“The foodborne outbreak investigation is essentially a scientific study that takes place in an extremely public and political atmosphere, compressed in a relatively short period of time.”

Epidemiology is the cornerstone of public health investigation and discovery. Public health practitioners rely on epidemiologic associations—often supported by statistics and laboratory evidence—to determine the source of foodborne disease outbreaks and implement control measures. Epidemiologic studies frequently provide new insights into emerging foodborne pathogens and food vehicles, and may serve as the basis for policy development and regulations. The purpose of this paper is to provide an overview of the principles and practices of epidemiology in the context of foodborne disease outbreaks.

I. Historical Perspective

John Snow (1813 – 1858) was an English physician now considered the father of modern epidemiology. He is best known for his investigation of the 1854 cholera epidemic in Soho, England. Snow source-tracked the cause of the outbreak by using maps to compare the distribution of ill (“cases”) and non-ill (“controls”) residents, and correlated his findings with information on different exposures such as air, food, and water at the time of the outbreak (person, place, time). He determined that the public water supply was the most likely cause of the outbreak, and bravely removed the Broad Street pump handle to prevent new illnesses. He took this public health action despite intense skepticism and political pressure. Notably, Snow’s epidemiologic study pre-dated the laboratory methods needed to diagnose the cause of the illnesses, an infectious bacterium named Vibrio cholera decades later.

A current definition of epidemiology is "the study of the distribution and determinants of health-related states in specified populations, and the application of this study to control health problems." Over 150 years since Snow’s work on the cholera epidemic in London, epidemiologic studies continue to be used for food and waterborne disease surveillance and outbreak investigation. While the

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scientific methods have advanced, the original art of shoe-leather epidemiology that correlates person, place, and time to implicate a source is done on a daily basis by health departments around the world.

Path to Causation
It has been said that epidemiology is an imperfect science. Indeed, epidemiologic studies identify an association between an exposure and an outcome, but do not prove causation. Application of statistical approaches measures the strength of the association. Despite its limitations, the principles and practices of epidemiology have proven to be invaluable in the prevention and control of diseases in both human and animal populations. This is especially true in situations where classical experimental studies are either too time-consuming or unethical to conduct.

II. Foodborne Disease Surveillance

The purpose of surveillance is to monitor trends, guide prevention efforts, and detect outbreaks. In the US, certain communicable diseases and conditions including foodborne infections and intoxications must be reported by health care providers and/or clinical laboratories to the local or state health department. Although legally required in most states, disease reporting is essentially a passive system. Statistics on individual cases of reportable foodborne diseases are collected at the local level (county, city, parish, etc.) and reported to the state health department, which then voluntarily reports outbreak statistics to the CDC. The CDC maintains an electronic Foodborne Outbreak Reporting System (eFORS) database available to the public online at OutbreakNet. CDC is obligated to report certain foodborne disease outbreaks to the World Health Organization to comply with International Health Regulations.

Burden of Illness
The Centers for Disease Control and Prevention (CDC) estimate that there are 48 million illnesses, 128,000 hospitalizations, and 3,000 deaths annually due to foodborne illness in the US (Scallan et al, 2011). Approximately 1 in every 6 Americans suffer from foodborne illness each year. The majority of
Foodborne infections are self-limiting and usually involve an acute gastroenteritis (e.g., fever, cramps, diarrhea, vomiting) that lasts for 2-5 days with full recovery. However, some pathogens and toxins can cause life-threatening illness, long-term health problems, and death. Certain populations are more susceptible, especially children, the elderly, and persons with compromised immune systems.

There are over 250 pathogens and toxins that can be transmitted by food. The most common are norovirus, *Salmonella*, *E. coli* O157, *Campylobacter*, *Listeria*, and *Toxoplasma* (Scallan et al, 2011). Historically, animal-based food products (e.g., uncooked ground beef or poultry, unpasteurized milk) have been most often associated with foodborne disease outbreaks. In recent years, large multi-state outbreaks of foodborne infections linked to newly recognized vehicles have become more common. For example, 12 of 26 multi-state outbreaks compiled by the CDC from 2006-2010, were linked to new food vehicles as shown in **bold** below.

