Outbreak Investigation Case Series

Commercially Distributed Food Vehicles

In-depth, behind-the-scenes analyses of foodborne outbreak investigations

Introduction

This series focuses on investigations of outbreaks caused by commercially distributed food items and detected through pathogen–specific surveillance. The etiologic agents often are *Salmonella*, Shiga toxin-producing *E. coli* (STEC), or *Listeria monocytogenes*, but other pathogens are sometimes responsible. The primary target audience is foodborne disease epidemiologists who investigate (or are training to do so) these types of outbreaks, but others might find this series informative as well.

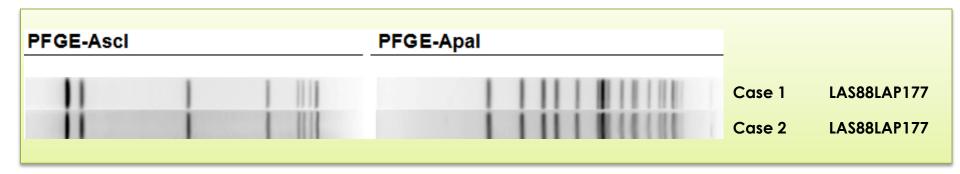
The primary focus of this series is methods used by epidemiologists (in concert with their co-investigators) to generate, develop, and confirm hypotheses about the outbreak vehicle. Descriptions will generally begin with the detection of a cluster (typically by molecular subtyping of submitted clinical isolates at a public health lab) and end when the food source is identified to a level of certainty/confidence that public health interventions are implemented. While this outbreak occurred when pulsed field gel electrophoresis was the subtyping method used by public health laboratories, the lessons are still applicable now that whole genome sequencing is the subtyping method.

From an epidemiologist's perspective, the overall goal in these types of investigations is to document a sufficiently specific food exposure in a sufficiently high proportion of cases that one can confidently conclude that the food item of interest is the outbreak vehicle. This series will use outbreak examples that detail the exact process and methods that led investigators to that "threshold of confidence" that prompted them to take action. What were the epidemiologists thinking and doing day-by-day, case-by-case, and step-by-step as the investigation progressed, leading up to the attainment of that threshold of confidence? How were leads identified, and how did investigators decide when and how aggressively to follow a particular lead? The nuances, complexities, obstacles, and decision nodes involved in these types of investigations are nearly impossible to fully describe in the limited space of a peer-reviewed manuscript (plus, many excellent investigations are never published). It is our objective to capture all of the important methodological intricacies of selected particularly speedy or effective investigations using a detailed timeline format. We strongly encourage our audience to read the published investigation manuscript (when one exists) before going through our description. We hope that our descriptions will be a useful, educational supplement to the characterization of the investigation.

Listeria monocytogenes-Multistate Outbreak Associated with Soft Cheese, 2013

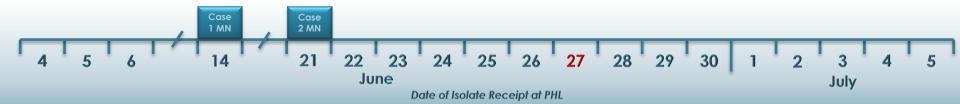
This story starts with the receipt of two clinical *Listeria monocytogenes* (LM) isolates at the Minnesota Department of Health (MDH) Public Health Laboratory (PHL) on June 13 and June 20, 2013 (submission of clinical LM isolates to MDH is mandatory in Minnesota). By June 27, subtyping of the two cases' LM isolates revealed that they were indistinguishable by pulsed-field gel electrophoresis (PFGE). The MDH PHL notified MDH foodborne epidemiologists, and a cluster investigation was initiated.

Two restriction enzymes are used routinely on LM isolates in Minnesota. The isolates were given the Minnesota 2-enzyme subtype designation LAS88LAP177 (national PulseNet designation GX6A16.0016/GX6A12.0003).



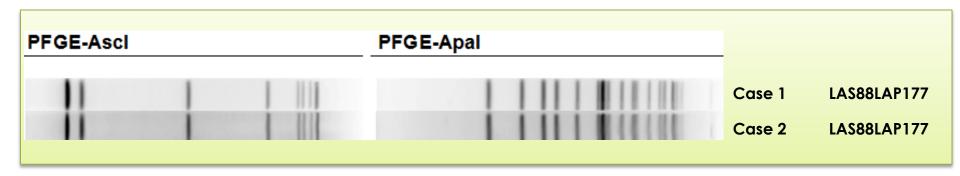
What are two initial questions an epidemiologist should consider once receiving these laboratory subtyping results?

