Centers for Disease Control and Prevention
Epidemiology Program Office
Case Studies in Applied Epidemiology
No. 873-703

An Epidemic of Thyrotoxicosis

Student's Guide

Learning Objectives
After completing this case study, the participant should be able to:

- ☐ List the key tasks involved in investigating epidemics of unknown cause;
- ☐ Describe the roles, responsibilities, and relationships of federal versus state public health agencies in a field investigation;
- ☐ Assign appropriate priority to key tasks during an investigation; and
- ☐ Describe jurisdictions of health agencies at various levels of government.

This case study was developed by Frederic Shaw in 1987. It has been revised and updated by Richard Dicker with input from the EIS Summer Course instructors.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

PART I

On the afternoon of June 16, 1985, an endocrinologist at the University of South Dakota, Sioux Falls, was examining a patient with recent-onset thyrotoxicosis (manifestations of excess thyroid hormone) when the patient mentioned that there were four other people in his small town with the same problem. The patient was the postmaster of Valley Springs, South Dakota (population 801).

Just a few days earlier, the endocrinologist had read an abstract of a CDC investigation describing an epidemic of painless thyroiditis in York County, Nebraska, in early 1984. Although the cause was never determined, the most likely etiology was believed to be viral infection.

By speaking with other local physicians, the endocrinologist identified seven other patients with possible thyrotoxicosis. Six of the patients lived in Valley Springs, and two lived in southwest Minnesota. All exhibited classic symptoms of thyrotoxicosis (anxiety, shortness of breath, palpitations, rapid heart beat, weight loss), and all had markedly elevated thyroxine (T_4) levels. All but one had abnormally low radioiodine thyroid uptakes. The endocrinologist called CDC and provided the EIS Officer with the information summarized in the line listing below.

Table 1. Line listing of patients with clinical thyrotoxicosis reported to CDC on initial telephone call, June 18, 1985

Patient	Age	Sex	Residence	Onset date	Max. T_4*	24-hr. RAIU (%)†
1	53	M	Valley Springs, S.D.	3-84	>20	0.6
2	34	F	Valley Springs, S.D.	5-85	18	17.0
3	57	M	Beaver Creek, S.D.	5-85	22	1.0
4	41	F	Valley Springs, S.D.	5-85	18	2.6
5	76	F	Valley Springs, S.D.	6-85	14	7.8
6	?	M	Luverne, Minn.	6-85	"high"	1.0
7	29	M	Valley Springs, S.D.	?	27	2.2
8	?	M	Luverne, Minn.	?	"high"	"low"

* Normal range = 5-12.
† RAIU - radioactive iodine uptake; normal range = 10%-35%.

Question 1: Place yourself in the role of the EIS Officer. Can you say that an epidemic exists?

Question 2: What additional information might you try to collect on the phone call?

Question 3: Which of the following tasks are appropriate next steps to take? Which are not appropriate? Why or why not?

a. Review information with your supervisor in Atlanta.
b. Contact the state epidemiologist in South Dakota.
c. Book an airline flight to Sioux Falls.
d. Contact state health departments in neighboring states.
e. Contact local health departments in areas affected by the outbreak to identify more cases.
f. Contact physicians in communities affected by the outbreak to identify more cases.

Additional discussions involved the EIS Officer, the South Dakota State Epidemiologist, the Director of the South Dakota Department of Health Communicable Disease Program, and CDC staff. The South Dakota State Epidemiologist invited CDC to send a team to investigate the cluster in Valley Springs. Accordingly, the EIS Officer and a medical student departed from Atlanta for Sioux Falls, South Dakota, on June 23 to assist the state health department in an investigation.

On the airplane, the Officer and medical student reviewed the differential diagnosis for thyrotoxicosis, as summarized in Table 2.