**2006 - E. coli O157 and bagged spinach**
2006 - *E. coli* O157 and shredded lettuce (restaurant chain A)
2006 - *E. coli* O157 and shredded lettuce (restaurant chain B)
2006 - **Botulism and commercial pasteurized carrot juice**
2006 - *Salmonella* and fresh tomatoes
2007 - *E. coli* O157 and frozen pizza
2007 - **Salmonella** and peanut butter
2007 - *Salmonella* and a vegetarian snack food
2007 - *Salmonella* and dry dog food
2007 - *Salmonella* and microwaveable pot pies
2007 - *Salmonella* and dry puffed breakfast cereal
2007 - *E. coli* O157 and ground beef
2007 - **Botulism and canned chili sauce**
2008 - *Salmonella* and cantaloupe
2008 - *E. coli* O157 and ground beef
2008 - *Salmonella* and fresh produce items
2009 - *Salmonella* and peanut butter containing foods
2009 - **Salmonella** and imported white pepper
2009 - *Salmonella* and alfalfa sprouts
2009 - **E. coli O157 and prepackaged cookie dough**
2009 - Multidrug resistant *Salmonella* and ground beef (x2)
2009 - *E. coli* O157 and blade tenderized steaks
2009 - **Salmonella** and salami made with contaminated pepper
2010 - *E. coli* O145 and romaine lettuce
2010 - *Salmonella* and alfalfa sprouts
2010 - **Salmonella** and frozen meals

According to surveillance statistics from 2007 (the most recent summary of reported foodborne disease outbreaks in the US), an etiologic agent and/or food vehicle were identified in less than half of the foodborne outbreak investigations. The burden of illness pyramid shown below illustrates why reported outbreaks and illnesses are just the “tip of the iceberg.”
The CDC also conducts an active surveillance system called **FoodNet** in collaboration with 10 state or local health departments around the country. The project utilizes epidemiologists to actively look for foodborne infections through regular contact with health care providers and laboratories. They find cases that may have otherwise been missed through the passive surveillance system. The also conduct special projects designed to identify new food vehicles, risk factors, and other emerging issues in the epidemiology of foodborne infections.

### III. Foodborne Disease Outbreak Investigation

**Outbreak Detection**

A *foodborne or waterborne outbreak* is defined as occurring when two or more unrelated people get the same illness from the same contaminated food or drink. Localized outbreaks are usually recognized by a hospital seeing an increased number of gastroenteritis illnesses, or when the local public health nurse or epidemiologist notices an increase in the expected number of case reports for a foodborne pathogen. Sometimes the patients themselves recognize the outbreak if they were all sickened following a common event such as an office picnic or wedding reception. Outbreaks are occasionally identified via consumer complaint hotlines. The specific steps and timeline of an outbreak investigation are listed in Appendix I and II, respectively.

**The Outbreak Response Team**

In the US, the response to public health emergencies usually begins at the local/county/city level and progresses to the state and federal levels depending on the scope of the problem. Federal agencies become involved in foodborne disease outbreak investigations when they are invited by the state health department, the outbreak is multi-state, or the outbreak involves a federally regulated product. Typically, the State Epidemiologist will make a formal request for assistance from CDC, who will then provide expert(s) in epidemiology or other disciplines depending on the nature of the investigation. Epidemiologists from the health departments and CDC are primarily responsible for
case-patient finding and studies to identify the cause of the outbreak, although they sometimes get involved in traceback and environmental investigations.

Responsibilities of local, state, and federal agencies in foodborne disease surveillance and outbreak investigation in the US

<table>
<thead>
<tr>
<th>Responsibility</th>
<th>Local*</th>
<th>State</th>
<th>CDC</th>
<th>FDA &amp; USDA FSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food safety regulation and policy</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Human disease surveillance</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Food product testing/surveillance</td>
<td>No</td>
<td>Sometimes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Outbreak detection &amp; investigation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Traceback/trace-forward</td>
<td>Sometimes</td>
<td>Yes</td>
<td>Sometimes</td>
<td>Yes</td>
</tr>
<tr>
<td>Product recalls</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Food safety consumer education</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Food safety industry guidance</td>
<td>Sometimes</td>
<td>Sometimes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Local environmental health departments are usually responsible for food safety oversight of restaurants and other food service establishments.

When a state asks for assistance from CDC, they usually send an Epidemic Intelligence Service Officer (EISO). EISOs are most often physicians, but may also be veterinarians, PhD-level epidemiologists, or from related disciplines. Below is a representative example of a multi-disciplinary team that could be involved in a large outbreak:

- Physicians (often have an MPH or equivalent degree)
- Public health nurses
- Microbiologists
- Epidemiologists
- Veterinarians (often have an MPH or equivalent degree)
- Food Scientists
- Environmental Health Specialists
- Consumer Safety Officers
- Food and Drug Investigators
- Biostatisticians
- Public Health Educators
- Information officers (public relations)

IV. Descriptive Epidemiology

At the beginning of an outbreak investigation, the epidemiology team summarizes patient (case) data based on person, place, and time. This is accomplished through unbiased interviews using standardized public health questionnaires. Most health departments use pathogen- or syndrome-
specific case report forms, if available. Foodborne disease case report forms vary from state-to-state, but each contain essential information on patient demographics, medical history, signs and symptoms, laboratory results, treatment, and hospitalization. The epidemiologic portion of the case report form may include food and water exposures, meals eaten inside and outside the home, group exposures (e.g., day-care, nursing home), animal contact, travel history, and household contacts. The foods asked about include those most commonly associated with the specific disease. Some examples of foodborne diseases and food histories are shown in the links below (click on the name to see the Case Report form).

