The Pan African Medical Journal

An Epidemic of Spastic Paraparesis of Unknown Aetiology in Northern Mozambique

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African Case Studies in Public Health

Participants' Guide

An Epidemic of Spastic Paraparesis of Unknown Aetiology in Northern Mozambique

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Abstract

This case study is based on a real-life outbreak investigation undertaken in Mozambique in 1981. This case study describes and promotes one particular approach to unknown disease outbreak investigation. Investigational procedures, however, may vary depending on location and outbreak. It is anticipated that the epidemiologist investigating an unknown disease outbreak will work within the framework of a "multidisciplinary investigation team". It is through the collaborative efforts of this team, with each member playing a critical role, that outbreak investigations are successfully completed. Some aspects of the original outbreak and investigation have, however, been altered to assist in meeting the desired teaching objectives and to allow completion of the case study in less than 3 hours.

How to Use the Case Study

General instructions: Case studies in applied epidemiology allow students to practice applying epidemiologic skills in the classroom to address real-world public health problems. The case studies are used as a vital component of an applied epidemiology curriculum, rather than as stand-alone tools. They are ideally suited to reinforcing principles and skills already covered in a lecture or in background reading.

Ideally, 1 or 2 instructors facilitate the case study for 8 to 20 students in a classroom or conference room. The instructor directs a participant to read aloud a paragraph or two, going around the room and giving each participant a chance to read. When the participant reads a question, the instructor directs all participants to perform calculations, construct graphs, or engage in a discussion of the answer. Sometimes, the instructor can split the class to play different roles or take different sides in answering the question. As a result, participants learn from each other, not just from the instructors. Additional instructor's notes are included with each question.

The instructors must keep Part 4 of the student guide (last 6 pages) as a separate handout. Do not let students see Part 4 until after they have completed Part 3.

Audience: Residents in Field Epidemiology Training Programs (FETPs), Field Epidemiology and Laboratory Training Programs (FELTPs), Epidemic Intelligence Service (EIS) programs and others who will be engaged in conducting field studies involving humans, or who are interested in this topic.

Prerequisites: Before using this case study, participants should have working knowledge of descriptive epidemiology, epidemic curves, measures of association, study design, and outbreak investigation. The student will also benefit from having some familiarity with paralysis of unknown aetiology, or unknown disease outbreaks investigation techniques, but will be likely to rely heavily on others with greater expertise in these areas in a real-life outbreak situation.

Materials needed: A calculator, the case control study student guide

Level of training and associated public health activity: Basic to intermediate, i.e., this case study could be used in an introductory course in field epidemiology – outbreak investigation

Time required: Approximately 3 hours

Language: English

Participant's Guide

Goal of Case Study: To investigate an unknown disease using a community-based strategy, and to discuss how this strategy can be used to develop informed policies for improving surveillance data quality in local, low-resource settings

Learning Objectives - After completion of this case study, the participants should be able to:

1. Analyse and prioritise needs for investigation of an outbreak of unknown aetiology
2. Identify types of causative agents that could cause an epidemic-prone disease
3. Identify the strengths of a multidisciplinary team in outbreak investigation and control
4. Adapt the process of outbreak investigation for a specific outbreak
5. Explain the importance and process of community involvement in surveillance
6. Construct an appropriate case definition
7. Identify and describe the appropriate study design and interpret the results for study
8. Formulate public health responses from the findings of the analytic study

Introduction

The first report of the outbreak of spastic paraparesis came from the remote health centre of Cavá in Nampula Province, northern Mozambique, on 13th August 1981. The Nampula Provincial Department informed the Department of Surveillance at Ministry of Health (MOH) on 21st August 1981 by telex (Figure 1). On learning of the telex, the Minister of Health convened an emergency meeting and sent a team to the field.

Figure 1. Telex received at the Ministry of Health, Mozambique, 21st August, 1981

Telex

Polio outbreak, Memba District

38 cases, Hyperreflexia

Provincial Department of Health, Nampula

21st August, 1981

According to the telex, officials in Namupla suspected poliomyelitis. Poliomyelitis is an infectious disease caused by wild polio virus types 1, 2 and 3, predominantly transmitted through ingestion of infected faecal matter. The initial symptoms include fever, fatigue, headache, vomiting, neck stiffness and pain in the limbs. It affects mainly children under five years of age. Less than 1% of the infected cases develop irreversible flaccid paralyisis [1–3]. However, the report of hyperreflexia among the cases was not compatible with polio. This called for an investigation into a possibly unknown disease.