Table 2. Causes of Thyrotoxicosis

I. Disorders associated with thyroid hyperfunction (usually associated with increased radioactive iodine uptake.)

   A. Excess production of Thyroid Stimulating Hormone (TSH)
   B. Abnormal thyroid stimulation
      1. Graves' disease
      2. Trophoblastic tumor
   C. Intrinsic thyroid autonomy
      1. Hyperfunctioning adenoma
      2. Toxic multinodular goiter

II. Disorders not associated with thyroid hyperfunction (usually associated with decreased radioactive iodine uptake)

   A. Disorders of hormone storage
      1. Subacute granulomatous thyroiditis
      2. Subacute lymphocytic thyroiditis (painless thyroiditis)
         a. sporadic
         b. postpartum
      3. Chronic thyroiditis with transient thyrotoxicosis
   B. Extrathyroid source of hormone
      1. Thyrotoxicosis factitia
      2. Ectopic thyroid tissue

III. Jod-Basedow disease – iodine-induced hyperthyroidism (usually associated with decreased radioactive iodine uptake)

Note: Jod-Basedow disease is the only form of hyperthyroidism that has been well-documented to occur in epidemic form. However, it has not appeared in the United States in 50 years.

The endocrinologist met the CDC investigators at the airport and gave them additional information about the area. Valley Springs, S.D., is located about 15 miles east of Sioux Falls on Interstate 90. Luverne, Minn. (population 4,568), lies 10 miles to the east of Valley Springs. The economy of the entire area is agricultural and is based on the production of beef cattle. There are no physicians in Valley Springs. Luverne has one medical clinic and a community hospital. Specialty referrals for the entire area are generally made to Sioux Falls.

At this point, the investigative team included the endocrinologist, staff from the South Dakota Health Department, the EIS Officer, and the medical student.

Question 4: Which of the following steps would you take now, and which should wait for later? Explain why.

a. Set up a control program.
b. Set up a case-finding strategy.
c. Generate etiologic hypotheses.
d. Interview the known case-patients.
e. Create a case definition.
f. Perform etiologic epidemiologic studies using the eight case-patients already known.
g. Contact the Minnesota State Epidemiologist regarding the two Minnesota cases.
h. Confirm the diagnosis.

Question 5: The state health officials want to proceed by conducting additional case finding, to determine the extent of the problem. Your supervisor wants you to conduct a quick case-control study to try and identify possible etiologies. What do you do?

Question 6: Are there any outbreak situations in which setting up a control program would precede further epidemiologic investigations? If yes, give an example.

The investigators decided to start the investigation by interviewing the eight known case-patients in order to verify the disease process and to look for obvious etiologic clues. They took blood specimens from the case-patients as well as from their family members.

Question 7: Was it appropriate to obtain blood specimens from case-patients and family members at this point in this investigation? Why or why not?

The eight interviews produced no valuable etiologic clues. The case-patients were geographically clustered but seemed to have no identifiable common exposures. Blood specimens from case-patients and their family members underwent a variety of tests, including tests for virus-specific antibodies, T_4, free T_4, T_3 resin uptake, and T_3. While waiting for the blood test results, the team decided that the next step should be to increase case ascertainment.

Question 8: What case-finding method(s) might you use?

Since radioactive-iodine-uptake scans were performed in only two facilities in the entire area, two hospitals in Sioux Falls, the team decided to begin case ascertainment by reviewing the results of all uptakes done there in the past year. They identified 33 patients with abnormally low uptakes. These patients were clustered around Luverne, Minnesota.

Question 9: How might you proceed?

PART II

Following discussions with the Minnesota State Epidemiologist, the Minnesota Department of Health joined the investigation. The investigators visited the only source of health care in Luverne, a clinic. The medical director of the clinic stated that he had seen an unusual number of elevated T_4's lately, but said that he had ascribed the phenomenon to laboratory error. Team members reviewed the charts of all clinic patients with elevated T_4's in the past year. They interviewed and obtained blood from all these patients and their families.

