Breakfast Session:

Practical Approach to Addressing Microbial Data Deviations

Kim Sobien, MBA

Senior Consultant - Microbiology

ValSource

PDA Parenteral Drug Association

PDA Aseptic Manufacturing Excellence Conference 2024

CONNECTING PEOPLE SCIENCE AND REGULATION®

Introduction

Kim Sobien is a Microbiology Senior Consultant with ValSource, Inc. Her pharmaceutical industry career encompasses a breadth of quality, compliance, and technical experience with injectable pharmaceutical products. She has expertise in microbiology, sterility assurance, contamination control, investigations, capability building, and inspection readiness.

Kim has a BS in Microbiology from the University of Wisconsin–La Crosse and a Master of Business (MBA) degree with an emphasis in Global Management from the University of Phoenix. She is an active member of the Parenteral Drug Association (PDA) and the PDA Southeast Chapter, Co-Lead for the PDA EM/Microbiology Interest group, and a past co-chair and committee member for the PDA Pharmaceutical Microbiology Conference. She also participates on several ASTM E55.06 “Microbial and Sterility Assurance” subcommittees.

ksobien@valsource.com

VALSOURCE

With thanks to Paula Peacos

Agenda

Overview of MDDIs – What, Why, Who, and When

Phases of a MDDI – Phase I and II

A Brief Word on Microbial Identification

Root Cause Analysis and Impact Assessment

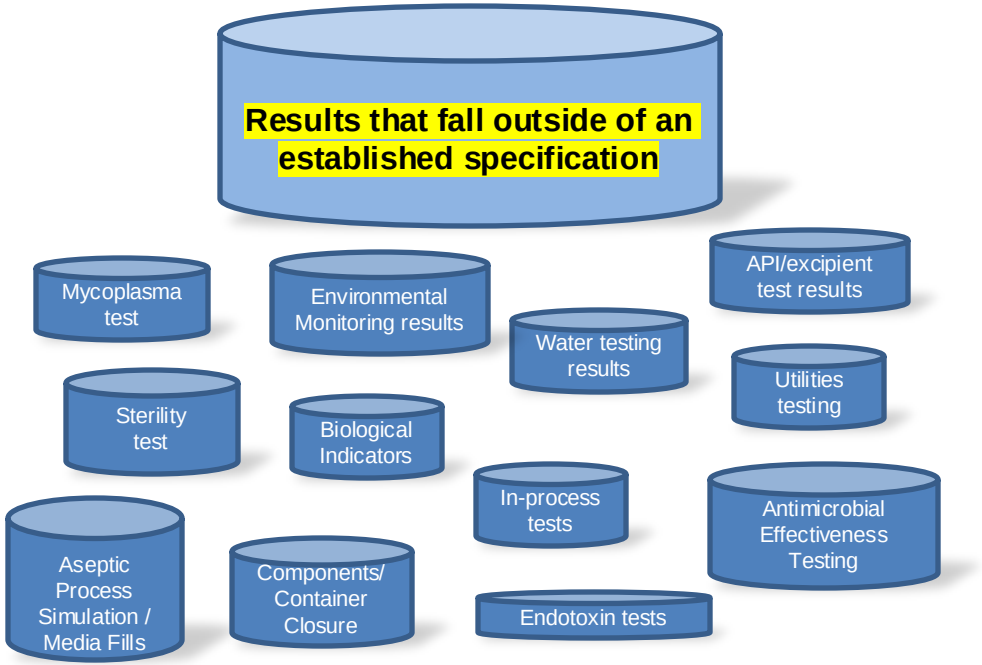
Executive Summary

Practical Application – Interactive Activity

Quick Survey

- How many attendees author investigations?
- How many attendees support investigations?
- If you write investigations, are you a Microbiologist?
- Have you ever had an investigation where you didn't find the exact root cause?
- What's the weirdest microorganism you've ever seen in an investigation?

Microbial Data Deviation Investigations
MDDI – What are they and why do we perform them?

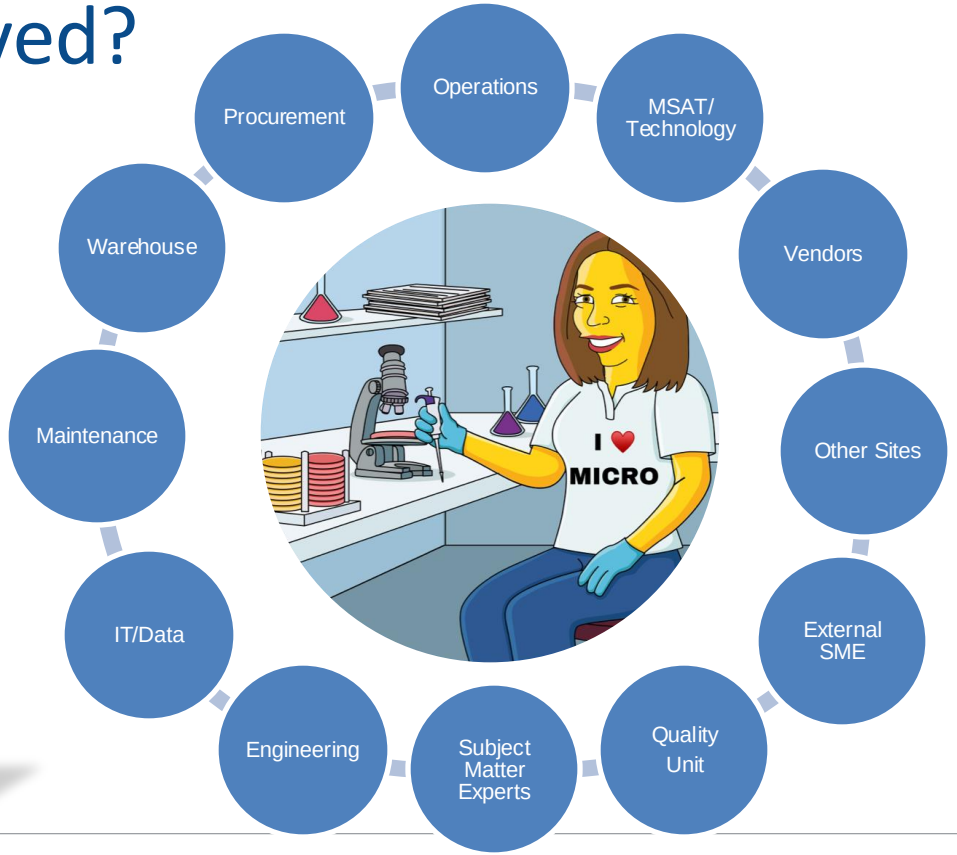


Why? *(list is not all inclusive)*

- Ensure and enhance patient safety
- Regulatory requirement
- Memory fades quickly
- Details are important
- Documentation is power
- Part of a robust continuous improvement program
- Improve inspection outcomes
- Better understand process/reduce future deviations

MDDI – Who is involved?

