



**Centers for Disease Control and Prevention
Epidemiology Program Office
Case Studies in Applied Epidemiology
No. 912-303**

Suspected Legionnaires' Disease in Bogalusa

Student's Guide

Learning Objectives

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

- Discuss the relationship between and roles of state-based and Atlanta-based EIS officers in a field investigation;
- Develop an epidemiologic case definition;
- Calculate power for a case-control study;
- Describe different sources of controls for a community-based outbreak.

This case study is based on an investigation conducted in 1989 by the Louisiana Department of Health and Hospitals and the Centers for Disease Control. This case study was developed in 1991 by Frank Mahoney, John Horan, and Richard Dicker. The current (1998) version was updated and edited by Richard Dicker, with comments and input from the 1998 EIS Summer Course instructors.



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



PART I

On October 31, 1989, the Louisiana Department of Health and Hospitals (LDHH) was notified by two physicians in Bogalusa, Louisiana that over 50 cases of acute pneumonia had occurred among local residents. Most cases had occurred within a 3-week interval from mid- to late October. All cases had occurred in adults. Six persons had died.

Clinical histories from several patients suggested that the illness may have been Legionnaires' disease, caused by infection with the bacterium *Legionella pneumophila*.

You are the EIS Officer assigned to the Epidemiology Section of the LDHH.

Question 1: If you had taken this call, what additional information would you request over the telephone?

Serologic testing of several patients during the initial phase of illness had been negative for *Legionella* antibody. No sputum specimens had

been collected for Legionnaires' testing, since the hospital's laboratory was not able to perform the tests.

Question 2: In general, besides a true outbreak, what else can account for a sudden increase in the number of cases of a particular disease to be reported to a health department?

Question 3: Assuming you will depart for Bogalusa to conduct a field investigation, what sorts of preparations do you need to make?

To refresh their knowledge of Legionnaires' disease, the investigators turned to **Control of Communicable Diseases in Man, fifteenth edition**, the edition available at the time. The following is abstracted from that handbook:

Legionnaires' disease, or legionellosis, is characterized by pneumonia caused by the bacterium Legionella pneumophila. The incubation period ranges from 2 to 10 days. The disease often begins with anorexia [loss of appetite], malaise [fatigue and overall sense of poor well-being], myalgias [muscle aches and soreness], and headache, followed by rapidly rising fever and chills. Chest X-rays typically show patchy areas of consolidation. The diagnosis is confirmed by:

- 1) isolation of the organism on special media; or
- 2) demonstration by immunofluorescent stain of involved tissue or respiratory secretions; or
- 3) fourfold or greater increase in titers between acute and convalescent phase serum samples, or
- 4) a single high titer (>1:256) in a patient with a compatible clinical course.

[In 1999, the diagnosis may be made by detecting antigens to serogroup 1 in urine.]

Cases of legionnaires' disease occur sporadically [individually] and in outbreaks. The reservoir of the causative organism is primarily aqueous, such as hot water systems, air conditioning cooling towers, and evaporator condensers. The mode of transmission is

airborne via aerosol-producing devices. Risk factors for serious illness include increasing age, especially in smokers; diabetes, chronic lung disease, renal disease or cancer; or immunocompromised patients. The usual male-to-female ratio is about 2.5:1.

Bogalusa is located in Washington Parish and has a population of about 16,000 persons. The largest employer is a paper mill located in the center of town adjacent to the main street. The paper mill includes five prominent industrial cooling towers. The mill also has three paper machines that emit large volumes of aerosol along the main street in town. Many persons suspected the cooling towers and/or paper machines to be the cause of the outbreak, since they were prominent sources of outdoor aerosols. Attention was also directed at a few public buildings with cooling towers, since they were potential sources of indoor aerosol.

Bogalusa is served by a 98-bed private hospital (hospital A) and a 60-bed public hospital (hospital B). Three additional hospitals are located in the surrounding parish. All of the reported cases were from Hospital A.

