



Acute Renal Failure and a Long Night in Haiti

Participant's Guide

Learning Objectives

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

- Describe the questions and decisions to be addressed before departing on a field investigation;
- List the steps of an outbreak investigation;
- List the components of a case definition;
- Discuss the role of epidemiologic evidence in public health decision-making.

This case study is based on an investigation conducted in 1996 as EPI-AID 96-47 by EIS Officers Kate O'Brien and Joel Selanikio.¹ This case study was developed in 1997 by Richard Dicker and Linda Dicker. The current version was updated and edited by Richard Dicker, with comments from the 1998 EIS Summer Course Instructors.



PART I

In mid-May 1996, an EIS Officer in the Division of Bacterial and Mycotic Diseases at CDC received a call from a physician in the Haiti Ministry of Health. He reported that, in the past six months, roughly 30 children had been admitted to a hospital in Haiti with acute renal failure. The children ranged in age from less than one month to 13 years. Only one child was known to have survived.

Haiti, with a population of 6.8 million people and an estimated gross domestic product of \$225 per capita, is considered the poorest country in the

western hemisphere. The infant mortality rate is 74 per thousand live births, and 46% of the population is less than 15 years of age. Among adults, the unemployment rate is 50%, and only 13% have ready access to potable water.

Given the context of living conditions in Haiti and the frequency of illness and death among children, clusters of disease may not be recognized unless they are large or unusual. The outbreak of deaths from acute renal failure appeared to be both.

Question 1: What questions would you ask to characterize the outbreak?

Question 2: If you anticipate receiving and responding to a request for assistance, what jurisdictional questions about might you ask?

Acute renal failure (ARF) means that the kidneys have stopped filtering urea and other waste products from the blood.

The EIS Officer reviewed the causes of acute renal failure, as shown in the table below.

Table 1. Main Categories of Acute Renal Failure²

- I. Prerenal events (leading to decreased blood flow to the kidneys)
 - A. Absolute decrease in effective blood flow - e.g., due to hemorrhage, gastrointestinal fluid loss (diarrhea, vomiting), renal losses (e.g., from diuretics)
 - B. Relative decrease in effective blood flow - e.g., due to sepsis, anaphylaxis, vasodilatory drugs, or anesthetic agents
 - C. Myocardial failure - e.g., due to myocardial infarction, pulmonary embolism, congestive heart failure
 - D. Disruption of renal autoregulation - e.g., due to angiotensin-converting-enzyme (ACE) inhibitors
 - E. Occlusion of renal artery or renal vein
- II. Renal or intrinsic events
 - A. Acute Tubular Necrosis, e.g., due to
 - 1. ischemia (mainly as a consequence of prerenal events)
 - 2. toxins, including nephrotoxic antibiotics (gentamicin, kanamycin), heavy metals (mercury, cisplatin), solvents (carbon tetrachloride, ethylene glycol), radiographic contrast agents, and others
 - B. Interstitial nephritis related to drugs (methicillin), infection, or cancer (lymphoma, leukemia, sarcoidosis)
 - C. Acute glomerulonephritis or small-vessel vasculitis due to connective-tissue disorders, malignant hypertension, toxemia of pregnancy, and other disorders
- III. Postrenal events (obstructive uropathy)
 - A. upper urinary tract obstruction - ureteral obstruction
 - B. lower urinary tract obstruction - bladder-outlet obstruction

The Ministry physician reported that, at autopsy, the kidneys showed "...acute tubular necrosis with evidence of regeneration," consistent with a toxic etiology.

CDC's National Center for Environmental Health (NCEH) has programmatic responsibility for environmental and toxic exposures.

Question 3: Given that the cause is suspected to be toxic but the call came into the Division of Bacterial and Mycotic Diseases (DBMD), who should respond to a request for assistance?

On June 13, CDC received an official request through appropriate channels for assistance in this outbreak.

Question 4: What might be the objectives of the mission?

