

Division C Problem I: Disease Detectives Investigate an Outbreak of Cryptosporidium

Emerging infectious diseases pose important public health problems for both the developed and developing world. Many new or previously unrecognized bacterial, fungal, viral and parasitic diseases have emerged within the past two decades. At the same time, many once-controlled infections have re-emerged or become resistant to antimicrobial therapy. This emergence is the result of changes in society, technology, the environment, and the microbes themselves, and these changes have had often unpredictable consequences. Important factors influencing emergence include changes in human demographics and behavior, changes in technology and industry, changes in economic development and land use, increasing and rapid international travel and commerce, microbial adaptation and change, and the breakdown of public health measures.

Early in the spring of 1993, a widespread outbreak of acute watery diarrhea among the residents of Milwaukee, Wisconsin was detected. This massive outbreak of watery diarrhea was caused by *Cryptosporidium parvum* oocysts that passed through the filtration system of one of the city's water-treatment plants. *Cryptosporidium* has been recognized as a common cause of waterborne disease outbreaks (recreational and drinking water). Due to its high resistance to chlorine disinfection methods, prevention measures focus on reducing the introduction of oocysts into source water and removal of oocysts by filtration. During this outbreak, researchers estimated that over 400,000 residents became ill with diarrhea, nausea, vomiting, abdominal cramps, and/or fever between March 1 and May 30th, 1993.

On April 5, 1993, the Wisconsin Division of Health was contacted by the Milwaukee Department of Health after reports widespread absenteeism among hospital employees, students, and schoolteachers due to gastrointestinal illness. The following problem covers two separate investigations of this outbreak.

Note: All answers and work should be placed on the answer sheet. Any work or answers on the exam will not be scored.

1. (3 pts) Disease detectives use three pieces of information to characterize an outbreak. What are they?
 - a.
 - b.
 - c.

On April 7, two laboratories identified *Cryptosporidium* oocysts in stool samples from seven adult residents of the Milwaukee area. Beginning that day (April 7), surveillance for enteric pathogens was begun among fourteen clinical laboratories in Milwaukee County. Previously, all fourteen laboratories routinely tested all stool specimens submitted for bacterial culture for *Salmonella*, *Shigella*, and *Campylobacter*. Before April 7, 12 of the 14 laboratories tested for *Cryptosporidium* only at the request of a physician.

During the period from March 1 through April 16, 1993, a total of 2300 stool specimens were submitted to the fourteen clinical laboratories in the Milwaukee vicinity for routine culture for bacterial enteric pathogens. Twenty specimens were positive for *Salmonella*, ten for *Shigella*, and eleven for *Campylobacter*. From March 1 through April 6, 12 of 42 stool specimens tested for *Cryptosporidium* were positive; from April 8 through April 16, 331 of 1009 specimens were positive.

2. (9 pts) Calculate the prevalence of the following pathogens. Show your work and round to 2 decimal places.

