1990 EIS SUMMER COURSE

LISTERIOSIS IN COSTA RICA

Objectives

Following this exercise, the student should be able to:

1. Describe CDC, State or Country, local and hospital roles and relationships during an investigation;
2. Describe uses and limitations of numerator data;
3. Describe sources and uses of data in a hospital-based investigation;
4. Formulate a case definition in an outbreak investigation;
5. Generate hypotheses regarding exposure and disease.

PART I

On July 27, 1989, the director of the laboratory at the National Children's Hospital, a referral hospital in San Jose, Costa Rica, visited the CDC while attending a meeting in Atlanta. She wanted to discuss 8 babies who had been treated at the Children's Hospital for listeriosis so far that summer. The babies had been delivered at General Hospital A, were sent home apparently well, and then presented to the Children's Hospital a few days later. One infant died and one became paralyzed from an intracranial hemorrhage. The laboratory director wants to know if the CDC can help investigate the problem. She will call from Costa Rica on her return to discuss the cluster of cases.

QUESTION 1: What questions might you ask in a conference call with the laboratory director?

The Children's Hospital is a 400 bed pediatric referral hospital with no obstetrical services. The Children's Hospital draws patients from all of Costa Rica. The microbiology lab there reports 2-3 isolates of Listeria monocytogenes per year.

General Hospital A is a 1000 bed public facility with adult and pediatric services. The laboratory in General Hospital A reports 1-2 isolates of listeria per year in all ages. Approximately 10,000 babies are delivered each year in General Hospital A. Their obstetrical service performs the most deliveries of any hospital in San Jose, but there are several other hospitals with maternity services.

In the United States, perinatal listeriosis occurs in 12 infants/100,000 live births.

QUESTION 2: What factors might account for the apparent increase in L. monocytogenes isolates?

QUESTION 3: Do you think there is a real outbreak? Is there sufficient evidence to pursue the investigation?

On August 3, 1989, after the lab director has discussed the outbreak further with the infection control committee, obstetrical service, laboratory director and hospital administrator at General Hospital A, the CDC was invited to assist in an epidemiologic investigation. On August 7 an invitation from the Ministry of Health arrived at CDC and an EIS officer departed for Costa Rica the same day.

QUESTION 4: Place yourself in the role of the EIS officer. What would you do before you got on the plane? With whom would you want to meet upon your arrival in Costa Rica?

QUESTION 5: What initial information and materials would you seek?

At both the Children's Hospital and General Hospital A, L. monocytogenes is identified using gram stain, beta-hemolysis, motility, and a standard panel of biochemical tests. The Children's hospital had isolated L. monocytogenes from blood and/or spinal fluid of 10 infants in 1989. The monthly isolations are shown below.

Listeria isolated from CSF and blood,
Costa Rican Children's Hospital, 1989

Month (1989)	LM culture from CSF	LM culture from blood	Other organism from CSF
January	1	0	1
February	0	0	9
March	0	0	14
April	0	0	16
May	0	1	13
June	7	5 *	11
July	0	0	19

* 4 of these 5 patients also had L. monocytogenes in CSF

All 8 infants from whom L. monocytogenes was isolated at the Children's Hospital in June had been delivered at the General Hospital A. The infants with listeriosis in January and May had been delivered at Hospitals B and C, and had listeriosis at birth.

General Hospital A had isolated L. monocytogenes from 3 additional infants (two in June and one in July) and from one adult in 1989. No other hospitals in the area had isolated L. monocytogenes during 1989.

QUESTION 6: What rates might you want to examine to further evaluate the situation? What would you use as your denominator(s)?

There are two distinct forms of perinatal listeriosis: early and late onset disease. Early onset disease arises from transplacental transmission of Listeria. Intrauterine infection may result in stillbirth, preterm labor, or an infant who is born with neonatal sepsis. The vast majority of infants with early onset disease present with symptoms within 24 hours of birth. Clusters of early onset listeriosis can herald the presence of a community outbreak of foodborne disease; pregnant women who eat a contaminated food may deliver an infant with early onset disease 2-6 weeks later.

A second form of perinatal listeriosis, late onset disease, occurs in infants who are born well and present with illness several days to several weeks after birth. Late onset infection can be due to nosocomial exposures or exposures encountered in the home environment after birth. Clusters of late onset infection are usually nosocomial, but little is known about transmission and risk factors. Although the incubation period for late onset disease is not known, it probably is greater than 2 days.

After review of surveillance and laboratory information, the EIS officer decided to focus the investigation on the infants born at General Hospital A. Information on monthly deliveries of live infants, premature deliveries, and stillbirths were collected from the obstetrical service at Hospital A.