Before departing, the CDC investigators had to make many decisions and preparations, which could be grouped under the headings of

Epidemiologic Issues; Supplies and Equipment; Investigative Team Composition, Roles, Responsibilities; and Administrative Issues.

Question 5: Before departing, what decisions and preparations in these four categories must be made?

Question 6: Before departing, review the steps of an outbreak investigation.

On June 14, an EIS Officer from DBMD departed for Haiti. She was joined shortly thereafter by an EIS Officer from NCEH.

Upon arrival, the EIS Officer met with Embassy, Ministry, and Hospital officials. She learned that, prior to November 1995, no children with acute renal failure had been admitted to Port-au-Prince's primary children's hospital, Hopital Universitaire d'Etat de Haiti (HUEH), in the past

five years. In November, 2 children were admitted with ARF. An additional 30 children have been admitted since then, and the number of cases seems to be increasing each month. All patients were less than 14 years of age, and most were younger than 5 years old. All children had had a prodromal illness, most often characterized by fever and a variety of other symptoms, including diarrhea, vomiting, cough and abdominal pain. All but one child had died.

Question 7: How do you generate hypotheses?

Question 8: Develop a case definition for this investigation.

Some members of the Ministry wanted the investigative team to determine the extent and scope of the outbreak, while others wanted the team to focus its attention on finding the cause,

using cases already known. Yet a third faction wanted the team to make recommendations about what to do to "stop the epidemic."

Question 9: Discuss these perspectives. Are there any outbreak situations in which setting up a control program would **precede** further epidemiologic investigations? If yes, give an example.

Question 10: How might you address the differences in perspective and opinion about where to focus your efforts?

Question 11: How would you determine the extent of the outbreak?

PART II

The investigators defined a case as “confirmed” if it met all of the following criteria:

- Clinical: acute renal failure (defined as anuria or creatinine > 1.0 mg/dL) for at least 24 hours with no other known cause
- Time: date of admission or date of diagnosis on or after November 1, 1995
- Place: Haiti resident or visitor
- Person: age < 18 years

A case was categorized as “possible” if no chart or maternal interview had been completed, or if the cause of ARF was not clearly idiopathic.

Investigators searched for cases in a number of ways. First, they reviewed a line listing of recent cases that had already been compiled by the Ministry. Second, they asked physicians at HUEH to recall any ARF patients, since the hospital had no admission or discharge log book and no means for systematically searching medical records. Third, they met with and solicited case reports from private practitioners in the Port-au-Prince Pediatric Society at a meeting called to discuss the epidemic. Fourth, the Ministry prompted active case finding at several other large medical centers outside Port-au-Prince. Finally, field health workers collected reports of cases from the public.

Early on, the investigators considered a wide variety of hypotheses, which could be grouped in four categories:

- Infections (leptospirosis, group A streptococcus, *E. coli* O157:H7, hantavirus, influenza, legionnaire’s disease, malaria)
- Ingestions (fava beans, almond extract, amphetamines, salicylates, glycerol, quinidine)
- Toxins (hydrocarbons, chlorinated hydrocarbons, ethylene glycol, diethylene glycol, phenol, analine, acetaminophen, heavy metals, herbal remedies, pesticides)
- Bites (spider, snake)

However, based on the febrile prodrome, age distribution of the patients, and the kidney pathology findings, the investigators felt that the leading hypotheses were an infectious agent, a toxin in the environment, or a toxin contained in a pediatric medication. Investigators planned to conduct a systematic interview with each child’s mother or caretaker to collect detailed information about the child’s exposures and illness prior to onset of renal failure. One investigator suggested that, at the same time, they should collect samples and bottles of medications used by the child during the two weeks prior to onset of ARF, which might be helpful in evaluating the third hypothesis.

Question 12a: Is it reasonable to ask for samples of medications, even though it is relatively early in the investigation and medications are only one of three active hypotheses?

Question 12b: If you do plan to collect samples, what issues must you consider?