Laboratory results from the blood taken from the first 15 case-patients were now available. As expected, all had elevated free T_4's. The team was startled to find, however, that 75% of asymptomatic family members of case-patients also had elevated T_4's.

The total number of case-patients with unexplained thyrotoxicosis was now 28. About five to eight new cases per week were being recognized at the Luverne clinic. Patients' symptoms are shown in Table 3.

Table 3. Distribution of symptoms among patients with thyrotoxicosis, Luverne Clinic, 1985

Major symptom	Percent with symptom	Major symptom	Percent with symptom
Fatigue	92	Nervousness	60
Weakness	83	Sleeplessness	51
Tachycardia or palpitations	79	Headaches	45
Shortness of breath	68	Heat intolerance	38
Weight loss	66	Excessive sweating	34
Tremor	62	Diarrhea	16

The investigators agreed to widen case finding to define the extent of the outbreak. They decided to review patients' records from the medical clinics in five communities in southwestern Minnesota around Luverne, in southeastern South Dakota, and in northwestern Iowa for the previous 18 months. The team also planned to contact by telephone all physicians in eight counties in southwestern Minnesota and question them about the occurrence of thyrotoxicosis among their patients in the past 6 months. In addition, the investigators decided to send letters to all physicians in South Dakota and southwestern Minnesota describing the outbreak and requesting them to report suspected cases to their state health departments.

In order to do this, team members decided that they needed a more formal case definition.

Question 10: Write the case definition that you would now use during widened case surveillance. How might this definition differ from the case definition you might use in a case-control study of the same illness?

PART III

A case was defined as an illness characterized by the presence of one or more values for T_4, free T_4, or T_3 that were at least 25% higher than the upper limit of normal in the laboratory in which the test was performed, and included two or more of the following symptoms: sleeplessness, nervousness, headache, increased heart rate or palpitations, shortness of breath, fatigue, excessive sweating, tremor, diarrhea, heat intolerance, or weight loss. Patients were excluded if they had Graves' disease or if they had received thyroid hormone-replacement therapy during the 2 months before diagnosis.

Question 11: What are the advantages and disadvantages of this case definition?

Widened surveillance produced additional cases (total N = 121). An age-sex breakdown of cases, an epidemic curve, and an incidence map are shown in Table 4.

Table 4. Age and sex distribution of 121 patients with thyrotoxicosis, Minnesota and South Dakota

Age group (years)	Males	Females	Total No.	Total (%)
0-9	1	1	2	(2)
10-19	3	5	8	(7)
20-29	7	8	15	(12)
30-39	15	14	29	(24)
40-49	8	10	18	(15)
50-59	16	6	22	(18)
60-69	9	5	14	(12)
70+	3	10	13	(11)
Total	62	59	121	(100)

Figure 1. Number of cases of thyrotoxicosis by month of onset of symptoms, Minnesota, South Dakota, and Iowa, February 1984 – August 1985 (n=121)