Month (1989)	Infants born at Hosp A with lab confirmed listeriosis	Total live births	Attack rate
January	0	744	____
February	0	666	____
March	0	694	____
April	0	770	____
May	0	903	____
June	10	577	____
July	1	780	____
Total	11	5134	____

Month (1989)	Prematurity births #	Rate	Stillbirths #	Ratio
January	52	____	95	____
February	59	____	82	____
March	48	____	90	____
April	54	____	100	____
May	62	____	115	____
June	41	____	73	____
July	62	____	98	____
Total	378	____	653	____

QUESTION 7: **Calculate monthly and overall attack rates of listeriosis at Hospital A. Calculate the monthly and overall rates of premature births at hospital A. Calculate the monthly and overall ratio of stillbirth to total live births.**

QUESTION 8: **Interpret these data.**

QUESTION 9: **What information about the case-patients would you collect?**

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PART II

The following line listing presents some of the information collected on infants born at General Hospital A with neonatal listeriosis.

Line listing

ID	Sex	Culture date	Symptom date	DOB	Delivery type	Delivery site	Outcome	Admitting symptoms
10	F	6/2	6/2	6/2	spont	Del rm	Lived	dyspnea
01	M	6/8	6/8	6/2	c-section	OR	Lived	fever
08	F	6/15	6/15	6/8	spont	Emerg rm	Died	dyspnea
02	F	6/15	6/12	6/8	spont	Del rm	Lived	fever
11	F	6/15	6/15	6/11	c-section	OR	Lived	dyspnea, pneumonia
03	F	6/22	6/20	6/14	c-section	OR	Lived	fever
04	M	6/22	6/21	6/14	spont	Del rm	Lived	fever
05	F	6/22	6/18	6/15	c-section	OR	Lived	fever
06	M	6/22	6/20	6/15	c-section	OR	Lived	dyspnea, pneumonia
07	M	6/23	6/19	6/16	forceps	Del rm	Lived	fever
12	M	7/21	7/21	7/21	spont	Del rm	Died	dyspnea

QUESTION 10: Construct an epidemic curve.

QUESTION 11: Analyze the cases in terms of time, place, and person. What hypotheses do these data suggest? (If none, how would you go about generating hypotheses?)

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PART III

In discussions with personnel at General Hospital A, the EIS officer learned that renovations in the obstetrical suites in the hospital had disrupted usual procedures during the month of June. During this time, the regular staff performed procedures in provisional rooms. The staff thought that the outbreak was somehow related to the renovations.

The very high attack rate and close temporal clustering of neonatal cases seemed most consistent with a continuing common source outbreak.

QUESTION 12: What type of study would you conduct to test this hypothesis?

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PART IV

The EIS officer decided to do a case control study to investigate potential exposures that might have caused the outbreak.

QUESTION 13: What case definition would you use?

QUESTION 14: How would you identify controls?

A case control study was performed. A nosocomial or outbreak-associated case was defined as an infant from whom L. monocytogenes was isolated from a sterile site more than 48 hours after birth. A random number table and the birth log book were used to select 36 control infants from among infants born between June 2 and June 23 (the period during which at least one outbreak-associated case or case-mother was in the hospital).

Some of the results are shown:

Exposure	Cases n=9 (%)	Controls n=36 (%)
Alcohol cord care	9 (100%)	36 (100%)
Ambu-bag resuscitation	2 (22%)	1 (3%)
Antibiotic eyedrops	9 (100%)	36 (100%)
Banked human milk	1 (11%)	2 (5%)
BCG injection	7 (78%)	25 (69%)
Caesarian delivery	5 (55%)	9 (25%)
General anesthesia	5 (55%)	8 (22%)
Intravenous catheter	0 (0%)	0 (0%)
Intrapartum antibiotics	0 (0%)	7 (19%)
Mineral oil bath	9 (100%)	36 (100%)
Suction equipment	2 (22%)	3 (8%)
Supplemental oxygen	3 (33%)	6 (17%)
Vitamin K injection	9 (100%)	36 (100%)

QUESTION 15: Construct 2-by-2 tables for the information presented above. Calculate measures of association.

QUESTION 16: Is the information consistent with a common source outbreak?

QUESTION 17: What hypotheses could explain the observation that cases and controls did not differ significantly in exposure to the items listed?

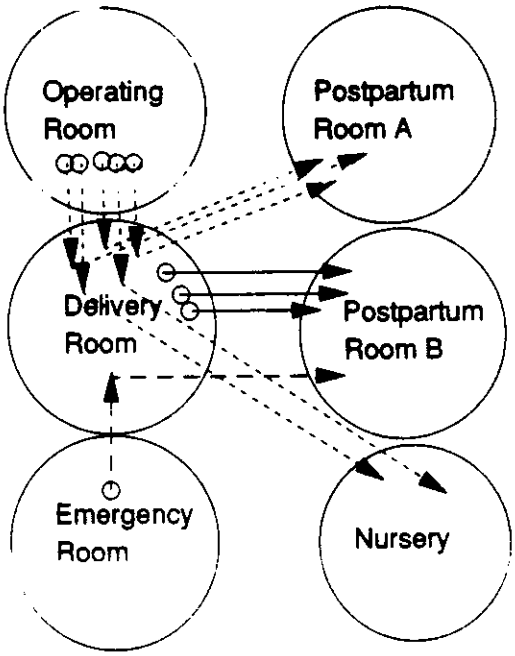
The case control study found no statistically significant difference in exposures between cases and controls. Exposures which were common among cases were also common among controls. In addition, review of staff work schedules and obstetrical logs showed that 15 different obstetrical personnel had attended the delivery of the 9 cases, with no single individual present for more than 2 deliveries.