Botulism
E. coli O157
Salmonella

Food history section of California’s E. coli, other STEC, shiga toxin positive feces, and/or HUS Case Report Form

The epidemiologist uses information from the case report forms (or other questionnaires) to create a line list with relevant data oriented by person (e.g., age, ethnicity, etc.), place (widespread or locally contained), and time. Time is portrayed as an epidemic curve with onset of illness (x axis) plotted against number of illnesses. The shape of the epidemic curve will suggest whether the outbreak is due to a point source or a common source.

Point Source Outbreak: People are exposed to the source over a limited, defined period of time. For example, a food poisoning event linked to a wedding reception dinner. The epidemic curve rises rapidly and contains a definite peak, followed by a gradual decline as shown in the figure below:
Common Continuous Source Outbreak: People are exposed to the source over a prolonged period of time. Large, multi-state common source outbreaks often trace to a widely distributed food product. In these outbreaks, the down slope of the epidemic curve may be very sharp if the common source is removed, or the curve gradually drops off if the outbreak is allowed to exhaust itself. The 2006 *E. coli* O157:H7 outbreak linked to fresh spinach is an example of a common source outbreak.

**Epidemic curve of confirmed cases of *E. coli* O157:H7, cluster 0609mlEXH-2, by date of illness onset, as of January 4, 2007 (N=198*)**

*198 confirmed cases with reported date of initial symptom onset

V. Hypothesis Generation

Findings from the patient interviews and laboratory diagnostic tests are used to establish a case definition (suspect, confirmed probable). The epidemiologist may use several strategies to then identify exposures that the ill persons have in common. For most enteric pathogens (Appendix III), they will ask about exposures 7 days before the onset of illness. However, some pathogens or toxins have much shorter or longer incubation periods (time from exposure to illness). The epidemiologist will interview the patient (or parent) over the phone, or may conduct a home visit.
They will review the responses to determine if there are commonalities among the patients such as food items, restaurants, stores, activities, or other factors.

If the source is a novel food vehicle, it may not be apparent by just comparing interview notes and case report forms. In that situation, the next step is to administer more detailed, structured questionnaires asking about many food items (“shotgun”, “trolling”, “trawling”). Intensive open-ended hypothesis generation questionnaires may also be used to attempt to find a common exposure. Other techniques include home visits and looking in the refrigerator and pantry. Comparison of patient shopper card information is very useful if the source is a food sold in grocery stores.

VI. Analytical Epidemiology

Once a common exposure is suspected, the hypothesis is tested using statistical analyses (analytical epidemiology). The epidemiologist uses comparison groups, which provide baseline data to measure the strength of the relationship between exposure and outcome. In foodborne disease outbreak investigation, there are two types of study design used alone or in combination depending on the nature of the outbreak.

**Cohort**: A study in which individuals with differing exposures to a risk factor (e.g. eating the implicated food) are identified and then observed for the occurrence of certain health effects (e.g. clinical symptoms) over some period. Cohort studies are usually used for outbreaks in small, well-defined populations in which all persons exposed can be identified. For example, all persons attending a wedding reception dinner (the “cohort”) may be interviewed to determine whether they became ill after the reception, and to identify what foods they had consumed. The questionnaire for a cohort study is developed based on the menu.

