patients' *Salmonella* isolates to PulseNet should be decreased, improved interview formats should be used, and interviews that identify restaurant clusters should be conducted sooner. Conducting and completing interviews with a standardized questionnaire in a timely manner remains a critical deficiency during multistate outbreak investigations, partly because such interviews can lead to identification of clusters. Questionnaire data are typically submitted by facsimile to CDC for lack of a flexible and rapidly configurable electronic data gathering platform.

**Step 4: Testing the Hypotheses**

A hypothesis should be tested to determine if the source has been correctly identified. Investigators use many methods to test their hypotheses. Two main methods are analytic epidemiologic studies and food testing. Case-control studies or cohort studies are the most common type of analytic study conducted so investigators can analyze information collected...
from ill persons and comparable well persons to see whether ill persons are more likely than people who did not get sick to have eaten a certain food or to report a particular exposure. Controls for a case-control study may be matched on geography to ensure that cases or ill persons and controls or well persons had the same opportunities for exposure to a contaminated food item. One method to geographically match is to use a reverse digit dialing protocol. A case address is entered into an online directory (such as www.whitepages.com), then a reverse address search is conducted to identify phone numbers for neighbors in that geographic area. Duplicate phone numbers and businesses are excluded.

If eating a particular food is reported more often by sick people than by well people, it may be associated with illness. Using statistical tests, the investigators can determine the strength of the association (i.e., how likely it is to have occurred by chance alone), and whether more than one food might be involved. Investigators look at many factors when interpreting results from these studies. These include frequencies of exposure to a specific food item, strength of the statistical association, dose-response relationships, the food’s production, preparation and service, and the food’s distribution.

Food testing can provide useful information and help to support a hypothesis. Finding bacteria with the same DNA fingerprint in an unopened package of food and in the stool samples of people in the outbreak can be convincing evidence of a source of illness. However, relying on food testing can also lead to results that are confusing or unhelpful. This is the case for several reasons. First, food items with a short shelf life, such as produce, are often no longer available by
the time the outbreak is known, so they cannot be tested. Second, even if the actual suspected food is available, the pathogen may be difficult to detect. This is because the pathogen may have decreased in number since the outbreak or other organisms may have overgrown the pathogen as the food started to spoil. Also, the pathogen may have been in only one portion of the food. A sample taken from a portion that was not contaminated will have a negative test result. So, a negative result does not rule out this food as a source of illness or the cause of the outbreak. Leftover foods or foods in open containers may have been contaminated after the outbreak or from contact with the food that actually caused the outbreak. Lastly, some pathogens cannot be detected in food because there is no established test that can detect the pathogen in the suspect food.

Sometimes in testing hypotheses, investigators find no statistical association between the illnesses and any particular food. This is not unusual, even when all the clues clearly point to foodborne transmission. In fact, investigators identify a specific food as the source of illness in about half of the foodborne outbreaks reported to CDC. Not finding a link between a specific food and illness can happen for several reasons. One reason is that public health officials may have learned of the outbreak so long after it occurred that they could not do a full investigation. There may have been competing priorities or not enough staff and other resources to do a full investigation. An initial investigation may not have led to a specific food hypothesis, so no analytic study was done or the initial hypothesis could have been wrong. An analytic study may have been done, but it did not find a specific food exposure because the number of illnesses to analyze was small, because multiple food items were contaminated, or because the food was a
"stealth food." Stealth foods are those that people may eat but are unlikely to remember. Examples include garnishes, condiments on sandwiches, and ingredients that are part of a food item (e.g., the filling in a snack cracker). Food testing did not find any pathogen related to the outbreak, or food testing may not have been done at all.

When no statistical association is found, it does not mean that the illness or outbreak was not foodborne. It means only that the source could not be determined. If the outbreak has ended, the source of the outbreak is declared unknown. If people are still getting sick, investigators must keep gathering information and studying results to find the food that is causing the illnesses.

