

An Independent Review of FDA's Foodborne Outbreak Response Processes

By Craig W. Hedberg, PhD
Professor, University of Minnesota School of Public Health
Co-Director, Minnesota Integrated Food Safety Center of Excellence
Minneapolis, MN

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FDA organizational acronyms cited in this report

| | |
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| CFSAN | Center for Food Safety and Applied Nutrition |
| CORE | Coordinated Outbreak Response and Evaluation (CORE) Network |
| DPS | Division of Produce Safety |
| OC | Office of Compliance |
| OFS | Office of Food Safety |
| OFPR | Office of Food Policy and Response |
| ORA | Office of Regulatory Affairs |

Executive Summary

As the federal food regulatory agency with oversight for the large majority of commercially distributed foods, FDA plays a key role in conducting multistate outbreak investigations and in translating investigation results into prevention activities. The importance of this role is highlighted in the development of FDA's blueprint for the future, the "New Era of Smarter Food Safety."

The development of whole genome sequencing (WGS) has improved foodborne illness surveillance and led to the recognition that some pathogenic strains are causing reoccurring, emerging, and persisting (REP) food safety problems. Outbreaks of shigatoxin-producing *E. coli* associated with leafy green vegetables have been a particular concern in recent years.

FDA established the Coordinated Outbreak Response and Evaluation (CORE) Network to coordinate its outbreak response efforts with subject matter experts from the Center for Food Safety and Applied Nutrition (CFSAN), the Office of Regulatory Affairs (ORA) and Centers for Disease Prevention and Control (CDC). CORE Teams take food exposure information from CDC, make assignments for record and sample collection by ORA field staff, and identify outbreak sources through the convergence of product distributions across multiple legs of a traceback, supported by epidemiology and laboratory data. Tracebacks are time and labor intensive and frequently limited by inadequate records and comingling of product in distribution. Efforts are made to identify farm sources, or production sources depending on the commodity, so that farm or facility visits, and environmental assessments can be made to identify the source of the contamination event. In some outbreak response efforts, root cause investigations are conducted to collect information that can be used "to develop and recommend risk mitigation strategies for industry to reduce the risk of repeated food contamination events." (FDA, Office of Regulatory Affairs, Procedure Manual for Fresh Produce Root Cause Investigation).

A review of FDA's outbreak response activities was conducted to explore the dynamics of FDA's relationships with federal, state and industry partners during and after these investigations. The review included documents related to outbreak investigation procedures, policies, and outcomes with interviews of key stakeholders identified by FDA.

Findings and recommendations presented in the report were related to the following areas:

- Initiation of the outbreak investigation and assignment of investigation tasks.
- Role of CORE in traceback activities.
- Factors used to determine whether or not to conduct a root cause investigation.
- Translation of outbreak investigation findings to prevention activities.
- Evaluation activities and systems improvement.

The report reached the following conclusions:

FDA has made considerable investments in recent years to improve its outbreak investigation processes with the establishment of CORE. Its integration of activities through an incident command system has provided a structure for coordinating traceback activities across FDA. The process of making record collection assignments involves multiple steps that must be coordinated across different parts of the agency, with inherent delays built into the process. Technological and operational innovations provide opportunities to shorten response times. In particular, the identification of REP strains and reoccurring

outbreak settings provide investigators with ready hypotheses to test at first recognition of the outbreak.

Improvements in outbreak detection will continue to advance with application of WGS to surveillance of pathogens by public health agencies. Turn-around times in public health laboratories have limited the speed of outbreak detection, but these have decreased in states with adequate resources to perform WGS in real time. Improving the capacity of state and local public health epidemiologists to conduct detailed exposure interviews may depend on additional support through CDC's epidemiology and laboratory capacity (ELC) grants. While ELC grants are not within FDA's jurisdiction, helping to ensure the effective coordination of federal outbreak response resources is.

Because tracebacks require exposure assessments conducted by state and local health departments, the speed and effectiveness of FDA activities will always depend on the capacity of the public health system. Expanding the number and distribution of FDA-supported Rapid Response Teams (RRTs) to enhance coordination of investigation activities between FDA and state partners is warranted.

A complementary method of outbreak identification, through environmental and food product sampling by FDA or a federal or state regulatory partner, is becoming more common. When a reportable foodborne pathogen is identified, a search of PulseNet data for matching human isolates may indicate the occurrence of a foodborne outbreak. Investigation of the human case exposures is needed to confirm the source of such a "retrospective" outbreak. This depends on the same public health resources needed for conventional surveillance activities.

A key implication of the expanding use of WGS for foodborne illness surveillance will be the need to investigate more frequent but smaller clusters of cases. Prioritizing traceback of small clusters can lead to earlier detection of outbreaks before they manifest as large, multistate outbreaks. However, this would likely increase the need for informational tracebacks early in the hypothesis generation process. This could be accomplished either by more formal engagement of CORE Response while clusters are still being followed by the Signals Team, earlier transfer of cluster investigations to CORE Response Teams or more formal reliance on CDC and state partners to conduct these informational tracebacks.

The development of improved traceability with electronic records could significantly reduce the burden of investigation required to collect records to document the movement of products in a traceback. This would both speed up tracebacks and permit a larger range of products to be traced. At the same time, prioritizing traceback analyses based on the probability of product availability would improve the efficiency of source identification and better inform the transition from response to prevention. Establishing performance measures for outbreak response activities and outcomes should be established within the CORE database system.

Resource constraints are a limiting factor in many outbreak investigations. Staffing levels for CORE, the Office of Regulatory Affairs (ORA) investigators, produce safety specialists, laboratory support systems and other program areas are not adequate to respond to the growing number of outbreaks associated with REP strains and recurrent settings. Consideration for how to add capacity to CORE and increase the ability of CORE Response Teams to directly interact with outbreak investigation partners outside of FDA is warranted.

Farm visits and sample collections have become an increasing part of outbreak investigations involving REP strains and recurrent settings. Getting to farms while produce is still being grown and harvested has been a challenge. For most produce associated outbreaks, the majority of cases have already occurred by the time the outbreak is recognized. Environmental assessments conducted during these visits, but after the outbreak has ended still need to document conditions that can be directly related to the specific event, and also put them into context of the larger population of similar outbreaks that have been investigated. Integration of these data should be viewed as a routine investigation method. This could help identify factors, such as the presence of animal production facilities on lands adjacent to produce fields that can be compared across multiple investigations and evaluated during applied research studies and long-term environmental assessments. These *post hoc* environmental assessments can also help develop plans for seasonal surveillance during subsequent harvests.

Earlier and more open communication with industry, public health and regulatory partners would enhance the collaborative nature of outbreak investigations and likely produce meaningful results faster. Trust between partners is needed to effectively solve problems and identify solutions. While there remain questions about how, when and to whom information can be disclosed, the default setting should be to disclose information whenever it can advance the progress of the investigation. Outside of specific regulatory directives, behavioral change by industry requires the understanding of investigation findings and insights on how to implement changes within existing production systems. Timely release of investigation findings to the public and discussion of the implications of the findings directly with the affected industry is critical for effective communication and widespread acceptance of results. While the New Era of Smarter Food Safety seeks to “bend the curve” of foodborne illness, successful outbreak investigations can lead to better prevention methods that may lead to “canceling the curve” of many potential outbreaks.

The final section of the report contains the conclusions and a series of recommendations developed by the author.

1. Purpose and scope of independent review

This independent review of FDA's foodborne outbreak response processes was intended to identify barriers to enhance the speed, effectiveness, coordination, and communication of outbreak investigations.

The review encompassed FDA roles and responsibilities, processes, priorities, decision trees, and procedures for outbreak response in specific areas:

1. Product Tracing
2. Root Cause Investigations
3. Use of CORE data for surveillance

The review was not intended to be a comprehensive audit of FDA outbreak response activities. It was intended to provide an objective assessment of the structural and functional capacity to support, participate in or lead multistate foodborne illness outbreak investigation activities. In particular, it was intended to explore the dynamics of FDA's relationships with federal, state and industry partners during and after these investigations.

2. Approach

The author reviewed documents related to outbreak investigation procedures, policies and outcomes (Appendix 1) and interviewed FDA staff involved in outbreak response throughout the agency, as well as federal partners (CDC/USDA), several state partners and industry experts (Appendix 2). Regular discussions were held with RADM David Goldman, Chief Medical Officer for the FDA's Office of Food Policy and Response (OFPR), to review progress, establish priorities and seek assistance in conducting the review.

| Table 1: Key questions to address during external review. |
|--|
| 1. Initiation of outbreak investigation and assignment of investigation tasks. |
| 2. Traceback activities <ol style="list-style-type: none">How clusters were identified and prioritized for traceback.Investigation protocol that governed traceback efforts.Scope of document requests in traceback.Timelines in completing tracebacks.Incorporation of traceback results into epidemiologic analyses. |
| 3. Root cause investigations <ol style="list-style-type: none">Factors used to determine whether or not to conduct root cause investigation.Timelines for initiating and conducting root cause investigation.Information return on investment. |
| 4. Potential use of CORE data to supplement NORS data. |

| Table 2: Key events for review. |
|--|
| 1. <i>E. coli</i> O157:H7 in romaine lettuce. |
| 2. 2020 <i>Salmonella</i> Newport in onions. |
| 3. 2020 <i>Salmonella</i> Enteritidis in peaches. |
| 4. 2020 <i>Salmonella</i> Stanley in wood ear mushrooms. |

Although the review was intended to encompass the participation of all parts of FDA in responding to foodborne illness outbreaks, much of the focus was centered on the FDA's [Coordinated Outbreak Response and Evaluation \(CORE\) Network](#), which was established in 2011. CORE was organized as a centralized FDA resource to facilitate outbreak detection, response, and prevention activities. It was intended to be a primary point of contact with investigators from CDC and other federal partners. It was also intended to coordinate investigation activities with other FDA offices.

Interviews with FDA staff and external stakeholders sought to describe the operations of CORE, how CORE Teams interact with FDA and external partners, how CORE has changed FDA's response to foodborne outbreak investigations, and how the results of CORE's investigations are translated into prevention measures. Interview subjects were invited to provide their subjective assessments of CORE's role in FDA's outbreak response activities. This included assessing the strengths of existing systems and identifying potential gaps and areas for improvement, both within CORE and across the FDA.

Reviews of outbreak-associated documents were conducted to validate interview responses and provide objective measures of CORE and FDA response activities.

Outbreaks associated with fresh produce were selected as review priorities for several reasons. Outbreaks of shigatoxin-producing *E. coli* (STEC) associated with leafy green vegetables have emerged as reoccurring and persisting problems. The identification of reoccurring, emerging, and persisting (REP) strains of foodborne pathogens has been highlighted by CDC since whole-genome sequencing has become the standard of practice for molecular subtyping in foodborne disease surveillance (Tack, et al. MMWR Morb Mortal Wkly Rep 2020;69:509–514. DOI: <http://dx.doi.org/10.15585/mmwr.mm6917a1>). Furthermore, the Interagency Food Safety Analytics Collaboration (IFSAC) attributed 50% of *E. coli* O157:H7 infections in 2018 to vegetable row crops, a category that is largely comprised of leafy green vegetables (Interagency Food Safety Analytics Collaboration. <https://www.cdc.gov/foodsafety/ifsac/pdf/P19-2018-report-TriAgency-508.pdf>). Similarly, an increasing number of multistate foodborne *Salmonella* outbreaks have been associated with fresh produce vehicles, with seeded vegetables, fruits, and other produce accounting for 35% of *Salmonella* infections in 2018. Finally, several multistate outbreaks associated with fresh produce vehicles were investigated in 2020. It was thought that these would provide a rich and recent series of events that would reflect current practices for which memories would be fresh and documents readily available.

Findings of this review are presented in the following order:

- Initiation of the outbreak investigation and assignment of investigation tasks.
- Role of CORE in traceback activities.
- Factors used to determine whether or not to conduct root cause investigation.
- Translation of outbreak investigation findings to prevention activities.
- Evaluation activities and systems improvement.