A food-specific attack rate table is constructed, comparing symptoms among those who consumed a particular food to those who did not consume that food. To compute the attack rate, divide the number who became ill by the number who ate the food item and multiply by 100. A ratio of the two attack rates, known as the relative risk (RR), is calculated. Below is an example of a food-specific attack rate table:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Ate lettuce</th>
<th>Did not eat lettuce</th>
<th>RR</th>
<th>95% CI</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>73 (33%)</td>
<td>1 (3%)</td>
<td>11.7</td>
<td>1.7-81.8</td>
<td>0.0002</td>
</tr>
<tr>
<td>Fever</td>
<td>41 (18%)</td>
<td>1 (3%)</td>
<td>6.6</td>
<td>0.9-46.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Diarrhea &amp; Fever</td>
<td>40 (18%)</td>
<td>0 (0%)</td>
<td>Und</td>
<td>2.39-</td>
<td>0.006</td>
</tr>
<tr>
<td>Cramps</td>
<td>56 (25%)</td>
<td>1 (3%)</td>
<td>9.0</td>
<td>1.3-63.0</td>
<td>0.003</td>
</tr>
<tr>
<td>Chills</td>
<td>47 (21%)</td>
<td>1 (3%)</td>
<td>7.6</td>
<td>1.1-53.1</td>
<td>0.009</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30 (13%)</td>
<td>1 (3%)</td>
<td>4.8</td>
<td>0.7-34.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Cough</td>
<td>27 (12%)</td>
<td>4 (11%)</td>
<td>1.1</td>
<td>0.4-2.9</td>
<td>0.57</td>
</tr>
<tr>
<td>Headache</td>
<td>61 (27%)</td>
<td>6 (17%)</td>
<td>1.6</td>
<td>0.9-3.5</td>
<td>0.18</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>35 (16%)</td>
<td>5 (14%)</td>
<td>1.1</td>
<td>0.5-2.7</td>
<td>0.79</td>
</tr>
</tbody>
</table>
Case-Control: A study that compares persons with the disease (cases) to another group of people from the same population who do not have the disease (controls) is referred to as a case control study. Case-control studies are used for outbreaks involving a less defined population (community or common source outbreaks). Food exposures of the two groups are compared using a standardized, structured questionnaire. In more complex and geographically widespread investigations (for example, multi-state outbreaks involving multi-ingredient foods such as salsa), it may be necessary to conduct more than one case-control study. For example, CDC may conduct a case-control study using cases from across the country, while a specific state may conduct a separate case-control study only among customers of a specific restaurant implicated during the investigation.

Selection of controls is critically important in designing a case-control study. Controls are often matched by age to avoid confounding, especially when the sample size is small. Confounding in statistics is when an extraneous variable produces a false positive result (in this case, incorrectly implicating a food). Depending on the nature of the outbreak, non-ill controls may come from several places:

- Neighborhood controls identified through random digit dialing using the case’s area code and first 3 digits of their phone number
- Meal companions
- Family members or friends of cases
- People who attended an implicated event

Unlike cohort studies, attack rates and relative risk cannot be calculated because the total population at risk is unknown. The odds ratio (OR) is used instead as an estimate of relative risk. The OR is calculated by constructing a 2 x 2 table as shown in the example below:

\[
\begin{array}{c|cc|c}
 & \text{Cases (ill)} & \text{Controls (not ill)} & \text{Total} \\
\hline
\text{Ate lettuce} & 8 \ (a) & 6 \ (b) & 14 \ (a+b) \\
\text{Did not eat lettuce} & 11 \ (c) & 27 \ (d) & 38 \ (c+d) \\
\hline
\text{Total} & 19 \ (a+c) & 33 \ (b+d) & 52
\end{array}
\]

Odds Ratio (OR) formula = \(\frac{a \times d}{b \times c}\)
In this case the OR = \( \frac{8 \times 27}{11 \times 6} = 3.3 \)

Interpretation: cases were 3.3 times as likely to have consumed lettuce when compared with controls.

**Statistical Significance Testing:** The RR or OR by themselves are not measures of statistical significance. To confirm that the result did not occur by chance alone (usually at a 95% confidence level), a chi-square or other test is done. The result is reported as a confidence interval and p-value. If the confidence interval includes 1.0, there is no difference between the two groups. The P-value is the probability that the result occurred by chance; lower p-values indicate that the result is statistically significant (e.g., p-value < 0.05).

**VII. Molecular Epidemiology**

Advances in laboratory methods, especially those emerging from the molecular revolution, have enhanced the ability to source-track outbreaks across the food continuum. In some recent produce-related outbreaks (sprouts, spinach, shredded lettuce, peppers), investigators have been able to identify the outbreak strain from the patient to the product, and even back to the farm. However, it is worth noting that finding the outbreak strain (“smoking gun”) in an implicated food product provides strong evidence to support an epidemiologic association, but is not a mandatory requirement to take action to prevent additional illnesses. Indeed, when Snow did his epidemiologic investigation 150 years ago, he did not have laboratory tests to identify the cholera bacteria in the public water supply – the epidemiologic findings were sufficient to recommend “removing the pump handle” to prevent future illnesses.