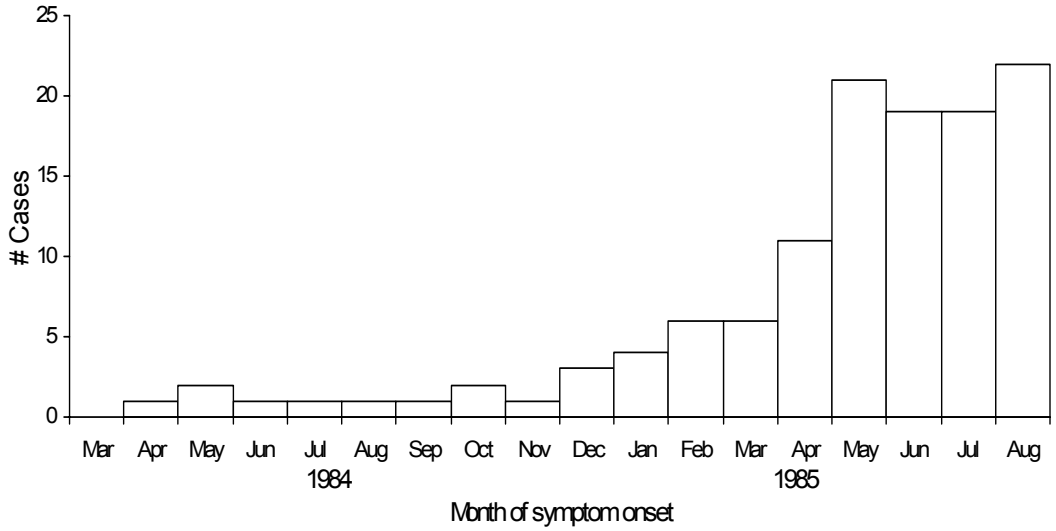


Figure 2. Number of cases of thyrotoxicosis by month of diagnosis, Minnesota, South Dakota, and Iowa, February 1984 – August 1985 (n=121)

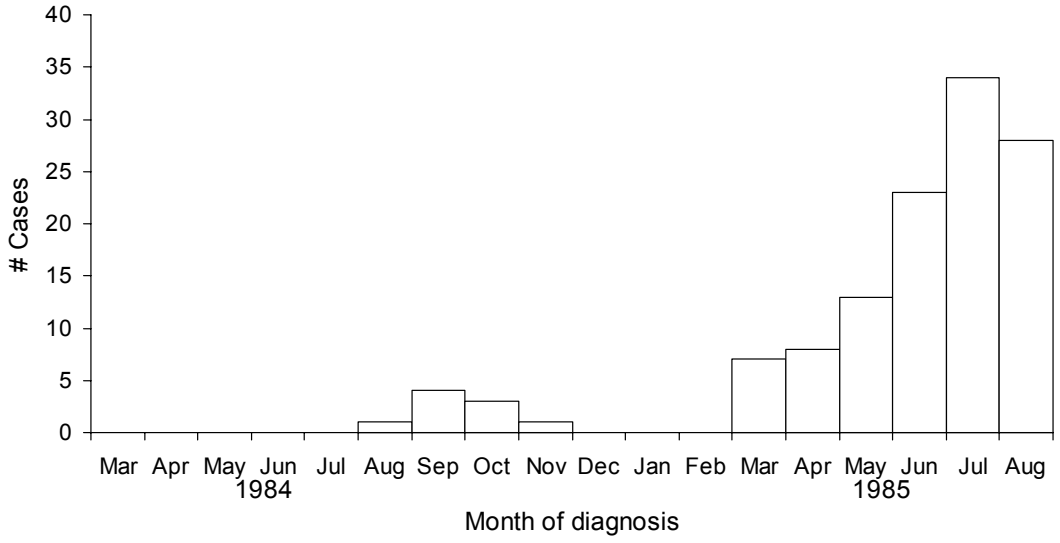
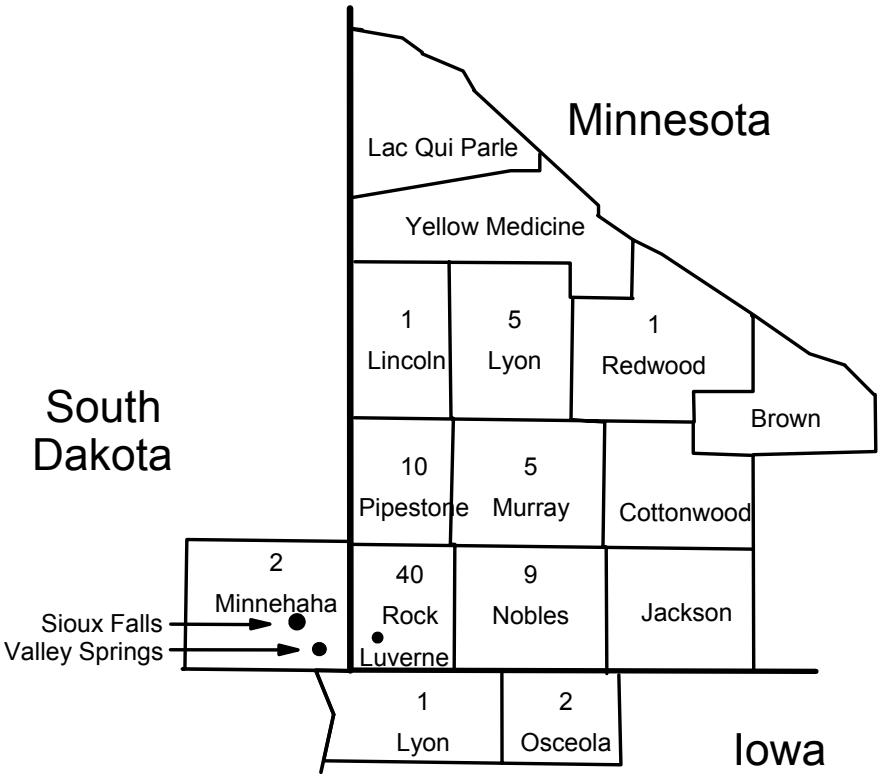