PART III

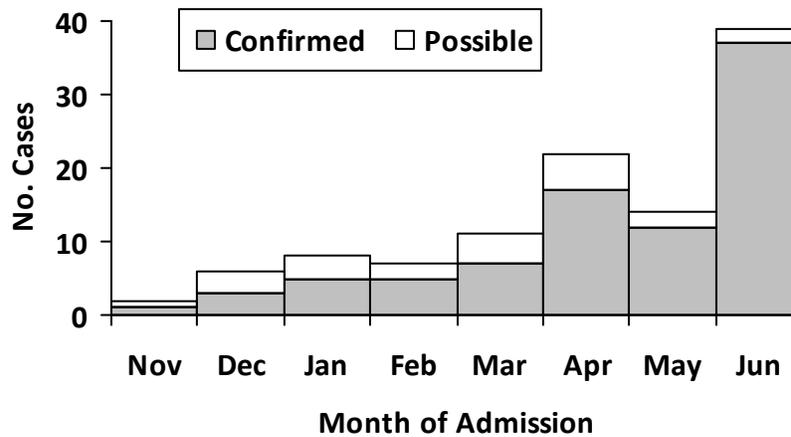
By interviewing parents and reviewing hospital charts, the investigators collected detailed information about each child's exposures and illness prior to onset of ARF. They also collected samples or empty bottles of all the medications used by the child in the two weeks prior to onset of renal failure.

Investigators identified 87 confirmed and 22 possible cases. Clinically, the children presented

not only with acute renal failure but with evidence of multiorgan toxicity such as hepatitis, pancreatitis, encephalopathy, and respiratory failure.

The number of cases by month of onset is shown in the following figure.

Figure 1. Month of hospital admission of acute renal failure cases, Haiti, November 1995 – July 1996



Question 13: With which outbreak pattern (point source, continuous or intermittent common source, propagated / person-to-person, etc.) is the epidemic curve most compatible?

The age distribution is shown in the figure below. Sixty-five percent of the 109 cases were male. Although many of the case-patients had siblings

in the age group affected by the outbreak, only one family had two cases among siblings.

Figure 2. Age distribution of acute renal failure cases, Haiti, November 1995 – July 1996

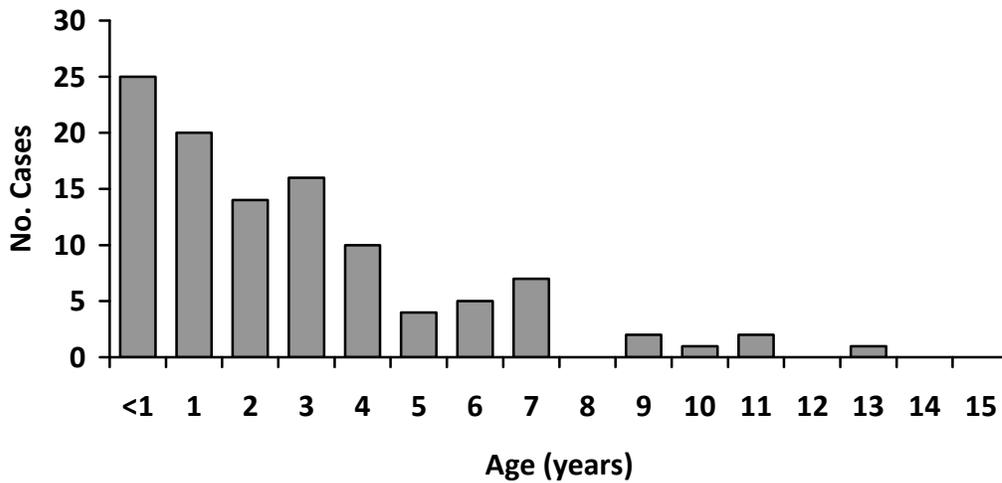


Figure 3. Map of Haiti's Departments



Of Haiti's 9 geopolitical units called *departments*, the Ouest Department, which includes Port-au-Prince, accounted for 88% of the cases. The 3 northern departments, one of which includes Haiti's second largest city, had no cases at all. The remaining cases were scattered among 4 other departments.

