CENTERS FOR DISEASE CONTROL, EPIDEMIC INTELLIGENCE SERVICE
New England Epidemiology Institute, 1992

AN EPIDEMIC DISEASE IN SOUTH CAROLINA

Objectives

After completing this case study, the student should be able to:

1. Apply the principles of descriptive epidemiology (time, place, person) in the investigation of a disease outbreak.
2. Characterize the epidemiology of a disease with appropriate tables, graphs, and charts, and generate hypotheses related to etiology.
3. Portray the relationships between descriptive epidemiologic characteristics and their roles in disease transmission and pathogenesis.

PART I

Note to Participants

You may be familiar with this epidemic from previous courses or reading. In the spirit of the "unknown" nature of this exercise, please do not reveal the identity or etiology of this disease to your colleagues.

INTRODUCTION

Over a period of years, physicians in the rural southeastern United States reported the occurrence of a disease that had not been recognized previously. Since reporting was required in only one state, and since medical services were limited, recording of the incidence of this disease was irregular.

BACKGROUND

The disease in question, although easily diagnosed on clinical grounds, was of unknown etiology at the time. Pathogenesis, mode of spread, immunity, and the role of social and environmental factors were matters of controversy. Many theories concerning the nature of the disease were proposed.

In an effort to determine the extent of the disease, a questionnaire was mailed to all practicing physicians in eight states in the Southeast regarding the number of cases they had seen in the preceding 5 years. Only one-fourth of the physicians responded. They reported an increase from 622 to 7,017 cases over the 5-year interval.

The following year, a U.S. Public Health Service epidemiologist was assigned to investigate the epidemic. After some preliminary observations, a field survey was conducted to determine the extent and the nature of the disease.

QUESTION 1: Into what general etiologic categories might one divide diseases that can occur in epidemic form?

INVESTIGATION

The survey was conducted in a five-county region in northwestern South Carolina where the disease was prevalent. The survey area included 24 mill towns with populations from 500 to 1,500. These villages varied widely in their sanitary status. Some had public water supplies, some had sewage systems, some had both, and some had neither. The survey was confined to a single racial group and comprised primarily wage earners and their families.

In each village, bi-weekly visits were made to each household over a period of 1 year to look for cases. The name, age, gender, and marital status of each member were recorded. The occurrence of the disease was determined by history and examination. Questionable cases were referred to one of the directors of the study who had considerable experience in diagnosing the disease.

QUESTION 2: What categories of information would you want in order to characterize the epidemic?

QUESTION 3: Review and graph the data in Tables 1 and 2.

QUESTION 4: Discuss the epidemiologic characteristics of the disease illustrated in your graphs.

Table 1
Cases of The Disease by Month of Onset in 24 Villages
Surveyed for One Year (Population 22,653)

Month	Number of cases	Rate per 1000*
January	0	0
February	4	0.2
March	28	1.2
April	120	5.5
May	310	13.7
June	432	19.7
July	154	6.8
August	57	2.5
September	28	1.3
October	14	0.6
November	0	0
December	0	0

* Adjusted to 31-day month.

Note: In individual villages, incidence peaked in different months.

Table 2
Incidence of The Disease by Age and Gender
in 24 Villages Surveyed for One Year

Age group (years)	Males			Females		
	Population*	# Cases	Rate per 1,000	Population*	# Cases	Rate per 1,000
<1	327	0	0	365	0	0
1	233	2	8.6	205	1	4.9
2	408	30	73.5	365	16	43.8
3	368	26	70.7	331	28	84.6
4	348	33	94.8	321	32	99.7
5 - 9	1,574	193	122.6	1,531	174	113.7
10 - 14	1,329	131	98.6	1,276	95	74.5
15 - 19	1,212	4	3.3	1,510	17	11.3
20 - 24	1,055	1	.9	1,280	51	39.8
25 - 29	882	1	1.1	997	75	75.2
30 - 34	779	4	5.1	720	47	65.3
35 - 39	639	4	6.3	646	51	78.9
40 - 44	469	10	21.3	485	34	70.1
45 - 49	372	7	18.8	343	18	52.5
50 - 54	263	13	49.4	263	12	45.6
55 - 59	200	5	25.0	228	6	26.3
60 - 64	164	9	53.6	153	3	19.6
65 - 69	106	4	37.7	105	2	19.1
≥70	80	6	75.0	114	2	17.5
Total	10,812	483	44.7	11,238	664	59.1

* As enumerated between May 1 and July 15.