Question 1: What kind of expertise does the outbreak investigation team require?

Question 2: Before departing, what preparations and decisions should be made with regards to:

a. The epidemiologic / scientific aspects of the investigation?
b. Supplies and equipment?
c. Investigative team composition, role, responsibilities?
d. Administrative issues?

In the provincial capital, the investigation team met the provincial health authorities. The provincial health authorities were experienced in investigating cholera epidemics, and they had immediately begun an outbreak investigation. The two teams worked on a joint outbreak investigation strategy and travelled to the coastal city of Nacala.

After arriving at the local hospital in Nacala, the investigation team met two doctors who had carried out a preliminary investigation and verified initial suspicions that the clinical presentation and history of cases were not compatible with a diagnosis of poliomyelitis.

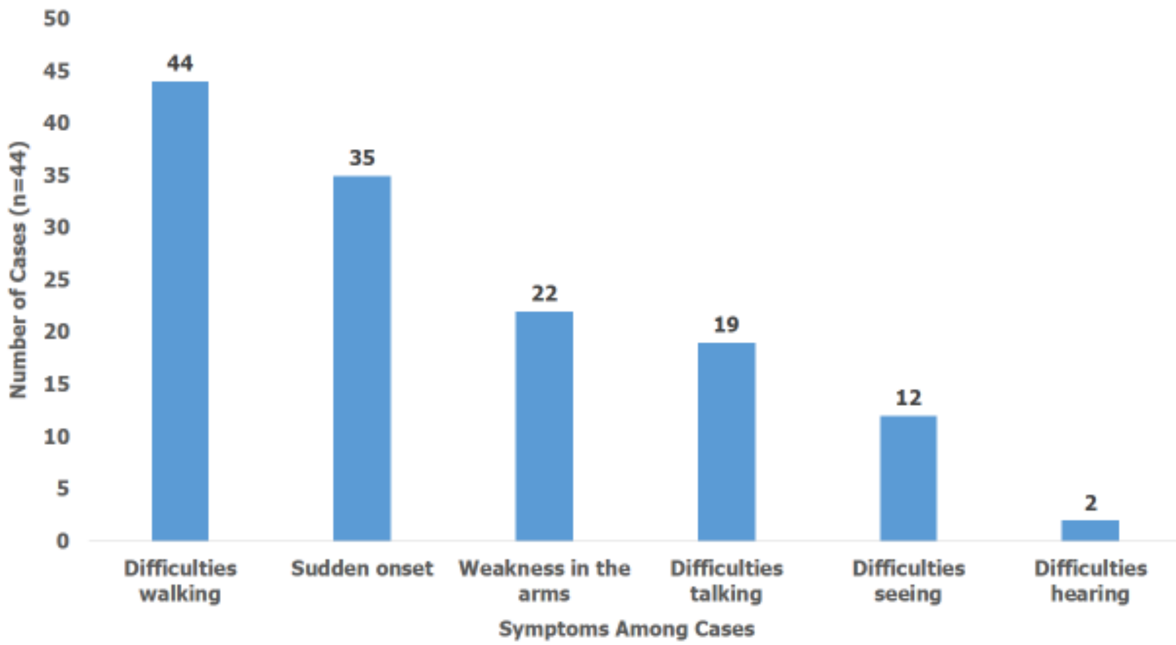
Of great concern was a continuing rapid increase in the number of cases, over a wide geographical area. Most cases were in the remote district of Memba (Figure 2), which was drought-prone and had suffered from low rainfall in the past two years.

Figure 2. Location of Memba District in Namupla Province, Mozambique [4]

Question 3: What kind of information would you need in order to describe the outbreak?

The investigation team set off the next day for Memba, accompanied by a doctor from Nacala. They visited a small health centre filled with patients, mostly young women and children, with paralysed limbs, as well as a district hospital. The team recorded histories and examined the patients at both facilities and obtained details for 44 patients (Figure 3).