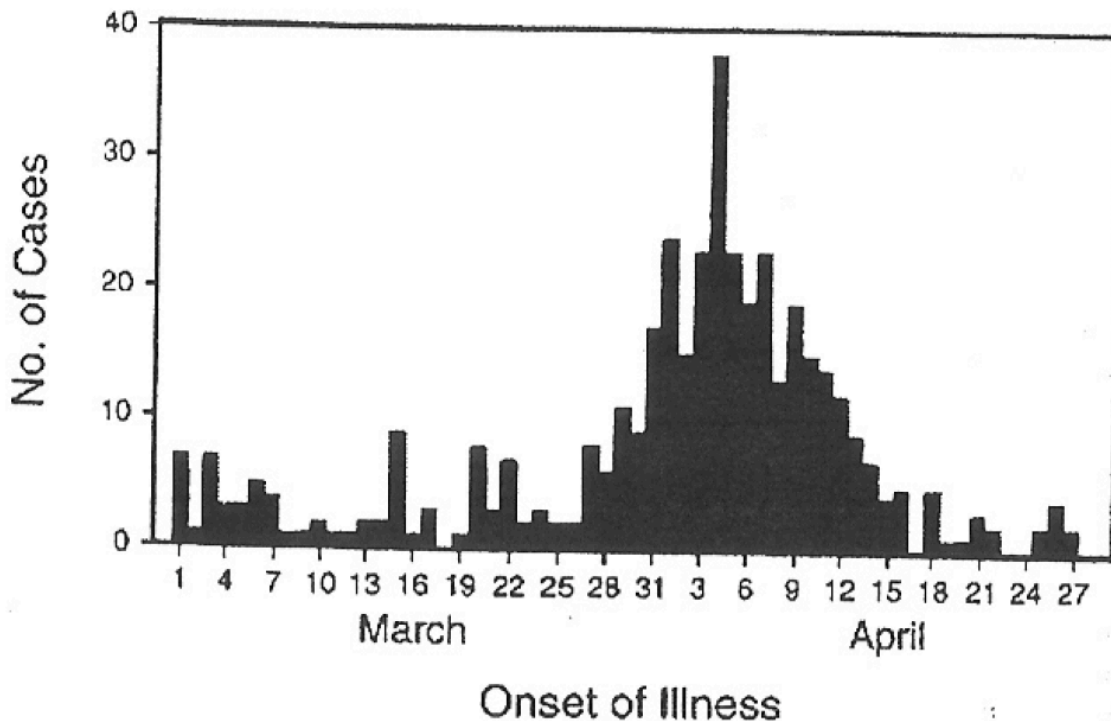
- a. *Salmonella*
- b. *Campylobacter*
- c. *Cryptosporidium* (April 8 through April 16)

3. (4 pts) Choose the most appropriate confirmed case definition from the below.

- a. A resident of the Milwaukee area with laboratory confirmed *Cryptosporidium* infection in Milwaukee, Wisconsin from March 1-May 30th, 1993.
- b. A resident of the Milwaukee area with laboratory confirmed *Cryptosporidium* in Milwaukee, Wisconsin from April 7-May 30th, 1993.
- c. A person with some or all of the following symptoms: diarrhea, nausea, vomiting, abdominal cramps, and fever in Milwaukee, Wisconsin from March 1-May 30th, 1993.
- d. A person with laboratory confirmed *Cryptosporidium* infection in Milwaukee, Wisconsin from April 7-May 30th, 1993.
- e. A resident of the Milwaukee area with some or all of the following symptoms: diarrhea, nausea, vomiting abdominal cramps, and/or fever from March 1-May 30th.

4. (4 pts) Choose the most appropriate probable case definition from the below.
- A resident of the Milwaukee area with laboratory confirmed *Cryptosporidium* and with the following symptoms: diarrhea, nausea, vomiting, abdominal cramps, and fever in Milwaukee, Wisconsin from March 1-May 30th, 1993.
 - A person with the some or all of following symptoms: diarrhea, nausea, vomiting, abdominal cramps, and fever in Milwaukee, Wisconsin from April 7-May 30th, 1993.
 - A resident of the Milwaukee area with some or all off the following symptoms: diarrhea, nausea, vomiting, abdominal cramps, and fever in Milwaukee, Wisconsin from March 1-May 30th, 1993.
 - A person with laboratory confirmed *Cryptosporidium* in Milwaukee, Wisconsin from April 7-May 30th, 1993.
 - A resident of the Milwaukee area with some or all of the following symptoms: diarrhea, nausea, vomiting abdominal cramps, and fever in Milwaukee, Wisconsin from April 7-May 30th, 1993.

Figure 1: Reported Date of the Onset of Watery Diarrhea during the Period from March 1 through April 28, 1993, in 436 Cases of Infection Identified by a Random-Digit Telephone Survey of the Greater Milwaukee Area.