Move to the next page to see what the investigators were thinking...



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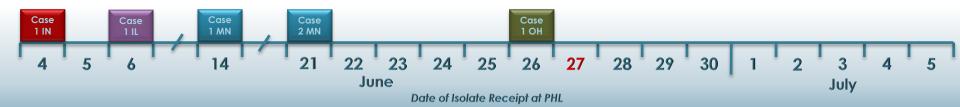


How common is the PFGE pattern?

• Less than 20 LM cases are identified in Minnesota each year, and this PFGE pattern combination had not been seen previously in MN. This suggested that this cluster represented a true common source outbreak.

Are there other cases with this PFGE pattern in other states?

A PulseNet search revealed that there were recent 2-enzyme PFGE matches among clinical isolates from Indiana, Illinois, and
Ohio (see epi curve below). Nationally this was a common pattern combination and not above baseline; however, the
Minnesota specific information suggested that this was indeed a common source outbreak. Although not a large outbreak at
this point, the geographic distribution of cases suggests a widely distributed food item was responsible and as such an
aggressive investigation was warranted.

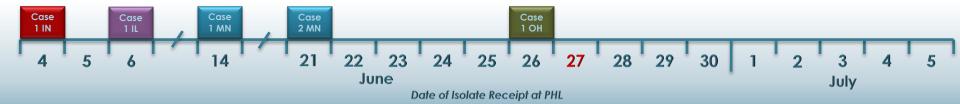


Characteristics of the five cases:

- Median age, 55 years (range, 31 67 years)
- 4 (80%) Female
 - 1 was pregnant and miscarried
- All 5 (100%) were hospitalized
- 1 (20%) died
 - 58 year-old with metastatic lung cancer

What are you thinking at this point?

Move to the next page to see what the investigators were thinking...

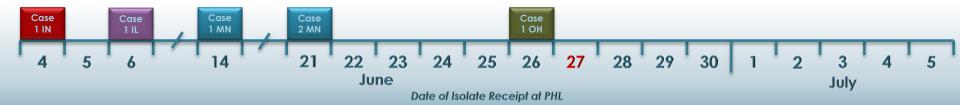


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Assessment:

The age distribution of the cases is not unusual for LM. However, the high proportion of female cases is noteworthy.

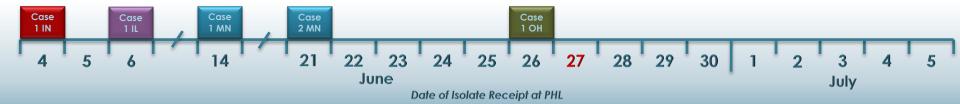


<u>Team Diarrhea</u> had already interviewed both Minnesota cases with the national <u>Listeria Initiative Case Report Form</u>. MDH does not wait for PFGE subtyping results before attempting to interview *Listeria* cases. The first case had been interviewed on June 19:

MN Case 1 Exposures

- He said he likely ate brie from a grocery store but couldn't recall which grocery store it was purchased from or what brand it was.
- He also ate goat cheese at a restaurant.
- He likely ate pastrami from a grocery store but didn't remember the brand name.
- He ate a generic brand of potato salad from a grocery store.

	Ate (=1)	Likely Ate (=2)	Likely did NOT eat (=3)	Did NOT eat (=4)	If ate or likely ate, How often?	If ate or likely ate, Where was it purchased? Name(s) of store/restaurant/venue: (choose all types that apply) (all names that apply)	Types or brands: (all that apply)
Brie	1	2	3	4		Grocery store Deli/small market Restaurant Other venue Don't know Was this item purchased from a deli counter at any of the sites? Yes No Yoon't know	MICHEM
Goat MM	POXA POE	2	3	4	☐ ~ 1-2 x/month ☐ ~ 1x/week ☐ ~ 2-4x/week ☐ ~ 5-7x/week ☐ not sure	Grocery store Deli/small market Restaurant Other venue Don't know Was this item purchased from a deli counter at any of the sites? Yes No Don't know	
Pastrami/ Corned peef	1 Gover	2	3	4	~ 1-2 x/month	Grocery store Deli/small market Restaurant Other venue Don't know Was this item purchased from a deli counter at any of the sites?	d) inknow
READY-TO-EAT SALADS: In the 4 week period, did you eat any of the following ready-to-eat, deli-style salads (that were NOT PREPARED AT HOME)? Likely Did did NOT dikely ate, Ate Likely NOT eat How often? How often? How often? Where was it purchased? Name(s) of store/restaurant/venue: Types or brands:							
	(=1)_	Ate (=2)				(choose all types that apply) (all names that apply)	(all that apply)
Potato salad	(1)	2	3	4	X ~ 1-2 x/month ~ 1x/week ~ 2-4x/week ~ 5-7x/week not sure	Grocery store Deli/small market Restaurant Other venue Don't know Was this item purchased from a deli counter at any of the sites? Yes Don't know	Generic



