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Original Research Article

Yellow fever outbreak in Plateau state, Nigeria: A re-emerging disease or a case of misdiagnosis over the years?

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Abstract

Background: The first reported Yellow fever outbreak in Nigeria occurred in 1931.The latest outbreak in Nigeria, commenced in September 2017. It is active in seven states and suspected cases have been reported in sixteen states, inclusive of Plateau state. The last reported outbreak in Plateau state occurred in Jos in 1969 with an estimated 100,000 cases.

Materials and Methods: The cases and health workers involved in management were interviewed. Hospital records, laboratory and surveillance data were reviewed.

Results: **Case 1:** A 6-year-old girl from Tudun-Wada, Jos Plateau state presented with fever (38.6^{o}C), abdominal pain, sore throat and jaundice. Liver function test (AST: 398U/L, ALT: 96U/L). Treatment included ribavirin, ceftriaxone, anti-oxidants, intravenous fluids, blood transfusion. ELISA-IgM was positive for YF, but negative on PNRT.

Case 2: A 10-year-old boy from the same family with *case 1* presented with fever (39.0^{o}C), abdominal pain, diarrhoea and jaundice. Liver function test (AST: 315 U/L, ALT: 126U/L). Treatment is same as *case 1* plus metronidazole. ELISA-IgM was positive for YF, but negative on PNRT, while PCR was positive for Lassa fever.

Twenty-three contacts (17 healthcare workers, 6 family members) were traced and daily monitoring instituted.

Conclusion: The potential for a major urban outbreak of Yellow Fever in Plateau state and Nigeria is already present. Advocacy, health education and enforcement of vector control measures need to be intensified by the State Ministry of Health. Surveillance for rapid case finding and proactive vaccination also need to be intensified to forestall a disaster.

Keywords: Yellow fever, outbreak, Plateau, Nigeria.

1. Introduction

Yellow fever (YF) is an acute viral haemorrhagic disease caused by a *Flavivirus* which is transmitted to humans by the bites of infected *Aedes* and *Haemogogus* mosquitoes. [1] The virus is endemic in tropical areas of Africa, Central and South America. In the 17th and 19th centuries, YF outbreaks occurred in North America and Europe, leading to high mortality and morbidity. [1,2] Annually, an estimated 200,000 YF cases and 30,000 deaths occur globally. [1,2] The incubation period for YF is between 3 to 6 days, followed by infection that can occur in one or two phases. The symptoms in the first, "acute", phase usually include fever, muscle ache, backache, headache, shivers, loss of appetite, nausea or vomiting. Most patients improve and their symptoms disappear after 3 to 4 days.[1] However, 15% of patients enter a second, more toxic phase within 24 hours of the initial remission. Symptoms include return of high fever, jaundice, decreased urination, abdominal pain with vomiting, bleeding from the mouth, nose, eyes or stomach, delirium and seizures. Half of the patients who enter the toxic phase die within 10 to 14 days, the rest recover without significant organ damage.[1] YF is difficult to diagnose, especially during the early stages. It can be confused with severe malaria, dengue fever, leptospirosis, viral hepatitis (fulminating forms of hepatitis B and D), West Nile and Zika viruses. The diagnosis of YF is made by detection of the virus, or of its genetic material in serum or tissue using virus isolation or Reverse transcription polymerase chain reaction (RT-PCR). It can also be made by means of serological testing for the

detection of antibodies: Enzyme Linked Immunosorbent Assay (ELISA) or Plaque Reduction Neutralization Test (PRNT).[1] There is no cure for YF, treatment involves symptomatic treatment. Vaccination therefore remains the most effective from of prevention. [1]

Nigeria is a country with high risk of YF transmission.[3] The first reported YF outbreak in Nigeria occurred in 1931 with eight reported cases.[3,4] Subsequent outbreaks have occurred in various parts of the country with some notable epidemics occurring between 1952-53 in the Eastern region, 1969 in the Jos region and 1986-87 in the Southern region. [3,5,6] Pockets of other outbreaks have occurred in Nigeria over the years. In 2017, Nigeria experienced a YF outbreak with confirmed cases reported in six states (Kano, Kebbi, Kogi, Kwara, Nasarawa and Zamfara) and suspected cases reported in 16 states (Abia, Anambra, Borno, Edo, Enugu, Kano, Katsina, Kogi, Kwara, Kebbi, Lagos, Nasarawa, Niger, Oyo, Plateau, and Zamfara).[7] In 2018, the number of states with active YF increased to seven (Niger). This should not come as a surprise because over the last 10 years, there has been an increase in the number of countries reporting YF to the World Health Organisation (WHO), especially in West Africa where 93 % of the countries notified cases in the past 4 years, a 30% increase compared to the period 1995-1999.[8]