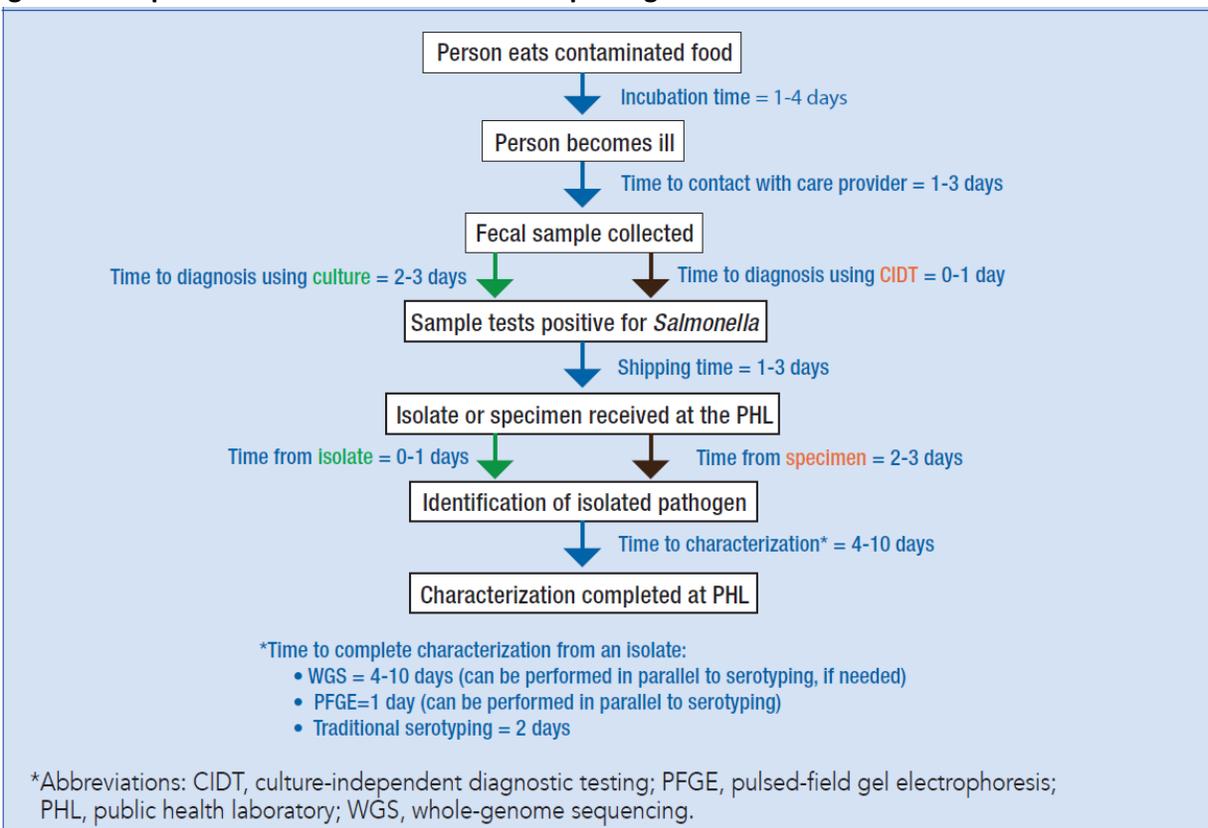
The final section of the report contains conclusions and the author's recommendations to enhance the speed, effectiveness, coordination, and communication of outbreak investigations based on his in-depth interviews and review of internal and external documents.

3. Findings

Initiation of the outbreak investigation and assignment of investigation tasks. Illnesses caused by foodborne pathogens such as *Salmonella*, STEC or *Listeria monocytogenes* are reportable to local or state health agencies according to the specific communicable disease reporting rules of the state. Most cases are diagnosed by clinical laboratories, and the laboratory or clinician who ordered the test (or both) reports the case. If the diagnosis was made by isolating the agent, the isolate is usually submitted to the public health laboratory for confirmation and further characterization by WGS. If the diagnosis was made by culture independent diagnostic testing (CIDT), retained clinical samples need to be cultured, either by the clinical laboratory or the public health laboratory, to obtain an isolate for further characterization by WGS. Results of WGS are reported to CDC through PulseNet.

As demonstrated in the following figure, the time from specimen collection to WGS may run from 9-24 days. Thus, cases are not typically linked to a possible cluster until 2-4 weeks after exposure to the source of contamination. Individual cases may be interviewed by local or state public health officials within days of diagnosis to identify potential exposure settings such as child-care facilities or restaurants that may require intervention. In some states, all cases are routinely interviewed to assess potential exposure sources, whether or not they have been linked to a cluster.

Figure 1. Sample timeline for *Salmonella* case reporting.



Source: CIFOR Guidelines for Foodborne Disease Outbreak Response, third edition (<https://cifor.us/downloads/clearinghouse/CIFOR-Guidelines-Complete-third-Ed.-FINAL.pdf>)

Multistate outbreak investigations are generally initiated following the detection of a cluster of illnesses caused by pathogens that appear to be closely related by WGS. Initial review of cases by age, gender, geographic location, and date of onset is conducted to characterize the scope and spread of the outbreak. For example, among the outbreaks included in this review, initial detections were made with as few as 10 cases in three states (*S. Newport*, onions), 11 cases in four states (*S. Stanley*, wood ear mushrooms), and 16 cases in six states (*S. Enteritidis*, peaches) for the *Salmonella* outbreaks and between 5-7 cases in 2-4 states for the *E. coli* O157:H7 outbreaks associated with leafy greens. These initial multi-state clusters represented as little as 1% of total cases (*S. Newport*, onions) to as much as 70% of total cases in the smallest of the leafy green outbreaks. However, across all of these outbreaks, 48-100% of cases ultimately included in outbreak totals had experienced onset of illness by the time that the outbreak was initially recognized. These results highlight both the dynamic nature of the outbreaks and the challenges of rapidly identifying the source. Turn-around times on WGS in Public Health Laboratories are a limiting factor in outbreak recognition.

Previous exposure sources associated with the agent are reviewed to identify food vehicles implicated in previous outbreaks and isolation of the agent from animals, food, or environmental samples. Thus, leafy greens were suspected as potential vehicles for the *E. coli* O157:H7 outbreaks. *S. Enteritidis* outbreaks have primarily been associated with eggs and chicken meat while *S. Newport* and *S. Stanley* have been associated with a variety of animal products and seeded vegetables. Because none of these relationships are exclusive, preliminary exposure histories collected during routine interviews by local and state health departments are reviewed and National Hypothesis Generating Questionnaires (NHGQ) are used to collect information on a broad range of food and non-food sources (National Hypothesis Generating Questionnaire http://cifor.us/downloads/clearinghouse/NHGQ_v2_OMB0920_0997.pdf). Of particular interest is the identification of sub-clusters of cases who may have eaten at the same restaurant or chain of restaurants. These sub-clusters are important because they allow investigators to focus on foods common to the cluster setting (Smith K, *et al.* Product Tracing in Epidemiologic Investigations of Outbreaks due to Commercially Distributed Food Items – Utility, Application, and Considerations (<http://mnfoodsafetycoe.umn.edu/wp-content/uploads/2015/10/Product-Tracing-in-Epidemiologic-Investigations.pdf>)). In two of the outbreaks included in this review (*E. coli* O157:H7, salad kit; *S. Enteritidis*, peaches) the implicated food item was rapidly identified because initially interviewed cases obtained the products through a single retail grocery chain. Restaurant chain-associated sub-clusters provided initial points of service for traceback in several other investigations.

Descriptive data regarding the outbreak and *a priori* hypotheses are reviewed by epidemiologists at CDC in conjunction with the reporting states and federal regulatory partners, FDA, and USDA-Food Safety Inspection Service (FSIS) (Memorandum of Understanding Between the Food and Drug Administration and the Centers for Disease Control and Prevention. MOU 225-14-017). In some instances, when a specific food commodity is suspected, CDC will convene a group of industry specialists to generate hypotheses as to possible sources. The FDA CORE Signals Team participates in initial assessments and the analysis of NHGQs and case clusters before a specific food item is suspected or implicated. The FDA Office of Food Safety (OFS) subject matter experts may be consulted regarding specific commodities.

During these early phases of the investigation, while hypothesis generating interviews are being conducted, informational tracebacks are needed to establish whether a commonly eaten food item, such as chicken, lettuce, or tomatoes may have come from a single source. These informational tracebacks need to be rapidly conducted and incorporated into epidemiologic studies. Detailed product

source information collected during routine case investigations and hypothesis generating interviews is needed to be able to distinguish whether a particular type of leafy green or brand of peanut butter, for example, may be associated with illnesses. For commonly eaten foods such as lettuce, peanut butter or chicken, additional details beyond the commodity level are needed to assess the likelihood that a specific product is involved in the outbreak. Much of this activity occurs during the early stages of the outbreak investigation, when the CORE Signals Team is evaluating data in conjunction with CDC and state partners. Informational traceback data may be obtained “through phone calls, emails, spreadsheets, and official documentation” (FDA CORE Response Desktop SOP Traceback Investigations).

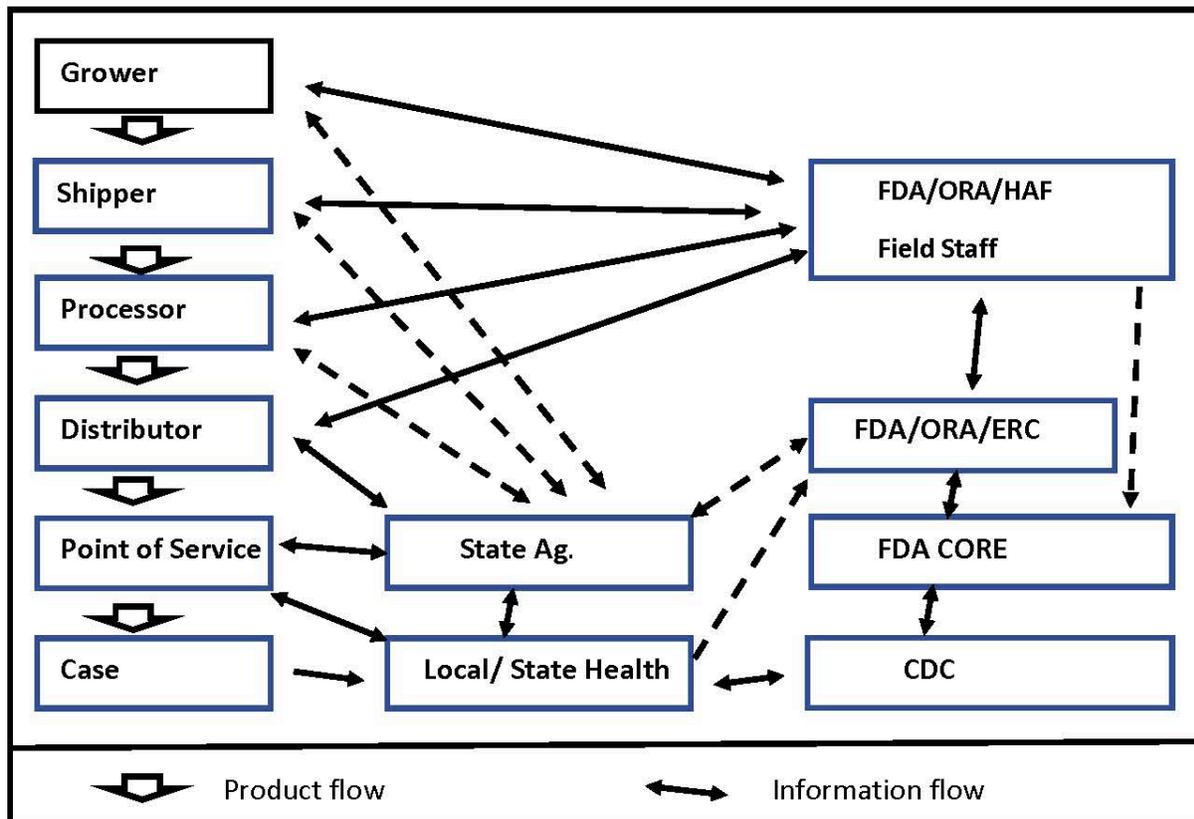
Local and state health officials and state departments of agriculture typically initiate these informational tracebacks by calling or visiting points of service or distributors. However, when the distribution chain leads out of their jurisdiction, CDC and FDA may be asked to assist. CDC does not typically play a direct role in contacting companies to facilitate these informational tracebacks. There are no written protocols for conducting an informational traceback (Guide to Traceback of Fresh Fruits and Vegetables implicated in Epidemiological Investigations). FDA CORE assists, but these requests typically come before the investigation has been transferred to a CORE Response Team, and the CORE Signals Team is not adequately staffed or intended to conduct detailed product tracebacks.

At the point at which a food item regulated by FDA is implicated, or suspected, FDA responsibility for the investigation is transferred from FDA CORE Signals to one of four FDA CORE Response Teams, to conduct an informational traceback or initiate a more formal regulatory traceback. For example, the November 2019 investigation of *E. coli* O157:H7 infections was transferred to CORE Response Team 2 because the identified strain had been historically linked to leafy greens and romaine from the Santa Maria, CA growing region (*E. coli* O157:H7/Romaine lettuce/Nov 2019 (EON-406461) Incident Summary Report).

Role of CORE in traceback activities. An FDA CORE Response Team is assigned to each outbreak investigation. Each response team has a Team Leader and five members. Teams operate under an incident command system (ICS) structure with incident lead, planning lead and operations lead roles rotated among team members during different outbreak responses. The incident lead serves as the primary point of contact with CDC, the planning lead is tasked to set up meetings and maintain meeting notes and documents. The operations lead communicates with District Emergency Response Coordinators (ERC), issues assignments and analyzes records. A schematic of how traceback information moves is depicted in Figure 2.