Lead
Investigator



Notification = Within 24 hours of discovery, in a formal manner, such as opening an investigation in an electronic database.
Notify area owner, Manufacturing, Quality Assurance

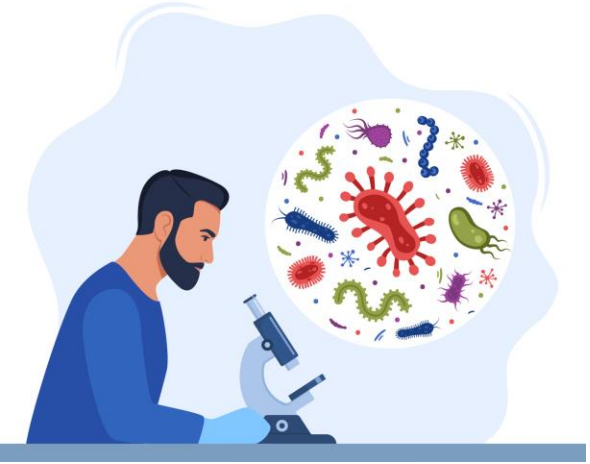
MDDI – When?

Consider:

- Exceeded ACTION limits
- Exceeded ALERT limits →
- Trends
- Nature of microbial Identification
- Aberrant Data (outside of the norm)

Annex 1:
"If alert levels are exceeded, operating procedures should prescribe assessment and follow-up, which should include consideration of an investigation and/or corrective actions to avoid any further deterioration of the environment."

MDDI – Phase I - Laboratory



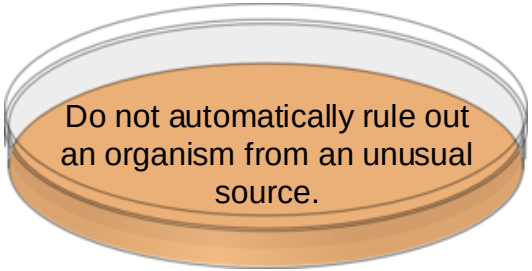
- Determine validity of the sample or test
- Sample collection and handling/storage
- Review assay trend history and SOP
- Observe testing practices
- Look at Equipment
- Interview operators
- Re-perform calculations
- Assess the microbial identification (nature, history)
- Review materials and documents used for testing
- GEMBA of the laboratory

MDDI – Phase II - Manufacturing

- Review sampling technique and location*
- Review manufacturing and personnel history*
- Interview operators*
- Assess the batch record*
- Review materials and documents used for production*
- GEMBA of the production area(s)*
- Determine root cause*

**involve the Microbiologist*!

MDDI – Microbial Identification



Correct organism identification is *critical*

Level of identification should be commensurate with risk to product and patient *(but strongly consider FULL characterization to include Genus and species)*

Need to identify the source of the organism and its potential impact

The amount of information determines the usefulness of the laboratory investigation

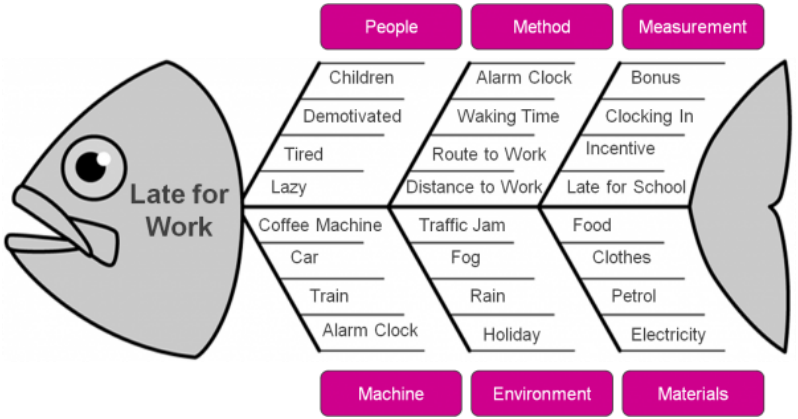
Be sure the information comes from an appropriate reference.

MDDI – Root Cause Analysis

How were the existing control systems breached?

Fishbone/6M

Area	Examples
Milieu (Environment or "Mother Nature")	• Facility design • Environmental factors • Power failures
Machine (Equipment)	• Improper or inadequate equipment • Equipment failure • Certification or calibration inadequate or missing
Method	• Inadequate, inaccurate, or missing procedure or test method • Resource planning, prioritization, scheduling inadequate
Measure	• Specification inadequate or incorrect • Statistical calculation not appropriate for the application
Manpower (People)	• Failure to follow procedure • Incomplete or missing records or data • Insufficient attention to detail and alertness • Improper or inadequate training • Inadequate staffing
Material	• Identity • Quantity • Quality

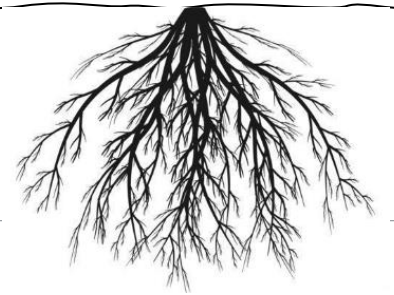


Record ALL inputs – not just the ones you think are the cause.
Record your thought process!

Consider other RCA methods like 5 Whys, Is/Is Not, GEMBA

MDDI – Root Cause Analysis

- **Root Cause**
  - The true underlying cause for the deviation
- **Probable Cause**
  - A factor (or combination of factors) that cause an abnormal event but cannot be fully verified by objective evidence
- **Contributing Cause**
  - Elements that either were necessary, in addition to the root cause for an event to occur, or that increased the event's impact