The risk of large and uncontrollable outbreaks in urban areas in Africa is more likely than ever. Many African cities now have an increasing number of overcrowded, informal settlements, or 'shanty towns', characterized by low-grade housing, poor roads, inadequate water supplies, sanitation and waste management services. Most people who live here have no access to running water and store drinking water in containers which often serve as breeding sites for the mosquito *Aedes aegypti*. The lack of public sanitation services in these cities prevent the removal of other artificial breeding sites such as metal cans, tires or broken-down vehicles.[8]

2. Materials and Methods

2.1 Study Area

Plateau state is in Nigeria's middle belt. It has an area of 26,899 square kilometres, an estimated population of about three million people and is located between latitude 80°24'N and longitude 80°32' and 100°38' east.[9] The state is named after the picturesque Jos, the state capital, a mountainous area in the north, with captivating rock formations. The altitude ranges from around 1,200 meters (about 4000 feet) to a peak of 1,829 metres above sea level in the Shere Hills range near Jos. The state is surrounded by Bauchi to the north east, Kaduna to the North West, Nasarawa to the South West and Taraba to the South East. It has an annual temperature between 18 and 22°C. The people are predominantly farmers. Tribes like Berom, Taroh, Ngas and others make up about forty languages.[9]

2.2 Study Design

This was a case series report conducted on the YF outbreak in Plateau state by interviewing the cases, contacts and health workers involved in the management. Hospital records, laboratory and surveillance data from the Plateau State Epidemiological Unit were reviewed.

2.3 Operational definitions [1,7]

- A suspected case is any person with acute onset of fever, with jaundice appearing within 14 days of onset of the first symptoms.
- A probable case is a suspected case; and one of the following: presence of yellow fever IgM antibody in the absence of yellow fever immunization within 30 days before onset of illness; or positive post-mortem liver histopathology; or epidemiological link to a confirmed case or an outbreak.
- A confirmed case is a probable case; and absence of yellow fever immunization within 30 days before onset of illness; and one of the following: detection of yellow fever-specific IgM; or detection of fourfold increase in yellow fever IgM, or IgG antibody titres between acute and convalescent serum samples, or both; or detection of yellow fever-specific neutralizing antibodies or absence of yellow fever immunization within 14 days before onset of illness; and one of the following: detection of yellow fever virus genome in blood or other organs by PCR; or detection of yellow fever antigen in blood, liver or other organs by immunoassay; or isolation of yellow fever virus.

Confirmatory laboratory diagnosis was made by Enzyme Linked Immunosorbent Assay Immunoglobulin M (ELISA-IgM). This was performed at the Central Public Health Laboratory, Lagos state. The same samples were then sent to the WHO Reference Regional Laboratory in Dakar, Senegal for formal confirmation by Plaque Reduction Neutralization Test (PRNT).[10]

2.4 Ethical Consideration

Ethical approval was obtained from the Health Research Ethics Committee, Jos University Teaching Hospital and Plateau State Ministry of Health (SMoH), Nigeria for the study to be carried out.

3. Results

On 29th September 2017, two patients presented to Bingham University Teaching Hospital with two weeks history of ill-health.

Case 1: A 6-year-old girl from Tudun-Wada, Jos Plateau state presented with fever, abdominal pain, sore throat, nausea, and jaundice. On physical examination, symptoms include fever (38.6°C) conjunctival pallor, an inflamed pharynx and coated tongue, transmitted chest sounds, a tender abdomen with a liver span of 2-3cm below the

coastal margin and a weight of 18 kg (90 % of expected). For children aged 1-6 years, the formula: 2n + 8 (where n = age in years) was applied.[11] Laboratory investigations revealed packed cell volume: 18%, white blood cell count: 3,200mm^3 (neutrophils 60%, lymphocytes 37%, monocytes 16%, eosinophils 1%, basophils 1%), platelet count: 42x10^3/uL, Liver function test: Aspartate aminotransferase (AST) 398U/L, Alanine aminotransferase (ALT) 96U/L, urinalysis (glucose +). Electrolytes, Urea and Creatinine (EUC): Na^+ 145mmol/L, K^+ 4.1mmol/L, Cl^- 113mmo/L, Cr^- 12umol/L. Confirmatory test for YF was positive by ELISA-IgM. On admission, serial weighing and temperature charts were kept (figure 1). Treatment included intravenous Ribavirin (30mg/kg/day), ceftriaxone, vitamin C and E, intravenous fluids, paracetamol, blood transfusion and nutritional rehabilitation. The patient was discharged after 18 days with a weight of 15.9kg (79.5% of expected), temperature 37^{o}C, packed cell volume (PCV) of 26%, Aspartate aminotransferase (AST) 56U/L and Alanine aminotransferase (ALT) 22U/L.