Communications and traceback assignments. FDA has begun to post details of outbreak investigation activities coordinated by CORE Response Teams on a publicly available investigation table (<https://www.fda.gov/food/outbreaks-foodborne-illness/investigations-foodborne-illness-outbreaks>). Increasing the transparency of outbreak investigations should enhance awareness of public health and potentially affected industry partners to facilitate improved collaboration on traceback activities.

Figure 2. Schematic of information flow in traceback investigation.



As depicted in Figure 2, regulatory tracebacks are time and labor intensive. CORE initiates document requests via assignments to ORA District Offices and field staff may make document requests by email, telephone, or in person. Each point of service (POS) may lead to multiple distributors, processors, shippers, and growers. Depending on the commodity and distribution network, a single leg of a traceback may involve firms in multiple FDA Districts. Follow-up within districts is arranged and managed at the district level. Firms may be asked to provide electronic records of shipments, invoices, bills of lading and other documents. Many small firms do not have electronic record-keeping systems that can generate these documents. In some instances, discrepancies in electronic records have resulted in the need to obtain copies of original shipping documents. Thus, many requests for traceback records result in the collection of large numbers of documents that must be organized and abstracted to produce useful information. FDA staff anticipate that the implementation of the FDA Food Safety Modernization Act (FSMA), section 204, proposed rule for food traceability should streamline traceback record collections by defining critical tracking events and standardizing data elements, which will allow for development of electronic reporting protocols.

Because of the current investigative burden of tracebacks, attempts are made to prioritize the identification of clusters that are most likely to yield actionable information. Criteria for selecting illness sub-clusters for investigation include:

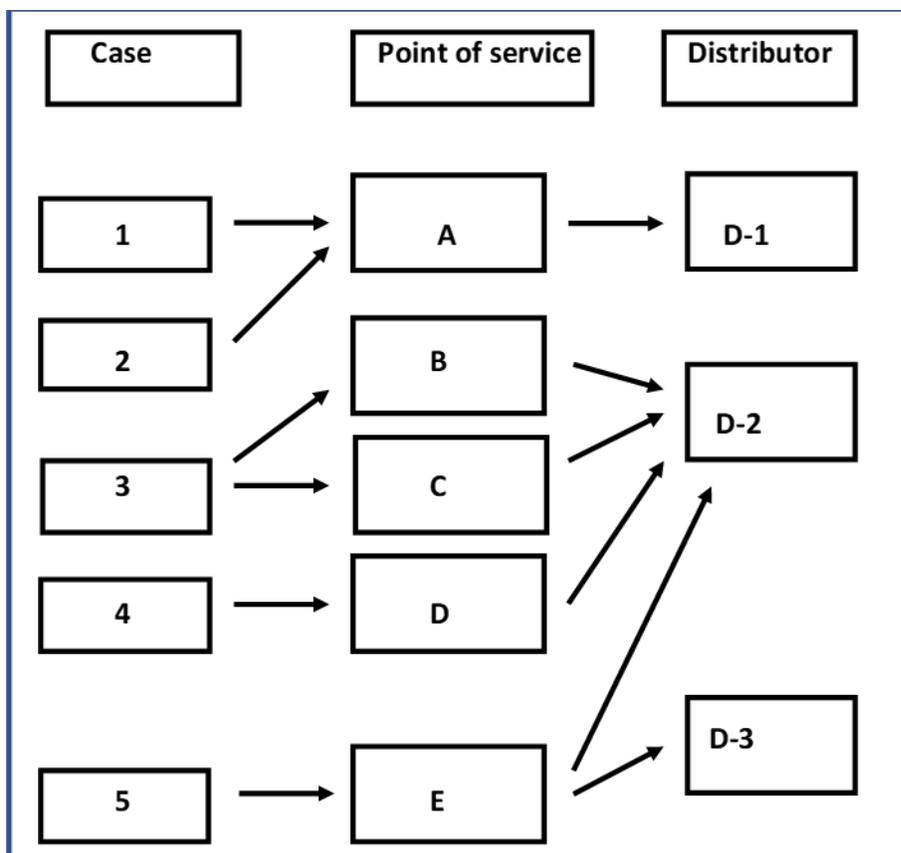
- The case isolate is closely related to the outbreak strain by WGS,
- A reliable food history is available for the case,
- The case reported few, or preferably one, exposure to the suspected food prior to illness onset,

- Verifiable purchase dates can be obtained through receipts, loyalty cards, shopper cards, or other documentation.

The more cases associated with the sub-cluster, the stronger the evidence that the contaminated product was sold at the particular point of service. (Irvin K, *et al.* An Overview of Traceback Investigations and Three Case Studies of Recent Outbreaks of Escherichia coli O157:H7 Infections Linked to Romaine Lettuce. *J Food Prot.* 2021. doi: 10.4315/JFP-21-112. Online ahead of print). Increasing the specificity of exposure information can help narrow the scope of tracebacks.

A simplified schematic of prioritization of a traceback is presented in Figure 3. In this figure, cases 1 and 2 share a unique exposure to point of service A. Because other cases were distributed among multiple other points of service with no clustering, point of service A would receive priority for traceback.

Figure 3. Schematic of prioritization of traceback.



Ideal traceback conditions are rarely achievable during actual outbreak investigations. During the outbreak of *S. Newport* infections associated with red onions, a regulatory traceback was initiated for four legs at 10 points of service. These four legs represented 26 cases. The main factor used to identify the legs was having more than one case at a single point of service with exposure to red onions (Outbreak Investigation of *Salmonella* Newport: Red Onions (July 2020) <https://www.fda.gov/food/outbreaks-foodborne-illness/outbreak-investigation-salmonella-newport-red-onions-july-2020>). In this traceback, onions from Thomson International, Inc. were identified in each of the four legs. Two legs each involved four separate points of service and the tracebacks yielded

detailed information on potential lots and field level data. However, the other two legs each involved only one point of service and included limited product lot or field source information. The tracebacks converged on one producer but were not able to converge on a product lot or field source of production. Lack of convergence at production levels limits the ability to focus root cause investigations on likely contamination pathways to determine how and why the outbreak occurred.

Scope of document requests in traceback. Document requests in traceback investigations are intended to cover the availability of products at the point of service when cases were likely exposed. These timeframes may vary by product type and shelf life, but frequently include two weeks at the point of service for known meal dates and three weeks at the point of service for onset dates of illness when the specific meal date is not known. Because multiple cases at a single point of service are likely to have meal dates over several days or possibly weeks, the document requests may frequently cover time frames up to a month for individual points of service. For distributors serving multiple points of service the corresponding document requests would cover the range of exposure windows for the individual points of service. The temporal variability in the search window potentially increases with each step backwards in the traceback. Thus, many tracebacks feature very broad records requests, which are a frequent source of concern for the companies pulling records.

Within these exposure windows, all potential sources are assessed to identify convergence on a particular source of supply. Because of the size of these exposure windows, products with a relatively high rate of consumption and resupply may introduce considerable “noise” into the analysis. That is, the actual contaminated product may appear to be just one of many possible sources identified as potentially available at the point of service. Alternative approaches in which higher probabilities of availability based on proximity to consumption are being developed. These efforts to quantify tracing scores using critical tracking events would reduce uncertainty in the traceback and reduce the number of documents that would be needed to evaluate in each traceback (Weiser AA, *et al.* (2016) Food Chain-Lab: A Trace-Back and Trace-Forward Tool Developed and Applied during Food-Borne Disease Outbreak Investigations in Germany and Europe. PLoS ONE 11(3): e0151977.

<https://doi.org/10.1371/journal.pone.0151977>).

Timelines in completing tracebacks. Assignments made for record collections in regulatory tracebacks may be initiated by email, telephone call or in person. Although records may be supplied as searchable spreadsheets, records may need to be reviewed on site. Depending on the scope of the record request, the point of service, distributor, shipper, or other operator may need time to compile the requested information and deliver it for review. In general, responses to requests that are completed within 1-2 days are considered timely. In a series of requests associated with outbreaks from 2019-2020 that were reviewed, the median response time was within 2 days and ranged from 0-14 days. In October 2020, Fresh Express Inc received a warning letter that noted delays in responding to FDA requests for documents in a traceback investigation related to an outbreak of cyclosporiasis (WARNING LETTER Fresh Express Inc - Div of Chiquita Brands MARCS-CMS 609899 — OCTOBER 20, 2020.

<https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/fresh-express-inc-609899-div-chiquita-brands>). CORE response teams assemble the collected data, update product flow/traceback diagrams and make additional assignments as needed. Assignment dates are tracked in the CORE incident database. While response times may be tracked internally within individual investigations, there is no corresponding field in the CORE data base for response dates to facilitate systematic evaluation of response times across traceback events.

Factors used to determine whether or not to conduct root cause investigation. The Procedure Manual for Fresh Produce Root Cause Investigation (RCI) establishes a detailed process for initiating and conducting a RCI. The procedure manual was jointly developed by CFSAN’s Office of Food Safety (OFS)/Division of Produce Safety (DPS), CORE and the Office of Regulatory Affairs (ORA). Thus, it represents the collaboration of three of the major FDA groups involved in foodborne outbreak investigation and response. The Manual defines a RCI as “an in-depth, multi-disciplinary, systems-based investigation of firms, products, and the environment, intending to determine how the environment may have contributed to the introduction, proliferation, and transmission of pathogens or other hazards that caused illnesses or fresh produce contamination.” Initiating a RCI requires consultation between FDA partners including ORA Headquarters, CFSAN’s Office of Compliance (OC), and CORE. If there is agreement to conduct the RCI, a *Request to Initiate an RCI* memorandum is drafted to “define the specific mission, expected objective outcomes and how success will be measured, expected timeframe of execution, estimate of resources required and overall scope of the RCI.” The RCI is intended to produce an “outward facing summary of activities, observations, conclusions and recommendations for the general public.”

In practice, it appears that many produce-related outbreak investigations involve some level of environmental assessment that is conducted to investigate growing, harvesting, packing, and holding operations outside of formal RCI procedures (Memorandum: Date: 9/10/2020 Firm: Thomson International, Inc. (Holtville). Subject: Outbreak Investigation. FEI: 3017219425. <https://www.fda.gov/media/146374/download>). There is not always a clear distinction between focused regulatory investigations to complete particular assignments made in response to traceback activities and broader searches for answers that may be viewed as “research”. Absent the activation of a formal RCI process, extra assignments may be seen to compete with other regulatory activities and viewed as drains on resources without clearly defined outcomes or expectations of success. These deployments involve considerable logistical challenges in moving personnel and equipment.

Extending record collections, environmental assessments, and environmental and product sampling beyond the scope of initial outbreak investigation response assignments may be important for extending the value of epidemiologic investigations and for identifying root causes. For example, following the investigation of a nationwide S. Enteritidis outbreak associated with Schwan’s ice cream, documentation of ice cream pre-mix transportation factors identified cross-contamination between raw liquid egg and pasteurized pre-mix in tanker trailers used to deliver the pre-mix to the packaging plant. Although environmental samples taken at the plant or from a few trucks were negative, the epidemiologic findings supported product contamination results and led to changes in regulations regarding transportation of food ingredients (Hennessy TW, *et al.* A national outbreak of Salmonella enteritidis infections from ice cream. The Investigation Team. N Engl J Med. 1996 May 16;334(20):1281-6.).

Given the challenges inherent in identifying farms and fields during the course of outbreak investigations, it is not reasonable to expect to be able to link every case to a specific source, or to isolate the outbreak-associated strains from product or environmental samples collected from the farms. The biology of the organisms and ecology of the fields challenges the limits of our laboratory methods. This is compounded by the lack of access to animal and environmental samples from adjacent fields managed by different owners. However, as outbreak scenarios are repeated and outbreak-associated strains reoccur, the patterns of observations across multiple outbreaks becomes meaningful and interpretable. Placing those observations into an epidemiologic context may be the key to

developing more effective prevention strategies. For example, in the S. Newport outbreak associated with onions, environmental assessments with microbiological testing conducted after the outbreak, combined with the author's re-evaluation of traceback data (see p.44) suggested that the Holtville growing region was the likely source of contaminated onions in the S. Newport outbreak. Although, no "smoking gun" in the form of the specific outbreak-associated strain was isolated from product or environmental samples from Holtville was found, the balance of evidence is consistent with the epidemiology of the outbreak. These findings provided important information for industry action to prevent future outbreaks (*Salmonella* Newport/Red Onion/Jul 2020 (EON-432687) Incident Summary Report).

Translation of outbreak investigation findings to prevention activities. Coordination of outbreak investigation activities begins with CDC and the states. As hypotheses develop regarding possible sources of exposure, commodity-specific SMEs with FDA are engaged, and specific segments of industry may be contacted to explore how the scope of the outbreak may relate to current production and distribution practices within the industry. This early engagement with industry has become more common in the context of reoccurring or persisting strains of pathogens, such as with *E. coli* O157:H7 in leafy greens. Engagement with industry throughout the investigation process is important to ensure that contextual information about the outbreak is shared between FDA, CDC, state partner investigators and the industry experts who will be critical to implementing potential changes to production practices.