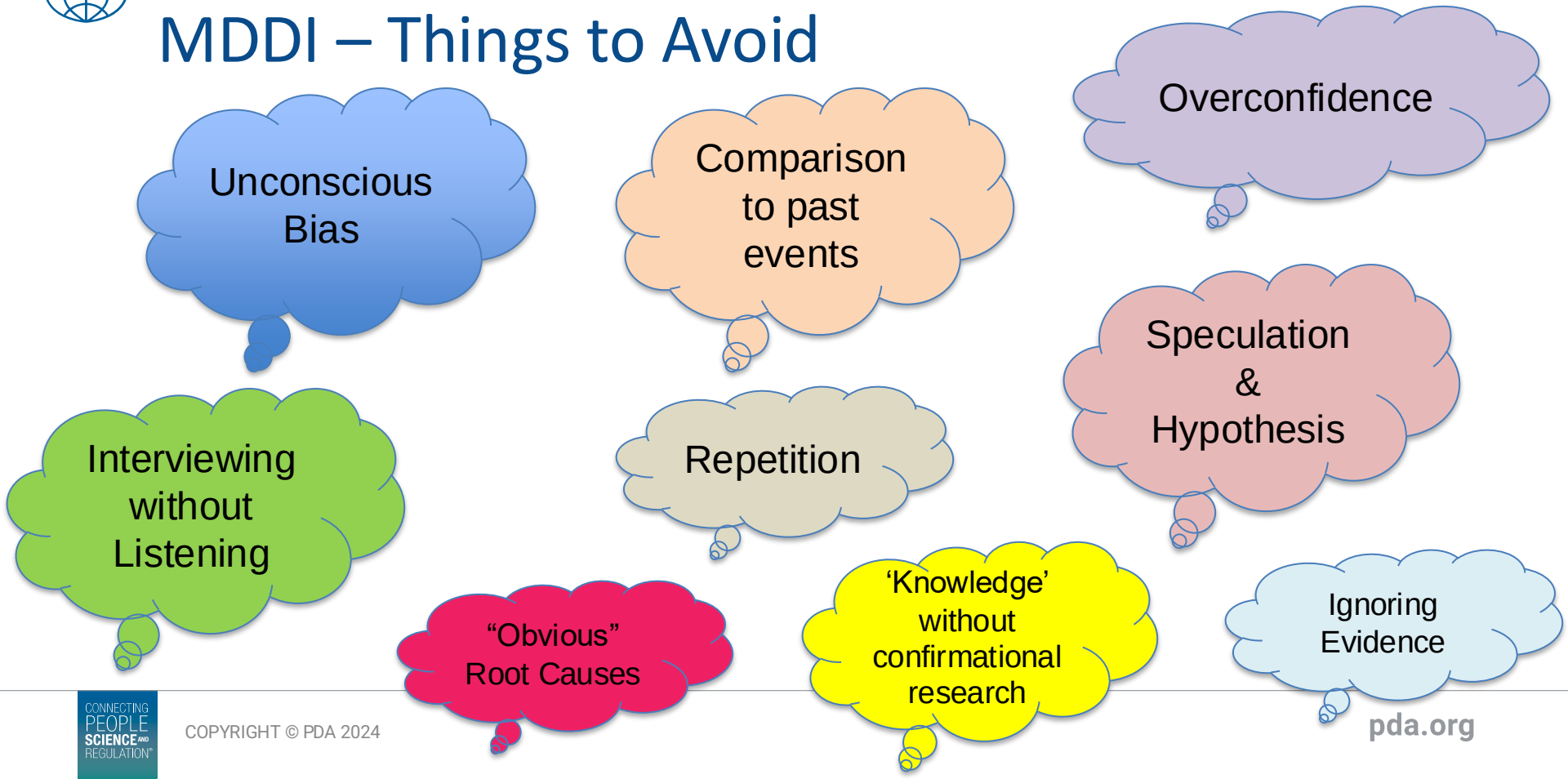


MDDI –Impact Assessment

Considerations in determining potential impact:

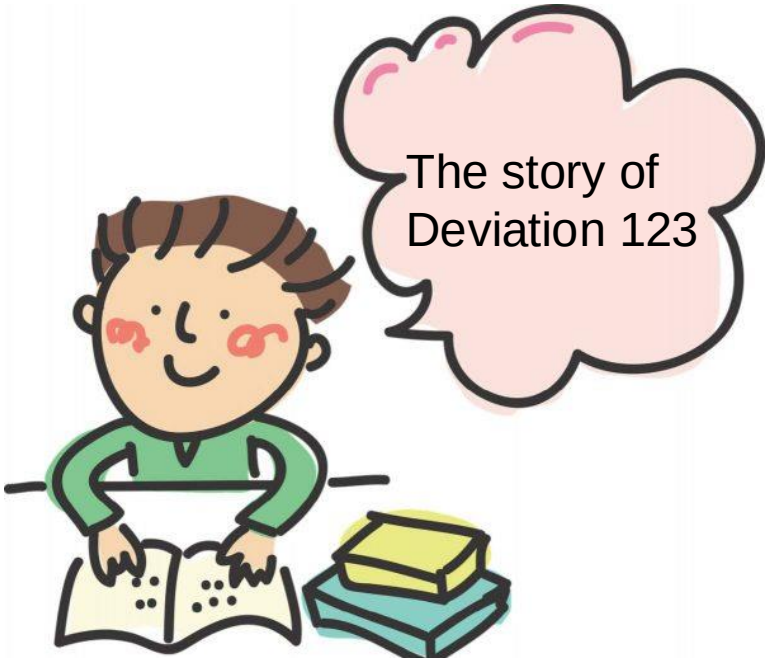
- Target patient population (pediatric, geriatric, immuno-compromised)
- Product Type and Route of Administration
- Ability to Proliferate (in the product and/or in the patient)
- Toxins (endotoxin, exotoxins, mycotoxins, aflatoxins
- Presence of Preservatives and Anti-microbial agents
- Open vs. Closed System
- Stage of Manufacturing Process (any downstream filtration or terminal sterilization?)
- Could other batches or processes be impacted?
- Organism persistence (spores, biofilms)
- Sample Collection Process
- Known resistance to antibiotics
- Quantify how much is present
- Pathogenicity (obligate, opportunistic, non-pathogenic)
- Batch Interventions

MDDI – Things to Avoid



MDDI – Executive Summary

- The executive summary should succinctly tell the story of the investigation:
- When (on DATE)
- What (X was observed, X occurred, X was deviated from)
- Who
- What was supposed to have happened (per SOP)
- What was the impact (batches)
- What was done about it
- Is there a trend?
- The summary should stand alone if you didn't read any more of the investigation.



MDDI – Executive Summary Example

Surface contact environmental monitoring of site 123.F04 (floor location #4 contact sample in room 123) on 01OCT2024 resulted in an observation of 176 CFU. The number of recovered CFU exceeds the action level of 100 CFU per SOP EM003216. The microbial identification results is Bacillus thuringiensis, a spore-forming environmental bacteria. There were no other recoveries from environmental monitoring of room 123 on 01OCT2024. Historical data does not indicate a trend in recovery at this location, in this room, or for this microorganism. Corrective action was taken by performing an additional sporicide application per SOP CLN001247 on 10OCT2024. No additional recoveries from this sampling location have occurred in the 30 days following the sample date. Future EM of the site will be monitored closely for the next 30 days for recurrence.