Figure 3. Symptoms Observers Among Cases, Memba District, August 1981



They found that the disease varied in severity among patients (Figure 4); some of the worst cases had paralysed arms, were blind, and had difficulty in hearing. In the following two months, the investigation team confirmed the existence of a large epidemic of spastic paraparesis and investigated its possible causes.

Initially, the team suspected the disease to be of viral origin. Blood, urine, and cerebral spinal fluid (CSF) samples were collected for laboratory testing overseas. The team also interviewed community members who indicated that they were suffering a severe drought affecting agricultural production. The only surviving food crop was bitter cassava. The food shortage was so extreme that some families were forced to eat cassava peel.

Figure 4. Children affected with spastic paraparesis

Question 4: What are possible aetiologies for a disease like this? Explain why.

Question 5: Given the characteristics of the cases and resources available, what steps of an outbreak investigation are more critical in case of unknown disease? Explain your choices.

Question 6: In addition to the MOH at this level of investigation, which organisations could provide support for this specific outbreak? Specify the type of support. What types of stakeholders can help in each case?

Part 1

Memba District was remote, and its provincial and district health authorities lacked transport as well as other resources.

Question 7a: What strategies could you use to detect cases in the remote affected areas?

Question 7b: What considerations do you need to take into account in order to successfully implement the above strategies?

Due to the serious nature of the epidemic, the health department collaborated with political and administrative authorities to arrange transportation and logistics. These authorities also mobilised local community leaders and community members to find cases. The investigation team generated a case definition for community-based surveillance.

Question 8: What are characteristics of case definitions for: a) community-based case finding, b) suspected cases, c) probable cases, and d) confirmed cases?

The initial case definition for community case finding was: Patient with difficulty walking since the last rainy season (March- April 1981). Active case detection was based on close collaboration with community leaders, who commissioned brigades and asked them to search for and register community members who had difficulty walking since the last rainy season, including their name and house location.

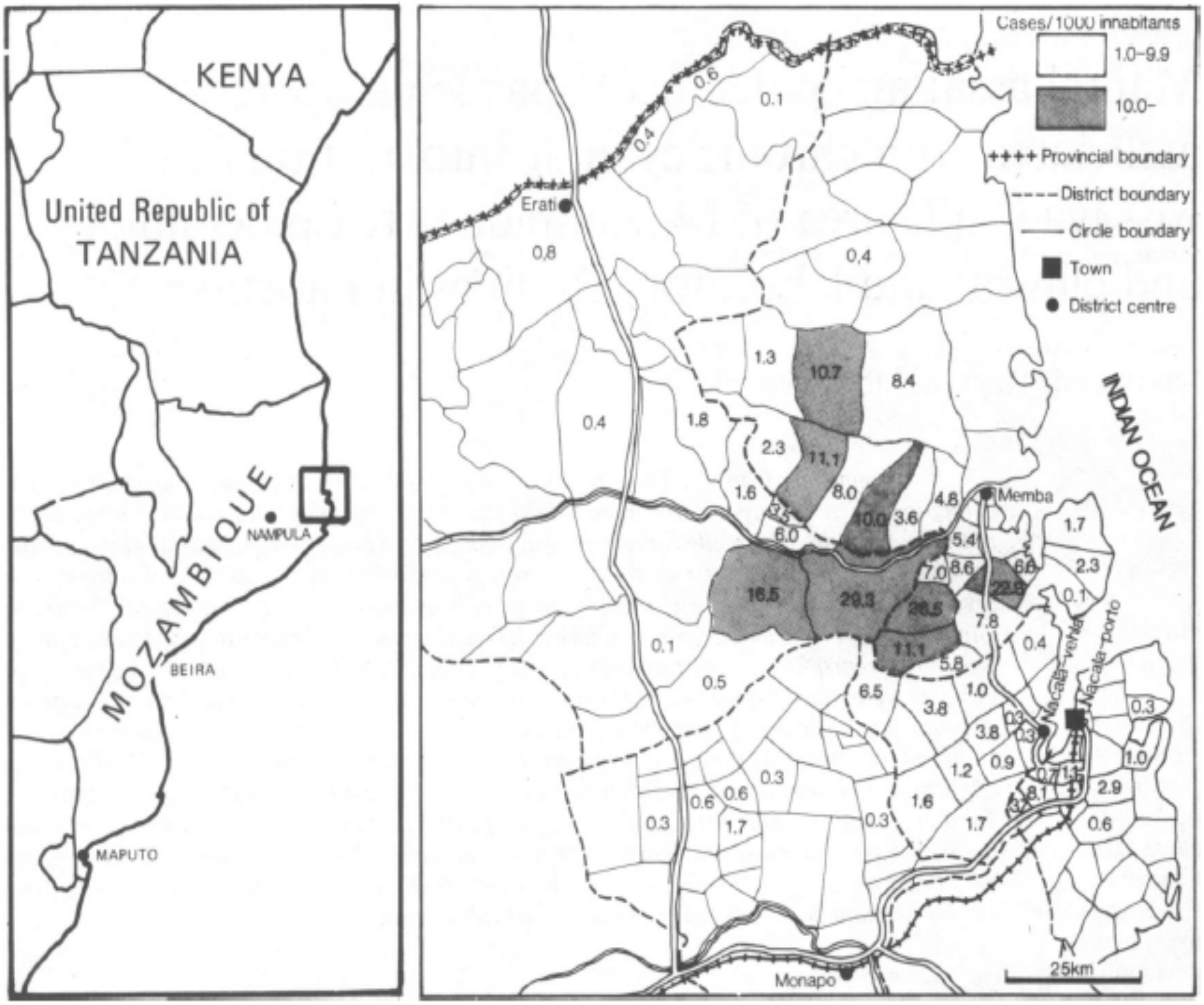
A brigade member was required to visit the identified patients in their homes and record on a form details such as age, sex, dwelling place, symptoms, and time of onset. Most cases were easy to identify. When doubts arose, people were referred to the local health facility where a doctor performed a more thorough neurological examination of signs, such as sensory level.