Consultation with FDA to facilitate outbreak investigations involving fresh produce has been promoted by the produce industry (Produce Industry Partnership with FDA/CDC to Investigate Illness Outbreaks-Draft Proposal). The industry has also advanced its own evaluation of outbreak associated data (An Analysis of 2016-2019 Outbreaks Linked by Whole Genome Sequencing. United Fresh Produce Association). These efforts to complement internal agency reviews and publications that seek to synthesize information learned from outbreak investigations and special studies are conducted to explain outbreak findings (Marshall KE, et al. Lessons Learned from a Decade of Investigations of Shiga Toxin-Producing *Escherichia coli* Outbreaks Linked to Leafy Greens, United States and Canada. *Emerg Infect Dis.* 2020;26(10):2319-2328. <https://dx.doi.org/10.3201/eid2610.191418> ; Coulombe G, et al. Outbreaks of *Escherichia coli* O157:H7 Infections Linked to Romaine Lettuce in Canada from 2008 to 2018: An Analysis of Food Safety Context. *J Food Prot.* 2020 Aug 1;83(8):1444-1462. doi: 10.4315/JFP-20-029. <https://doi.org/10.4315/JFP-20-029>; Bottichio L, et al. Shiga Toxin-Producing *Escherichia coli* Infections Associated With Romaine Lettuce-United States, 2018. *Clin Infect Dis.* 2020 Nov 5;71(8):e323-e330. doi: 10.1093/cid/ciz1182; Thao S, et al. Enhanced formation of shiga toxin-producing *Escherichia coli* persister variants in environments relevant to leafy greens production. *Food Microbiol.* 2019 Dec;84:103241. doi: 10.1016/j.fm.2019.103241. Epub 2019 Jun 14. PMID: 31421768; Maguire M, et al. Precision long-read metagenomics sequencing for food safety by detection and assembly of Shiga toxin-producing *Escherichia coli* in irrigation water. *PLoS One.* 2021 Jan 14;16(1):e0245172. doi: 10.1371/journal.pone.0245172).

Evaluation activities and systems improvement. The New Era of Smarter Food Safety-Blueprint for the Future embodies a number of initiatives to improve foodborne outbreak response (New Era of Smarter Food Safety. FDA's Blueprint for the Future (<https://www.fda.gov/food/new-era-smarter-food-safety/new-era-smarter-food-safety-blueprint>). Implementation of the blueprint will be a long process that depends on technological and operational innovation. Several elements that will have impacts in the near term are highlighted below.

- A key element of this is the development of tech-enabled traceability. Requirements for additional traceability records for foods that have been frequently associated with foodborne outbreaks have been identified on a food traceability list. Firms that manufacture, process, pack or hold these foods will be required to establish and maintain records containing key data elements associated with critical tracking events (Food Traceability List (<https://www.fda.gov/media/145050/download>)). Making these records available within 24 hours in an electronic spreadsheet will greatly speed up the traceback process. In addition, if the time and labor constraints associated with tracebacks was substantially reduced, it would make it feasible to include many additional points of service or legs in the tracebacks that are conducted. The success of this effort will initially depend on data quality issues and the confidence that field staff and CORE have in the reported data.
- Another technological advance is the development and use of artificial intelligence (AI) to improve predictive analytics capabilities. A project has been developed to incorporate AI to improve the import screening tool PREDICT to identify contaminated shipments of imported foods (Incorporating Outbreak and Recall Data Streams in Predict Model). In particular, this project will assess the incorporation of outbreak data managed by CORE. Characteristics of outbreaks, implicated food items and production variables associated with these food items may provide important flags for the identification of other foods in commerce that may pose a risk for foodborne illness if not removed from the marketplace.
- Coupled with these efforts to focus on prevention is the development of a framework to map the process of moving from outbreak to prevention by the Office for Food Safety. This mapping process clearly establishes relationships between CORE, CFSAN and OFPR. The process maintains the role of CORE Signals in outbreak detection and CORE Response in outbreak management and resolution. With the transfer of the incident to CORE Outbreak Evaluation for preparing recommendations and data aggregation, OFS Prevention would convene subject matter experts (SMEs) to evaluate policy, research, and education gaps. A key element of the approach would be the expectation for OFS prevention to develop a draft prevention strategy within 30 days, seek alignment across the Agency on the recommended strategy, and then subsequently execute the strategy in conjunction with internal and external partners, including industry. Following the implementation of the strategy, compliance status would be monitored to determine whether the strategy led to improvement or not. If improvement was not observed, the strategy would be re-evaluated and updated. This approach would standardize the process of transition from outbreak response to prevention, clarify roles and reinforce the importance of each of the partners in their role.
- An important effort to improve communication with external partners and to improve the transparency of outbreak response activities has been the development of the table listing outbreak investigations being managed by FDA's CORE Response Teams Investigations of Foodborne Illness Outbreaks (<https://www.fda.gov/food/outbreaks-foodborne-illness/investigations-foodborne-illness-outbreaks>). This table provides access to information on the date the investigation was posted, the pathogen, any product(s) linked to illnesses (if any), the number of cases, the investigation status, whether a traceback, onsite inspection, sample collection and analysis, or recall has been initiated, and the outbreak status. Investigation partners and the public can use this information to monitor the progress of the outbreak investigation. The availability of this information is intended to increase the visibility

of outbreak investigation activities and provide incentives to all internal and external partners to work efficiently in a cooperative manner to effectively respond to the outbreak.

4. Themes that emerged from interviews

There were common themes that emerged from the different groups of stakeholders interviewed. Major issues that were raised by multiple stakeholders are presented first, followed by the summaries from the individual stakeholder groups.

Major issues:

- Communication with investigation partners and industry. There is a perception that a culture of withholding information goes beyond actual legal restraints on sharing information. This affects many aspects of outbreak investigation and response.
- Informational tracebacks are a critical part of hypothesis generation during the earliest stages of outbreak investigations. However, CORE does not have an established procedure to conduct tracebacks until an incident has been transferred to a Response Team. This is typically after a food item has been implicated, or it is caused by a REP strain previously linked to an FDA regulated food item.
- The incident command structure (ICS) structure that CORE operates under has improved the standardization of outbreak response activities but imposes built in time delays to the investigation. Greater flexibility for Response Teams to interact directly with state partners could enhance the efficiency of outbreak responses.
- The collection of electronic records for traceback is increasing, but their use is qualified by concerns about data accuracy. The goal of source convergence over the limited number of traceback legs available during each investigation amplifies the cost of potential data errors.
- The processes for transferring investigations from CORE Response to Outbreak Evaluation and for initiating Environmental Assessments (EAs) or RCIs needs clarification and standardization. There is a tension between initiating efforts to identify a “smoking gun” and efforts to more broadly identify why the event happened. Transitioning from response to prevention requires putting the individual outbreak events into a larger epidemiological context.
- Lack of resources. The number of concurrent investigations frequently stretches the capacity of CORE. ORA PSN investigators and supporting program areas risk burnout due to the number of concurrent and consecutive farm investigations and sample collections associated with REP strain and other produce-related outbreaks.

Summaries by stakeholder group:

- **FDA CORE.** It was noted that CORE has established Team structures and workflow based on divisions of labor under an incident command system.
 - A single Signals Team is tasked to coordinate with CDC to assess preliminary information about clusters identified through WGS sequencing at CDC. Although one Team member is assigned to follow each cluster, a recent challenge noted is a shortage of staff to follow new clusters due to the increased precision of cluster definition by WGS. While the Signals Team may participate in hypothesis generation with CDC, they do not generally participate in traceback activities.
 - Four Response Teams have been established. Response Team leads communicate with each other on a regular basis, but each Response Team is responsible for its own outbreak investigations. It was noted that for each response there are three leads identified: an incident lead to serve as the point of contact with CDC investigators, a planning lead to set up and

document meetings, and an operations lead to communicate with the Emergency Response Coordinators (ERCs) in the Divisions and issue assignments and analyze records. These roles were noted to rotate among the Response Team members to help ensure that all Team members are familiar all roles and prevent “burn out” from repeatedly performing the same tasks in each investigation. Thus, a single Response Team member could simultaneously serve as incident lead, planning lead and operations lead for three separate investigations.

- It was noted that incidents are transferred to a Response Team based on the judgment that the outbreak is caused by a food item regulated by FDA and coordination of traceback efforts is needed. The Response Team occupies a central role in assessing exposure information collected by Local and State Health Departments and CDC to initiate assignments for record collection by ORA field staff with the goal to collect information as soon as possible and to take tracebacks to the farm level to get boots on the ground for additional investigations.
 - Although using ICS for making assignments for record collection has improved standardization of the process, it was noted that working through ERC and field staff affects the speed of data collection. CORE has intermediaries for 90% of interactions, and Response Team members would welcome more direct access to state partners.
 - In addition, collection of electronic records and spreadsheets with requested information has improved the speed and effectiveness of tracebacks, compared to older approaches and looking at paper records. However, there are concerns about data entry errors on spreadsheets. In addition, there is inconsistent use of terminology by companies that frequently needs to be clarified when reviewing electronic data. The need for follow-up to clarify data questions undermines the value of speed in obtaining the electronic records.
 - At the end of the response activities, the incident is transferred to Outbreak Evaluation. This process typically precedes a formal EA or RCI, which may be conducted by the Office of Compliance (OC) and Office of Food Safety (OFS). There is a lack of clarity on post-response roles for CORE versus OFS. There is no process for integrating results of the EA into a re-evaluation of the traceback. Inferences from tracebacks are frequently limited by uncertainty.
 - CORE notes it is developing an outbreak analytics platform, with the first phase being to automate everything from the CORE Data Dictionary. CORE is seeking guidance on helping to determine the usefulness of many of the data elements being collected. The second phase would be to pull in outside data relevant to improving the speed and effectiveness of outbreak responses. The third phase would be to share the platform with external partners to increase transparency of investigation processes and improve the usefulness of data to inform policy.
 - In addition to coordinating the activities of the Signals, Response and Evaluation, Analytics and Communications Teams, the leadership of FDA CORE seeks to maintain strong working relationships with CDC, the states and industry. To do this they frequently represent FDA and CORE in national Food Safety meetings.
- *FDA ORA.* It was noted that CORE issues the assignments and ORA implements. This is viewed as appropriate since field staff doing routine inspections are more aware of conditions within specific facilities. ORA prioritizes inspections based on results of previous inspections and the occurrence of outbreaks. It was further noted that CORE is only one key to effective ORA response. For example, the opportunity of SMEs to participate in developing sampling assignments has allowed ORA Produce Safety Network (PSN) investigators to be in the field within 24 hours of receiving the

assignment. Because of increasing numbers of outbreaks associated with produce, and the need for more EA associated with REP strains and recurring outbreaks with leafy greens, ORA effectively doubled the size of its PSN over the past year.

- EA and RCI represent important transitions to prevention, and investigators are always interested in getting to the root cause. However, there are concerns about investigations moving into the realm of research. When the outbreak appears to be winding down, it is not clear how far efforts should be made to find the “smoking gun”. ORA needs to maintain other inspection activities. There are concerns that decisions made at an operational level based on considerations of available resources and likely outcomes may be overruled by leadership for reasons that may not be clearly communicated.
 - There are numerous logistical and procedural challenges to conducting on-farm investigations. Multiple simultaneous or serial field assignments in areas with no FDA office mean that field staff spend considerable time on logistics to maintain needed supplies. Repeated field assignments among a limited number of investigators increases stress and risk of investigator burn out. This concern was exacerbated during the COVID-19 pandemic, where travel restrictions meant that volunteers needed to be recruited to fulfil field assignments. CORE assignments may include many questions submitted by SMEs from several different offices. These questions may be duplicative of each other or the standard field investigation questionnaire (FIQ) and may distract from efforts to focus on identifying a root cause. Coordination and communication with state partners needs to be maintained to avoid jurisdictional conflict.
 - Key limitations to conducting on-farm investigations include the timeliness of traceback such that implicated fields are frequently fallow by the time of the investigation, the size and complexity of produce operations and lack of access to adjacent land.
- *Other FDA Offices.* In CFSAN, the Office of Food Safety (OFS) houses the Division of Produce Safety. Produce safety experts in the Division of Produce Safety, based in the Produce Safety Network (PSN), work with growers on policy implementation, rather than conducting on farm investigations as part of an outbreak response. To further the development of a preventive framework, there is a need to get answers faster. Two big data advances, WGS and traceability are critical to this effort. If a clearer picture of causation can be developed, it is more likely that industry will follow. This will also be critical to leverage state agriculture sector’s support for industry to push better production practices.
- FDA is not resourced to conduct surveillance for food safety hazards in produce. CFSAN PSN needs to increase its expertise base and add capacity to develop partnerships with state partners and industry that can help promote applied research to address food safety problems and promote development of food safety culture.
 - OFS maintains experts from every aisle of the grocery store and works alongside CORE to provide SME assistance.
 - Process improvements are needed to transition from immediate outbreak response to prevention. There is a strong desire to identify the “smoking gun” by getting boots on the ground quickly. However, identifying the smoking gun may not identify why the event happened, which is the key to prevention.