**Step 5: Finding the Point of Contamination and Source of the Food**

If a likely source is identified, investigators may also do an environmental assessment or evaluation to find out how the food was contaminated. The assessment could involve one food facility or several. If the people who got sick ate food prepared in only one kitchen, it is likely the contamination occurred in that kitchen. Investigators interview the people who prepared the food to find out the ingredients used, the steps followed in preparing the food, and the temperatures used to prepare and hold the food. They look at the health practices and training of the workers and at the cleanliness of the kitchen. They also check the health status of the workers at the time the exposures took place. In a commercial or institutional kitchen, they look at past inspection reports to see if there has been a history of problems.
If an outbreak is linked to a food prepared in a number of different kitchens (like hamburgers from many stores of the same chain) or to a food that was bought from many stores and eaten without further preparation (like peanut butter), it is likely that contamination happened somewhere in the food production chain before the final kitchen. In that case, investigators do a “source traceback” to find out where contamination occurred (Figure 2).

Figure 2: Finding the Point of Contamination and Source of the Food.

Tracebacks typically start from several ill persons or restaurants to see whether and where the food production chain comes to a common point. Finding this point helps to define where
contamination occurred and can help to confirm the hypothesis. Investigators ask about suppliers of the suspect food item for stores, restaurants, or cafeterias where they believe the suspect food was bought or eaten. They then ask food suppliers where they received the suspect food item from, and so on. They study purchase and shipment information to find food items that are most closely associated with the illnesses.

These steps usually involve local or state environmental health specialists. For widespread or severe outbreaks, they often involve state environmental health specialists or other state public health officials and investigators from the Food and Drug Administration (FDA), U.S. Department of Agriculture (USDA), and CDC. Information from the environmental assessment and source traceback suggests ways to control the outbreak and prevent similar outbreaks from happening in the future.

**Step 6: Controlling an Outbreak**

Once a food is found to be the source of illness, control measures may be needed right away. If contaminated food stays on store shelves, in restaurant kitchens, or in home pantries, more people may get sick. Outbreak control measures might include requiring specific measures to clean and disinfect food facilities, temporarily closing a restaurant or processing plant, recalling food items, telling the public how to make the food safe or to avoid it completely, or telling consumers to throw away the suspect food from their pantry or refrigerator.
Public health officials may decide on control measures on the basis of strong epidemiological evidence on the disease’s origin, spread, and development. They do not need to wait for proof of contamination from the laboratory. This practice can result in earlier action to protect the public’s health. As officials learn more during the investigation, they may change, focus, or expand control measures and advice to the public.

**Step 7: Deciding an Outbreak is Over**

An outbreak ends when the number of new illnesses reported drops back to the number normally expected. The epidemic curve helps investigators see that illnesses are declining. Even when illnesses from the outbreak appear to have stopped, public health officials still continue surveillance for a few weeks to be sure cases don’t start to increase again. If that happens, they continue or restart their investigation. It could be that the source was not completely controlled, or that a second contamination involving another food or location is linked to the first outbreak.

**Step 8: Preventing Future Outbreaks**

The ultimate goal for public health and food safety officials is not just stopping outbreaks once they occur, but preventing them from happening in the first place. Long-term prevention of foodborne outbreaks takes the actions of many partners in the food production chain, stretching from farm to table. Some prevention measures include quality assurance programs at egg farms, safe agricultural practices for produce farmers, efforts to keep shellfish harvest beds free of sewage contamination, inspection systems at meat processing plants, use of pasteurization,
canning, cooking, irradiation, and other steps to kill pathogens in food processing, buyer specifications for food safety in food purchasing contracts, training for restaurant managers and food workers about food safety and sanitation measures, proper hand-washing procedures, and the importance of giving food workers paid sick leave, and food safety education for consumers.