MDDI – Use Your Resources!

PDA Technical Report 88: Microbial Data Deviation Investigations in the Pharmaceutical Industry (2022). Accessed from https://www.pda.org/publications/pda-technical-reports

LightsOnData (2018)"How to use the fishbone diagram to determine data quality root causes". Accessed from http://www.lightsondata.com/how-to-fishbone-diagram-data-quality-root-causes/

Astromskis, S., Janes, A., Sillitti, A., & Succi, G. (2013) "Implementing Organization-wide Gemba using Non-invasive Process Mining". Cutter IT Journal, 26(4), 32-39. Accessed from https://www.researchgate.net/profile/Alberto_Sillitti/publication/290560376_Implementing_organization-wide_gemba_using_noninvasive_process_mining/links/57c699c608aefc4af34b22a0.pdf

MindTools, Management Training and Leadership Training. "Online "5 Whys: Getting to the Root of a Problem Quickly" Accessed from https://www.mindtools.com/pages/article/newTMC_5W.html

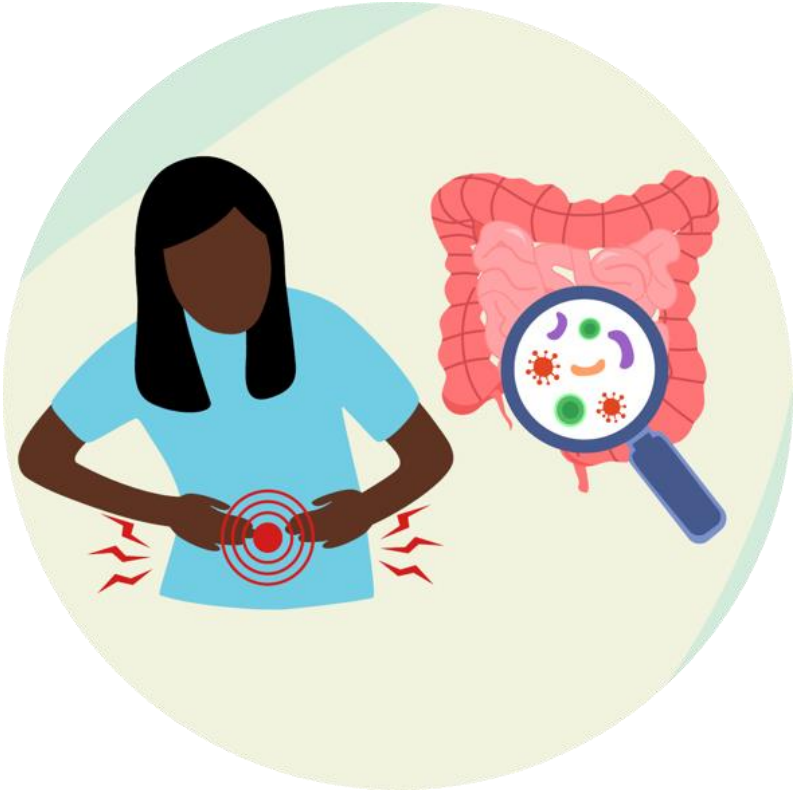
Interactive Exercise – Contamination at the Dinner Party!

The scene: Last night, you hosted a lovely dinner party for 20 of your closest friends.

After everyone left, and cleanup was finished, you went off to bed.

The situation: around 5 am, you wake up with nausea, vomiting, cramps, dizziness, and a fever of 105 degrees.

Your partner takes you to the hospital and you're diagnosed with…



Food Poisoning!!

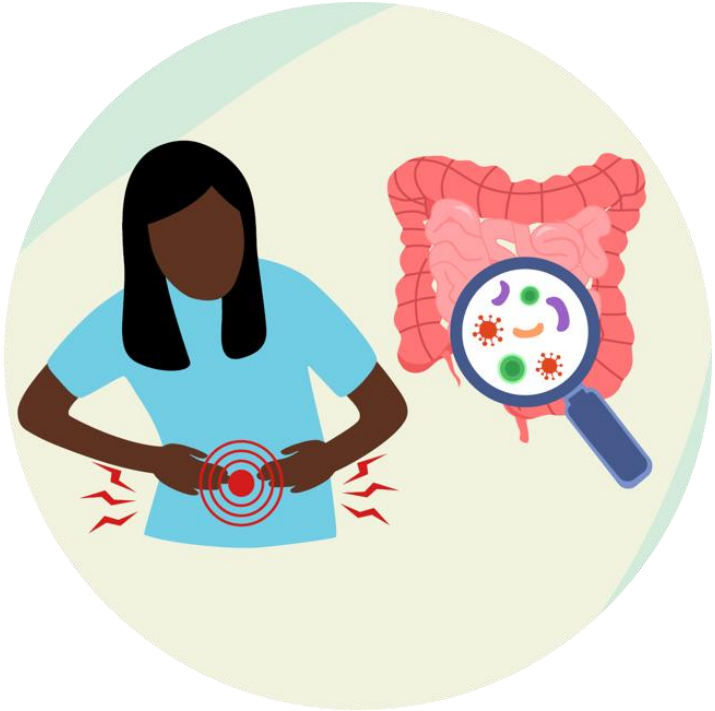
Oh no!! How could this have happened??

Let's investigate!

What was on the menu?

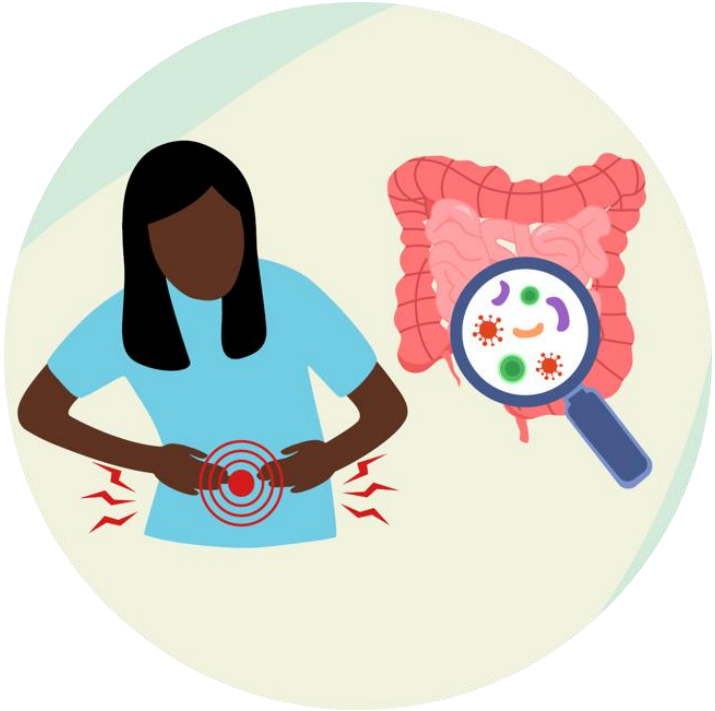
- Geena brought a green salad
- Paul brought potato salad
- Chuck brought chicken wings
- Jamie brought Jello with fruit
- Virginia brought a vegetable platter with dip
- Stacie brought shrimp cocktail
- Christine brought coleslaw
- Brad brought baked beans
- Cathy brought her famous homemade cheesecake
- Betty brought store-bought brownies and red velvet cake
- Sally brought soft drinks and wine
- Kevin brought paper plates, utensils, and napkins
- You hosted the party and provided hot dogs, hamburgers, buns, ketchup, mustard, mayo, pickles, relish, onions, and beer