- During the active response, farm investigations are conducted to collect data and samples that may identify sources of contamination and potentially lead to a large scale, long term RCI. Post response, there may be follow-up investigations or longitudinal studies and non-regulatory research to address unanswered questions. While ORA inspectors participate in active outbreak investigations, they are discouraged from participating in longitudinal studies.
 - The transfer of incidents from CORE Response Teams to CORE Outbreak Evaluation provides an opportunity to examine the whole record of the outbreak to develop prevention strategies in conjunction with CDC. At the end of an outbreak, CORE creates recommendations which are forwarded to OFS for inclusion in their prevention plans.
- The Office of Food Policy and Response reviews all of FDA's outbreak response activities to identify strategies to integrate activities across the agency, accommodate new technology, and set up processes and policies to make things work better. Those interviewed raised the following points:
 - There are many inefficiencies built into the system beginning with state investigations. Interviews may not be conducted in a timely manner and public health laboratories may batch test case specimens. Because of constraints on FDA communications and regulatory tracebacks, CDC and the states could do more informational tracebacks and situational discussions with industry.
 - There is a need to better integrate Rapid Response Teams (RRTs) in outbreak responses and ensure that RRTs have the capacity to assist investigations in all states.
 - Tracebacks generate a lot of data in different formats that cannot easily be connected for analysis. Current practices assign equal probabilities across shelf life of product. Attempts are made to build the traceback piece by piece to ensure precision of the traceback. Structuring supply chain data and putting it into a common platform can facilitate quantitative analysis. Prioritizing tracebacks based on probability of availability would improve efficiency of tracebacks.
 - Developing predictive analytics; a cumulative oversight model for imported foods is being developed that could be benchmarked against domestic inspections. Protocols for working with foreign counterparts are being developed. Working to develop approaches for industry to share block chain traceability data with government during outbreak settings. Looking to integrate data from CORE into analytical models.
- *Federal partners.* The importance of weekly tri-agency calls between CDC, FDA, and USDA-FSIS to review cluster and outbreak investigations was noted. This provides situational awareness for regulatory agencies. FDA and USDA-FSIS liaisons co-located with CDC also work together in the early assessment of outbreaks and to facilitate planning.
 - There is little cross-over between FDA and USDA-FSIS on specific investigations, and if FDA regulated product implicated in an outbreak is used in an FSIS-regulated facility, there is no formal mechanism for FDA to notify USDA-FSIS. USDA-FSIS staff in the facility are typically notified by the company that they have received recalled product.
 - It was noted that USDA-FSIS has applied epidemiology staff in the Office of Public Health Science (OPHS) that conduct product tracebacks in outbreak investigations similar to FDA CORE, and

these applied epidemiology staff may be invited to FDA CORE tactics calls. Tactics calls provide opportunities for discussion on priorities for traceback.

- USDA-FSIS noted several differences in their approach to outbreak investigations. They do not distinguish between informational and regulatory tracebacks. Information is collected by applied epidemiology staff from OPHS rather than by field inspection staff. When they request additional information at a federal establishment or retail, they work with CDC to provide talking points so that consistent information is shared. They do not have 20.88 agreements with individual collaborators but have a mechanism to allow OPHS to share information with state partners with approval of the Assistant Administrator and the Director of the Office of Field Operations Recall Management and Technical Analysis Division (FSIS Directive 2620.5). USDA-FSIS also posts information on active investigations to an outbreak table (<https://www.fsis.usda.gov/food-safety/foodborne-illness-and-disease/outbreaks/outbreak-investigations-response>) and includes a link to after action review reports for some completed investigations.
- The Outbreak Response and Prevention Branch (ORPB) at CDC works closely with CORE during outbreak investigations. Good working relationships have been established and it was noted that interagency cooperation has never been better. This was attributed in part to the maturation and stability of leadership within CORE.
- There have been considerable advances in CDC's approach to cluster detection and response. The use of WGS has led to greater specificity and precision in cluster definition. The routine use of detailed hypothesis generating questionnaires and binomial comparisons of specific exposures to FoodNet population survey data has led to rapid refinement of hypotheses. Experience from earlier investigations has improved identification of epidemiologic patterns associated with various commodities. Identifying that a cluster has a "produce signal" allows investigators to add specific modules of questions to probe on produce sources.
- These innovations and earlier engagement between ORPB and CORE have led to earlier and more successful initiation of tracebacks. It was noted that there is more general acceptance that tracebacks are an integral part of investigations and not something to start after a food item has been definitively implicated. There has been more willingness to trace small clusters and individual cases. There has been an increased willingness to trace more than one food item at the start of the investigation. There is a greater willingness to put resources on the ground.
- Several limitations and areas for improvement were noted. FDA relies on scarce field resources and coordination with states that also have limited resources and different priorities. Depending on investigators who are busy with routine inspections to also do field assessments inevitably slows things down. There remain challenges to initiating tracebacks during the early stages of investigation when there are multiple potential vehicles. There are opportunities to develop more holistic analyses of tracebacks, to better reflect the probability distributions of exposure among reported cases. While there are more field assessments being conducted for outbreaks associated with REP strains, there is a need for better environmental and hydrologic understanding of landscapes to assess relationships between the implicated and adjacent fields and associated land use practices. This should include standardizing the process for initiating environmental assessments and codifying information about REP strains to facilitate analyses of environmental data across different outbreaks. A protocol to facilitate testing of animals on adjacent lands is needed.

- *State partners.* The role of RRTs and their importance in coordinating investigations at a state level was emphasized. Resources at both federal and state levels are seen as limiting factors in the increasing need for environmental assessments associated with REP strains. A small group of specialists are at risk for burn out due to frequent field assignments. RRTs serve as “force multipliers” and should be expanded to all states. In addition, RRTs may have the ability to develop protocols to facilitate access to animal and environmental samples from independent operations nearby implicated produce fields. There is also a need within agriculture to treat fresh produce as a ready-to-eat food and increase the knowledge base of produce safety measures across states.
 - Opportunities for prevention should be enhanced. Performance measures should focus on outcomes rather than processes. Particularly for REP strains, the anticipated recurrence of an outbreak should lead to targeted retail product sampling as well as heightened surveillance for human illnesses. In addition, there need to be better processes for FDA to act on food and environmental sampling results generated independently by states. The triggers for initiating a RCI are not clear.
 - Issues of communication between FDA and states, and with the public were raised. Concerns about commercial confidential information are cited as a barrier to sharing information. In responding to outbreaks, the public health benefits of disclosing information should be given greater weight. Transparency in communications would benefit all parties.
 - Although CORE has standardized many response activities and effectively uses Emergency Response Coordinators to coordinate with FDA field staff and state regulatory partners, there is not always a clear consensus on priorities, resource allocations, objectives, and timelines for response activities.

- *Industry.* There were important differences expressed by food retailers versus primary producers. At the retail level, most contact is initiated by state agencies. There is variability among the states, but in general there was a sense that FDA and state regulators were forthcoming with information about the outbreak and investigation and were willing to work with the company to identify information needs. This appears to correspond to the role of retailers in being “pass throughs” for the contaminated produce. However, producers noted a lack of willingness on the part of FDA to share information about the investigation. Variability among FDA investigators was also noted with inconsistency in questions asked and expectations for time frames for requested information.
 - There was a very strong desire expressed for more information on the distribution of cases by onset date and location. Industry representatives suggested that their knowledge of supply chains could be matched to outbreak distribution patterns to refine hypotheses. It was noted that some companies have conducted extensive environmental and product testing, in addition to their supply chain knowledge that is not being used.
 - There was an overall level of frustration voiced regarding the coordination of investigations. While the addition of CORE was viewed positively, there were concerns about disconnects between CORE and ORA field staff. This was a particular concern of large produce companies that may appear in multiple tracebacks across different outbreaks and get contacted frequently by different investigators. In addition, managing information between FDA and the various states that initiate traceback investigations and test products independently of FDA was viewed as a challenge.

- The scope of date ranges for shipment data in traceback investigations was raised as a concern. Requests for data on shipments extending over periods of six weeks are common. Companies simultaneously try to produce the extensive shipment data and work with customers to identify narrower ranges of likely products. Large producers typically conduct internal investigations parallel to the public health and regulatory investigations.
- It was noted that some segments of the industry may be in denial about food safety concerns. However, there have been multiple industrywide efforts to explore root causes of produce-associated outbreaks and to communicate best practices for prevention.

5. Conclusions and Recommendations

FDA has made considerable investments in recent years to improve its outbreak investigation processes with the establishment of CORE. Its integration of activities through an incident command system has provided a structure for coordinating traceback activities across FDA. The process of making record collection assignments involves multiple steps that must be coordinated across different parts of the agency, with inherent delays built into the process. Technological and operational innovations provide opportunities to shorten response times. In particular, the identification of REP strains and reoccurring outbreak settings provide investigators with ready hypotheses to test at first recognition of the outbreak.

Improvements in outbreak detection will continue to advance with application of WGS to surveillance of pathogens under surveillance by public health agencies. Turn-around times in public health laboratories have limited the speed of outbreak detection, but these have decreased in states with adequate resources to perform WGS in real time. Improving the capacity of state and local public health epidemiologists to conduct detailed exposure interviews may depend on additional support through CDC's epidemiology and laboratory capacity (ELC) grants. While ELC grants are not within FDA's jurisdiction, helping ensure the effective coordination of federal outbreak response resources is.

Because tracebacks require exposure assessments conducted by state and local health departments, the speed and effectiveness of FDA activities will always depend on the capacity of the public health system. Expanding the number and distribution of FDA-supported RRTs to enhance coordination of investigation activities between FDA and state partners is warranted.

A complementary method of outbreak identification, through environmental and food product sampling by FDA or a federal or state regulatory partner, is becoming more common. When a reportable foodborne pathogen is identified, a search of PulseNet data for matching human isolates may indicate the occurrence of a foodborne outbreak. Investigation of the human case exposures is needed to confirm the source of such a "retrospective" outbreak. This depends on the same public health resources needed for conventional surveillance activities.

A key implication of the expanding use of WGS for foodborne illness surveillance will be the need to investigate more frequent but smaller clusters of cases. Prioritizing traceback of small clusters can lead to earlier detection of outbreaks before they manifest as large, multistate outbreaks. However, this would likely increase the need for informational tracebacks early in the hypothesis generation process. This could be accomplished either by more formal engagement of CORE Response while clusters are still being followed by the Signals Team, earlier transfer of cluster investigations to CORE Response Teams or more formal reliance on CDC and state partners to conduct these informational tracebacks.

The development of improved traceability with electronic records could significantly reduce the burden of investigation required to collect records to document the movement of products in a traceback. This would both speed up tracebacks and permit a larger range of products to be traced. At the same time, prioritizing traceback analyses based on the probability of product availability would improve the efficiency of source identification and better inform the transition from response to prevention.

Establishing performance measures for outbreak response activities and outcomes should be established within the CORE database system.

Resource constraints are a limiting factor in many outbreak investigations. Staffing levels for CORE, ORA investigators, produce safety specialists, laboratory support systems, and other program areas are not adequate to respond to the growing number of outbreaks associated with REP strains and recurrent settings. Consideration for how to add capacity to CORE and increase the ability of CORE Teams to directly interact with outbreak investigation partners outside of FDA is warranted.

Farm visits and sample collections have become an increasing part of outbreak investigations involving REP strains and recurrent settings. Getting to farms while produce is still being grown and harvested has been a challenge. For most produce associated outbreaks, the majority of cases have already occurred by the time the outbreak is recognized. Environmental assessments conducted during these visits, but after the outbreak has ended still need to document conditions that can be directly related to the specific event, and also put them into context of the larger population of similar outbreaks that have been investigated. Integration of these data should be viewed as a routine investigation method. This could help identify factors, such as the presence of animal production facilities on lands adjacent to produce fields that can be compared across multiple investigations and evaluated during applied research studies and long-term environmental assessments. These *post hoc* environmental assessments can also help develop plans for seasonal surveillance during subsequent harvests.

Earlier and more open communication with industry, public health and regulatory partners would enhance the collaborative nature of outbreak investigations and likely produce meaningful results faster. Trust between partners is needed to effectively solve problems and identify solutions. While there remain questions about how, when and to whom information can be disclosed, the default setting should be to disclose information whenever it can advance the progress of the investigation. Outside of specific regulatory directives, behavioral change by industry requires the understanding of investigation findings and insights on how to implement changes within existing production systems. Timely release of investigation findings to the public and discussion of the implications of the findings directly with the affected industry is critical for effective communication and widespread acceptance of results. While the New Era of Smarter Food Safety seeks to “bend the curve” of foodborne illness, successful outbreak investigations can lead to better prevention methods that may lead to “canceling the curve” of many potential outbreaks

Based on the findings of this review the following recommendations are made to enhance the speed, effectiveness, coordination, and communication of outbreak investigations.