5. (3 pts) Figure 1 shows the highest number of cases was reported on April 4th. A boil-water advisory was instituted on April 7th, What is the most likely reason for the spike in cases on the 9th, if the boil-water advisory was expected to reduce the number of new cases?

- a. Because of the incubation period, cases that were diagnosed on April 9th were probably infected before the boil order was instituted.
- b. The media attention surrounding the outbreak and the boil-order may have led to increased doctor visits/diagnosis
- c. Beginning April 7th, 14 labs (rather than two) regularly tested stool samples for *Cryptosporidium*, and more cases were diagnosed.
- d. Both B and C
- e. All of the above

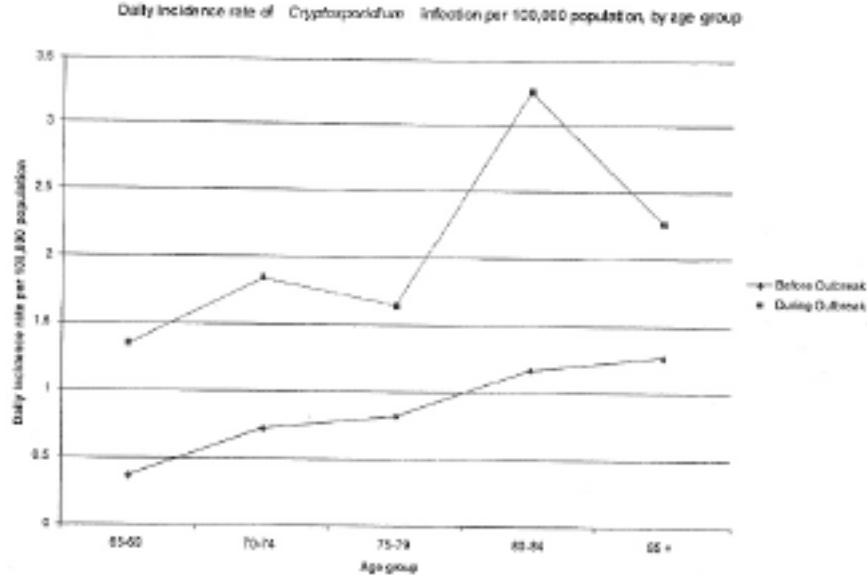
Table 1. Daily rates of gastroenteritis-related emergency room visits and hospitalizations per 100,000 elderly persons by age category before and during the 1993 outbreak of cryptosporidiosis, Milwaukee, Wisconsin.

Age Group	Elderly Population	Before Outbreak (452 days)		During Outbreak (28 days)	
		Number of Cases	Daily rate per 100,000	Number of Cases	Daily rate per 100,000
65-69	38,561	66	(A)	15	1.35
70-74	33,019	108	0.72	(B)	1.84
75-79	26,188	(C)	0.82	12	1.64
80-84	17,584	9	1.17	16	(D)
85+	(E)	81	1.27	9	2.27
65-85+	13,502	445	0.75	69	1.89

6. (12 pts) Fill in the blanks in the above table.

- a.
- b.
- c.
- d.
- e.

Figure 2



7. (3 pts) What kind of relationship between age and the incidence rate is shown before the outbreak? Write the letters of ALL correct answers.

- a. Linear
- b. Inverse
- c. Proportional
- d. Positive
- e. None of the above

8. (1 pt) Does this relationship hold true during the outbreak? Yes or No.

9. (2 pts) Which of the following provides a possible explanation of the relationship between age and incidence rate during the outbreak?

- a. Differences in risk factors among age groups (Le. other illnesses or conditions that made them more susceptible to cryptosporidium)
- b. Differences in the number of exposures among age groups to cryptosporidium
- c. Differences in the levels of exposure among age groups to cryptosporidium
- d. A, B and C are correct
- e. None of the above

Figure 3



Figure 4



10. (3pts) The above maps of gastrointestinal illness (GIH) in the elderly before- and during-outbreak. *Cryptosporidium* cases were obtained by disease detectives.