**Statistical Considerations in Foodborne Disease Outbreak Investigations**

Outbreak identification and investigation takes place in the context of a stream of information about cases of human illness. The minimum amount of information typically consists of data on time, location, and type of illness. Sometimes this is available at the individual level and sometimes it is available only at the group level. The precision of each dimension can vary (e.g., time as day, week, or month; location as address, county, or state; type as illness, salmonellosis, salmonellosis of known serotype, salmonellosis of known serotype and PFGE pattern). This stream of “surveillance” data does not contain information about which illnesses share a common cause, whether foodborne or otherwise. It does contain the basis for defining a “cluster” or cases of illness that have a common type at some level (e.g. serotype or PFGE pattern) and are close together in time, location, or both to a degree that is unusual. It is important to note that whatever notion of cluster one applies to identify a cluster of illnesses, that notion need bear no relationship to common cause. To identify cases of illness as members of a cluster is to propose a hypothesis. The cluster may consist of:

- Unrelated cases (the cluster does not become an outbreak)
- Some cases from an outbreak and some unrelated cases (the cluster goes beyond the outbreak)
• All of the cases from an outbreak (the cluster is the outbreak)
• A subset of the cases from an outbreak (the outbreak goes beyond the cluster)
• More complicated scenarios involving mixtures of multiple outbreaks and unrelated cases.

The relationship between designating a set of cases as a cluster and verifying a common cause can be enormously complex. A cluster embodies some notion of closeness, but our stated measures are not on the same scale. Type is a categorical measure while time and location are continuous measures, at least conceptually. Clusters are initially limited to illnesses of a single type, and closeness is within type. (A type classification that is too fine, meaning illnesses with a common cause frequently show different type, will then potentially require a second stage wherein single-type clusters with common cause are combined.) Closeness to a degree that is unusual is a relative notion; one must establish a baseline. Ideally that would derive from a surveillance stream that is known to contain only sporadic cases of illness. No such stream exists because not all historical cases have been investigated and even if they had been investigated, proving the negative, that no causal link exists between them, is impossible. So, we choose an imperfect baseline. We then establish a threshold for “sufficiently unusual” as to suggest common cause. This is an action threshold; it might be set low if there are very few clusters to investigate, and it should be set relatively high if investigating one cluster means not investigating another. In either case we would like the threshold to sort against scenario 1) above and against scenario 2) to the extent that the fraction of related cases is so low as to preclude identifying their common cause. It is epidemiologically important to note that scenario of all of the cases from an outbreak (i.e., the cluster is the outbreak) is not necessarily the ideal. In the
outbreak of *Salmonella* Saintpaul infections described in this paper, clusters linked to restaurants/events existed within the overall outbreak, and the ability to narrow the investigation of exposures among those restricted groups facilitated the identification of a common cause, at least for those cluster types. In identifying clusters linked to restaurants/events, extrapolating to the larger group required further epidemiological argument. Finally, biological and epidemiological differences in pathogens and agents that cause outbreaks and specifically foodborne outbreaks require that the operational understanding of the relationship between cluster and outbreak must be developed separately at the pathogen/agent level; each presents its own problems.

Outbreak investigations and especially large-scale investigations where new cases of illness are being identified produce a highly contingent body of information, and can't really be understood in terms of the statistics of randomized controlled experiments, clinical trials, or even static blocks of observational data. The primary objective for foodborne outbreak investigations is a positive test result with a (narrowly defined) PFGE pattern matching that of confirmed human illness from an unopened food container, or some other clear basis for causal connection. Subsequent positive environmental samples from a production facility or farm are also important in developing “causal” links. In an outbreak where new cases are occurring, finding a positive food sample is the guiding objective, and while exploratory epidemiology is the key tool to identify candidate foods for testing, traditional inferential statistical methods are not possible. The reason is that traditional statistics is not adequate to describe the process. To begin with the initial hypotheses are informed by the experiences of the haphazard set of initial investigators at the state or local level and the disparate investigative models. Those hypotheses are modified
through conversation and informal data sharing. The modified hypotheses are used to inform questionnaires for further case information gathering, but also parallel informal traceback and other investigative activities. The revised hypotheses are then explored by querying both new cases, but also the cases that gave rise to the hypotheses themselves, typically because of a dearth of accessible new cases. New questions are often piggy-backed onto existing instruments as accumulating data is analyzed. In active publicized outbreaks, cases and controls receive information that may affect their responses to questions about their exposures, complicating the fact that there is a known potential for differential rates of exposure misclassification. As in the outbreak of *Salmonella* Saintpaul infections described in this paper, clusters linked to restaurants/events are often analyzed separately, and sequentially as they are identified, with data from one informing investigations of others. Epidemiological studies take place in parallel with one another and with various forms of exploratory and confirmatory traceback. There are no standard statistical tools capable of objectively summarizing the body of accumulating information in a complex foodborne outbreak. The tools we use, we use knowingly violating most if not all of their basic assumptions. Our goal in so doing is to maintain an ordering on the weight of evidence for the competing hypotheses that exist at any point in time during the investigation. We attempt to control or adjust for sources of bias, confounding, and data dependence as consistently as possible, knowing that we fall short. We perform as much sensitivity analysis as is practical in a real-time setting, and initiate validation studies in some outbreaks, but the flow of the investigation often makes these artificial in that testing information may be available before or as the studies are launched. Investigation of foodborne outbreaks is still as much art as science, and the steps outlined above are still being tested and refined. Each
outbreak is unique, and each step of its investigation must be treated accordingly. Statistical summary of the evidence gathered remains a subjective process.