QUESTION 5: Using Table 3 below, compare the rates of disease between married and single women.

Table 3
Incidence of The Disease Among Women by Marital Status and by Age

Age group (years)	Married women			Single women		
	Population	# Cases	Cases per 1,000 pop.	Population	# Cases	Cases per 1,000 pop.
16-29	1,905	89	46.7	1,487	16	10.7
30-49	1,684	98	58.2	141	4	28.4
50+	387	4	10.3	26	0	0
Total	3,976	191	48.0	1,654	20	12.1

QUESTION 6: Using Table 4, calculate the overall attack rates for:

a. Mill workers and non-mill workers (regardless of gender).
b. Female mill and non-mill workers.
c. Male mill and non-mill workers.

Table 4
Incidence of The Disease by Occupation, Age, and Gender

Gender	Mill worker?	Age group (years)	Ill	Well	Total	Attack rate (%)
Female	Yes	<10	0	0	0	-
		10-19	2	330	332	0.6
		20-29	4	194	198	2.0
		30-44	2	93	95	2.1
		45-54	0	9	9	0
		>55	0	5	5	0
Female	No	<10	28	577	605	4.6
		10-19	5	200	205	2.4
		20-29	12	204	216	5.6
		30-44	16	220	236	6.8
		45-49	4	91	95	4.2
		>55	1	92	93	1.1
Male	Yes	<10	0	0	0	-
		10-19	3	355	358	0.8
		20-29	1	361	362	0.3
		30-44	3	318	321	0.9
		45-54	0	93	93	0
		>55	1	51	52	1.9
Male	No	<10	23	629	652	3.5
		10-19	4	161	165	2.4
		20-29	1	12	13	7.7
		30-44	0	10	10	0
		45-54	1	14	15	6.7
		>55	4	26	30	13.3

QUESTION 6d: What other types of comparisons can be made using the data in Table 4?

Use Table 5 to answer the following questions.

QUESTION 7a: What is the overall attack rate for the disease in the community?

QUESTION 7b: What proportion of households are affected with the disease in the community?

QUESTION 7c: What is the risk that other individuals in a household that already has a case will also have the disease?

QUESTION 7d: What are the average household sizes for affected and for unaffected households?

Table 5
Population and Number of Households Affected by The Disease
Over a 9-Month Period in 7 South Carolina Villages

Total population	4,399
• Population in affected households	424
• Population in unaffected households	3,975
Total number of cases	115
• Number of first cases in affected households	77
• Number of additional cases in affected households (subsequent cases in a household after the first case)	38
Total number of households	798

QUESTION 7e: Interpret the above results.

The investigators analyzed the incidence of the disease by socioeconomic status, as shown in Table 6.

Table 6
Incidence of The Disease by Economic Status
in 24 Villages* Surveyed for 1 Year

Family socioeconomic status	Cases	Population	Rate per 1,000
Stratum 1 (lowest)	99	796	124.4
Stratum 2	240	2,888	83.1
Stratum 3	260	4,868	53.4
Stratum 4	177	5,035	35.2
Stratum 5	132	5,549	23.8
Stratum 6	23	1,832	12.6
Stratum 7 (highest)	2	769	2.6
Total	933	21,737	42.9