- What plant is the most likely source of the contaminated water during the outbreak?
- What information in the map(s) supports this?

To determine the extent of the outbreak, disease detectives conducted a telephone survey of households in the greater Milwaukee area and four surrounding counties. Using the random-digit dialing method, 814 households were contacted with 613 households completing interviews. Interviews were done from April 28 to May 2. A probable case of *Cryptosporidium* infection was defined as the onset of watery diarrhea during the period of March 1 through April 28, 1993. The 613 households were similar to the 601,458 households reported in 1990 Census, in terms of sex, age, and geographic distributions of people in the greater Milwaukee area and the number of members per household.

Residential zip codes were used to assign each person to one of four regions: southern, northern, middle and non-Milwaukee water works region (non-MWW). Regions were defined by which water plant predominately serviced that area. The north regions received water from the northern plant and the south from the southern plant. The middle zone residents received water from either plant depending on demand while the non-MWW region received water from outside the MWW service area.

Table 2. Rate of Watery Diarrhea from March 1 through April 28, 1993, among Respondents in a Random-Digit Telephone Survey of Households in the Greater Milwaukee Area, According to Sex, Age, and Water Works Region.

Characteristic	No. of Respondents	No. Reporting Watery Diarrhea	Attack Rate (%)
Total	1663	436	26
Sex			
Male	783	193	(A)
Female	877	243	28
Unknown	3	0	
Age (yr)			
< 9	255	49	19
10-19	240	63	26
20-29	202	61	30
30-39	308	104	34
40-49	(B)	74	32
50-59	149	37	25
60-70	106	24	23
> 70	155	22	14
Unknown	20	2	10
Water Works Region			
MWW	790	309	39
Southern	359	186	(C)
Middle Zone	129	42	33
Northern	312	81	26
Non-MWW	873	(D)	15

11. (3 pts) Why was it important that the 613 survey households were similar to the total number of greater Milwaukee residents in regards to age, sex, geographic distribution, and number of members per household?

12. (12 pts) Fill in the blanks in the above table.

- Male (Round to 1 decimal place)
- 40-49 age group (Round to the closest whole number)
- Southern (Round to 1 decimal place)
- Non-MWW service area (Round to the closest whole number)

13. (9 pts) Calculate the relative risks for the southern, middle zone, and northern regions. Show your work. Round your answer to 1 decimal place.

- southern region
- middle zone
- northern region

14. (3 pts) Using your answer in 13a, in one sentence interpret the relative risk of those who received water from the southern water plant and *Cryptosporidium* infection and those that did not.

15. (1 pt) Do the findings in number 13 support the information found in the maps (Figures 3 and 4) in question 9? Yes or No.

16. (7 pts) The rate of watery diarrhea among survey participants was 26 percent. The total population of the greater Milwaukee area during the outbreak period (March and April 1993) was 1,610,000. The background rate for cases of watery bacteria not attributed to cryptosporidium per month is 0.5%.

a. How many total people can be estimated to have had watery diarrhea during the survey period? Show your work.

b. How many people can be estimated to have had watery diarrhea that could be attributed to this outbreak. Show your work.

17. (5 pts) Suppose laboratory confirmation of infection was the only method used to include individuals as a case associated with the outbreak.

a. Would the number of outbreak associated cases be over or underestimated?

b. Give two reasons a person with Cryptosporidium infection would be missed.

18. (4 pts) Give two ways that residents who received water outside the MWW service area may have been exposed to Cryptosporidium.