**Outbreak Investigations: Informing Prevention of Foodborne Diseases**

Outbreak investigations play a key role in preventing foodborne diseases. Investigations may find new pathogens, new food vehicles, and unsuspected gaps in the food safety system. They can improve scientific understanding of how the contamination occurred at specific points in the food supply chain, if it may occur again, and how it may be reduced or prevented. Outbreak investigations also offer opportunities for different authorities and professionals to work together and may reveal points at which the public health system can be improved. Often outbreak investigations raise questions that need research to better understand how contamination occurs and how it can be prevented or reduced. The result of outbreak investigations and additional research should be better practices in industry, regulations and enforcement by the regulatory agencies, and consumer understanding, all of which should reduce the number of foodborne illnesses that occur.
Figure 3. Number of restaurant clusters by week of first meal consumed by case-patient with identifiers linking clusters with analytic studies to Table 2, United States, April 1 to September 4, 2008 (n=37)

NOTE: By the time the first restaurant cluster was reported to CDC on June 4th, 77 PFGE-confirmed cases and 20 cases pending PFGE had been reported to CDC, and many more had occurred that were not yet reported.
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<td>Hypothesis generating interviews conducted</td>
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<td>First multistate case-control study (Study 1)</td>
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<td>Investigation of restaurant cluster in Wichita Falls, TX (Cluster E)</td>
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<td>Second multistate case-control study (Study 2)</td>
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### Figure 4: Timeline of Events – Nationwide Outbreak of *Salmonella* Serotype Saintpaul Infections, by week, 2008