Recommendations

- FDA has been working with CDC and USDA-FSIS to increase the sensitivity and timeliness of outbreak detection based on surveillance of WGS patterns among human, food, animal, and environmental isolates of foodborne pathogens. Going forward, FDA should routinely enter WGS data from FDA labs into PulseNet and refine automated search algorithms to:
 - Detect temporal clusters suggesting the occurrence of an outbreak due to commercial distribution of a contaminated food product.
 - Identify human illnesses associated with contaminated food, animal, or environmental samples through PulseNet.
 - Provide historical context between current detected clusters and previously detected events.

Because the source of an outbreak is generally not predictable before its investigation, federal partners should routinely share cluster detections with one another. A common platform, such as CDC's SEDRIC, should be used by all partners to visualize case distributions.

- FDA already works with CDC and USDA-FSIS to identify reoccurring, emerging, and persisting REP strains of pathogens and food items that have been associated with them. In the future:
 - These should be incorporated as *a priori* hypotheses in outbreak investigations and used to target retail product sampling during outbreaks associated with these strains.
 - FDA should coordinate with state partners on retail product sampling.
- FDA should work with CDC and state partners to develop a formal protocol to conduct informational tracebacks to support epidemiological investigations needed to identify suspected food items. While the early stages of investigations, including hypothesis generation and exposure assessment of cases are primarily conducted by state and local health agencies, with CDC coordination for multistate investigations, many investigations require some source tracing of products to help identify a likely vehicle. At this stage of the investigation, before the outbreak has been transferred to a CORE Response Team, there is uncertainty over roles and responsibilities for conducting informational tracebacks. While CORE does conduct and support some informational tracebacks, a written protocol would clarify differences in roles and responsibilities between partners for informational and regulatory tracebacks. This would facilitate more efficient collection of data earlier in the investigation.
- FDA already posts details of outbreak investigation activities being conducted by CORE Response Teams on its publicly available outbreak investigation table. FDA should build on these efforts.
 - FDA should coordinate with CDC to provide case distribution maps and epi-curves as part of the posting.
 - At the conclusion of the investigation, FDA should provide links to a summary of CORE investigation results and other investigation reports published about the outbreak, to enhance the usefulness of the table for external partners
 - FDA should work with CDC and USDA-FSIS to develop a standard set of data elements that can be publicly released for all outbreak investigations being conducted without regard to regulatory jurisdiction.

Increasing transparency of outbreak investigations should enhance awareness among public health and potentially affected industry partners to facilitate improved collaboration on investigation activities.

- FDA has been working to narrow the scope of regulatory tracebacks and reduce the burden of record review and analysis. Additional efforts should include:
 - Work with retailers, CDC, and state partners to document purchase histories using shopper loyalty cards or recreating electronic receipts of credit card purchases.
 - Continue to focus on tracebacks from sub-clusters of cases linked to retail stores and food service establishment and encourage CDC, state, and local partners to conduct ingredient-specific case-control studies within subclusters when possible.

- Narrow the scope of tracebacks by prioritizing shipments with higher probabilities for being a source, rather than equally weighting all shipments within a designated timeframe of interest.
- As FDA prepares to implement FSMA Section 204, rule on traceability, it should work with industry groups to define standards and protocols for electronic submission of data elements.
 - Standards should be developed to allow for interoperability across multiple proprietary systems. However, the development of electronic reporting may exacerbate differences in the timeliness and effectiveness of tracing back information from large retailers, distributors, and producers, compared to smaller, independent operators across the supply chain. The development of electronic health records in medicine and electronic reporting of reportable disease information followed a long development process and is not universal.
 - While fully interoperable systems are developed, FDA should continue to promote delivery of traceback data in the most readily analyzable formats available.
- As the capacity of companies to provide electronic data increases, FDA should re-evaluate the process that CORE uses to make field assignments and information requests. If companies can respond to requests and provide data directly to CORE, it may not be necessary for emergency response coordinators (ERC) in field offices to be intermediaries in making the requests. If so, ORA field staff could focus investigations on firms that lack resources to provide electronic data.
 - Evaluate the need for additional CORE staff that may be required to manage the increased data resulting from electronic records requests and the increased numbers of investigations that could be generated as more, smaller clusters of foodborne pathogens are identified by WGS.
 - Evaluate the potential to expand the scope of CORE responsibilities for direct interaction with state partners and industry sources, similar to the role of the USDA-FSIS Office of Public Health Science (OPHS).
 - Evaluate prioritization schemes for clusters identified by WGS, including REP strain, cluster size and density of case distributions over time.
- Tracebacks are conducted to identify convergences that may indicate a possible source of contamination or a node through which contaminated product has passed.
 - While convergences are defined as points in the supply chain where multiple traceback legs share a commonality, CORE should develop a process for weighting the importance of different legs, particularly in the context of investigations involving REP strains. A traceback leg including multiple points of service should be weighted more heavily than a traceback leg with a single point of service. When coupled with *a priori* hypotheses associated with REP strains, this could facilitate more rapid identification of farm sources to target for environmental assessment.
 - While tracebacks are conducted to identify convergences as targets for additional investigations, results of these further investigations should be evaluated against the traceback to identify factors that may be associated with the outbreak. For example, in the 1994 outbreak of *Salmonella* Enteritidis associated with commercially distributed ice cream, production records linked to case-associated products identified cross contamination between unpasteurized liquid egg and pasteurized ice cream mix during transportation as the cause of the outbreak (Hennessy, 1996).

- As the traceability rule and technology tools to enhance traceback are implemented, alternative methods for assembling and visualizing supply chain data should be evaluated to enhance the efficiency and efficacy of product tracing.
- When feasible, farm visits and environmental assessments should be conducted to evaluate farms implicated as sources for outbreaks involving REP strains.
 - If it is not feasible to conduct an environmental assessment, data should be collected on farm characteristics that have been associated with previous outbreaks.
 - Because it is not feasible to conduct a full root cause analysis for each outbreak investigation, repeated observations over multiple investigations should be conducted and analyzed to provide insights into the reoccurrence of specific contributing factors.
- In transitioning from outbreak response to prevention, CORE Response Teams, Outbreak Evaluation, and OFS Prevention should continue to jointly review findings from the individual outbreak investigation in the context of findings from investigations of outbreaks associated with similar pathogen-food and settings pairs to identify emerging trends that can be shared with industry partners.
 - FDA should develop a process to share outcomes of investigations with industry experts to facilitate development of important learnings to share with industry more broadly.
 - When a root cause investigation (RCI) is conducted, a public facing summary should be posted to a web-accessible repository of RCIs.
- Performance measures should be developed to evaluate the timeliness and effectiveness of investigation activities.
 - A key set of data elements for investigation timelines should be identified. For example, time from traceback information request to receipt of documents could be analyzed to evaluate the impact of electronic data collection, compared to document retrieval. Evaluation of timeline elements should be incorporated into after action review reports.
 - FDA should consult with CDC, state, and academic partners (such as the Council to Improve Foodborne Outbreak Response (CIFOR) <https://cifor.us>, and the Integrated Food Safety Centers of Excellence <https://foodsafetycoe.org/>) to identify critical timeline elements that can be tracked to facilitate performance improvement.
 - Standard analysis queries should be programmed to run on the CORE database, to identify operational bottlenecks, target areas for improvement across multiple investigations, and assess performance over time
- FDA should plan to increase the investigative capacity of CORE, the Produce Safety Network and state partners to manage anticipated increases in demand for tracebacks, farm visits and environmental assessments associated with increased numbers of clusters identified by WGS, and increased analysis of electronic traceback records. Consideration should be given to expanding the number and distribution of FDA-supported Rapid Response Teams to enhance coordination of investigation activities between FDA and state partners.

Appendix 1: List of documents reviewed

FDA

1. New Era of Smarter Food Safety. FDA's Blueprint for the Future (<https://www.fda.gov/food/new-era-smarter-food-safety/new-era-smarter-food-safety-blueprint>)
2. Memorandum of Understanding Between the Food and Drug Administration and the Centers for Disease Control and Prevention. MOU 225-14-017
3. Guide to Traceback of Fresh Fruits and Vegetables implicated in Epidemiological Investigations
4. Procedure manual for Fresh Produce Root Cause Investigations (RCI)
5. About the CORE Network (<https://www.fda.gov/food/outbreaks-foodborne-illness/about-core-network>)
6. FDA CORE Organization Chart
7. FDA CORE Response Desktop SOP Traceback Investigations
8. FDA CORE Traceback Cluster Criteria, attachment to FDA CORE Response Desktop SOP Traceback Investigations
9. CORE Incident Data Dictionary
10. Food Traceability Proposed Rule At-A-Glance - FDA (<https://www.fda.gov/media/142303/download>)
11. Food Traceability List (<https://www.fda.gov/media/145050/download>)
12. Investigations of Foodborne Illness Outbreaks (<https://www.fda.gov/food/outbreaks-foodborne-illness/investigations-foodborne-illness-outbreaks>)
13. Office of Regulatory Science Produce Timeframe for Food and Feed Laboratories
14. Incorporating Outbreak and Recall Data Streams in Predict Model
15. Environmental Assessment of Factors Potentially Contributing to the Contamination of Romaine Lettuce Implicated in a Multi-State Outbreak of E. coli O157:H7 (<https://www.fda.gov/food/outbreaks-foodborne-illness/environmental-assessment-factors-potentially-contributing-contamination-romaine-lettuce-implicated>)
16. Memorandum to the File on the Environmental Assessment; Yuma 2018 E.7 Outbreak Associated with Romaine Lettuce. (<https://www.fda.gov/media/117512/download>)
17. Letter to State Agriculture Officials and the Leafy Greens Industry Concerning the Environmental Assessment (<https://www.fda.gov/media/117511/download>)
18. Microbiological Surveillance Sampling: FY19 Romaine Lettuce at Commercial Coolers in Yuma, Arizona (<https://www.fda.gov/food/sampling-protect-food-supply/microbiological-surveillance-sampling-fy19-romaine-lettuce-commercial-coolers-yuma-arizona>)
19. FDA Outbreak Response: Fall 2019 E. coli O157:H7 in romaine lettuce (Power Point presentation)
20. E. coli O157:H7/Romaine lettuce/Nov 2019 (EON-406461) Incident Summary Report.
21. Outbreak Investigation of E. coli: Romaine from Salinas, California (November 2019) (<https://www.fda.gov/food/outbreaks-foodborne-illness/outbreak-investigation-e-coli-romaine-salinas-california-november-2019>)
22. E. coli O157:H7/Leafy greens (suspect)/November 2019 (EON-408527) Incident Summary Report.

23. Outbreak Investigation of E. coli: Salad Mix (December 2019)
(<https://www.fda.gov/food/outbreaks-foodborne-illness/outbreak-investigation-e-coli-salad-mix-december-2019>)
24. Investigation Report: Factors Potentially Contributing to the Contamination of Romaine Lettuce Implicated in the Three Outbreaks of E. coli O157:H7 During the Fall of 2019
(<https://www.fda.gov/media/138238/download>)
25. Outbreak Investigation of E. coli -Leafy Greens (December 2020)
(<https://www.fda.gov/food/outbreaks-foodborne-illness/outbreak-investigation-e-coli-leafy-greens-december-2020>)
26. Outbreak Investigation of E. coli O157:H7: Unknown Food (Fall 2020)
(<https://www.fda.gov/food/outbreaks-foodborne-illness/outbreak-investigation-e-coli-o157h7-unknown-food-fall-2020>)
27. Salmonella Newport/Red Onion/Jul 2020 (EON-432687) Incident Summary Report
28. Outbreak Investigation of Salmonella Newport: Red Onions (July 2020)
(<https://www.fda.gov/food/outbreaks-foodborne-illness/outbreak-investigation-salmonella-newport-red-onions-july-2020>)
29. Salmonella Enteritidis/Peaches/Aug 2020 (EON-435502) Incident Summary Report
30. Outbreak Investigation of Salmonella Enteritidis: Peaches (August 2020)
(<https://www.fda.gov/food/outbreaks-foodborne-illness/outbreak-investigation-salmonella-enteritidis-peaches-august-2020>)
31. Salmonella Stanley/Wood Ear Mushrooms/Apr 2020 (EON-438485) Incident Summary Report
32. Outbreak Investigation of Salmonella Stanley: Wood Ear Mushrooms - Dried Fungus (September 2020) (<https://www.fda.gov/food/outbreaks-foodborne-illness/outbreak-investigation-salmonella-stanley-wood-ear-mushrooms-dried-fungus-september-2020>)
33. Outbreak Investigation of Cyclospora: Bagged Salads (June 2020)
(<https://www.fda.gov/food/outbreaks-foodborne-illness/outbreak-investigation-cyclospora-bagged-salads-june-2020>)
34. WARNING LETTER Fresh Express Inc - Div of Chiquita Brands MARCS-CMS 609899 — OCTOBER 20, 2020. (<https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/fresh-express-inc-609899-div-chiquita-brands>)
35. Memorandum: Date: 9/10/2020 Firm: Thomson International, Inc. (Holtville). Subject: Outbreak Investigation. FEI: 3017219425 <https://www.fda.gov/media/146374/download>
36. TITLE 21--FOOD AND DRUGS CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES, SUBCHAPTER A -- GENERAL PART 20 -- PUBLIC INFORMATION Subpart E - Limitations on Exemptions, Sec. 20.88 Communications with State and local government officials.
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=20.88L>
37. [2020 Leafy Greens STEC Action Plan](https://www.fda.gov/food/foodborne-pathogens/leafy-greens-stec-action-plan) <https://www.fda.gov/food/foodborne-pathogens/leafy-greens-stec-action-plan>