Molecular epidemiology is a relatively new field that combines the tools of traditional epidemiology (case-finding, questionnaires, statistics) with the tools of molecular biology (DNA fingerprinting, bioinformatics). **PulseNet**, an application of molecular epidemiology, is the national molecular subtyping network for foodborne disease surveillance in the US. It was created to address the challenges of detecting geographically widespread common source outbreaks. Pulsed-field gel electrophoresis (PFGE) is the “gold standard” method for molecular epidemiologic studies of foodborne pathogens. PFGE analysis is a macro restriction-based subtyping method where rare-cutting enzymes are used to digest genomic DNA; the fragments are then visualized on a gel. The CDC PulseNet protocols typically require a primary enzyme (for example, \( Xba-1 \)) to initially compare strains. A secondary enzyme (for example, \( Bln-1 \)) is used to generate more fragments and confirm the genetic relatedness of the strains. Patterns are compared using specialized cluster analysis software (GelCompar II, BioRad).

PFGE analysis is performed in public health laboratories around the country by microbiologists specifically trained by CDC in standard PulseNet protocols. State and local microbiologists submit PFGE patterns from their communities electronically to CDC. The database at CDC searches for similar patterns in the past 2-4 months. When a cluster of indistinguishable patterns is identified, PulseNet sends a notification to participants. Regulatory agencies also submit strains isolated from food product surveillance testing. At this time, PulseNet protocols are available for 5 foodborne pathogens: Salmonella, Shigella, E. coli O157, Campylobacter, and Listeria. Over 75 public health and regulatory (e.g., USDA FSIS, FDA) laboratories currently participate in PulseNet.
Pulsed-field gel electrophoresis (PFGE) patterns submitted to CDC's PulseNet. The red box shows a cluster of indistinguishable patterns that may indicate an outbreak.

In some outbreaks, additional molecular typing methods are used. For example, multilocus variable number tandem repeat (VNTR) analysis (MLVA) is a sequence-based method being used by some states and CDC during foodborne disease outbreaks. MLVA originates from human forensic science, and exploits a phenomenon of repetitive DNA that occurs in the genomes of many different organisms including humans. DNA base pairs sometimes line-up in repeat patterns (motifs) at a certain place (locus) in the genome. For example, the “Vhed1” locus of E. coli O157 repeats the “TGGCTC” motif; the number of times this motif repeats varies depending on the strain. Analysis of repeat motifs is done for many different loci in the genome (for example, 7 to 11 for E. coli O157), which creates a DNA fingerprint for the individual strain. These patterns can be used as an epidemiologic tool (linking isolates from humans, foods, and the environment), or used for long-term evolution and population genetics studies.

MLVA is not used as widely as PFGE analysis in regional public health laboratories. In order to perform MLVA, the public health laboratory must have an automated sequencer and have trained microbiologists to perform the test and interpret the results. The overall advantages of MLVA and
other DNA sequence-based methods are their reproducibility and portability among laboratories. Furthermore, the methods are relatively easy to standardize and do not rely on potentially ambiguous interpretations of gel patterns, which can be a problem with PFGE analysis.

10 loci MLVA measures numbers of tandem repeats (TR) in 10 different sites in an \textit{E. coli} O157:H7 strain genome\textsuperscript{2}.

\textbf{VIII. Conclusions}

In summary, epidemiology is a discipline that utilizes both quantitative (science) and qualitative (art) approaches. Regardless of whether the foodborne disease outbreak is linked to a local church picnic, or a large international outbreak, the value of the epidemiologic findings is ultimately dependent on the skill and expertise of the investigation team. In Part 2 of this paper, a fictional scenario of a multi-state outbreak on the west coast will be used to illustrate the principles and practices in epidemiology highlighted in Part 1.

IX. References and Resources

Procedures and Guidelines


Outbreak Investigations


APPENDIX I

THE 10 STEPS OF A FOODBORNE DISEASE OUTBREAK INVESTIGATION

Once an outbreak is suspected, whether it was identified locally or nationally, there are fundamental steps followed by all jurisdictions:

Step 1. Prepare to investigate
a. Identify outbreak investigation team
b. Review scientific literature
c. Notify appropriate state and local entities
d. Determine if immediate control measures are needed

Step 2. Verify the diagnosis and confirm outbreak
a. Get laboratory confirmation (see Appendix I)
b. Collect stool and/or vomitus specimens from ill persons
c. Collect any suspect food or drinks, if available
d. Perform bacteriologic, virologic or parasitic testing at the public health reference laboratory
e. Submit bacterial isolates from patients or environmental samples to the state public health lab or CDC for DNA fingerprinting/Pulse Field Gel Electrophoresis (PFGE)
f. Notify the medical and surrounding public health communities of the outbreak and request that possibly related cases be tested and reported