Case 2: A 10-year-old boy from the same family as *case 1* presented with fever, abdominal pain, diarrhoea, vomiting and jaundice. On physical examination, symptoms included a temperature of (39.0^{o}C, conjunctival pallor, a tender abdomen with a liver span of 3-4cm below the coastal margin and a weight of 24kg (68.6% of expected). For children aged 7-12 years, the formula: 7n-5/2, (where n = age in years) was used. [11] Laboratory investigations revealed packed cell volume: 13%, white blood cell count: 11,800mm^3 (neutrophils 79%, lymphocytes 32%, monocytes 16%, eosinophils 1%, basophils 1%), platelet count: 50x10^3/uL, Liver function test: AST: 315U/L, ALT: 126U/L, urinalysis (protein ++, blood+, leucocytes +), EUC: Na^+ 149mmol/L, K^+ 5.4mmol/L, Cl^- 115mmo/L, Cr^- 29umol/L. Confirmatory test for YF and Lassa fever were positive by ELISA-IgM and Polymerase Chain Reaction (PCR) respectively. On admission, serial weighing and temperature charts were kept (figure 1 and 2). Treatment included intravenous Ribavirin (30mg/kg/day), ceftriaxone, metronidazole, artesunate, gentamicin, vitamin C and E, intravenous fluids, paracetamol, blood transfusion and nutritional rehabilitation. The patient was discharged after 18 days with a weight of 24.2kg (69.1% of expected), temperature 37.3^{o}C, of 28%, AST 76U/L, ALT 41U/L.

Twenty-three contacts (17 healthcare workers, 6 family members) were traced and daily temperature monitoring instituted (table 2). None of the contacts developed any symptoms of YF.

Table 1: Information of contacts

SN	Sex	Age (years)	Type of contact	LGA	Relation to the cases
1	M	54	1,2,3,4	Jos/North	FM
2	F	31	1,2,3,4	Jos/North	FM
3	M	15	3,4	Jos/North	FM
4	M	26	3,4	Jos/North	FM
5	M	3	2,3,4	Jos/North	FM
6	M	13	3,4	Jos/North	FM
7	M	43	2	Jos/North	HW
8	M	43	2	Jos/North	HW
9	M	37	2	Jos/North	HW
10	M	46	2	Jos/North	HW
11	M	49	2	Jos/North	HW
12	F	36	2	Jos/Nor th	HW
13	F	47	2	Jos/North	HW
14	M	27	2	Jos/North	HW
15	F	37	2	Jos/North	HW
16	F	38	2	Jos/North	HW
17	F	38	3	Jos/North	HW
18	F	39	2	Jos/North	HW
19	F	53	2	Jos/North	HW
20	F	28	2	Jos/North	HW
21	F	37	3	Jos/North	HW
22	F	28	2	Jos/North	HW
23	F	57	3	Bassa	HW

M: Male, F: Female, LGA: Local Government Area, FM: Family member, HW: Health worker

Type of Contact [12]

1 = Touched body fluids of the case (blood, vomit, saliva, urine, feces)

2 = Had direct physical contact with the body of the case (alive or dead)

3 = Touched or cleaned the linens, clothes, or dishes of the case

4 = Slept or ate in the same household as the case

Figure 1: Temperature trend in YF cases

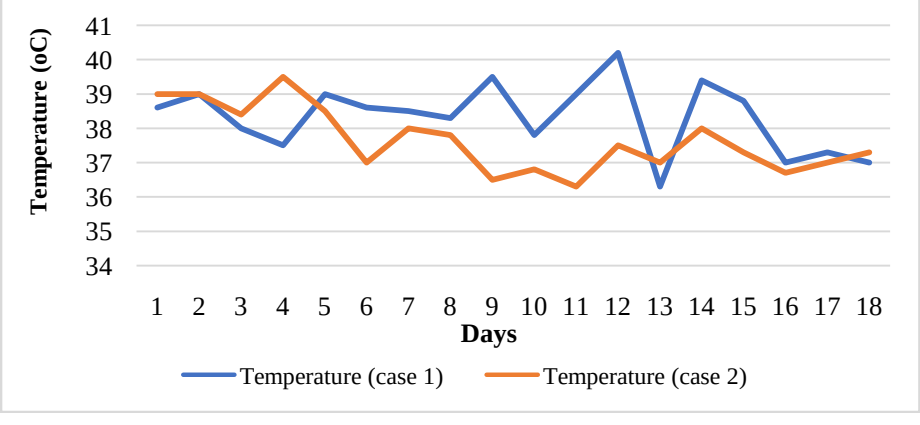
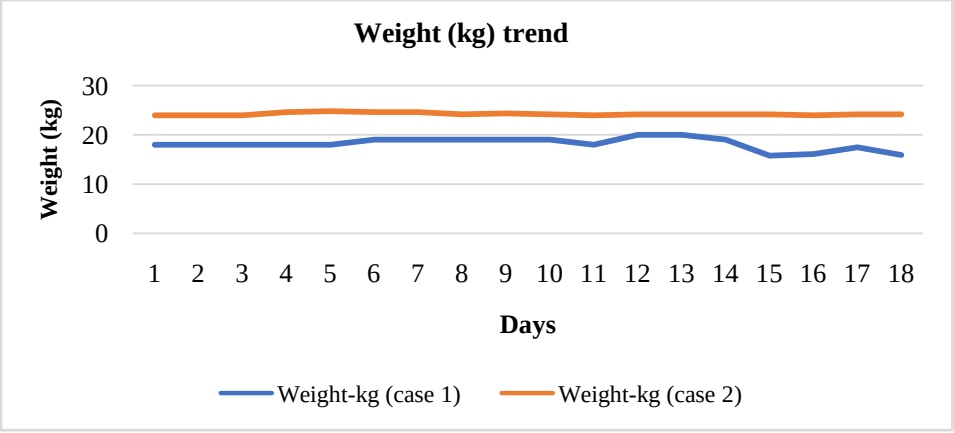