In most of the identified cases, the diagnosis was confirmed as spastic paraparesis. Other neurological diseases common in Mozambique, such as poliomyelitis, were diagnosed in a few cases. In total, 1102 cases were identified in 5 districts from the beginning of the investigation up to the end of October 1981 (Table 1), with an attack rate of 0.1 – 29.0/1000 habitants (Figure 5). There were no cases in district capitals.

Table 1. Total Number of Cases Identified per District, Mozambique, 1981

District	Number of Cases
Memba	772
Nacala-a-Velha	98
Nacala-Porto	45
Monapo	16
Erati	171
Total	1102

Figure 5. Attack rate of spastic paraparesis, Mozambique, August 1981 [5]



The team analysed the situation in Memba in more detail. Of the 772 cases notified, 764 cases had the syndrome compatible with spastic paraparesis (locally known as "mantakassa" – the word for paralysis in the local dialect of the Macua language). The distribution of cases according to time and person in Memba district is presented below (Figures 6-7).

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Figure 6. Distribution of spastic paraparesis cases by time in Memba District, May- October 1981

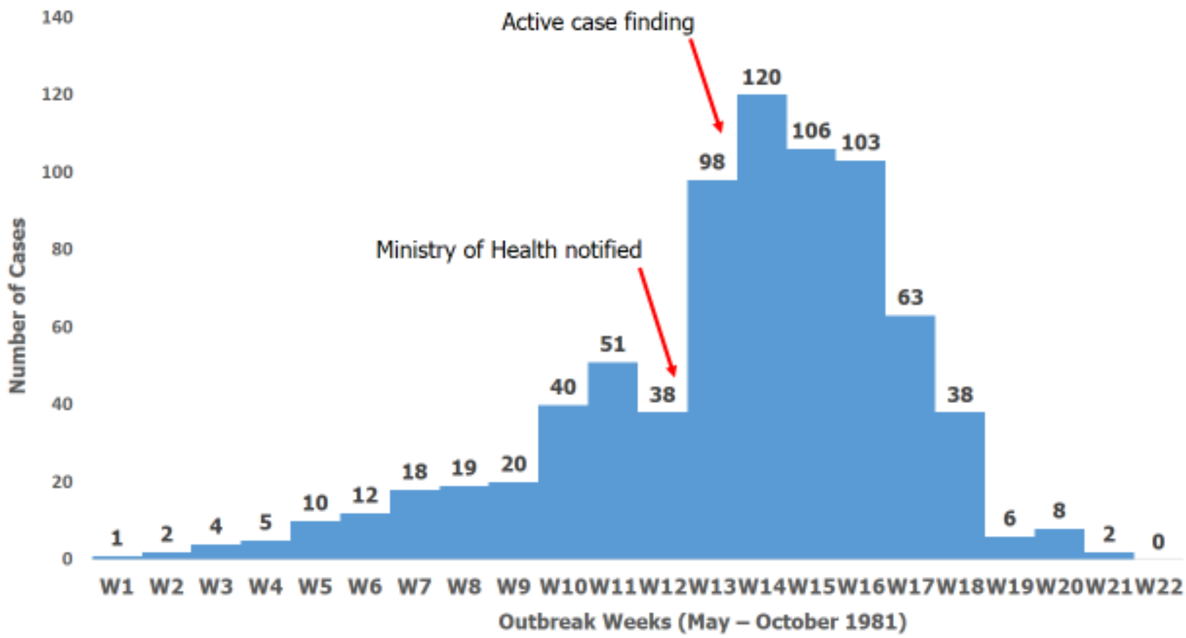
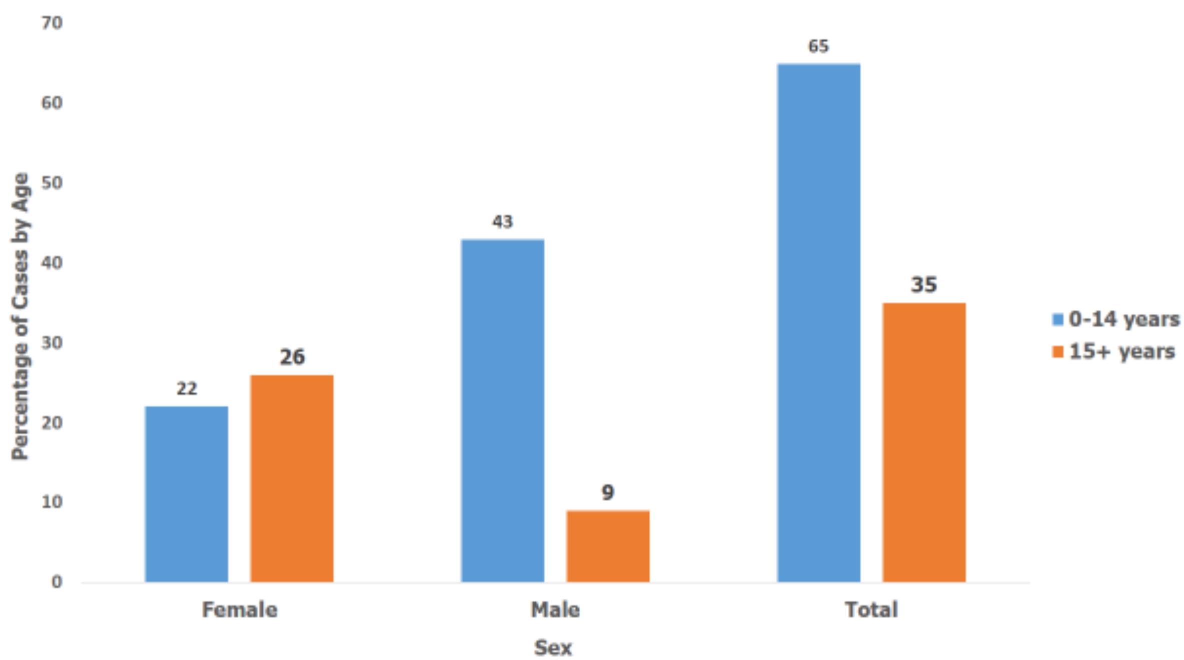


Figure 7. Distribution of cases of spastic paraparesis by sex and age, Memba District (n=764)



Question 9: What kind of observation can you make about the characteristics of the disease from the data presented above?

Investigators noticed a frequent clustering of cases in families. This information inclined the team to believe that the disease was transmitted by one family member to the next. The team was afraid that a failure to diagnose the cause of disease could prove catastrophic if the epidemic spread further.