The number of patients discharged with a diagnosis of pneumonia at Hospital A since January 1986 is shown in Table 1. Between January 1986 and September 1989, only one pneumonia patient had been diagnosed as having Legionnaires' disease.

Table 1. Number of Patients with a Diagnosis of Pneumonia Discharged from Hospital A by Month, 1986-1989

	<u>1986</u>	<u>1987</u>	<u>1988</u>	<u>1989</u>
January	12	20	21	16
February	14	19	26	19
March	7	21	8	27
April	12	10	11	13
May	8	10	10	9
June	4	11	11	6
July	5	5	9	8
August	5	9	12	7
September	6	7	13	8
October	15	8	10	70
November	?	8	11	
December	?	11	20	
Total	88	139	162	183

Review of charts of pneumonia patients at Hospital A during October revealed that many patients had fever, weakness, lethargy, and mental confusion. Some patients had a dry cough, and several reported having watery

diarrhea. Chest X-rays showed patchy infiltrates indicative of pneumonia. Most patients were residents of Bogalusa or the surrounding areas of Washington Parish.

Question 4: Develop a case definition for this outbreak.

Question 5: Would you look for additional cases? How? Do you need to find every case?

Question 6: You are asked to address the hospital staff. What might you tell them?

Discussions were held among staff of the LDHH and the CDC. LDHH felt capable of conducting the epidemiologic investigation, but requested assistance with laboratory support. CDC proposed that an EIS Officer from Atlanta assist

in the epidemiologic investigation and that CDC provide laboratory support. The field investigation team arrived in Bogalusa on November 8.

Question 7: Given that Louisiana had its own epidemiologists including a field EIS officer, what issues should be decided up front?

PART II

Discussions were held among staff of the Louisiana health department and the CDC. The health department felt capable of conducting the epidemiologic investigation, but requested assistance with laboratory support. A second EIS Officer was sent from Atlanta to assist in the investigation, and CDC provided laboratory support. The field investigation team arrived in Bogalusa on November 8.

The investigators set up active surveillance for case-finding at all five local hospitals in the Bogalusa area. In addition, they used a standard questionnaire to abstract information from the medical records of all persons admitted or discharged with a diagnosis of pneumonia, respiratory distress, or possible Legionnaires' disease (LD) since October 1, 1989.

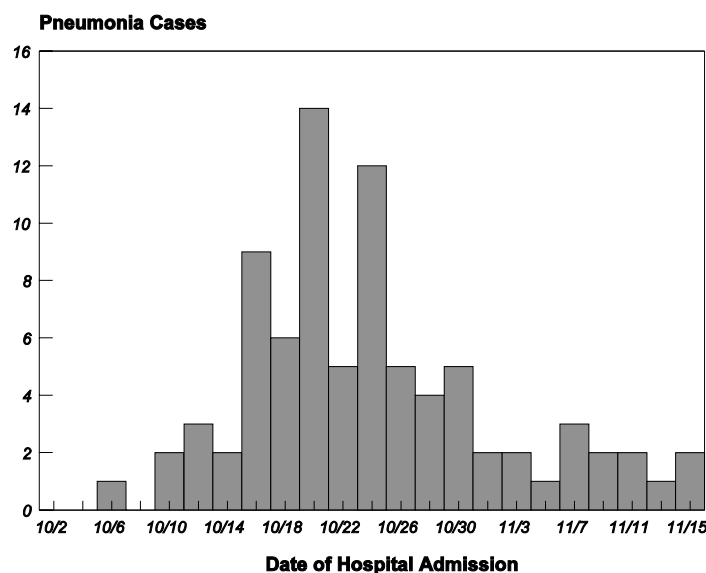
Investigators defined a possible case of LD as an illness in a resident or visitor of Washington Parish, ≥ 20 years of age, admitted to one of the 5 local hospitals after October 1, 1989, with an X-ray consistent with pneumonia. A confirmed case had to meet the criteria for a possible

case, plus have laboratory evidence of LD (four-fold rise in antibody titer, a single convalescent antibody titer $\geq 1:256$, positive urine antigen test, positive sputum culture, or positive biopsy).