Appendix 1: List of documents reviewed

External

1. CIFOR Guidelines for Foodborne Disease Outbreak Response, third edition (<https://cifor.us/downloads/clearinghouse/CIFOR-Guidelines-Complete-third-Ed.-FINAL.pdf>)
2. Marshall KE, Nguyen T, Ablan M, et al. Investigations of Possible Multistate Outbreaks of Salmonella, Shiga Toxin–Producing Escherichia coli, and Listeria monocytogenes Infections — United States, 2016. MMWR Surveill Summ 2020;69(No. SS-6):1–14. DOI: <http://dx.doi.org/10.15585/mmwr.ss6906a1>
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4. Interagency Food Safety Analytics Collaboration. Foodborne illness source attribution estimates for 2018 for Salmonella, Escherichia coli O157, Listeria monocytogenes, and Campylobacter using multi-year outbreak surveillance data, United States. Atlanta, Georgia and Washington, District of Columbia: U.S. Department of Health and Human Services, CDC, FDA, USDA/FSIS. 2020. <https://www.cdc.gov/foodsafety/ifsac/pdf/P19-2018-report-TriAgency-508.pdf>
5. Smith K, Miller B, Vierk K, Williams I, Hedberg C. Product Tracing in Epidemiologic Investigations of Outbreaks due to Commercially Distributed Food Items – Utility, Application, and Considerations (<http://mnfoodsafetycoe.umn.edu/wp-content/uploads/2015/10/Product-Tracing-in-Epidemiologic-Investigations.pdf>)
6. Traceback Information Gathering Worksheet (<http://mnfoodsafetycoe.umn.edu/resources/>)
7. Key Points: Product Tracing In Epidemiologic Investigations Of Outbreaks Due To Commercially Distributed Foods Part 1:When And How To Initiate (<http://mnfoodsafetycoe.umn.edu/wp-content/uploads/2016/09/Key-Points-Product-Tracing-In-Epi-Investigations-Part-1.pdf>)
8. Key Points: Product Tracing In Epidemiologic Investigations Of Outbreaks Due To Commercially Distributed Foods Part 2: Conducting The Trace (<http://mnfoodsafetycoe.umn.edu/wp-content/uploads/2016/09/Key-Points-Product-Tracing-In-Epi-Investigations-Part-2.pdf>)
9. Key Points: Obtaining Food Transaction Records From Credit/Debit Cards (<http://mnfoodsafetycoe.umn.edu/wp-content/uploads/2016/09/Key-Points-Food-transaction-records-from-cards.pdf>)
10. Key Points: Investigating Establishment Sub-Clusters (<http://mnfoodsafetycoe.umn.edu/wp-content/uploads/2014/10/Key-Points-Investigating-Restaurant-Subclusters3-FINAL.pdf>)
11. Outbreak of Salmonella Newport Infections Linked to Onions (<https://www.cdc.gov/salmonella/newport-07-20/index.html>)
12. Public Health Notice: Outbreak of Salmonella infections linked to red onions imported from the United States (<https://www.canada.ca/en/public-health/services/public-health-notice/2020/outbreak-salmonella-infections-under-investigation.html>)
13. Outbreak of Salmonella Enteritidis Infections Linked to Peaches (<https://www.cdc.gov/salmonella/enteritidis-08-20/index.html>)
14. Public Health Notice: Outbreak of Salmonella infections linked to peaches imported from the United States (<https://www.canada.ca/en/public-health/services/public-health-notice/2020/outbreak-salmonella-infections-peaches-imported-united-states.html>)

15. Outbreak of Salmonella Stanley Infections Linked to Wood Ear Mushrooms (<https://www.cdc.gov/salmonella/stanley-09-20/index.html>)
16. Outbreak of E. coli Infections – Unknown Source 1 (<https://www.cdc.gov/ecoli/2020/o157h7-10-20a/index.html>)
17. Outbreak of E. coli Infections Linked to Leafy Greens (<https://www.cdc.gov/ecoli/2020/o157h7-10-20b/index.html>)
18. Outbreak of E. coli Infections – Unknown Source 3 (<https://www.cdc.gov/ecoli/2020/o157h7-11-20/index.html>)
19. Outbreak of E. coli Infections Linked to Romaine Lettuce (<https://www.cdc.gov/ecoli/2019/o157h7-11-19/index.html>)
20. Outbreak of E. coli Infections Linked to Fresh Express Sunflower Crisp Chopped Salad Kits (<https://www.cdc.gov/ecoli/2019/o157h7-12-19/index.html>)
21. Public Health Notice: Outbreak of E. coli infections linked to Fresh Express brand Sunflower Crisp Chopped Salad Kits (<https://www.canada.ca/en/public-health/services/public-health-notice/2019/outbreak-e-coli-salad-kits.html>)
22. Outbreak of E. coli Infections Linked to Romaine Lettuce (<https://www.cdc.gov/ecoli/2018/o157h7-11-18/index.html>)
23. Public Health Notice – United States outbreak of E. coli infections linked to romaine lettuce with implications for Canadians (<https://www.canada.ca/en/public-health/services/public-health-notice/2019/outbreak-united-states-e-coli-infections-romaine-lettuce.html>)
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30. Produce Industry Partnership with FDA/CDC to Investigate Illness Outbreaks-Draft Proposal

31. An Analysis of 2016-2019 Outbreaks Linked by Whole Genome Sequencing. United Fresh Produce Association
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50. Council to Improve Foodborne Outbreak Response (CIFOR). <https://cifor.us/about>

51. Integrated Food Safety Centers of Excellence. <https://foodsafetycoe.org/>.

Appendix 2: List of stakeholders interviewed

FDA

- **Office of Chief Counsel**
 - Peter Beckerman, Deputy Chief Counsel for Program Review
- **Center for Food Safety and Applied Nutrition (CFSAN)**
 - Douglas Stearn, Deputy Director
 - Jim Gorny, Produce expert
- **Coordinated Outbreak Response and Evaluation (CORE)**
 - Stic Harris, Director
 - Kari Irvin, Deputy Director
 - Karen Blickenstaff, Response Staff Director
 - Brooke Whitney, Response Team 1
 - Angela Fields, Response Team 3
 - Lauren Singleton, Response Team 3 Lead
 - Sabina Reilly, Signals and Analysis Staff Director
 -
- **Office of Food Safety (OFS)**
 - Mark Moorman, Director
 - Stephen Hughes, OFS Prevention
 - Don Kautter, SME
 - Kurt Nolte, Produce Safety Network
- **Office of Food Policy and Response (OFPR)**
 - Frank Yiannis, Deputy Commissioner, Food Policy and Response
 - Caitlin Boon, Associate Commissioner, Food Policy and Response
 - Donald Prater, Associate Commissioner for Imported Food Safety
 - David Goldman, Chief Medical Officer
 - Carolyn Brickey, Senior Policy Analyst
 - Jeff Farrar, Federal State Relations
 - Andrew Kennedy, New Era Technology Team Leader
- **Office of Regulatory Affairs (ORA)**
 - Michael Rogers, Assistant Commissioner for Human and Animal Food Operations
 - Gerald Bromley, HAF West Division Director
 - Brittany Nork, Produce Safety Network, Supervisory CSO
 - Kevin Gerrity, Produce National Expert

External partners

- Matt Wise, CDC
- Robert Tauxe, CDC
- Kis Robertson Hale, FSIS
- Bonnie Kissler, FSIS
- Natalie Krout-Greenberg, California Department of Food and Agriculture

- Joe Reardon, North Carolina Department of Agriculture
- Ernie Julian, Rhode Island Department of Health
- Sandra Eskin, Pew Trusts
- Michael Roberson, Publix
- Natalie Dyenson, Dole
- Drew McDonald, Taylor Farms
- Jennifer McEntire, United Fresh Produce

Appendix 3: Background

In July 2020, FDA published its blueprint for the future: New Era of Smarter Food Safety (<https://www.fda.gov/food/new-era-smarter-food-safety/new-era-smarter-food-safety-blueprint>). This blueprint outlined the FDA approach to “leverage technology and other tools to create a safer and more digital, traceable food system.” The blueprint intended to build on the work FDA has done to build a more risk-based food safety system under the FDA Food Safety Modernization Act (FSMA). Importantly, the blueprint recognized that “smarter food safety is about more than just technology. It’s about simpler, more effective, and modern approaches and processes. It’s about leadership, creativity and culture”.

A recent report from CDC highlights the challenges of investigating multistate foodborne illness outbreaks (Marshall KE, et al. MMWR Surveill Summ 2020;69(No. SS-6):1–14. DOI: <http://dx.doi.org/10.15585/mmwr.ss6906a1>). During 2016, CDC was alerted to 230 possible multistate clusters of *Salmonella*, shiga-toxin producing *E. coli* (STEC), and *Listeria monocytogenes*. Of these, 216 were investigated, resulting in a median 24 investigations per week. Ultimately, 39 outbreaks were solved; a food item was confirmed in 18 and suspected in 10. Thus, considerable effort from federal, state, and local public health and food regulatory agencies is required to determine that an outbreak is occurring as well as to identify its source. The following table summarizes outbreak details for the 28 multistate outbreaks investigated in 2016 for which a common food source was implicated:

| Outbreak Characteristic | Median | Range |
|----------------------------------|--------|--------|
| Duration (days) of outbreak | 81 | 17-963 |
| Duration (days) of investigation | 70 | 23-245 |
| Number of cases | 14 | 2-70 |
| Number of states with cases | 8 | 2-24 |

(Marshall KE, et al. MMWR Surveill Summ 2020;69(No. SS-6):1–14. DOI: <http://dx.doi.org/10.15585/mmwr.ss6906a1>).

The CDC surveillance summary nicely details the phases of the multistate investigation process. FDA has an important role in each of these phases.

- 1. Detection phase.** Potential multistate outbreaks may be identified by review of PulseNet data by CDC or state public health laboratories, identification of pathogens in food or environmental samples by FDA, FSIS or a state department of agriculture, or by identification of outbreaks associated with events or establishments by state and local public health agencies.
FDA role: Detection of pathogens through regulatory testing of food or food environmental sampling. CORE Signals Team monitors external data streams to identify possible foodborne outbreaks.
- 2. Assessment phase.** Review of available information to determine the potential size and scope of the outbreak, and likelihood that a potential source can be identified.
FDA role: CORE Signals Team consults with CDC investigators to assess the developing situation.
- 3. Investigation and response phase.** Coordinated investigation involving CDC, state and local public health and food regulatory agencies, FDA CORE Response Teams, and USDA-FSIS Applied

Epidemiology staff from the Office of Public Health Science (OPHS). Exposure data collected from cases is used to guide traceback investigations and laboratory testing of food and environmental samples.

FDA role: CORE Response Teams work with epidemiologists at CDC to identify priorities for traceback, make assignments for record collection to inspectors with the Office of Regulatory Affairs (ORA), assemble collected information and report results back to CDC for incorporation into the outbreak analysis. Commodity specialists within CFSAN review available data to help guide investigations. ORA field staff collect product shipment information from firms, coordinate with state food regulators, and collect food and environmental samples for regulatory testing.

4. **Control phase.** Product specific interventions are implemented as needed. Public notifications of results to facilitate prevention. Root cause investigations and environmental assessments conducted.

FDA role: FDA recall coordinators oversee necessary recalls or market withdrawals. CORE Outbreak Evaluation Team gathers and analyzes outbreak prevention data. CFSAN Office of Food Safety commodity specialists analyze inspection results to recommend appropriate prevention measures that can be adopted by the industry.

Improving the speed and effectiveness of multistate outbreak investigations requires earlier detection that an outbreak is occurring, more rapid assessment of potential vehicles and modes of transmission, faster traceback of more food items, and environmental assessments of likely points of contamination. The challenges posed by reoccurring, emerging, and persisting (REP) strains requires a change in the dynamics of the outbreak investigation process. The conventional flow of hypothesis generation, hypothesis testing, source tracing and evaluation, has inherent limitations in the steps and pace of the investigation. REP strains present investigators with *a priori* hypotheses to test and groups of potential sources to evaluate. Environmental assessments of REP outbreaks need to encompass information from groups of related outbreaks rather than focus exclusively on the outbreak under investigation. All of this requires enhanced communication and collaboration between FDA, CDC, state and local public health and food regulatory agencies and the food producing, distribution, and service industries that are both the subject of investigations and the key to effective prevention and control of foodborne illnesses.