The deceased second case's spouse had been interviewed with the national <u>Listeria Initiative Case Report Form</u> on June 20:

MN Case 2 Exposures

- He reported that his spouse ate blue cheese from a grocery store, and had leftover cheese in the refrigerator.
- She also likely ate soft white cheddar cheese from a different grocery store.
- She likely ate pastrami from a grocery store but he could not remember the brand name.

· She ate potato salad from a deli.

	and the same of th	(date 4 weeks before) t	hrough / / (specimen collection/delivery date), did you eat any o	f the following CHEESES?
e,	Blue of 2 3 4 gorgonzola (1) 2 3 4 -NOT IN OVIGINAL PACKAGING -HUS LETTURES	☐ ~ 1x/week ☐ ~ 2-4x/week ☐ ~ 5-7x/week ☐ not sure	Restaurant Other venue Don't know Was this item purchased from a deli counter at any of the sites?	
	- this lettores		Yes No Don't know	
†	Other soft 1 (2) 3 4 white cheese (not cream, cottage, or ricotta - specify)	~ 1-2 x/month	Grocery store Deli/small market Restaurant Other venue Don't know Was this item purchased from a deli counter at any of the sites? Yes No Don't know	unite Chidder (Stt.) immulun brank
	Pastrami/ 1 (2) 3 4 beef -Mone leftover	~ 1-2 x/month ~ 1x/week ~ 2-4x/week ~ 5-7x/week not sure	Grocery store Deli/small market Restaurant Other venue Don't know Was this item purchased from a deli counter at any of the sites:	Mknam
	READY-TO-EAT SALADS: In the 4 week period, of Likely Did	lid you eat any of the f	following ready-to-eat, deli-style salads (that were NOT PREPARED AT HO	DME)?
	Makely Did Add NOT Ate Likely NOT eat (=1) Ate (=2) eat (=3) (=4)	If ate or likely ate, How often?	If ate or likely ate, Where was it purchased? (choose all types that apply) Name(s) of store/restaurant/venue: (all names that apply)	Types or brands: (all that apply)
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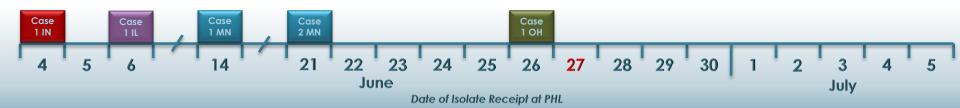


Summary of initial interviews of the two MN cases:

- Both cases ate multiple soft cheeses, from multiple grocery stores and one restaurant.
 - However, no commonalities were noted regarding the type of cheese or point of sale/service.
- Both cases likely ate pastrami, but from different grocery stores.
 - Neither case/proxy could recall the brand name.
- Both cases ate or likely ate potato salad.
 - Purchased from deli counters at different retail locations.
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What are you thinking at this point and what is your next step?

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Assessment:

At this point soft cheese, pastrami, and potato salad are interesting exposures. Pursuing additional details on all of these items is warranted. Therefore, cases or their proxys were called back. In addition, we requested the help of our Minnesota Department of Agriculture (MDA) colleagues to find out what types of potato salad were sold at each cases' deli/grocery store. Also, obtaining additional information from the cases in other states would help either support or rule out these exposures. So, the MN lead investigator reached out to the other states to obtain this information. Read on . . .



Listeria Initiative Case Report Forms for the Indiana, Illinois, and Ohio cases were reviewed and compared to the MN cases:

- No additional cases reported consuming pastrami or potato salad.
- All 5 cases reported soft cheeses:

State	Type of Soft Cheese	Point of Purchase	
IL Case 1	Cottage cheese, mozzarella, soft cheese	Grocery store	
IN Case 1	Havarti, Brie, blue	Grocery store, IN restaurant	What do you think about potato salad now? What do you make of all the different soft cheeses?
MN Case 1	Brie, goat cheese	Grocery store, MN restaurant	How could you determine whether soft cheese consumption among the outbreak cases is higher than expected?
MN Case 2	Blue, soft cheddar	Grocery store	Move to the next page to see what the investigators were thinking
OH Case 1	Feta, queso fresco, cottage cheese, mozzarella, cream cheese, goat cheese	Grocery store	



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What do you think about the potato salad now?