Interactive Exercise



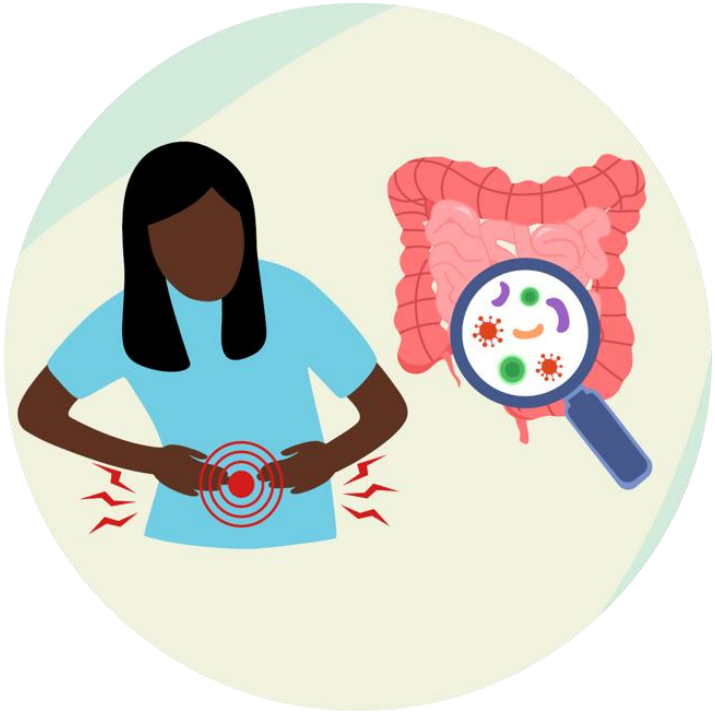
Step 1: Who's on your Investigation Team?

Interactive Exercise



Step 2: What data do we need to collect?

Interactive Exercise



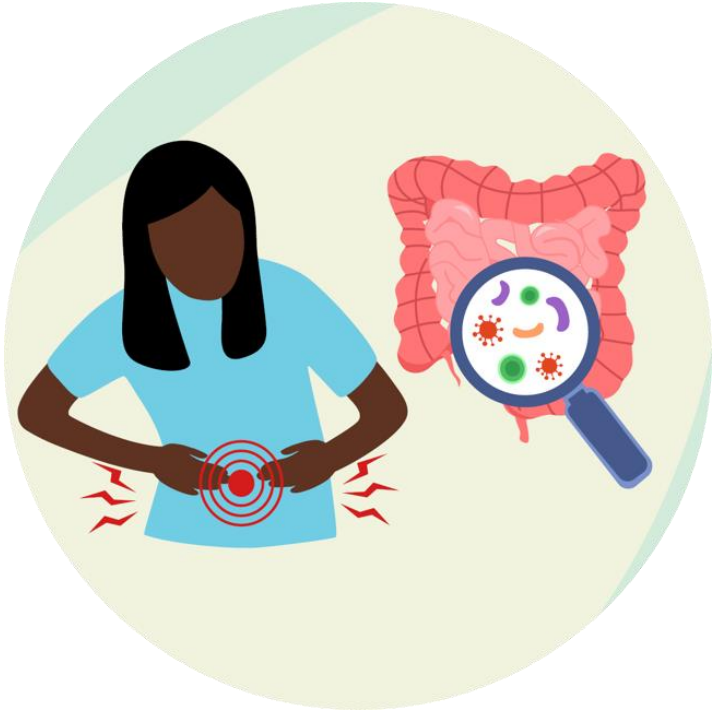
What did we find out?

Interviews: No other adults reported illness

(one person's child who did not attend had similar symptoms the day before the party)

Who do we notify?

Interactive Exercise

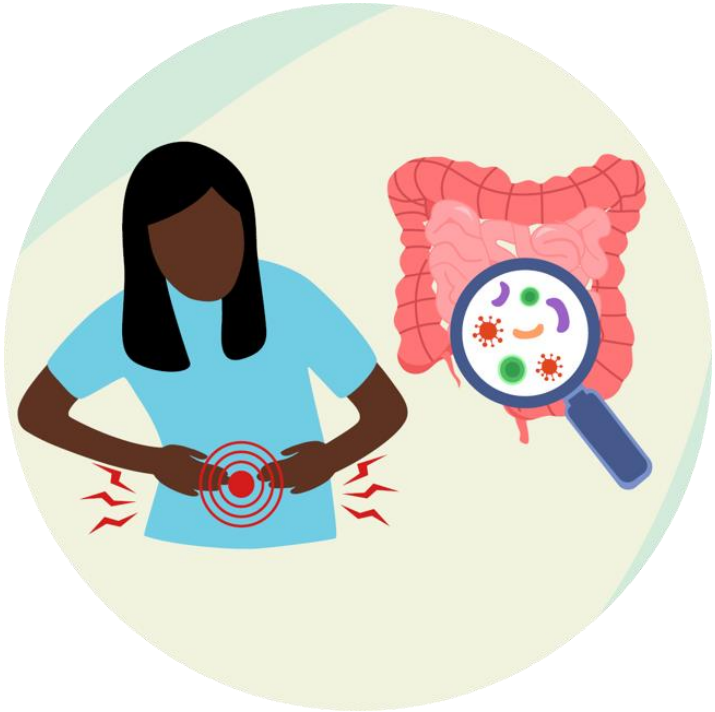


Phase I:

Let's look at "The Lab" (Your Kitchen)

What should we look at and do?