At this point, the investigators had begun to lean away from the infectious disease hypothesis. They decided to conduct an epidemiologic study to evaluate the two remaining hypotheses — a pediatric medication and an environmental exposure to a toxin.

Question 14: What type of study would you suggest?

Question 15: Whom would you choose for your comparison group?

Question 16: What types of information would you include on your data collection instrument?

PART IV

The investigators conducted a case-control study. Cases were children who met the definition for a confirmed case and whose mothers could be interviewed. Controls were children less than 18 years of age who were hospitalized at HUEH in mid-June for any reason other than renal failure, but who also had a

history of fever during their current illness. Mothers of both case- and control-children were asked about exposures during the two weeks before onset of illness. However, for some cases, that exposure period was months earlier, whereas for controls, the exposure period was just a few weeks ago.

Question 17: Do you see any potential problem with using controls' exposure histories in early June as the comparison for cases' exposure histories from earlier periods?

Investigators identified 453 different medications by history or collection. Two medications, both acetaminophen liquid preparations manufactured by a single local pharmaceutical company, were

the only ones associated with illness. The two-by-two table below shows the association between the two medications combined and illness.

Table 2. Exposure to Afebril or Valodon among Cases and Controls, Acute Renal Failure Investigation, Haiti, 1996

		CASES	CONTROLS	
EXPOSURE TO AFEBRIL or VALODON	YES	55	5	Odds ratio = 64.6 (95% CI = 17.6, 260.2)
	NO	8	47	
		63	52	

Question 18: Given the odds ratio of 64.6, do you think you have enough information to warn the public about consuming Afebril / Valodon? Why or why not?

While the epidemiologists were conducting the case-control study, laboratory scientists were furiously working to identify the toxic exposure. The epidemiologists had noted that all of the first five patients had taken Afebril or Valodon, so the laboratory focused on these medications. Meanwhile, children continued to be admitted with renal failure.

On Thursday June 20 at 11 a.m., 14 bottles collected from two case-households arrived by courier at the NCEH laboratory.

By 5 p.m. on Friday June 21, laboratorians had confirmed the presence of significant amounts of diethylene glycol (DEG) in a bottle of Afebril from one household and a bottle of Valodon from the other household. DEG, a known nephrotoxin and hepatotoxin, is used in industrial solvents and antifreeze. These results were communicated from CDC to the investigators in Haiti on a secure line at the pre-arranged time of 8 p.m. By 11 p.m., CDC had faxed written confirmation of substantial contamination.

Question 19: What action would you take at this time?

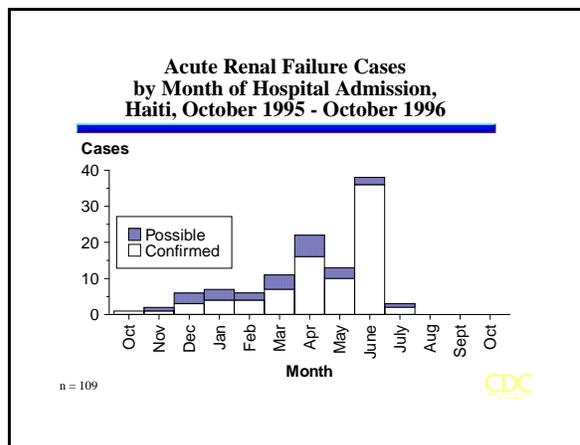
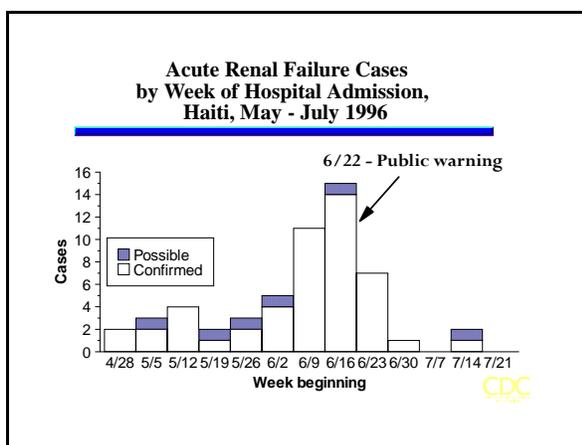
Part V - Conclusion