- **Primary finding/outcome**
  - Multistate outbreak of *Salmonella* Saintpaul identified and investigations to determine source initiated.
  - Interviews conducted for 19 case-patients on events, animal contact, travel, restaurants, sources of food at home, open-ended food history, and >200 food items including produce (tomatoes, lettuce, cilantro, bell peppers, other peppers), salsa, guacamole, and tortillas. Over 50% of case patients report consuming raw tomatoes, eggs, ice cream, potatoes, milk, tortillas, cold cereal, raw onion, salsa, ground beef, chicken, and lettuce.
  - Illness significantly associated with eating raw tomatoes [matched Odds Ratio (mOR)=5.6, 95% Confidence Interval (CI)=1.6–30.3] after adjusting for consumption of tortillas. Illness was not significantly associated with eating salsa (mOR=1.7, 95% CI=0.8–3.8), guacamole (mOR=1.6, 95% CI=0.7–3.5), or any other food item.
  - Illness significantly associated with eating certain types of tomatoes (June 3). Limited advisory recommending that consumers in New Mexico and Texas avoid eating certain types of tomatoes (June 3).
  - Tomato advisory expanded nationwide by FDA along with a reminder that they are often used in fresh salsa, guacamole, and pico de gallo and are part of fillings for tortillas (June 7).
  - Salsa implicated in menu level analysis; jalapeño peppers implicated in ingredient-level analysis. In a multivariate model containing raw tomatoes and raw jalapeño peppers as independent variables, only raw jalapeño peppers were independently associated with illness (mOR=25; 95% CI=3.4–infinity).
  - Garnish implicated in menu level analysis; jalapeño peppers implicated in ingredient-level analysis.
  - Illness was significantly associated with eating at a Mexican-style restaurant (mOR=4.6, 95% CI=2.1–infinity), and with eating pico de gallo (mOR=4.0, 95% CI=1.5–17.8), corn tortillas (mOR=2.3, 95% CI=1.2–5.0), and freshly prepared salsa (mOR=2.1, 95% CI=1.1–3.9). Illness was not independently associated with consumption of tomatoes, jalapeño peppers, cilantro, avocados, salsa, or onions, all of which were significantly associated on univariate analysis.
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<td>Investigation of restaurant cluster in north Texas (Cluster D - 2 restaurant locations)</td>
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<td>Investigation of restaurant cluster in Charlotte, NC (Cluster F)</td>
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<td>Centers for Disease Control and Prevention (CDC) sends two epidemiologists to US Food and Drug Administration (FDA) to assist with traceback investigations</td>
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<td>FDA conducts hot pepper traceback</td>
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<td>Nationwide hot pepper alert issued</td>
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<td>Texas case survey conducted</td>
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<td>Investigation of restaurant cluster in New York City, NY (Cluster B)</td>
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<td>Investigation of restaurant cluster in Central Texas (Cluster C)</td>
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<td>Household-based study in Arizona, New Mexico, and Navajo Nation (Study 3)</td>
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<td>On univariate analysis, illness in the household was significantly associated with having a raw jalapeño pepper in the household (mOR=2.9, 95% CI=1.2–7.6), and illness had a borderline association with having a raw serrano pepper in the household (mOR=0.9, 95% CI=0.4–2.1). Illness was not significantly associated with the presence of tomatoes, cilantro, or any other food item in the household. Illness was not associated with reported consumption of raw jalapeño peppers (mOR=1.7, 95% CI=0.6–4.9), raw serrano peppers (mOR=0.5, 95% CI=0.1–3.1), raw tomatoes (mOR=1.6, 95% CI=0.6–4.9), or any other food item.</td>
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<td>Investigation of restaurant cluster in East Texas (Cluster A)</td>
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<td>Investigation of restaurant cluster in Little Rock, AR (Cluster H)</td>
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<td>No food or ingredient implicated.</td>
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<td>FDA reports isolation of the outbreak strain from a jalapeño pepper sample obtained from a Texas distributor</td>
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<td>This was the first laboratory testing of raw produce that identified the outbreak strain confirming that jalapeño peppers were a vehicle for infections.</td>
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<td>FDA investigators travel to Mexico to inspect farms identified in traceback investigations</td>
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<td>Based on traceback findings for jalapeño peppers, FDA launched inspections at Farm A and Farm B in Mexico.</td>
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<td>FDA lifted advice to avoid certain types of raw tomatoes</td>
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<td>FDA lifted advice to avoid certain types of raw tomatoes.</td>
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<tr>
<td>Colorado Department of Public Health and Environment reports isolation of the outbreak strain from a jalapeño pepper sample collected from the household of a case-patient</td>
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<td>This was the second confirmation of the outbreak strain in jalapeño peppers, and the first jalapeño pepper from a case-patient household to yield the outbreak strain.</td>
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<td>FDA reports isolation of the outbreak strain from two environmental samples, agricultural water and serrano peppers from Mexican Farm B</td>
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<td>This was the first isolation of the outbreak strain from serrano peppers confirming that serrano peppers were also a vehicle for infections.</td>
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<td>FDA issues a warning not to eat peppers grown or packed in Mexico</td>
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<td>FDA issues a warning not to eat peppers grown or packed in Mexico (July 30).</td>
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<td>FDA lifts jalapeño and serrano pepper advisories</td>
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<td>The outbreak did not appear to be ongoing and contaminated peppers from implicated farms were no longer being harvested or distributed.</td>
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Intervention Activities Highlighted