 Potato salad was not reported by any of the 3 non-Minnesota cases, which seemed to rule it out as a cause of this outbreak. The same was true for pastrami.

What do you make of all the different soft cheeses?

 Soft cheeses are a well-established vehicle for listeriosis, but it can be difficult for cases to remember specific types of "fancy" cheeses.
 Several cases report brie, blue, and goat cheese.
 These exposures are definitely worth pursuing.

How could you determine whether soft cheese consumption among the outbreak cases is higher than expected?

 Because all LM cases nationally are interviewed with the same form, additional LM cases that do not have the outbreak PFGE pattern could serve as a comparison group in a case-case comparison study. This is one of the main features of the national Listeria Initiative.

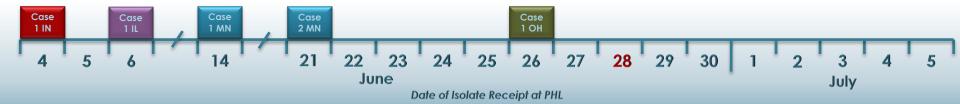


CDC epidemiologists conducted a case-case comparison study to compare outbreak case food consumption rates against estimated background consumption rates using non-outbreak associated LM cases.

- In this instance, sporadic LM cases from 2004-2013 interviewed with the same *Listeria* Initiative (LI) questionnaire were used as the comparison group.
- LM cases with the outbreak PFGE pattern (n=5) were significantly more likely than sporadic LM cases from 2004-2013 to have consumed:
 - Any soft cheese: odds ratio, 10.8; 95% confidence interval, 1.8 ∞
 - Brie: odds ratio, 16.8; 95% confidence interval, 1.2 235
 - Other soft cheese: odds ratio, 14.6; 95% confidence interval, 1.2 771
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Assessment:

Both soft cheese and yogurt are associated with illness in the case-case comparison study. Review of the initial interviews revealed that cases reported different brands of yogurt, diminishing the likelihood of yogurt being the source of the outbreak. Additional details such as brand, variety, and point of sale are needed to determine if some type of soft cheese is the outbreak vehicle.



JUNE 28 2:30 - 6:00 P.M. (DAY 2 OF INVESTIGATION)

Minnesota case 1 and the spouse of Minnesota case 2 were re-interviewed:

The spouse of MN case 2 reported that she had consumed blue cheese purchased from a local grocery store (Store A).

MN case 1 reported consuming a soft brie-like cheese that was part of a cheese plate served at a North Dakota restaurant.

- The Minnesota lead investigator contacted the restaurant chef, and he reported that the cheese plate included the following five cheeses:
 - Blue

- Gruyere

- Crave Brothers Les Frères

- Cheddar

- Manchester

The Minnesota lead investigator had contacted the other states with cases to learn specifics of their cases' exposures reported on their LI questionnaires.

At 4:10 p.m., Illinois reported that their case specifically mentioned consuming Crave Brothers Les Frères purchased at a chain grocery store (Store B).

At 5:50 p.m. the Indiana cases' LI questionnaire was reviewed.

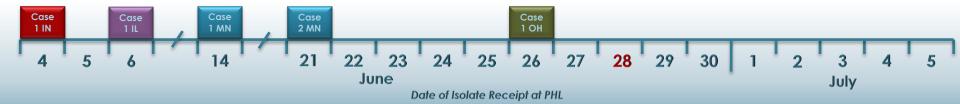
• They reported consuming a cheese plate from a restaurant in Indiana. A quick on-line search of the restaurant menu indicated that they served Crave Brothers Les Frères on cheese plates.

At 6:00 p.m. MDH was notified by CDC of non-human isolates in PulseNet that were indistinguishable from the outbreak PFGE pattern.

- The non-human isolates had been collected by the FDA in recent years.
- Of the 40 matching non-human isolates in PulseNet, 30 (75%) were from environmental samples collected from the Crave Brothers cheese production facility in 2010 and 2011.