Interactive Exercise

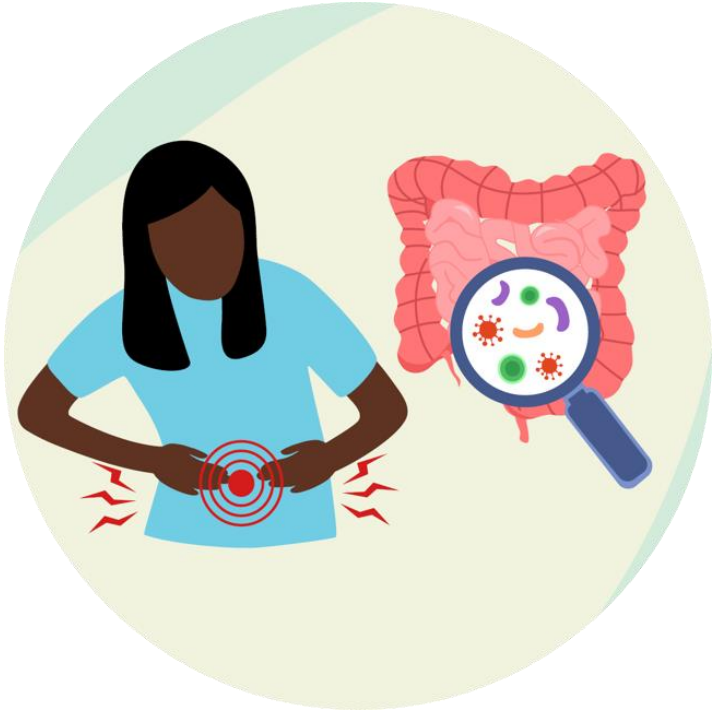


Phase II:

Let's look at "The Manufacturing Area" (Grocery Store, other people's kitchens)

What should we look at and do?

Interactive Exercise



GEMBA of the Grocery Store

What should we look for?
Who should we talk to?
What data can we collect?

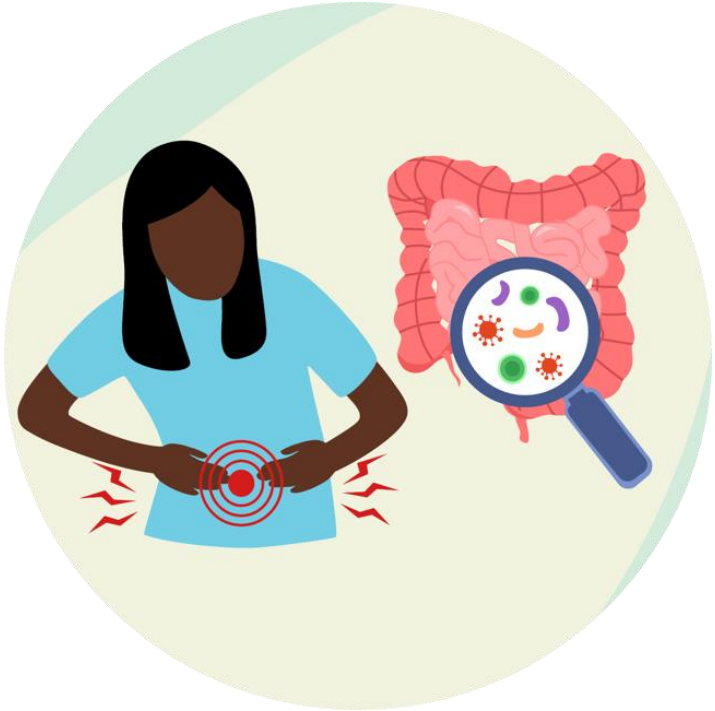
Interactive Exercise

“Operator” Interviews

- Stacie: I licked a spoon, and I think I put it into the dishwasher right after.
- Christine: I've made this food hundreds of times, I know I didn't mess anything up.
- Betty: I bought everything from the store, it was unopened & fresh when it got to the party.
- Paul: I followed my recipe to a 't' - it was made perfectly. I even washed each mixing bowl and measuring cup beforehand.
- Chuck: I work in a restaurant making chicken wings all day, I know how to properly fry chicken.

What else should we ask or observe?

Interactive Exercise

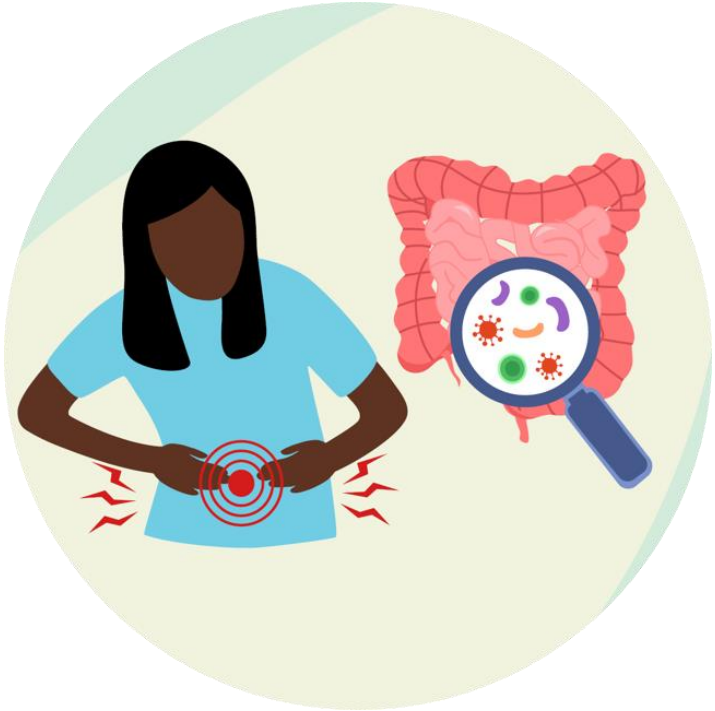


Microbial Identification

The ID is….*Salmonella*

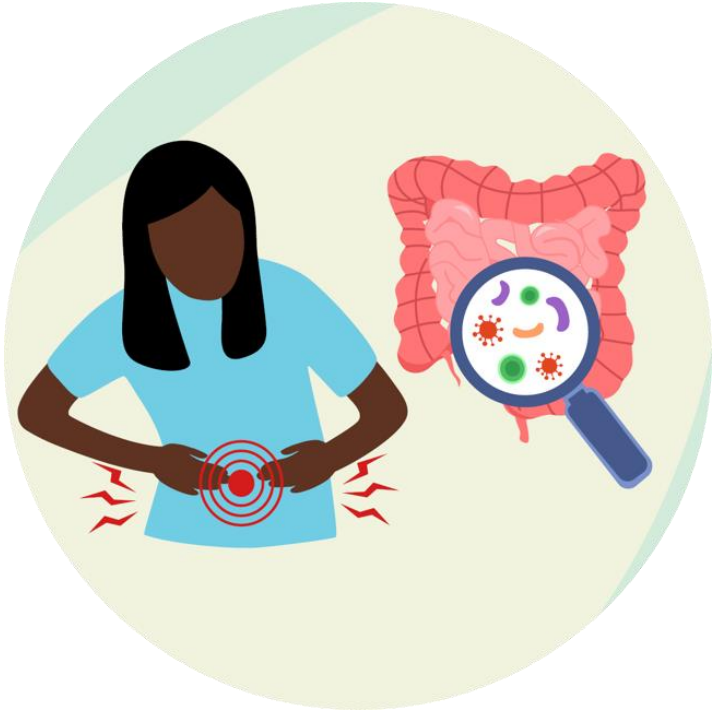
What do we know about this bacteria?