Problem II: Disease Detectives Investigate an Outbreak of Salmonella Typhimurium Phage type DT104

Antimicrobial resistance has become an emerging worldwide problem. Bacteria can become resistant to antibiotics through natural pathways such as mutation and gene transfer. However, our antimicrobial use has accelerated the emergence of resistant bacteria. Inappropriate use, extensive use of antibiotics in hospitals, and agricultural use create environments where selection and spread of resistant microbes is possible. Agriculture use (i.e. adding antibiotics to agricultural feed) has especially come under concern since many of the antibiotics used agriculturally are also used for treatment of infections in humans. Evidence of transmission of multidrug resistant bacteria found from livestock to humans and the national and global transport of food products has made this issue an emerging public health problem of growing importance.

Salmonella enterica serovar Typhimurium known as definitive phage type 104 (DT104) has become an increasing cause of food borne outbreaks in the United States. Salmonella Typhimurium DT104 was first associated with the use of antimicrobials in swine in Denmark but eventually spread throughout Europe and later to the US. Consumption of beef, pork and chicken has all been linked to infection. The following problem focuses on an outbreak of Salmonella Typhimurium DT104 associated with raw-milk Mexican cheese. Raw-milk cheese is traditionally made from unpasteurized milk. It is illegal to sell homemade raw-milk cheese; however, it is commonly sold via street vendors, flea markets, and small specialty markets.

In January of 1997, disease detectives in Yakima County, Washington noted an increase in salmonellosis among members of the county's Hispanic community. Laboratorians are required to submit cases of salmonellosis to the Washington State Department of Health laboratories for confirmation and typing.

Disease detectives use various study types to help explain a developing outbreak. In the above outbreak, disease detectives designed a study that would help them to identify exposures associated with infection by Salmonella Typhimurium.

19. (10 pts) Fill in the blank next to each of the following study characteristics with one of below study types.

- Cross-sectional
- Case-Control
- Experimental
- Cohort

- a. _____ Investigator determines through a controlled process the exposure for each individual (clinical trial) or community (community trial), and then tracks the individuals or communities over time to detect the effects of the exposure.
- b. _____ Can use a prospective (forward in time) or retrospective (backward in time) approach.
- c. _____ Uses odds ratio to quantify the relationship between exposure and disease.
- d. _____ Investigators measure the exposures and health outcomes of a sample of persons in a population simultaneously.
- e. _____ Selection of the appropriate comparison group is key to the strength of this design.
- f. _____ Investigator records whether each study participant is exposed or not, and then tracks the participants to see if they develop the disease of interest.
- g. _____ Considered the most rigorous of all study designs.
- h. _____ Investigators identify a group of people with a disease and a group of persons without disease.
- i. _____ Better suited for descriptive epidemiology than determining causation.
- j. _____ Uses relative risk to quantify the relationship between exposure and disease.

In this outbreak a case was defined as gastrointestinal illness in a Yakima County resident with illness onset on or after January 1, 1997, and a stool culture that yielded *Salmonella* Typhimurium. Disease detectives interviewed 22 case-patients and 61 age-matched neighborhood control subjects. Case-patients were asked about exposures in the 7 days before illness onset and control subjects about exposures in the 7 days preceding the interview. Patients and control subjects did not differ with respect to socioeconomic status, as measured by the presence of a telephone in the home, automobile ownership, the number of months worked by the primary wage earner, or mean family size ($P > .10$ for all comparisons).

20. (1 pt) What is the name of this type of study?

21. (8 pts) Which of the following statements are true about this study type? Write the letters of all that apply.

- a. Exposure is determined by recall or records
- b. Not ideal for rare exposures
- c. Used when the population is well-defined
- d. Can study multiple exposures at the same time
- e. Odds ratio does not measure risk directly
- f. Not vulnerable to bias
- g. All of the above

Table 1: Associations of Exposures Among Patients With Salmonella Typhimurium Infection and Controls, Yakima County, Washington, 1997

Food Exposure	Exposed Case-Patients	Total Case-Patients	Exposed Controls	Total Controls	Odds Ratio
Raw-Milk Mexican Style Cheese	17	22	17	61	(a)
Other Cheeses	7	22	21	59	0.84
Chorizo	2	22	18	61	(b)
Ground Beef	9	22	34	61	2.38
Other Beef	13	22	33	61	1.16
Raw Eggs	4	21	11	58	1.00