Step 3. Case definition
a. Establish a set of standard criteria for deciding who are the ill persons related to the outbreak (“case-patients”)
b. Narrow or broad (confirmed, probable, suspect)
c. DYNAMIC: may change during investigation

Step 4. Case finding
a. Conduct a systematic search for more case-patients based on case definition by contacting hospitals, clinical laboratories; consider a media release
b. Create a line list of possible cases (people exposed)

Step 5. Perform descriptive epidemiology
a. Tabulate and orient data: PERSON, PLACE, TIME
b. Calculate frequencies and map the distribution of the cases
d. Plot the onset of illness for all cases in an Epidemic Curve

Step 6. Hypothesis generation—the how and the why
a. Compare with known sources or similar outbreaks
b. Design questionnaire (trawling, trolling, shotgun, or hypothesis-generation)

Adapted from the Georgia Department of Community Health
Step 7. Evaluate hypothesis through statistics (analytical epidemiology)
   a. Perform epidemiologic study: cohort, case-control
   b. Compare risk factors among ill (cases) vs not ill (controls)

Step 8. Additional environmental studies
   a. Collect food, water, and/or environmental samples implicated during the epidemiologic investigations
   b. Conduct traceback and traceforward studies
   c. Investigate the distribution chain and determine the likely cause of the food contamination

Step 9. Implement control/prevention measure
   a. Coordinate with all stakeholders including regulatory and industry partners
   b. Develop strategies to prevent further or future illness

Step 10. Communicate findings
   a. Disseminate outbreak investigation report—internal and external audience
   b. Educate community, ill persons, restaurant staff, and public health staff
   c. Communicate with the food industry
APPENDIX II

SAMPLE TIMELINE FOR AN EPIDEMIOLOGIC INVESTIGATION OF FOODBORNE INFECTIONS.

1 - 7 days

Patient Eats Contaminated Food

Contact with health care system: 1 - 5 days

Patient Becomes III

Diagnosis: 1 - 3 days

Stool Sample Collected

Shipping: 0 - 7 days

E. coli O157 Identified

Public Health Lab Receives Sample

DNA fingerprinting: 2 - 10 days

Final report & recommendations

Case control study and traceback Days to months

Case Confirmed as Part of Outbreak

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*Adapted from powerpoint presentation courtesy of K. Neil, CDC.*
### APPENDIX III

**CHARACTERISTICS OF SELECTED FOODBORNE PATHOGENS AND TOXINS ASSOCIATED WITH HUMAN GASTROENTERITIS.**

<table>
<thead>
<tr>
<th>Onset of illness after eating suspect food (variable)</th>
<th>First predominant symptom</th>
<th>Suspect pathogen or toxin*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 hour</td>
<td>Upper gastrointestinal and neurological (tingling, numbness, dizziness, vision problems)</td>
<td>Shellfish toxins Organophosphates</td>
</tr>
<tr>
<td>1-6 hours</td>
<td>Upper gastrointestinal (nausea, vomiting)</td>
<td><em>Staphylococcus aureus</em> enterotoxin <em>Bacillus cereus</em> emetic toxin</td>
</tr>
<tr>
<td></td>
<td>Gastroenteritis +/- neurological (tingling, numbness, vision problems, paralysis)</td>
<td><em>Ciguatera</em> toxin Chlorinated hydrocarbons</td>
</tr>
<tr>
<td>6-24 hours</td>
<td>Lower gastrointestinal (diarrhea, cramps)</td>
<td><em>Bacillus cereus</em> enterotoxin</td>
</tr>
<tr>
<td></td>
<td>Lower gastrointestinal (putrefactive diarrhea)</td>
<td><em>Clostridium perfringens</em></td>
</tr>
<tr>
<td>12-48 hours</td>
<td>Vertigo, blurred vision, difficulty swallowing, descending bilateral paralysis +/- gastrointestinal symptoms</td>
<td><em>Clostridium botulinum</em></td>
</tr>
<tr>
<td></td>
<td>Upper (nausea, vomiting) and lower (diarrhea, cramps) gastrointestinal symptoms</td>
<td>Norovirus</td>
</tr>
<tr>
<td>1 – 7 days</td>
<td>Lower gastrointestinal (diarrhea sometimes bloody, abdominal cramps, headache, +/- fever), vomiting, nausea</td>
<td><em>Campylobacter</em> <em>E. coli O157</em> and other pathogenic <em>E. coli</em> species <em>Salmonella enterica</em> <em>Shigella</em> species <em>Vibrio parahaemolyticus</em> <em>Vibrio vulnificus</em> <em>Yersinia enterocolitica</em> <em>Yersinia pseudotuberculosis</em></td>
</tr>
<tr>
<td>2 to 10 days</td>
<td>Lower gastrointestinal (watery diarrhea, cramps)</td>
<td><em>Cryptosporidium parvum</em></td>
</tr>
<tr>
<td>10 to 30 days</td>
<td>Fever, malaise, nausea, jaundice (later)</td>
<td>Hepatitis A virus</td>
</tr>
<tr>
<td>1 to several weeks</td>
<td>Lower gastrointestinal (mucoid diarrhea, abdominal pain, weight loss)</td>
<td><em>Cyclospora cayetanensis</em> <em>Giardia lamblia</em> <em>Entamoeba histolytica</em></td>
</tr>
</tbody>
</table>