Interactive Exercise



What might be some examples of bias in our investigation?

Interactive Exercise

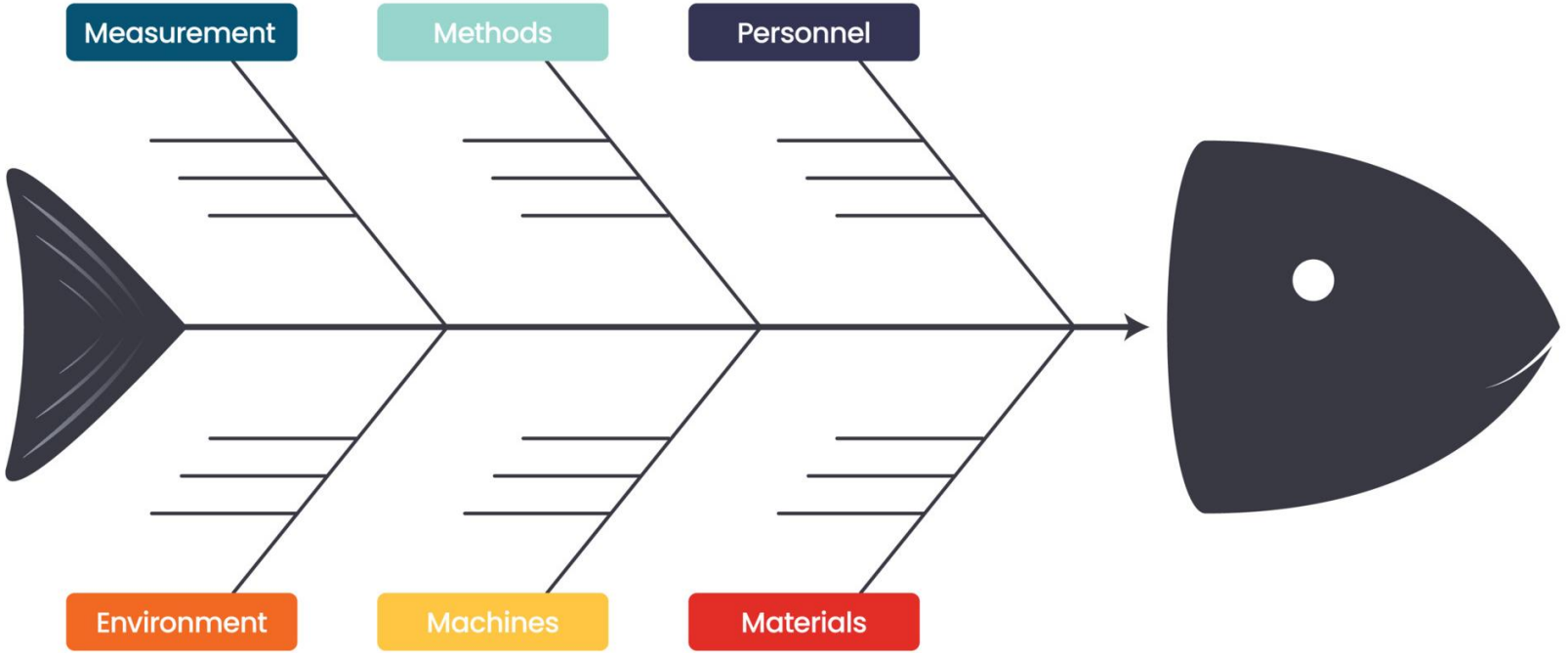


Root Cause Analysis

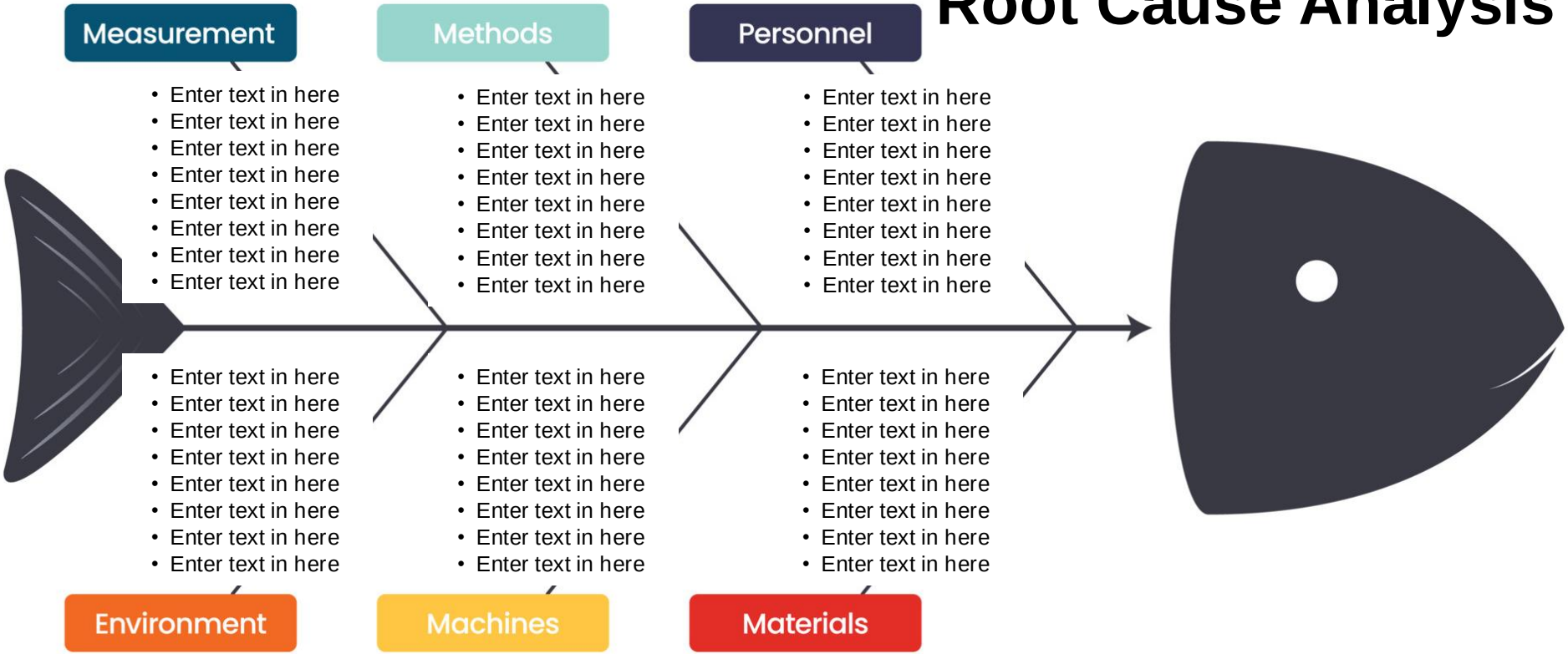
- 5 Whys
- Fishbone Analysis

Interactive Exercise

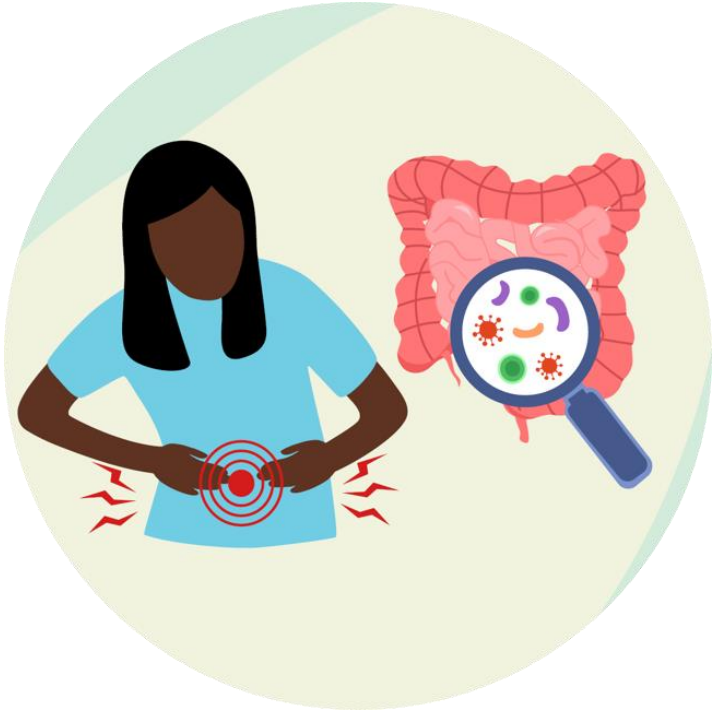
Root Cause Analysis



Root Cause Analysis

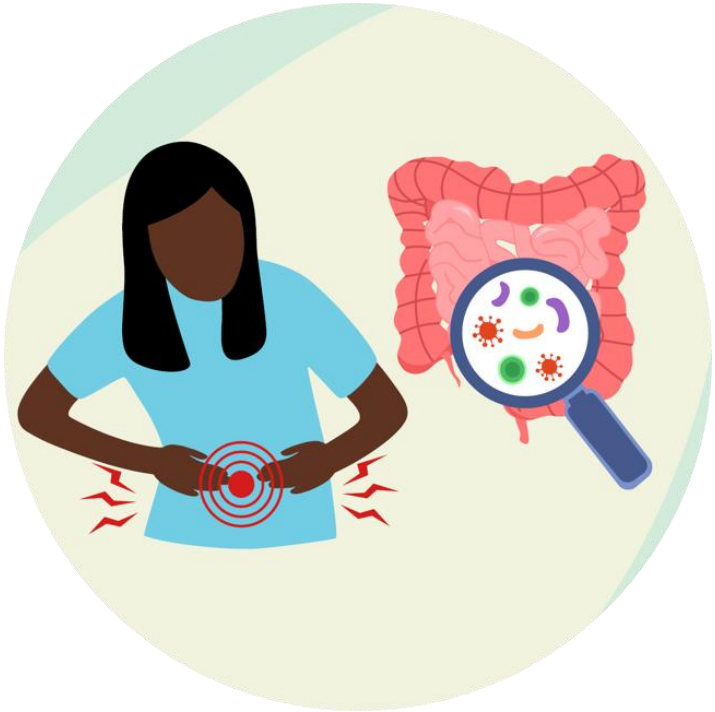


Interactive Exercise