Part 2

The team continued to collect blood, urine, and CSF specimens, and sent them to the capital (Maputo) and internationally for further analysis, though results had still not arrived. They also carried out a literature review to search for potential clues to the aetiology. The only similar cases were instances of lathyrism in India, Bangladesh, and Ethiopia, where spastic paraparesis was caused by eating the lathryrus pea (which does not exist in Mozambique) [6]. Some of the experts at the MoH argued for greater attention to the possibility of an insect vector. Every household was plagued by bedbugs and mosquitoes that frequently bit every night.

Question 10: What other kinds of samples should the team collect for laboratory testing? Why?

The team expanded to include a botanist and a nutritionist. Additional information about nutrition, socio-economic conditions, possible insect vectors and agriculture was collected, and the botanist identified wild plants that were consumed.

Some argued that public health officials should set up a special ward in the provincial capital to investigate the patients. But investigators felt that the answer was in the field, in the houses of patients. Only by looking at the community context could they understand this epidemic.

Question 11: Develop a hypothesis about the cause of the disease (either infectious or non-infectious) that could explain these findings.

Question 12: How might you test the hypothesis to confirm a dietary cause of the disease?

Question 13: What epidemiologic study design should be conducted to address this specific outbreak? Why? See Appendix 1 to review epidemiologic study designs.

The investigation team chose a communal village – Acordos de Lusaka – in Memba District for a more detailed study. This village was at the centre of one of the worst-hit areas. A house-to-house survey showed that 28 of the 815 inhabitants had developed the disease (Table 2) [3] .

Table 2. Spastic paraparesis incidence rate, "Acordos de Lusaka" village, Memba District, 1981 (n=815)

Age Group by Years	Sex	Cases	Population	Incidence Rate per 1000
0-14	Female	9	205	44
	Male	7	186	38
15-44	Female	10	169	59
	Male	1	120	8
45+	Female	1	55	18
	Male	0	80	0
Total		28	815	34

Question 14: Do we need a new case definition? Why or why not?

Question 15: What sources of controls would you use? How can the investigators match cases and controls?

The investigation team compared families with the disease with their neighbors who did not have the disease. Subjects in these families were matched by age and sex, consumption of cassava in the last 24 hours, median duration of time spent to dry cassava before consumption, access to food, and other nutritional habits.

Question 16: Which measure of association would you use to analyse the exposure data?

Table 3 presents the results related to food consumption and prior habits among case and control families in the communal village. Almost all of the affected families recalled onset of acute symptoms four to six hours after ingesting cassava from the recent harvest [3]. Investigators knew from the literature review that cassava contains cyanogenic glucosides [7].

Table 3. Summary of results describing food consumption and habits by affected and control families in Acordos de Lusaka, Memba District, October 1981

Variables	Affected Families (n=17)	Control Families (n=17)
Have eaten bitter cassava porridge in the last 24h	17	17
Have eaten dried uncooked cassava in the last 24h	16	6
Have eaten sauce containing cassava leaves in the last 24h	13	12
Have eaten cereals in the last 24h	1	1
Have eaten beans in the last 24h	1	7
Have eaten fish or meat	1	6
Have eaten wild plants in the last month	2	8
Member of the food cooperative	1	7
Depending on food donation from others	7	1
Median time to dry the cassava	7	7

Question 17: Calculate the OR and CI and interpret your results. Do the findings support the hypothesis? Which other information is important to clarify the aetiology?

Variables	Affected Families (n=17)	Control Families (n=17)	OR	CI (95%)
Have eaten bitter cassava porridge in the last 24h	17	17		
Have eaten dried uncooked cassava in the last 24h	16	6		
Have eaten sauce containing cassava leaves in the last 24h	13	12		
Have eaten cereals in the last 24h	1	1		
Have eaten beans in the last 24h	1	7		
Have eaten fish or meat	1	6		
Have eaten wild plants in the last month	2	8		
Member of the food cooperative	1	7		
Depending on food donation from others	7	1		
Median time to dry the cassava	7	7		

Part 3

The blood analysis results at the national level revealed anemia and eosinophilia. The CSF analysis was normal. Blood, urine and cerebrospinal fluids were negative for viruses. The urine toxicology for pesticides was also negative.