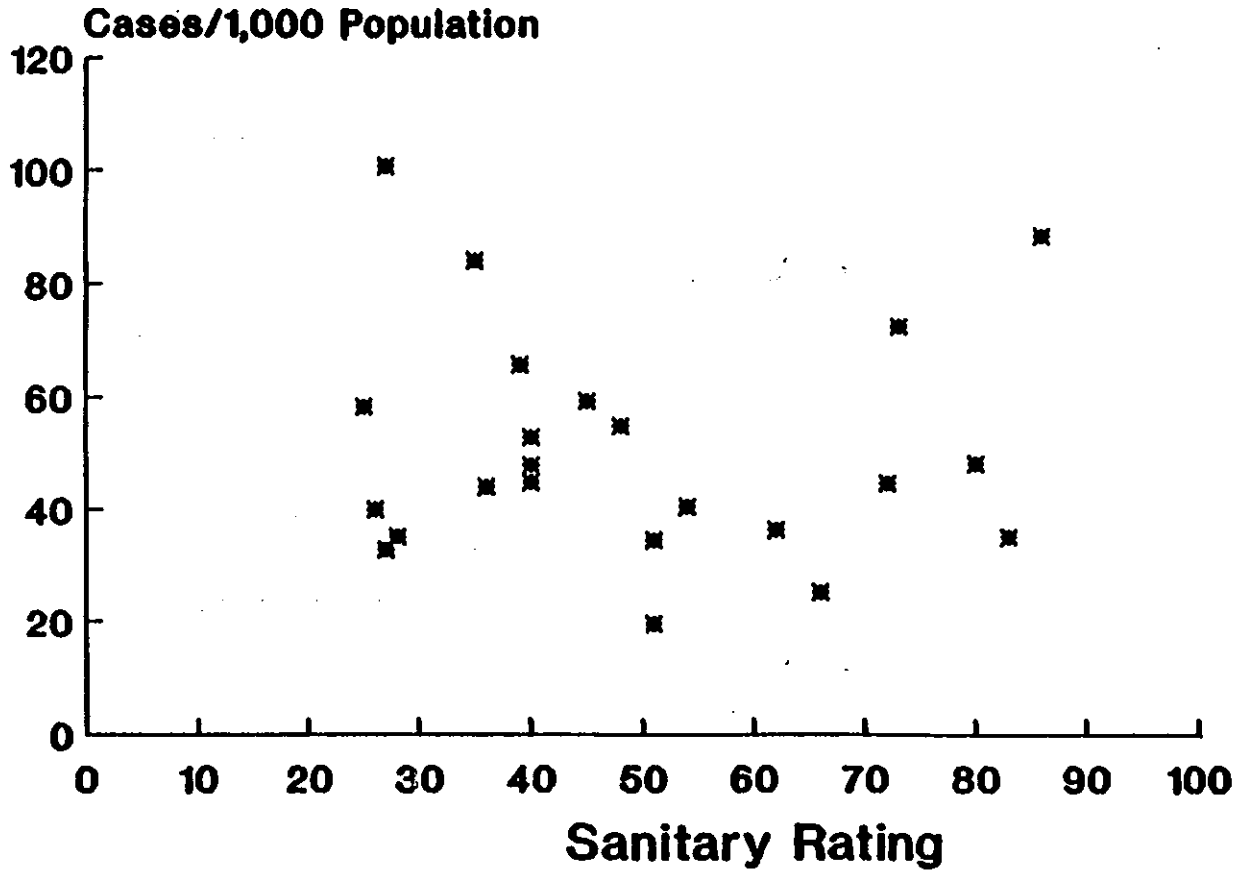
* Restricted to cases developing after 30 days of residence.

QUESTION 8a: Describe the effect of socioeconomic status, if any, on the disease.

QUESTION 8b: In general, what factors related to low socioeconomic status might influence the occurrence of disease?

The investigators also conducted sanitary surveys. Each village, as a unit, was rated for quality of general cleanliness, excreta disposal, and water supply. Figure 1 shows a scatter diagram of incidence of disease and sanitary rating for 24 villages. (On scatter diagram, high sanitary rating means good sanitation.)

Figure 1
Relationship of Incidence Rate of Unknown Disease
to Sanitary Rating of 24 Villages, South Carolina



QUESTION 9: Discuss the relationship between incidence of the disease and the sanitary rating.

QUESTION 10: Summarize the important epidemiologic characteristics of the disease determined at this point.