Figure 3. Incidence per 10,000 residents of thyrotoxicosis by county, Minnesota, South Dakota, and Iowa, February 1984 – August 1985



Sitting in a small country-western bar in Sioux Falls late at night in early September, the team members discussed their current hypotheses for the etiology of the outbreak on the basis of all the data accumulated so far. One member took a beer-dampened cocktail napkin and scratched out the major descriptive findings (time, place, person) that he knew about the cases so far.

Question 12: What would you write on the cocktail napkin?

Two nationally recognized thyroid experts were called in to provide consultation to the investigative team. After interviewing and examining several case-patients, they were perplexed by the outbreak but felt that the etiology was probably viral. Several team members favored iodine-induced hyperthyroidism as the most likely etiology; they felt that an accident might have occurred during the routine addition of iodine to flour. (An epidemic of thyrotoxicosis that occurred in Tasmania in the late 1960s was attributed to the addition of potassium iodate to commercially baked bread as a prophylactic measure against goiter.) They decided to conduct an etiologic study as the next logical step.

Question 13: Exactly what type of study would you propose? Why?

a. Additional in-depth interviews with the patients, perhaps as a group, since the investigators have speculations but no hypotheses supported by science, observation, or data.
b. A cross-sectional survey of a population-based sample of households in and around Luverne (questionnaire and blood for thyroid-function studies, iodine levels, and viral serology).
c. A retrospective cohort study. For example, define exposure as exposure to baked products that could contain toxic levels of iodine additives.
d. A prospective cohort study. For example, define exposure as exposure to baked products that could contain toxic levels of iodine additives.
e. A case-control study. For example, case-patients and control subjects would be asked about exposure to baked products and other foods which could contain toxic levels of iodine additives.
f. Random testing of all foods and liquids found in case-patients' kitchens for iodine levels and viral cultures.

PART IV

The investigators decided to carry out a case-control study. Case-patients were selected for the study if their illnesses fulfilled the case definition and if they had experienced the onset of symptoms in the previous six months. In households with more than one patient, only the family member with the earliest onset of symptoms was included in the study. The first 44 patients who met these criteria were enrolled.

Question 14: Do you agree with the decision to include only the earliest affected family member? Why or why not?

Question 15: Whom might you select as controls?

Question 16: What exposures would you ask about in the study?

PART V

Control subjects for the case-control study were randomly selected from local telephone directories and were matched to case-patients according to the following criteria: the same sex and telephone exchange, and age within 10 years of the corresponding patient if the patient was 30 years of age or older, and within 5 years if the patient was under 30 years of age.