By November 19, investigators had identified 83 patients who met the definition of possible LD (Figure 1). Fourteen of these patients had died without Legionella testing. Of the 83, 65% were female, and 28% were African-American. About three-fourths of the case-patients were residents of Bogalusa; about half (41) resided on the east side of town. Most case-patients had been admitted to the hospital in mid-October; few if any new cases were occurring in mid-November (Figure 1). To date, no sputum culture had shown growth for LD or other pathogens.

Before designing the analytic portion of the investigation, the investigators considered their leading hypotheses.

Figure 1. Number of cases of pneumonia by date of hospital admission, Bogalusa, 1989



Question 8: How does one generate plausible hypotheses to test in this type of investigation?

At this point in the investigation, the leading hypothesis was outdoor exposure to cooling towers, primarily because previous studies had demonstrated the role of cooling towers as sources of the *Legionella pneumophila* in other outbreaks, and there were several such towers in the town. However, rather than jumping to

conclusions based on this information alone, investigators began to compile a list of retail stores and other establishments which were frequently mentioned by some of the case-patients who had been interviewed. The investigators also noted the unusual preponderance of female cases.

Question 9: In this setting, what type of study would you use to test your hypotheses?

PART III

The investigators decided to conduct a case-control study to test their hypotheses. Sixty-six persons met the case definition for a possible case and were still alive. Laboratory results had

come back confirming Legionnaires' disease in 15 of these patients, and ruling out Legionnaires' disease in 10. Laboratory results for the remainder were pending.

Question 10: What case definition would you use for the case-control study?

Question 11: How does one go about determining an appropriate number of controls? What factors go into this determination?

Question 12: What are some possible sources of controls?

PART IV

The investigators decided to select controls from office records of physicians who admitted the cases.

Before conducting a study of a small number of cases, it is often useful to calculate the power or ability of a study to detect, at a statistically significant level, a particular odds ratio or difference between cases and controls.

The statistical power of a case-control study is influenced by 5 factors:

1. **n**, the number of cases;
2. **c**, the number of controls per case;
3. **OR**, the odds ratio in the source population worth detecting;

4. **p₀**, the proportion of exposed non-cases in the source population;
5. **α ("alpha")**, the desired level of significance. The corresponding 2-tailed **Z_α** from the normal distribution is used in the formulas, e.g., for α = 0.05, Z_α = 1.96.

The calculation of a study's power involves two steps. First, we calculate **Z_β** ("Z-beta"). Second, we determine the POWER, which is equal to 1-β, by looking up in a table of standard normal cumulative probabilities the cumulative probability associated with that Z_β.

A formula for calculating Z_β, with n cases and c controls per case, is given by:

$$Z_{\beta} = [n(p_1 - p_0)^2 / pq(1 + 1/c)]^{1/2} - Z_{\alpha}$$

where $p_1 = p_0 \text{OR} / [1 + p_0(\text{OR} - 1)]$ = proportion of cases exposed

$p = (p_1 + cp_0) / (1 + c)$ = proportion of all subjects exposed

and $q = 1 - p$

EXAMPLE

Suppose you were designing the case-control study to test the association between exposure to a particular water tower and Legionnaires' disease. You figure that you could enroll about 50 of the cases, and that about 14% of the town's population is exposed to the water tower in question. You might be able to afford (in terms of time and resources) to enroll 3 controls per case, and you were indoctrinated that α is always 0.05. Calculate the study's power to detect a true odds ratio of 2.0.