Two different commissions studied the evidence related to this disease. The first commission ended its investigation with these conclusions: "(1) According to the weight of evidence (the) disease (is) due to infection with a living micro-organism of unknown nature; (2) A possible location for this infection is the intestinal tract; and (3) Deficient animal protein in the diet may constitute a predisposing factor in the contraction of the disease."

Two years later, the second commission concluded that: "(1) The supposition that the ingestion of good or spoiled maize is the essential cause of (the disease) is not supported by our study; and (2) (The disease) is in all probability a specific infectious disease communicable from person to person by means at present unknown."

A year later, the commission presented the following at the annual meeting of the American Medical Association:

"In the group of incident cases most thoroughly studied, evidence of close association with a preexisting case was disclosed in more than 80 per cent.

"A house-to-house canvass of the homes of over 5,000 people living in six endemic foci of (the disease) failed to disclose any definite relation of the disease to any element of the diet.

"In these six villages new cases originated almost exclusively in a house in which a preexisting case was living, or next door to such a house, suggesting that the disease has spread from old cases as centers.

"So far as we have observed, (the disease) has spread most rapidly in districts where insanitary methods of sewage disposal have been in use."

QUESTION 11: For each of the epidemiologic characteristics of time, place, and person, which etiologic hypothesis (infectious vs. dietary) is more compatible with the data?

QUESTION 12: How might you test the infectious or dietary hypothesis about the cause of the disease?

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PART II

Many people postulated that an infectious agent was responsible for the disease. The epidemiologist carried out transmissibility studies that were described as follows:

> [The investigator] drew blood into a clean sterile syringe from the arm of a woman who was broken out and very sick with her first attack of [the disease] ... [He] shot a sixth of an ounce of the blood, still warm from the veins of the sick woman, under the skin of [his assistant's] left shoulder. [Then the assistant] shot a fifth of an ounce of the blood of the sick woman under the shoulder of [the investigator]. For two days the arms of these adventurers were stiff ... That was all.
>
> But [the investigator] was a glutton for proofs ... The [government] commission has said that [the disease] spread like typhoid fever, from the bowels of the suffering ones. On the 26th of April ... alone, he faced it... Here he stands, alone in this most grotesque of laboratories--the washroom of a Pullman car. Out of his pocket he takes a little vial. Into a pill mass with wheaten flour he makes up the contents of this tube--the intestinal discharge of a woman very sick with a true case of [the disease]. He swallows this dose. "And maybe the scales of the skin rash are contagious, too," says [the investigator], who is a thorough man. So for good measure he makes himself a powder from flour and the scaled-off skin from two more people sick with [the disease]. He swallows this powder...[1]

Using feces, urine, vomitus, and skin scales from patients, the investigator carried out additional similar experiments, called "filth parties," on himself and volunteers, including his wife and assistants. None of them came down with the disease.

In studies at mental institutions and orphanages where the disease was rampant, the investigator observed that none of the nurses or other ward personnel, even those attendants who lived on the ward, came down with the disease.

The investigator was convinced that this disease was not an infectious disease.

QUESTION 13: Do you agree with the investigator? Why?

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PART III

To investigate the possible role of diet, the investigators did a survey of all households in seven villages to compare the average daily consumption of various foodstuffs. Affected and non-affected households were identified. Table 8 shows the consumption pattern for four foods in these households.

Table 8. Consumption patterns of various foods by presence or absence of disease in the households in seven villages

	Affected	Non-affected	Total
Fresh meat			
high quantity	9	208	217
low quantity	52	472	524
TOTAL	61	680	741
Fresh milk			
high quantity	6	275	281
low quantity	50	396	446
TOTAL	56	671	727
Salt pork			
high quantity	29	289	318
low quantity	29	391	420
TOTAL	58	680	738
Syrup			
high quantity	18	231	249
low quantity	40	451	491
TOTAL	58	682	740

QUESTION 14: How would you analyze the data presented in Table 8?

QUESTION 15: Analyze the data in Table 8.

QUESTION 16: Interpret these results.