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5 Sources: [Guidelines for Foodborne Disease Outbreak Response](https://www.cdc.gov/ndph/doh/foodborne/disease_outbreak_response.html) (CIFOR) and [The Bad Bug Book](https://www.fda.gov) (FDA).
APPENDIX IV

GLOSSARY OF TERMS

**Attack rate:** Proportion of people becoming ill after a specified exposure.

**Case:** In a case-control study, an occurrence of illness as defined by investigators (also called case-patient).

**Case classification:** Gradations in the likelihood of being a case (e.g., possible, probably, confirmed). This is particularly useful where early reporting of cases is important and where there are difficulties in making definitive diagnoses (e.g., while specialized laboratory tests are pending).

**Case-control study:** Observational study in which subjects are enrolled on the basis of presence (cases) or absence (controls) of the disease of interest. Information is collected about earlier exposures and compared between cases and controls. Most often used in dispersed/diffuse foodborne disease outbreaks (e.g., multi-state outbreaks from widely distributed meat, produce and other foods/ingredients).

**Case definition:** A set of diagnostic criteria that must be fulfilled to be regarded as a case of a particular disease. Cases definitions can be based on clinical criteria, laboratory criteria, or a combination.

**Cohort study:** Observational study in which subjects are enrolled on the basis of presence (exposed) or absence (unexposed) of risk factors. Subjects are followed over time for development of a disease outcome of interest. Most often used in focal foodborne disease outbreak (e.g., church supper, wedding reception).

**Control:** In a case–control study, comparison group of persons without the disease under investigation.

**Epidemic curve:** A graph to show the time course of an epidemic by plotting the number of cases by their date of onset. The “epi curve” gives a simple visual display of the outbreak’s magnitude and time trend.

**Epidemiology:** The study of the distribution and determinants of health-related states in specified populations, and the application of this study to control health problems.

  **Analytical epidemiology:** The aspect of epidemiology concerned with the search for health-related causes and effects. Uses comparison groups, which provide baseline data to quantify the relationship between exposures and outcomes and to test hypotheses about causal relationships (e.g., case control and cohort studies).

  **Descriptive epidemiology:** The aspect of epidemiology concerned with organizing and summarizing health-related data according to time, place and person characteristics (e.g., epidemic curve, map, case-patient line listing).

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6 Adapted from CIFOR (2009) and WHO (2008).
**Foodborne disease**: Any disease caused by ingestion of contaminated food. Although some agents are more likely than others to be transmitted by food, identification of foodborne, waterborne, person-to-person, or animal-to-person transmission requires investigation. Furthermore, multiple modes of transmission may be involved in any single outbreak.

**Foodborne Disease Outbreak**: Two or more cases of a similar illness shown by an investigation to result from a common exposure, such as ingestion of a common food. An outbreak is a cluster with a clear association between cases, with or without a recognized common source or known vehicle.

**Foodborne disease surveillance**: Surveillance of diseases or conditions that might be foodborne. Thus, all diseases of enteric origin may be tracked by this mechanism, including norovirus infection (which involves substantial person-to-person transmission), listeriosis (which may have a diarrheal stage but generally is detected by blood culture), or botulism (which presents as neurologic disease).

**Foodborne intoxication**: Illness caused by ingestion of toxins produced in food by bacteria as a naturally occurring by-product of their metabolic processes.

**Foodnet “Atlas of Exposures”**: The results of periodic population-based surveys undertaken at selected sites in the United States. The survey collects information about exposures that might be associated with foodborne illnesses and can be used to estimate the background rate of different food exposures in the community.

**Incubation period**: The time interval between the initial contact with an infectious agent and the first appearance of symptoms associated with the infection.