Given: n = 50, c = 3, p₀ = 0.14, and OR = 2.0

$$p_1 = (0.14)(2.0) / [1 + 0.14(2.0 - 1)] = 0.246$$

$$p = [0.246 + (3)(0.14)] / (1 + 3) = 0.167$$

$$q = 1 - 0.167 = 0.834$$

$$Z_{\beta} = [50(0.246 - 0.14)^2 / (0.167)(0.834)(1 + 1/3)]^{1/2} - 1.96 = -0.221$$

$$\text{POWER } (1-\beta) = \text{cumulative probability of } -0.221 = 0.413$$

In other words, a study of 50 cases and 150 controls would be expected a priori (that is, based on the estimated exposure to the water tower of 14%) to have an approximately 41% chance of detecting a statistically significant association in the study, if the underlying association between water tower exposure and Legionnaires' disease in the population were 2.0.

Question 13: Using the formulas above, calculate the power of the study to detect an odds ratio of 2, 3, or 4 at an alpha of 0.05 using 2 controls per case, as indicated in the table below.

Table 2. Statistical Power of a Case-Control Study with $n=50$, $p_0=0.14$, and $\alpha=0.05$, for different control-to-case ratios and underlying associations

	Control-to-Case Ratio				
	1	2	3	4	10
OR = 2 ($p_1 = 0.246$)	0.25		0.41 (example)	0.45	0.51
OR = 3 ($p_1 = 0.328$)	0.59		0.82	0.84	0.88
OR = 4 ($p_1 = 0.394$)	0.84		0.96	0.97	0.98

Question 14: Discuss the pattern illustrated by the power estimates in the table.

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Z	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09
-3.8	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
-3.7	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
-3.6	0.0002	0.0002	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
-3.5	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002
-3.4	0.0003	0.0003	0.0003	0.0003	0.0003	0.0003	0.0003	0.0003	0.0003	0.0002
-3.3	0.0005	0.0005	0.0005	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004	0.0003
-3.2	0.0007	0.0007	0.0006	0.0006	0.0006	0.0006	0.0006	0.0005	0.0005	0.0005
-3.1	0.0010	0.0009	0.0009	0.0009	0.0008	0.0008	0.0008	0.0008	0.0007	0.0007
-3.0	0.0013	0.0013	0.0013	0.0012	0.0012	0.0011	0.0011	0.0011	0.0010	0.0010
-2.9	0.0019	0.0018	0.0018	0.0017	0.0016	0.0016	0.0015	0.0015	0.0014	0.0014
-2.8	0.0026	0.0025	0.0024	0.0023	0.0023	0.0022	0.0021	0.0021	0.0020	0.0019
-2.7	0.0035	0.0034	0.0033	0.0032	0.0031	0.0030	0.0029	0.0028	0.0027	0.0026
-2.6	0.0047	0.0045	0.0044	0.0043	0.0041	0.0040	0.0039	0.0038	0.0037	0.0036
-2.5	0.0062	0.0060	0.0059	0.0057	0.0055	0.0054	0.0052	0.0051	0.0049	0.0048
-2.4	0.0082	0.0080	0.0078	0.0075	0.0073	0.0071	0.0069	0.0068	0.0066	0.0064
-2.3	0.0107	0.0104	0.0102	0.0099	0.0096	0.0094	0.0091	0.0089	0.0087	0.0084
-2.2	0.0139	0.0136	0.0132	0.0129	0.0125	0.0122	0.0119	0.0116	0.0113	0.0110
-2.1	0.0179	0.0174	0.0170	0.0166	0.0162	0.0158	0.0154	0.0150	0.0146	0.0143
-2.0	0.0228	0.0222	0.0217	0.0212	0.0207	0.0202	0.0197	0.0192	0.0188	0.0183
-1.9	0.0287	0.0281	0.0274	0.0268	0.0262	0.0256	0.0250	0.0244	0.0239	0.0233
-1.8	0.0359	0.0351	0.0344	0.0336	0.0329	0.0322	0.0314	0.0307	0.0301	0.0294
-1.7	0.0446	0.0436	0.0427	0.0418	0.0409	0.0401	0.0392	0.0384	0.0375	0.0367
-1.6	0.0548	0.0537	0.0526	0.0516	0.0505	0.0495	0.0485	0.0475	0.0465	0.0455
-1.5	0.0668	0.0655	0.0643	0.0630	0.0618	0.0606	0.0594	0.0582	0.0571	0.0559
-1.4	0.0808	0.0793	0.0778	0.0764	0.0749	0.0735	0.0721	0.0708	0.0694	0.0681
-1.3	0.0968	0.0951	0.0934	0.0918	0.0901	0.0885	0.0869	0.0853	0.0838	0.0823
-1.2	0.1151	0.1131	0.1112	0.1093	0.1075	0.1056	0.1038	0.1020	0.1003	0.0985
-1.1	0.1357	0.1335	0.1314	0.1292	0.1271	0.1251	0.1230	0.1210	0.1190	0.1170
-1.0	0.1587	0.1562	0.1539	0.1515	0.1492	0.1469	0.1446	0.1423	0.1401	0.1379
-0.9	0.1841	0.1814	0.1788	0.1762	0.1736	0.1711	0.1685	0.1660	0.1635	0.1611
-0.8	0.2119	0.2090	0.2061	0.2033	0.2005	0.1977	0.1949	0.1922	0.1894	0.1867
-0.7	0.2420	0.2389	0.2358	0.2327	0.2296	0.2266	0.2236	0.2206	0.2177	0.2148
-0.6	0.2743	0.2709	0.2676	0.2643	0.2611	0.2578	0.2546	0.2514	0.2483	0.2451
-0.5	0.3085	0.3050	0.3015	0.2981	0.2946	0.2912	0.2877	0.2843	0.2810	0.2776
-0.4	0.3446	0.3409	0.3372	0.3336	0.3300	0.3264	0.3228	0.3192	0.3156	0.3121
-0.3	0.3821	0.3783	0.3745	0.3707	0.3669	0.3632	0.3594	0.3557	0.3520	0.3483
-0.2	0.4207	0.4168	0.4129*	0.4090	0.4052	0.4013	0.3974	0.3936	0.3897	0.3859
-0.1	0.4602	0.4562	0.4522	0.4483	0.4443	0.4404	0.4364	0.4325	0.4286	0.4247
0.0	0.5000	0.4960	0.4920	0.4880	0.4840	0.4801	0.4761	0.4721	0.4681	0.4641