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PART IV - CONCLUSION

The disease under investigation was pellagra. Pellagra was virtually unknown in the United States until 1907, although sporadic deaths were reported in 1889 and 1902. The first epidemic of pellagra occurred at the Mount Vernon (Alabama) Asylum for Negroes in 1906, with 85 cases and 53 deaths. Although pellagra was thought to be most prevalent in Georgia, North Carolina, South Carolina, Florida, Alabama, Mississippi, and Louisiana, these states did not participate in national mortality registration. Nonetheless, the number of reported deaths from participating states rose from none in 1904 to 1,015 in 1913.

Dr. Joseph Goldberger was requested by the Surgeon General to investigate the pellagra problem in March 1914. At that time the two leading schools of thought were the Italians, who thought the disease was caused by spoiled corn, and the Americans, who thought it was an infectious disease. Three observations made Goldberger suspect a nutritional disease:

1. Although the disease was endemic in asylums, attendants and professionals had never contracted a single case.
2. The disease was almost exclusively confined to the poor.
3. The disease was most common in rural areas.

In June 1914, Goldberger published his first report on his observations at the asylum in Milledgeville, Georgia, noting that professionals and attendants did not get pellagra. He noted significant dietary differences in the habits of the patients and non-patients, especially with regard to consumption of meat and milk.

In 1915, Goldberger instituted an enriched feeding program in two Mississippi orphanages that had a pellagra prevalence of 47%. As a result, no cases of pellagra occurred the following year among 103 patients. Also in 1915, Goldberger visited the Rankin State Penitentiary in Mississippi where no case of pellagra had ever been reported. He induced pellagra after 5 1/2 months among six out of 11 inmates by placing them on a diet containing no meat, milk, or fresh vegetables.

In 1916, Goldberger began trials of pellagra transmission. Using himself, his wife, and 12 other volunteers, he injected blood from pellagrous patients into healthy people. He also consumed a mixture of feces, urine, vomitus, and skin scales from pellagrous patients. Neither he nor the other subjects developed pellagra. Later that year, he initiated his South Carolina mill-town study-- first in seven villages, later in 24 villages.

From 1918 to 1926, Goldberger conducted studies to find pellagra-preventing (P-P) factor. He initially focused on amino acids. Tryptophan was shown to have some effect in preventing pellagra. He found that dried yeast had highest P-P activity. P-P appeared to be a water-soluble, heat-resistant substance, possibly a new B vitamin.

Economic hypothesis concerning appearance of pellagra in United States

In the early 1900s, many families in the rural South migrated from farms to small mill villages, and became dependent on wage earnings as a source of income. During the period 1900-1913, wages increased by less than 25%. During the economic depression from 1906-1911, wages actually decreased.

At the same time, food prices increased dramatically. Average food prices increased 50% from 1900 to 1913. These price increases, coupled with a decrease in locally available food as wage earners left the farm, made certain foods difficult to obtain.

Pellagra presented a significant public health problem as late as 1940 when 2,138 deaths were recorded.

Suggested Reading

Schultz MG. Joseph Goldberger and pellagra. *Am J Trop Med Hyg* 1977;26(5):1088-92.

Reference

1. DeKruif P. Hunger fighters. New York: Harcourt, Brace & Co. 1928:335-70.

Table 9. Factors accounting for the observed epidemiologic characteristics of The Disease (pellagra)

	Observed epidemiologic characteristic		Explanation
TIME	Seasonal variation	Summer peak	Disease identified by rash; sunlight exacerbated rash (possible explanation).
PERSON	Age and gender distribution	No case-patients <1 year of age	Preferential milk supplements and breast feeding.
		Increased incidence among children 1-14 years of age	Rapid growth rate with increased nutritional needs.
		Increased incidence among females 20-50 years of age	Increased demands of childbearing years: menses, pregnancy, lactation. Within family, were least likely to get nutritious food.
		Increased incidence among males >50 years of age	Unlikely to get supplemental food since no longer working.
	Marital status	Married women at increased risk	Marriage, child-bearing (see above).
	Socioeconomic status	Incidence inversely related to socioeconomic status	Protective foods more expensive.
	Occupation	Increased incidence among non-mill workers	Mills provided supplemental food.
PLACE	Affected households	Increased incidence among household members of a case-patient	Similar diets.