The investigators considered the possibility that host susceptibility rather than differential exposures determined which infants would develop listeriosis. Although little is known about the susceptibility of infants to late onset listeriosis, late onset neonatal infections with group B Streptococcus have been more extensively studied. To evaluate susceptibility to infection quantitatively, the investigators constructed a "susceptibility index" which combined risk factors that have been associated with late onset neonatal group B strep infection. The following index was used (one point given to each factor):

1. Birth weight < 2,500 gm
2. Maternal age < 20 or primiparous mother
3. 5 minute APGAR score < 7
4. Delivery by c-section
5. Respiratory distress at birth (chart documentation of difficulty breathing, meconium aspiration, or need for additional suctioning)

Cases were more than seven times as likely as controls to have a score of 2 or more. The difference between susceptibility in cases and controls might explain why only some infants became ill, even if all infants were exposed to a contaminated source.

To further evaluate the effect of hospital renovations and changes in delivery sites, investigators interviewed nursing personnel and reviewed information on patient location recorded in the charts. The following schematic was constructed to represent the path that each infant with nosocomial listeriosis took in moving through the hospital.



QUESTION 18: How do you interpret these findings?

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PART V - CONCLUSION

The hospital delivery room was the only site common to all babies who developed listeriosis. In the delivery room babies received antibiotic eyedrops, injections of Vitamin K, alcohol treatment of the umbilical cord, and mineral oil baths. Vials of antibiotics and Vitamin K were used up within 1-2 days, but babies who developed listeriosis were born over a 2 week period. Sterile disposable syringes were used on each infant. Alcohol used on the cord would be unlikely to support the growth of Listeria. The mineral oil used for the bath was stored in a large container and oil from the same container was used on all the infants. The oil contained no bacteriostatic agents. During a routine bath, oil came in contact with the baby's mouth, nose and mucous membranes. The oil was the only potential source to which all case infants were exposed that could support the growth of Listeria.

When General Hospital A first recognized the outbreak, cultures were collected from several sites. Initially the cultures were without growth, and they were sent to a referral laboratory where the specimens were processed using cold enrichment. This method takes advantage of the ability of Listeria to grow in the cold, but it may take months for cultures to grow. Culture of the oil from the delivery room grew L. monocytogenes with the same serotype and subtype as the outbreak strain.

During the outbreak period, the obstetrical suites in Hospital A were being renovated. Instead of deliveries occurring in 4 rooms with 4 sets of supplies being used, all babies were exposed to the same one set of supplies, including the same container of oil. The outbreak began after the June 2nd delivery of an infant born with maternally-acquired, early onset listeriosis. During this delivery, L. monocytogenes may have been introduced into the oil when the container was handled with contaminated hands. The outbreak ended after cleaning and disinfection took place, and when deliveries returned to the usual four rooms.

Mineral oil, which used to be prescribed for constipation, can cause lipoid pneumonia when inadvertently aspirated into the respiratory tree. Two features of the outbreak suggested that aspiration of oil might have contributed to invasive disease. First, although pulmonary listeriosis is extremely unusual in late onset disease, one third of nosocomial cases had presented with respiratory distress, pneumonia, and/or respiratory failure. Second, babies exposed to general anesthesia (during c-section) were more likely to develop listeriosis. The respiratory suppressant effects of anesthesia might have increased these babies' risk of aspirating oil applied on the face shortly after birth.

To evaluate the hypothesis that oil aspiration contributed to disease, autopsy material from an infant who died of listeriosis was reviewed. The lung tissue showed lipid-laden macrophages, consistent with lipoid pneumonia. Although pulmonary macrophages are the usual host defense against aspirated foreign bodies like mineral oil, L. monocytogenes is an intracellular pathogen which survives and multiplies within macrophages.

The following recommendations were made at the conclusion of the investigation:

1. The use of multidose containers in the delivery room should be minimized.

2. Precautions should be taken after a delivery to ensure that any replaceable materials which might have become contaminated are discarded and that multiuse equipment is sterilized.

3. Because of the risk of aspiration and the availability of acceptable alternatives (soap and water), mineral oil should not be used for bathing newborns. If used, the oil should not be applied on the face.

4. Neonatal listeriosis should be reported to facilitate prompt recognition of outbreaks. When listeriosis is diagnosed in a newborn, the infection control practitioner at the hospital of birth should be notified and surveillance for additional cases should be heightened.