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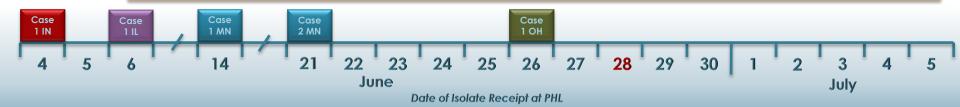
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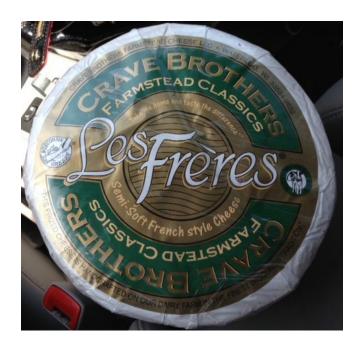
Assessment:

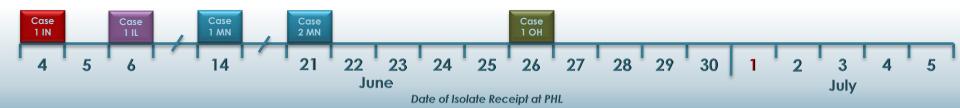
Investigators have a strong hypothesis that Crave Brothers Les Frères is the outbreak vehicle. What is the probability that three cases infected with the same strain of LM would have consumed the same brand and type of cheese by chance? Additionally, the outbreak strain of LM had also been isolated from environmental samples collected from the Crave Brothers production facility (albeit 2-3 years prior to the current outbreak).



JULY 1 (DAY 5 OF INVESTIGATION)

Crave Brothers cheese was collected for testing from two locations of the grocery chain where MN case 2 had purchased the product, and submitted to MDA for LM testing. In addition, leftover blue cheese, Irish cheddar, parmesan cheese, and an unknown hard cheese were collected for testing from MN case 2's home. To their credit, MDA laboratorians worked on a Saturday to set up the samples for testing.





JULY 3 (DAY 7 OF INVESTIGATION)

The Ohio case was re-interviewed:

• The case reported consuming a cheese plate served at a restaurant in Ohio, and an environmental health inspector confirmed that the cheese plate included Crave Brothers Petit Frère.

Enzyme-linked Fluorescent Assay (ELFA) results on the Crave Brothers cheese collected from grocery stores in Minnesota on July 1 and the leftover cheese collected from MN Case 2's home were available from MDA.

- Of 18 cheese samples submitted for testing, 4 were positive for LM, including:
 - 1 wedge of Crave Brothers Petite Frère with Truffles from one grocery store location in Minnesota.
 - 2 wedges of Crave Brothers Les Frères from another location of the same grocery store chain in Minnesota.
 - 1 wedge of blue cheese collected from MN Case 2's home.

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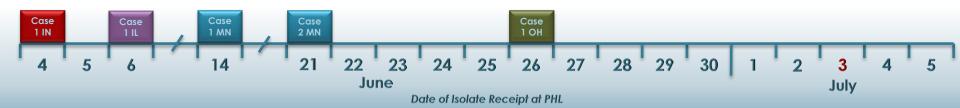
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 - 1 wedge of blue cheese collected from MN Case 2's home.

Assessment:

We have now reached that "threshold of confidence" that prompts a public health intervention. Four of five cases report the rare exposure of consuming cheese from the same small cheese producer, and LM with an indistinguishable PFGE pattern had previously been isolated from the cheese producer's facility. Additionally, these cheeses still represented an ongoing risk to the public. It is time to go public.

The blue cheese (from Case 2's home) that tested positive was not a Crave Brothers product. However, the rest of the evidence was so overwhelming that we moved forward, even with this inconsistency. Often, not every case lines up perfectly.



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The traceback investigation revealed that the cheeses had different distributors which indicated that the source of the contamination was the Crave Brothers plant.

MDH and MDA issued a joint press release warning consumers not to eat Crave Brothers Les Frères, Petit Frère, and Petit Frère with truffles.

Later that evening, Crave Brothers issued a voluntary nationwide recall of these cheeses.

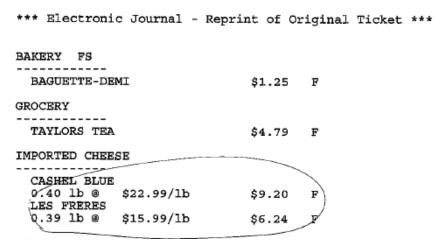


JULY 5-6 (DAY 9-10 OF INVESTIGATION)

PFGE results were available for the four LM isolates from cheese and they were all indistinguishable from the human case isolates.