* Use this table to find the power which corresponds to Z_{β} . For a given value of Z_{β} (say, -0.221), find that value to 1 decimal place in the left-most column (-0.2). The power will be in the -0.2 row. Now find the second decimal of your Z_{β} across the top row (0.02). The power is in that column. The power is at the intersection of the row and column you've identified (for -0.02 and 0.02, power = 0.41, or 41%).

PART V

The investigators decided to select two controls for each case from office records of the case-patient's physician. They enrolled a total of 28 cases and 56 controls. Cases and controls

were asked about exposures to cooling towers and nearby buildings. Some of these data are displayed in Table 3.

Table 3. Exposures to buildings, Legionnaires' disease outbreak, Louisiana, 1989

	Cases Exposed/Total (%)		Controls Exposed/Total (%)		Odds Ratio	P-value
<u>Indoor exposure to buildings with cooling towers</u>						
Retail Store A	3/28	(11%)	10/54	(19%)	0.5	0.5
Post Office	7/27	(26%)	12/50	(24%)	1.1	0.9
Hospital A	5/28	(18%)	12/54	(22%)	0.8	0.9
Hospital B	3/28	(11%)	7/56	(13%)	0.8	1.0
Paper Mill	2/28	(7%)	4/56	(7%)	1.0	1.0
<u>Outdoor exposure to stores near paper mill cooling towers</u>						
Retail Store A	3/28	(11%)	10/54	(19%)	0.5	0.5
Retail Store B	10/28	(36%)	15/52	(29%)	1.4	0.7
Retail Store D	5/28	(18%)	7/54	(13%)	1.5	0.5
Retail Store E	6/28	(21%)	9/54	(17%)	1.4	0.8
Restaurant A	2/26	(8%)	5/52	(10%)	0.8	1.0
Bank A	11/28	(39%)	19/53	(36%)	1.2	0.9
Butcher Store A	12/27	(44%)	10/54	(19%)	3.5	0.03
Any of the above	19/28	(68%)	33/56	(59%)	1.5	0.6
<u>Outdoor exposure to stores near other large cooling towers</u>						
Drug Store A	7/28	(25%)	15/55	(27%)	0.9	1.0
Drug Store B	13/28	(46%)	20/54	(37%)	1.5	0.6
Doctors Plaza A	2/27	(7%)	8/56	(14%)	0.5	0.5
Retail Store F	4/28	(14%)	6/54	(11%)	1.3	0.7
<u>Exposure to stores frequently reported by case-patients</u>						
Grocery Store A	25/27	(93%)	28/54	(52%)	11.6	<0.01
Grocery Store B	19/28	(68%)	23/54	(43%)	2.9	0.05
Retail Store C	22/28	(79%)	30/54	(56%)	2.9	0.07