Two hours after the phone call from CDC, the PAHO mission chief coordinated a meeting among the field investigators, the Haitian Minister of Health, the Chief of Police, and senior advisors of each. The American Ambassador was notified at 11 p.m. that the cause of the epidemic had been determined and that it involved one of the two major pharmaceutical companies in the country. At about 2 a.m. a representative of the pharmaceutical company arrived. After much discussion, all agreed that Afebril and Valodon should be pulled off the market immediately. At 5 a.m., a communications expert from the U.S. Embassy joined the meeting to assist in planning the recall and managing the public information campaign. By 7 a.m. the Minister of Health and the American Ambassador departed for the President's palace to present the information. At 8:30 a.m. the Minister issued a public announcement prohibiting the sale of the two implicated products, stating they had been accidentally contaminated with a poison.

A week later, when the DEG was traced back to contaminated glycerine, the pharmaceutical company recalled all 27 of their syrup products, whether they contained glycerine or not.

This announcement was followed by an intensive public information campaign over the next days and weeks on radio, television, and in newspapers throughout Haiti and in cities in the United States with large Haitian communities. In addition, fliers were distributed to all school children with information to take home to their families and notices were distributed to medical societies. Police checked and seized bottles of Afebril and Valodon bottles from pharmacies while the pharmaceutical company recalled the two products through their distributor network. A passive recall was also conducted whereby any individual or company could return bottles of the product to the company for a full refund. Finally all 10 departments were visited by Ministry of Health representatives to determine the extent of information received and to conduct spot checks of pharmacies in each department.

The figures below show that 7 patients with acute renal failure were admitted during the week after the announcement was made, and only 3 cases were identified subsequently. All had consumed Afebril or Valodon before the announcement of the recall. The epidemic appeared to have stopped.



To determine how Afebril and Valodon had become contaminated with diethylene glycol, staff from the Ministry of Health, CDC, and the U.S. Food and Drug Administration (FDA) conducted an investigation at the pharmaceutical firm, Company P.

Tests performed by CDC and FDA of medications provided by case-households and of other samples indicated that contamination of pediatric syrup had probably occurred during production from mid-July through mid-December 1995. The source of the DEG was glycerine, a common ingredient in pharmaceutical syrups which provide thickening and a sweet taste.

On June 27, 1995, Company C, an import company affiliated with Company P, received 72 drums of glycerine labeled as U.S.P. All drums were similar, made of blue plastic, with no lot numbers.

Company C transferred 62 of the 72 drums to Company P, which did not analyze the glycerine nor maintain records of when it was used in the production of syrups. Company C combined the remaining 10 drums with 4 drums from a second shipment of glycerine. Of these 14 drums, 2 were sold to the second pharmaceutical manufacturer in Haiti, and the remaining product was sold in small quantities to 11 pharmacies in the Port-au-Prince area. A small amount of glycerine from the 6/27/75 shipment was found at Company P. Analysis by the FDA indicated that this glycerine contained 24% DEG, 4% glycerine, 30% water, 20% sucrose, and 22% undetermined.

Eventually, the contaminated glycerine was traced back through distributors in Europe to a manufacturer in China. How and at what point the contamination occurred, and whether any other countries received DEG-contaminated glycerine remain unknown.

References

1. O'Brien KL, Selanikio JD, Hecdivert C, et al, for the Acute Renal Failure Investigation Team. Epidemic of pediatric deaths from acute renal failure caused by diethylene glycol poisoning. *JAMA* 1998;279:1175-1180.
2. Klahr S, Miller S. Acute oliguria. *New Engl J Med* 1998;338:671-675.
3. Goodman RA, Buehler JW, Koplan JP. The epidemiologic field investigation: science and judgment in public health practice. *Am J Epidemiol* 1989;132:9-16.