What about the outbreak case not linked to Crave Brothers cheese? It is not always possible to link every case in an outbreak directly to the implicated vehicle, but in this instance, the spouse of MN Case 2 called and said, "I think we bought the Petit Frère with truffles at the same time we bought the blue cheese." He reported that he did not have a receipt but had used a credit card to make the purchase.

An MDH epidemiologist contacted the grocery store and gave them the credit card transaction numbers, the date of the transaction, and the dollar amount of the transaction. Using this information the store was able to reprint the original receipt below.



Crave Brothers Les Frères was purchased at the same time as the blue cheese that subsequently was collected from the household of MN Case 2 and that tested positive for the outbreak strain of LM. Both cheeses were held in the same bag, and the blue cheese was contaminated by the Les Frères. At the time of the first interview, only the blue cheese was left and reported by MN Case 2's spouse. Now all 5 cases were epidemiologically linked to Crave Brothers cheese.



Epilogue

In the end, 5 outbreak cases were identified in Minnesota, Indiana, Illinois, and Ohio. In addition, subsequent whole genome sequencing efforts identified another likely case in Texas, but exposure information was not available. The use of the Listeria initiative questionnaire along with re-interviewing cases (or proxies) and calling restaurants to get specific details on cheese brand/type were critical in identifying the outbreak vehicle. The presence in PulseNet of matching environmental isolates from the cheese production plant was also a key supporting clue. This investigation resulted in perhaps the fastest identification of a commercially distributed food vehicle of a listeriosis outbreak: the cluster was detected in Minnesota on June 27 and public health interventions implemented on July 3 (6 days later). This was a remarkable accomplishment, especially with only 5 cases to work with. The rapidity of the investigation can be attributed primarily to the urgency displayed by the lead investigator and the aggressive acquisition of details on brands/types of soft cheese consumed, in collaboration with epidemiologists in the other affected states.

Reference: <u>Multistate Outbreak of Listeriosis</u> <u>Linked to Soft-Ripened Cheese</u>

Acknowledgments:

Mary Choi, Centers for Disease Control and Prevention, Illinois Department of Public Health, Ohio Department of Health, Indiana State Department of Health, Minnesota Department of Agriculture, and United States Food and Drug Administration, Wisconsin Department of Agriculture Trade and Consumer Protection

Summary of Key Investigation Lessons:

National outbreak detection algorithms are not always reliable at the individual state level. The outbreak **PFGE subtype** was common nationally and not above baseline. However, the subtype was **rare in Minnesota**, indicating that only 2 cases likely **represented a common source outbreak** that warranted aggressive follow-up; temporally associated isolates in other states with the same subtype were investigated like they were part of the outbreak (and they did turn out to be).

See: CIFOR Guidelines for Foodborne Disease Outbreak Response Chapter 4.2.9.2

➤ Obtaining detailed product information is often key to evaluating exposures that are reported by the majority of cases on the initial interview (in this outbreak soft cheeses, which required re-interview of cases and follow-up with multiple restaurants).

See: CIFOR Guidelines for Foodborne Disease Outbreak Response Chapter 4.2.10.3

➤ It is often necessary to call cases back (often more than once) to ask about an exposure again or to get more specific information (brand, type, point of sale, purchase date) on an exposure. Most people don't report all foods on 1st interview!

See: CIFOR Guidelines for Foodborne Disease Outbreak Response Chapter 4.2.10.3

See: CIFOR Guidelines for Foodborne Disease Outbreak Response Chapter 5.2.4.1.2

➤ The case-case comparison study conducted by CDC as part of the *Listeria*Initiative quickly quantified a strong signal for soft cheese, supporting the need for continued collection of details on brands/types of cheese consumed by cases.

See: CIFOR Guidelines for Foodborne Disease Outbreak Response Chapter 5.2.4.1.5

Matching food, animal, or environmental isolates in PulseNet can provide key clues in outbreak investigations.

See: CIFOR Guidelines for Foodborne Disease Outbreak Response Chapter 4.2.5

- > Grocery store receipts can sometimes be reprinted if the purchase was made with a credit card or debit card (i.e., even for stores that do not have loyalty programs). Please see our "Key Points" document for details on this topic.
- ➤ Outbreaks can be solved rapidly with very few cases. Success begins with the collection of very specific exposure details and rapid sharing of data between state and federal agencies.