22. (10 pts) Complete the two by two tables and calculate the odds ratio for the following exposures. Round to two decimal places

a. Raw-Milk Cheese

	Disease	No Disease
Exposed		
Unexposed		

b. Chorizo

	Disease	No Disease
Exposed		
Unexposed		

23. (3 pts) Using your answer from 22a, complete the following statement that describes the association between those who ate raw-milk cheese and Salmonella Typhimurium infection.

Persons who had eaten raw-milk cheese were (a) times (b more or less) likely to have developed a Salmonella Typhimurium infection than those who (c had or had not) eaten raw milk cheese.

- a.
- b.
- c.

24. (3 pts) At this point in the investigation can raw-milk cheese be identified as the source of the outbreak?

- a. Yes or No
- b. Assuming the odds ratio is not due to chance, why or why not can you identify raw-milk cheese as the source of the outbreak?

Due to the short shelf life of raw-milk Mexican-style short cheese (~1 week) no samples could be collected of the implicated cheese. However two producers of cheese eaten by ill persons were found. Both producers had purchased unpasteurized milk from the same dairy.

Salmonella isolates from enrolled cases included 19 that were PFGE pattern A (86%), none that were pattern B, and 3 that were pattern C (14%). 20 (91%) were resistant to ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline.

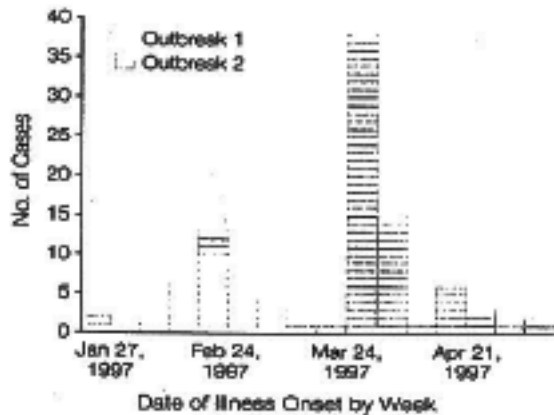
Cultures of milk from tanker trucks that transported unpasteurized milk from area dairies, including the implicated dairy, yielded Salmonella Typhimurium DT104 on 2 separate occasions. Laboratory testing revealed that isolates from the tanker trucks were PFGE pattern A and resistant to ampicillin, chloramphenicol, streptomycin, sulfamethoxazole, and tetracycline.

25. (2 pts) Why was it important that the Salmonella Typhimurium DT104 isolates from the unpasteurized milk collected from the tanker trucks and isolates from cases shared the same PFGE pattern and resistance pattern?

A similar outbreak among the Hispanic community of Santa Clara County and San Mateo County, California occurred in February 1997. Once again, the production of illegally distributed raw-milk cheese was implicated as the vehicle of the disease transmission. This outbreak was identified as being caused by Salmonella Typhimurium phage type DT104, variant Copenhagen.

One week into the investigation, a second concurrent outbreak was found. Isolates from this second outbreak were identified as Salmonella Typhimurium DT104 but a variant other than Copenhagen.

Figure 1: Cases of Salmonella Typhimurium Infections by Week of Onset



26. (1 pt) What name do disease detectives call the above graph?
27. (6 pts) The peak of
- Outbreak 1 occurs during the week of
 - Outbreak 2 occurs during the week of
28. (6 pts) Which of the following things can the graph (Figure 1) above help a disease detective do? Write the letter for ALL answers that apply.
- Identify clues about the pattern of disease spread
 - Determine the cause of the outbreak
 - Identify outliers
 - Deduce a probable time of exposure
 - Determine geographic distribution of cases
29. (6 pts) Give two examples of a public health intervention to prevent future outbreaks.