Question 15: Interpret these data.

PART VI

Additional epidemiologic analysis demonstrated a dose-response relationship between time spent in grocery store A and risk of disease. The investigators visited grocery store A and looked for potential sources of aerosolized water. An ultrasonic mist machine was operating over one section of the produce display. No one at grocery store A was familiar with the maintenance or operation of this

machine. Permission was obtained to culture a specimen of water from the reservoir of the misting device. The culture from the misting device contained *Legionella pneumophila* serotype 1 (LP-1). Cultures from various cooling towers around town also contain LP-1, but of different subtypes. The investigators were suspicious that this misting device may have been related to the outbreak.

Question 16: Do you think the basic criteria for causation have been satisfied?

Four additional activities were undertaken. A serosurvey was conducted among all grocery store employees in Bogalusa to determine antibody status against LP-1. A second case-control study was undertaken to determine if exposure to the misting device was associated with developing LD. Ten similar misting devices from other parts of the country were cultured. The investigators asked for permission to perform autopsies on two patients who had died of pneumonia early in the epidemic.

Employees at grocery store A were more likely to have elevated antibody titers (≥ 128) to

Legionella than employees at the other grocery stores (13/48 versus 7/75, prevalence ratio=2.9, $p=0.02$.) Analysis of the second case-control study revealed a significant association between disease and purchasing produce which was nearest the mister. Of the 10 mist machines from other parts of the country, 6 grew *Legionella*. Lung tissue from the two autopsied patients revealed *Legionella* of the same subtype as that found in grocery store A.

Until now, the news media had not been aware of the outbreak, the investigation, or the results.

Question 17: Who needs to know about these findings? How would you go about reporting the findings?

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PART VII - CONCLUSION

The investigators concluded that the misting device was the source of aerosols that caused the outbreak. They were reluctant to publish the results until the laboratory was able to demonstrate that viable *Legionella* could be isolated from aerosols produced by the machine. This was expected to take several weeks. In mid-December, the machine was removed from grocery store A and sent to CDC for further study. Since it was apparent that other mist machines were likely to be contaminated with *Legionella*, the FDA was notified. The FDA developed guidelines for maintaining these mist machines. In early January, the Bogalusa newspaper printed the first article about the outbreak, without knowing its cause. This story was quickly picked up by the New Orleans paper and national news services. Soon, Bogalusa was overrun by reporters wanting to find out the cause of the outbreak. They focused their attention on the paper mill in the center of town, and demanded to know the culture results from the cooling towers.

The LDHH Department issued a press release and a telephone message describing the mist machine findings. Grocery industry officials were notified about the potential problem in trade newspapers and at meetings. The telephone message became public and was widely quoted in newspaper articles.

The type of misting device implicated in the outbreak was new to the grocery industry. These misters produced a visible fog that attracted shoppers, but had no other practical use. They did not help to preserve produce. The health department received reports of similar types of machines used in other settings, such as amusement parks and indoor aquariums. The findings were published in the *MMWR* after laboratory staff were able to isolate *Legionella* organisms from aerosols produced by the machine.

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