**Odds ratio (OR)**: Measure of association that quantifies the relationship between an exposure and an outcome from an analytical epidemiologic study (usually a case-control study). Odds ratio describes the likelihood of exposure to the risk factor under investigation in both the diseased (case) and non-diseased (control) groups.

**OutbreakNet**: A national collaboration of epidemiologists and other public health officials who investigate outbreaks of foodborne, waterborne, and other enteric illnesses in the United States. The purpose of OutbreakNet is to ensure rapid, coordinated detection and response to multistate outbreaks of enteric diseases and promote comprehensive outbreak surveillance. Outbreak Response Protocol: A comprehensive document outlining the roles, responsibilities and required actions of all individuals and organizations involved in the investigation of a foodborne disease outbreak. Outbreak response protocols may be developed for a specific organization or may encompass multiple organizations and jurisdictions.

**p-value**: The probability of obtaining a test statistic at least as extreme as the one that was actually observed, assuming that the null hypothesis is true. One often "rejects the null hypothesis" when the p-value is less than the significance level α (Greek alpha), which is often 0.05 or 0.01. When the null hypothesis is rejected, the result is said to be statistically significant. In a foodborne outbreak investigation, the null hypothesis is that the suspect food (exposure) was not related to the outcome (infection).
**PulseNet**: An international surveillance network comprising national, state, and local public health and food-regulatory agency laboratories that conduct standardized molecular subtyping of foodborne disease pathogens (e.g., DNA fingerprinting) and maintain centrally accessible databases of patterns. PulseNet also functions as a communication hub for laboratories involved in food and foodborne disease monitoring.

**Relative risk (RR)**: A comparison of the rate of some health-related event such as illness or death in two groups (where one group is exposed while the other is not exposed to a risk factor).

**Reportable conditions (notifiable diseases)**: The list of diseases based on state laws or regulations that should be reported by health-care providers (e.g., physicians and their medical staff, laboratories, and hospitals) to local or state health agencies. The list of notifiable diseases and legal obligation for reporting differ from state to state. States can report notifiable diseases to CDC, which maintains a list of nationally notifiable diseases, but compliance is voluntary. CDC reports selected diseases to the World Health Organization in compliance with International Health Regulations.

**Sporadic case**: A case-patient not linked epidemiologically to other cases of the same illness. Single sporadic cases of extremely rare and serious conditions, such as gastrointestinal anthrax, botulism, or cholera, merit a detailed investigation as soon as possible, as though they were outbreaks, to prevent any further cases.

**Statistically significant**: In statistics, a result that is unlikely to have occurred by chance (see p-value).

**Surveillance**: The systematic collection, analysis, interpretation, and dissemination of data for public health action.

**Traceback**: The process by which the origin or source of a cluster of contaminated food is identified.

**Traceforward**: Tracking a recalled product from the origin or source through the distribution system.

**Trawling, trolling, shotgun or hypothesis-generating questionnaire**: A variety of interview forms designed to capture a wide range of exposures. These forms may be designed with embedded questions focused on disease-specific hypotheses (e.g., exposures previously associated with the pathogen or plausibly associated with the pathogen) as well as other food items and exposures that have not been associated with the pathogen, which may consolidate the hypothesis-generation and testing processes into a single step. For instance, the trawling questionnaire for an outbreak of *E. coli* O157:H7 infection may contain standardized questions about known transmission mechanisms for this agent, such as hamburger consumption, child-care attendance, recreational pool use, animal exposures, and other exposures identified in previous outbreaks which function as a priori hypotheses.
Michele Jay-Russell is currently a Project Director and Researcher at the Western Center for Food Safety at the University of California, Davis. Her research interests are in pre-harvest food safety and the interface between animal agriculture, wildlife, and the environment. Prior to joining the university, Dr. Jay-Russell was a Research Scientist with the Food and Drug Laboratory Branch at the California Department of Public Health. In this capacity, she was involved in many environmental and laboratory foodborne disease outbreak investigations including the 2006 farm investigation following the *E. coli* O157:H7 contamination of fresh, bagged baby spinach. She has also served as California’s State Public Health Veterinarian and Chief Epidemiologist for the Sacramento County Department of Health and Human Services. She has published and presented on numerous epidemiological investigations and surveillance programs in public health and food safety. In 2006-2007, she was awarded the California Department of Public Health Superior Accomplishment Award, the FDA Leveraging/Collaboration Award, and the International Association of Food Protection Innovation award. Dr. Jay-Russell received her Doctor of Veterinary Medicine and Masters of Preventive Veterinary Medicine in 1992; she completed her PhD in Microbiology from the University of California, Davis in 2011. Dr. Jay-Russell was board certified with the American College of Veterinary Preventive Medicine in 1997.