Appendix 4: Takeaways from outbreak investigations reviewed.

Investigation findings from several recent outbreak investigations were reviewed to highlight points related to the above findings. Key findings relating to investigation methods and their implications for investigation findings are summarized below.

- *E. coli* O157:H7 in romaine lettuce: In 2018 a large, multistate outbreak of *E. coli* O157:H7 was associated with romaine lettuce from the Yuma, AZ growing region. A total of 210 cases with 96 hospitalized and 5 deaths were reported for 36 states (CDC). Cases experienced onsets of illness from March 13 through June 6, 2018. FDA traceback activities identified 36 growing fields on 23 farms in AZ and CA as potential sources of contaminated lettuce (Memorandum to the file on the Environmental Assessment; Yuma 2018 *E. coli* O157:H7 Outbreak Associated with Romaine Lettuce). The environmental assessment (EA) found three samples of water from an irrigation canal were positive for the outbreak-associated strain. Information reviewed during the EA included the traceback leg associated with the grower, crops grown on adjacent fields, source of irrigation water, source of water of chemical applications, application of chemicals after a freeze in late February, use of biological soil amendments, evidence of animal intrusions, and unusual weather events were obtained for 21 farms (Memorandum to the file on the Environmental Assessment; Yuma 2018 *E. coli* O157:H7 Outbreak Associated with Romaine Lettuce). Of these 13 farms used water from the contaminated canal for irrigation. Seven of these used canal water to formulate chemical applications and applied chemicals to fields after a freeze in late February that may have damaged plants and increased their susceptibility to contamination (Memorandum to the file on the Environmental Assessment; Yuma 2018 *E. coli* O157:H7 Outbreak Associated with Romaine Lettuce). Importantly, at least one such farm was represented on each of the major legs of the traceback. Thus, this combination of conditions provides a reasonable pathway for contamination that caused the outbreak.

Based on document reviews and stakeholder interviews, it is not clear whether the traceback results were reevaluated in light of the EA survey findings and incorporated into the overall interpretation of the EA. Traceback data provide critical context for interpreting EA results. Not only are they important for identifying potential settings at which contamination occurred, they should be used to assess factors associated with that contamination event.

- *E. coli* O157:H7 in romaine lettuce: In November 2019, two multi-state outbreaks of *E. coli* O157:H7 infections were detected. The first involved 172 illnesses from 28 states and was associated with a strain historically linked to leafy greens (*E. coli* O157:H7/Romaine lettuce/Nov 2019 (EON-406461) Incident Summary Report). Based on this history the event was rapidly transferred to CORE Response Team 2 and coordinated investigation activities focused on leafy greens were initiated by CFSAN, ORA, CDC and state partners. The outbreak-associated strain was isolated from romaine lettuce from two patient-related product samples from MD and WI. Tracebacks were conducted for 15 points of service linked to 15 patients from seven states. These included points of service associated with the two positive samples. Tracebacks were limited by lack of receipts or confirmed purchase information, multiple leafy green exposures, and co-mingling of product from multiple production sources. Despite this, one grower was identified that could have supplied product to all but one of the POS during the time frame of interest. Environmental assessment of this grower

demonstrated cattle grazing in adjacent fields separated by an 800-foot buffer. No *E. coli* O157:H7 were isolated from environmental samples collected from the farm. Although the epidemiology, laboratory and traceback information suggest that romaine lettuce was the likely source of the outbreak, it was concluded that a single source of contamination could not be identified.

The second outbreak involved 10 illnesses from five states. Because CORE Response Team 2 was coordinating the investigation noted above, this investigation was also transferred to them (*E. coli* O157:H7/Leafy greens (suspect)/November 2019 (EON-408527) Incident Summary Report). Traceback was conducted for product consumed by three cases who shopped at three locations of a single grocery store chain. All three reported eating a Fresh Express Sunflower Crisp Chopped Salad, and one had a photograph of the packaging material that included a lot code. There was one farm source of romaine lettuce identified in common with the other investigation. However, because the outbreak was caused by an unrelated strain of *E. coli* O157:H7, and there were multiple other leafy green ingredients in the product, it was not possible to link the two events together.

Results of the first investigation suggested a likely common source that could not be linked unequivocally to all of the POS investigated. Given the limitations that exist in almost all tracebacks, total convergence on all legs of a traceback is unlikely to be achieved in any investigation. Given the time and cost of conducting a traceback with current policies and technology, relatively few legs of distribution can be traced during any investigation. The goal of complete convergence increases the likelihood that information errors at any point in the traceback will invalidate the bulk of the information collected. Multiple exposures and co-mingling of products produces tracebacks that are probability distributions rather than definite consumption histories. Interpreting tracebacks as probability distributions would reduce the cost of information errors in any individual leg of the traceback. It would also facilitate the development of analytical approaches that could accommodate the availability of the higher quality electronic records anticipated with implementation of traceability rules. If the time and labor costs of product tracing could be reduced by automated record queries, it would be theoretically feasible to trace the source of all products consumed by cases in each investigation.

- *2020 Salmonella Newport in onions*: During the summer of 2020, a very large multistate and international outbreak of *Salmonella* Newport infections was associated with onions grown by Thomson International, Inc. A total of 1,127 cases with 167 hospitalized were reported from 48 states. An additional 515 cases with 79 hospitalized were reported from seven Canadian provinces. Cases experience onset of illness from June 19 through September 11, 2020 (CDC). On July 13, FDA CORE Signals evaluated clusters of illnesses in coordination with CDC after notification by PulseNet on July 10. On July 21, the incident was transferred to CORE Response because it was a rapidly expanding multistate outbreak likely to be associated with a fresh produce item. On July 23, a regulatory traceback was initiated for 10 points of service (POS) that comprised four separate legs representing 26 confirmed cases. Thomson International, Inc. was identified as a common supplier for POS in all four traceback legs (*Salmonella* Newport/Red Onion/Jul 2020 EON #432687 Incident Summary Report). Each of the first two legs included four POS. The other two were for single POS. Results of tracebacks of the first two legs included details on growers, fields, harvest dates, pack dates, lot numbers and shipping dates. The third leg included some shipping date information but

no field-level information. The fourth leg included no lot information. Detailed lot information was not requested for these legs, because the implicated shipments were identified after records had been collected from Thomson International, Inc. (*Salmonella* Newport/Red Onion/Jul 2020 Traceback Investigation Summary EON 371142).

Based on traceback records, CORE identified three fields in Bakersfield, CA and one in Holtsville, CA where implicated lots were harvested. The traceback was limited by the availability and completeness of records at some points along the distribution chains. It was noted that “records at Thomson International, Inc. for field level information were known to be incorrect and information used in this traceback was the best information that the firm could identify” (*Salmonella* Newport/Red Onion/Jul 2020 Traceback Investigation Summary EON 371142). Subsequent EA and microbiological sampling were conducted in Bakersfield, CA and Holtsville, CA. No *Salmonella* were isolated from environmental samples collected in Bakersfield. *Salmonella* was isolated from 10 samples collected in Holtsville, CA. None of these were the outbreak-associated strain. No individual lots were found to be common to all POS identified in the first two legs of the traceback. One field in Bakersfield (R&G 161) and one in Holtsville, CA (Pepper 22) were potential sources for three of four POS in each of these legs.

A careful examination, by the author, of order numbers, packing dates and shipping dates identified a discrepancy for two shipments of onions. These two orders (0179308 and 0180808) had BOL shipping dates of June 12 and June 15, respectively. However, both indicated pack dates of June 16. These discrepancies are critical because they occurred at a transition between shipping onions harvested from Holtsville and onions harvested from Bakersfield. No Bakersfield onions were reportedly packed before June 16. Thus, if the shipping dates for these orders are correct, the onions were likely to have been harvested from the Pepper 22 field in Holtsville, CA. The shipping dates are consistent with the order numbers. The “08” at the end of the order numbers indicate that the orders were received during the week of June 8. Thus, results of the traceback indicating that the outbreak associated lots were harvested in Holtsville are consistent with the detection of *Salmonella* from environmental sampling in Holtsville after the end of the outbreak in identifying the Holtsville fields as a likely source for the outbreak. As with the outbreaks associated with romaine lettuce, careful integration of detailed traceback information provides critical context for interpreting outbreak results.

- *2020 Salmonella Enteritidis in peaches*: During the summer of 2020, a multistate and international outbreak of *Salmonella* Enteritidis infections was associated with peaches packed by Prima Wawona. A total of 101 cases with 28 hospitalized were reported from 17 states. Cases experienced onset of symptoms from June 29 through August 27, 2020 (CDC). On August 12, CDC notified CORE Signals of a cluster of 37 *S. Enteritidis* cases associated with pre-bagged peaches obtained from Aldi stores. On August 13, CDC hosted a call with States, reviewed preliminary exposure data and named peaches as a leading hypothesis. On August 14, FDA, CDC, and the Minnesota Department of Health reviewed exposure data with Aldi and requested additional information from the company. The incident was transferred to CORE Response on August 17 because it was a rapidly expanding multistate outbreak likely caused by an FDA-regulated food product (*Salmonella* Enteritidis/Peaches/Aug 2020 EON-435502 Incident Summary Report).

Traceback was initiated for 14 POS from six retail chains representing 18 cases. Traceback results were limited by lack of confirmed purchase information, peach variety consumed, discrepancies in information at two distribution centers and lack of information on specific shipments from distribution centers to retail locations (*Salmonella* Enteritidis/Peaches/Aug 2020 EON-435502 Incident Summary Report). Peaches from multiple Prima Wawona orchards were associated with shipments to various POS. A single source of contamination could not be identified. *Salmonella* spp. were isolated from samples including peach tree leaves collected from two Prima Wawona orchards. Although the outbreak-associated strains of *S. Enteritidis* were not isolated, *S. Alachua* closely related to isolates obtained from chicken samples were isolated from one orchard and *S. Montevideo* closely related to beef and cattle isolates were isolated from the other. Thus, traceback and environmental assessment results support the hypothesis that adjacent land use practices provided a likely source of contamination.

- *2020 Salmonella Stanley in wood ear mushrooms*: During 2020, a multistate outbreak of *Salmonella* Stanley infections was associated with wood ear mushrooms distributed by Wismettac Asian Foods, Inc. A total of 55 cases with six hospitalized were reported from 12 states. Cases experienced onset of symptoms from January 21 through September 19, 2020 (CDC). CDC initially notified CORE regarding a cluster of 13 cases in four states during April. The CA Department of Health investigated cases associated with three Asian restaurants (*Salmonella* Stanley/Wood Ear Mushrooms/Apr 2020 EON #43845 Incident Summary Report). The investigation focused on mung bean sprout exposure and no common source of supply was identified. The investigation was closed on June 2. It is not known if individual cases in GA, NJ, NV were interviewed to identify a potential common source.

On July 20, CDC reopened the cluster investigation after 11 additional cases were identified (*Salmonella* Stanley/Wood Ear Mushrooms/Apr 2020 EON #43845 Incident Summary Report). Newly identified cases frequently reported eating at ramen restaurants. On September 1, the CA Food and Drug Branch collected samples of mung beans and dried black fungus from a restaurant associated with four cases. The mung beans tested negative, but the fungus was presumptively positive for *Salmonella*, a finding that was subsequently confirmed to be the outbreak-associated strain. On September 11, the incident was transferred to CORE Response because it was a multistate outbreak associated with an FDA-regulated food product (*Salmonella* Stanley/Wood Ear Mushrooms/Apr 2020 EON #43845 Incident Summary Report). A regulatory traceback was initiated with two legs representing 11 cases. The traceback converged on Wismettac Asian Foods Inc., an importer and distributor of the implicated product that had been imported from China.

By the time the traceback was initiated, all but eight outbreak-associated cases had occurred. No cases experienced onset of symptoms at the time of or after the company's product recall, CDC, or FDA notifications. However, had the initial cluster investigation continued after failing to identify a common source of mung beans, it is possible that more than 60% of outbreak-associated cases could have been prevented. A lower threshold of action for CORE Response engagement could be useful in similar small outbreaks that appear to include multistate exposures.

- *Summary of key takeaways*: Review of the incident reports summarized above suggests the following:

- There is inherent ambiguity in tracebacks that is the result of patient dining preferences, inadequate documentation of exposure source details, and comingling of raw ingredients from multiple sources.
- The limited number of tracebacks conducted during an investigation increases the likelihood that information errors on any leg of the traceback could mask convergence across the legs of the traceback.
 - However, increasing the number of tracebacks and assessing the maximum likelihood of tracebacks based on probability distributions across the supply chain would increase opportunities to use traceback data to evaluate environmental assessment and microbiological testing results in an epidemiologic manner.
- The introduction of foodborne pathogens into fresh produce systems may happen on a sporadic basis from environmental reservoirs that limits the ability to detect the presence of the agent in subsequent environmental assessments.
 - However, the frequent finding of pathogens associated with animals, and animal production on land adjacent to produce farms suggests a likely causal pathway from contamination. The consistency of findings in aggregate compensates for the uncertainty in individual observations.