Just as the case-control study was getting under way, a new case-patient was diagnosed in Sioux Falls and was interviewed by some members of the investigative team. The woman, age 25, clearly had painless thyroiditis and hyperthyroidism. She lived in Sioux Falls but frequently visited a grocery store in Valley Springs, S.D., which her father owned. She sometimes purchased groceries there. Team members went to the store and interviewed the proprietor. All goods in the store were obtained from national distribution systems except two – chicken eggs and beef trimmings. The beef trimmings were obtained from a plant near Luverne. Some team members began to suspect that ingestion of beef may have been the source of the outbreak. They hypothesized that iodine contaminated the beef trimmings during processing, where it may have been used as a disinfectant.

Then, during the case-control study, one investigator visited a family of four people where all members of the family except one had illness fulfilling the case definition. The one unaffected member was a young boy who was a vegetarian. The family obtained its meat from the Luverne beef plant.

The results of the case-control study became available. The study showed that two factors were associated with illness – consumption of commercially processed chicken (odds ratio 2.3, p=0.03) and consumption of ground beef prepared by the Luverne plant (odds ratio 1.9, p=0.05). However, during the study, case-patients were not asked about the source of their beef in a uniform way; some team members suspected information bias.

Question 17: How would you obtain further data to test the hypothesis that ingestion of beef or poultry is the cause of the outbreak?

PART VI

The investigators decided to conduct a second case-control study to rule out any effect of information bias on the first case-control study and to obtain more information on specific exposures such as type of beef (hamburger, steak, roast) usually consumed and source of beef. The chicken was not implicated in the second study. Some of the results of the second case-control study are shown in Table 5.

Table 5. Matched-pair odds ratios for thyrotoxicosis and meat consumption

Factor	Matched-pair odds ratio
Ate hamburger from Plant A beef trim	23.0
Ate hamburger from privately slaughtered beef	0.08
Ate roast beef from Plant A	0.8
Ate roast beef from privately slaughtered beef	0.4
Ate steak from Plant A	0.9
Ate steak from privately slaughtered beef	0.6

Question 18: Interpret these results. How would you interpret the odds ratio of 0.08 for eating hamburger from privately slaughtered beef?

Question 19: What elements of causality, if any, were missing from the hamburger-thyrotoxicosis association at this point?

Question 20: What would be your recommendation regarding the beef plant now?

Question 21: In this setting, describe the jurisdictions and responsibilities of:

a. the State Epidemiologist.
b. the State Veterinarian.
c. CDC.
d. the United States Department of Agriculture.
e. the Food and Drug Administration.

PART VII - CONCLUSION

Investigators went to the Luverne plant. The following is excerpted from a report of the plant investigation:

"Two work shifts per day operated at Plant A, and approximately 800 animals were slaughtered and dressed during each shift. Before April 1983, thyroid glands were selectively removed and sold for use in the manufacture of thyroid extract. After that time, 'gullet trimming' was employed to harvest muscle from the bovine larynx. In this procedure, the larynx was placed vertically on a peg 1 meter above the floor. The sternothyroid and sternohyoid muscles were removed from the larynx with a downward slicing motion... This motion allowed portions of both lobes of the thyroid gland to be inadvertently included in the muscle trimming... Although the process of gullet trimming was performed by a limited number of employees, the presence of thyroid tissue in the neck trimmings could not be attributed to any one employee.

"...Among the 22 boxes of beef trimmings produced before the recall that were examined, thyroid tissue was found in all....No thyroid tissue was found in four boxes produced after gullet trimming was discontinued.

"When samples of the implicated beef were fed to volunteers, significant elevations of T_4 and T_3 occurred.

"On August 29, 1985, because of this investigation, the USDA issued a nationwide advisory that temporarily prohibited gullet trimming in all USDA-inspected plants that slaughter beef and pork."

That prohibition was later made permanent.

Reference

Hedberg CW, Fishbein DB, Janssen RS, Meyers B, et al. An outbreak of thyrotoxicosis caused by the consumption of bovine thyroid gland in ground beef. *N Engl J Med* 1987;316:993-8.