What seem like likely root causes at this point?

Interactive Exercise

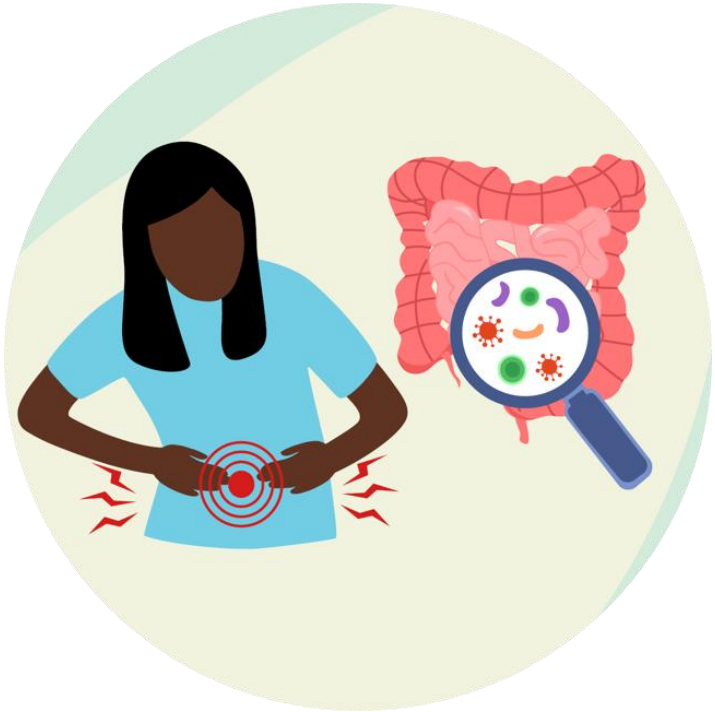


The Root Cause was Determined to be:

Unrefrigerated Potato Salad

(way to go, Paul!)

Interactive Exercise



What Corrective Actions could have been taken immediately?

What could we do to correct or prevent it from happening in the future?

ksobien@valsource.com

https://www.linkedin.com/in/kimsobien/