On the other hand, a total of 246 blood and serum specimens tested positive for extremely high levels of thiocyanate in cases (329 µmol/l average) versus controls (277 µmol/l average). The normal range of thiocyanate is 10-40 µmol/l for non-smokers and 70-150 µmol/l for smokers [5] [7]. Investigators discovered there were no significant age and sex differences and no correlation between the thiocyanate level and disease severity.

Question 18: In general, what factors might influence the occurrence of disease?

Cassava was the third largest source of carbohydrates in the tropics (after rice and maize), and its leaves have a high content of proteins and vitamins. It was the major staple food in the developing world, providing a basic diet for over half a billion people. This perennial tropical shrub is approximately one to three metres tall and may be either sweet or bitter. Bitter varieties contain large concentrations of cyanogenic glucosides, and must be processed to remove cyanoses before consumption. Incomplete processing can leave enough residual cyanide to cause acute cyanide intoxication, goiters, and even ataxia or partial paralysis and konzo [8].

Cassava is by far the most important human food source that uses cyanide as a defense mechanism against animals and marauding insects [8]. Cyanides are mostly metabolised in the body to thiocyanates and excreted in the urine. In affected areas, insufficient cassava processing was due to shortcuts in the normal methods in response to food shortages caused by drought or crop failure and cassava commercialisation.

The clinical, epidemiological and laboratory findings of this outbreak suggested that the disease was associated with cyanide intoxication and cassava consumption. However, it was not clear why the non-affected families also showed high thiocyanate levels.

After analysing the lab results and epidemiological characteristics of the outbreak, the investigation team considered the distribution of cases.

Continued on next page →

Question 19: Discuss the distribution of cases and the levels of thiocyanate:

a. Why do you think adult males and children < 3 years old were less affected by the disease than women of child bearing age and children >3 years old?
b. Why do you think both control and cases presented with high levels of thiocyanate in their urine?

Question 20: What action(s) would you suggest as a result of these findings?

Question 21: Do you agree with the procedures and methodology that the team used in this case? If such an outbreak happened in the future, what would you do differently? Why?

Conclusion

Konzo is a distinct neurological entity with selective upper motor neuron damage, characterised by an abrupt onset of an irreversible, non-progressive, and symmetrical spastic paralysis of the limbs. The disease is associated with prolonged high dietary cyanogen consumption from insufficiently processed roots of bitter cassava combined with a protein-deficient diet low in sulphur amino acids [8–10].

The konzo epidemic ran until the end of October 1981. Eventually 1,102 cases would be reported, spread over five districts in a total population of around 500,000. In the worst-affected villages, 1 in 30 people had the disease [3]. This disease was previously reported in some parts of Africa, with some cases initially reported as being of unknown origin, while other reports found an association with high cassava consumption and high thiocyanate blood levels [11,12].

Cassava contains cyanogenic glucosides, which cause cyanide poisoning when ingested; however, cyanogens can be removed by appropriate processing of cassava. Thiocyanate is the metabolic product of cyanide and is detectable through laboratory testing of urine samples if ingested. [5,10,13–15] In areas where cassava is routinely consumed and especially where outbreaks of spastic paraparesis have occurred, investigators could educate local villagers to avoid consuming under-processed bitter cassava to reduce risk of konzo [15].

Poverty is the main risk factor, and commercialisation, drought, or wars are the usual precipitators. The number of cases was probably underestimated, and the disease continues to be reported and is expanding to new areas of the continent. It has been noted that investigation of this disease requires the involvement of multidisciplinary teams, and its control requires a multi-sectoral approach, especially given its associated with poverty [8,16,17].