Figure 2: Weight trend in YF cases



4. Discussion

This outbreak is said to be the first reported outbreak of YF in Plateau state after the 1969 epidemic in Jos which had an estimate of 100,000 YF cases occurring.[4] In this current outbreak, prior to presentation at the hospital, the patients had contact with their 80-year-old ill grandmother, who eventually died following a history of persistent diarrhoea. Before her death, she was resident at Kwande Local Government Area (LGA), a border-town with Cameroon, which has been identified as a high risk YF area.[3,13]

The ages of the patients of six and ten years old were similar to the index case of the current Nigerian outbreak who was a seven-year-old girl from Ifelodun LGA, Kwara state. [5] She presented on 15th September, 2017 with fever, jaundice, abdominal pain, haematemesis, with no record of previous vaccination and no history of recent travel outside of the state in the 2 years prior to illness onset. The cases in this instance also presented with fever, jaundice, abdominal pain and history of recent travel, but no haematemesis with record of previous vaccination. None of these cases developed any severe manifestations; they both had full recovery with no complications.

The basic tests needed for laboratory confirmation of YF during an outbreak are ELISA to measure YF virus, IgM and RT-PCR. Other flaviruses such as Dengue virus, West Nile virus and Zika virus may give a false positive yellow fever ELISA result so, an ELISA panel for other expected flaviviruses, (as determined by local epidemiology) should be performed as a differential diagnosis.[14] Because strong cross-reactions occur between antibodies induced by Flavivirus infections, it is difficult to identify the exact pathogens. Hence, another confirmatory test, the PRNT is advantageous in regions where two or more flaviviruses circulate together.[15] The patients were laboratory confirmed at the Central Public Health Laboratory, Lagos by ELISA IgM (antibody) test, which was followed by the sero-neutralizing test (PRNT) for YF by the Institute Pasteur de Dakar, Senegal, a WHO regional reference laboratory for YF. The positive YF results returned negative on PRNT.[7] This was the case in some of the suspected cases found in some other states.[7] This led to the conclusion that the reported YF cases were not YF cases after all. These could have been Lassa fever or other Flaviviruses, as the male case also tested positive for Lassa fever at the Central Public Health Laboratory. There is no confirmation of the vector mosquito or mosquitoes involved in this wide-spread outbreak.[16]

The number of suspected cases continues to increase in Nigeria. This increase is attributed to an increasing number of overcrowded, informal settlements, or 'shanty towns', characterized by low-grade housing, poor roads, inadequate water supplies, sanitation and waste management services. Most people who live here have no access to running water and store drinking water in containers, which often serve as breeding sites for the mosquito *Aedes aegypti*. The absence and inadequate provision of public sanitation services in these cities prevent the removal of other artificial breeding sites such as metal cans, tires or broken-down vehicles. [8] This was confirmed by paying a visit to the residence of the Plateau cases. The house was in a poor sanitary condition, surrounded by overgrown bushes, presence of rat faeces and artificial breeding sites for mosquitoes. In the light of this, Plateau SMoH and relevant agencies like the Ministry of Works and Housing, Education, Environment and Water resources need to intensify advocacy, health education and enforcement of sanitation laws as vector control measures. Surveillance for rapid case finding and proactive vaccination also need to be intensified to forestall a disaster.

5. Conclusion

The potential for a major urban outbreak of Yellow Fever in Plateau state and Nigeria is already present. Hence, it is critical that a sustained response starts today. Plateau state ministry of health and relevant agencies need to intensify advocacy, health education and enforcement of sanitation laws as vector control measures. Surveillance for rapid case finding and proactive vaccination also need to be intensified to forestall a disaster.

Conflict of Interest

The authors have no conflicts of interest to declare.

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