Background Reading

Centers for Disease Control and Prevention. Section 2: Steps of an Outbreak Investigation. Principles of Epidemiology in Public Health Practice. 3rd ed. Atlanta, GA: CDC; 2012

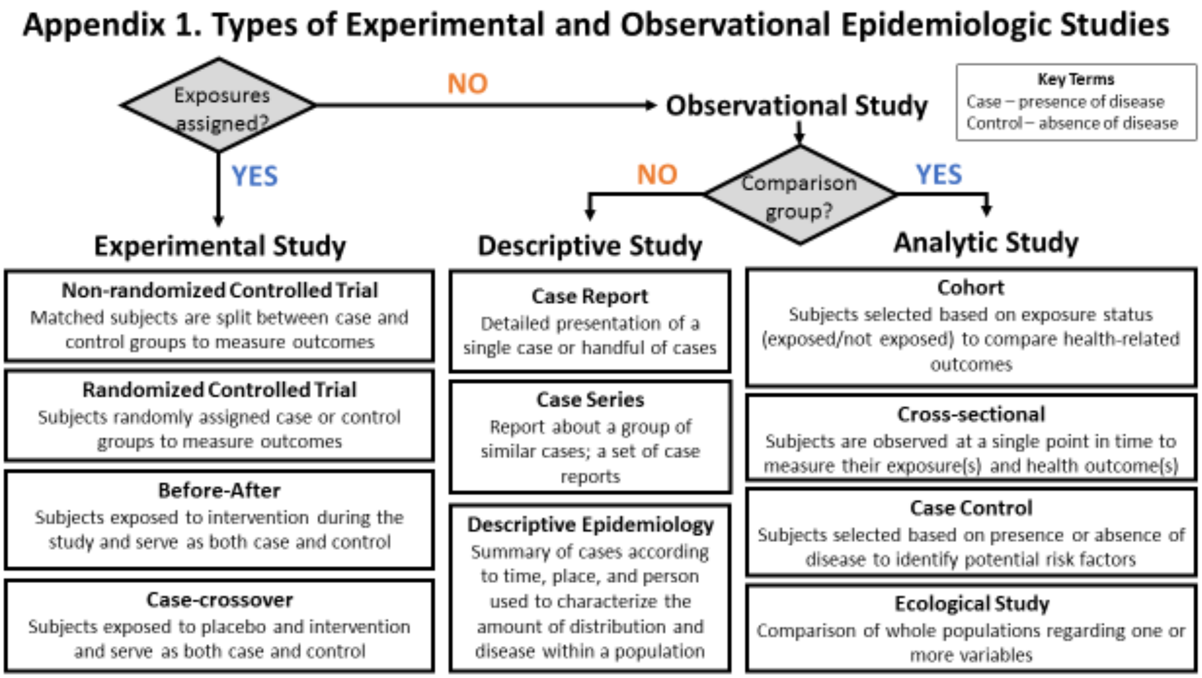
Acknowledgements

Training materials funded by: AFENET; The Centers for Disease Control and Prevention (National Center for Infectious Diseases); Emory University – Hubert Department of Global Health.

Acknowledgment: Esteves, António[1], Kulinski, Nicolai[2], Casadei, Enrico[3], Paul, Jansen[4], Martineli, António (deceased)[5], Rodrigues, Anne (deceased)[6]

[1]Nampula Provincial Health Department, [2]Ministry of Health; [3]Food and Water Hygiene laboratory - Ministry of Health, [4]Department of Traditional Medicine - Ministry of Health, [5]Microbiology Department, Faculty of Medicine – Eduardo Mondlane University, [6]Department of Nutrition - Ministry of Health.

Appendices



Source [18]

Glossary

Cassava – a staple source of food carbohydrates in the tropics, of which there are bitter and sweet varieties; also known as Brazilian arrow root, manioc, tapioca, and yucca [19]

Konzo – "a distinct form of tropical myelopathy characterised by abrupt onset of spastic pararesis"[8]

Lathyrism - a non-progressive bilateral symmetric paraparesis associated with consumption of grass pea – Lathyrus sativu

Mantakassa – the word for paralysis in the local dialect of the Macua language

Paraparesis – "a partial paralysis of the lower extremities"[20]

Poliomyelitis – a highly infectious viral disease spread most commonly through person-to-person faecal-oral contact and less often by contaminated food and water that may cause one or more of the following symptoms: fever, fatigue, headache, vomiting, stiff back, painful limbs, and paralysis [21]

Telex – messages sent over long distances using a telephone line to be printed by a special machine on the receiving line [22]

Thiocyanate – "a compound that consists of the chemical group SCN bonded by the sulfur atom to a group or an atom other than a hydrogen atom" [23]

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