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Case report

The role of the laboratory in outbreak investigation of viral haemorrhagic fever in Nigeria, 2014

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Abstract

On 26th March 2014, a newspaper published an article on the death of a 15 year old female student who attended a private university in Nasarawa state from suspected VHF; presumably Ebola. We investigated to know the cause of death, identified the agent and the source and proposed recommendations. We defined a suspected a case of Viral Haemorrhagic Fever (VHF) as any person with onset of fever and no response to usual causes of fever and at least one of the following signs: bloody diarrhoea, bleeding from gums, bleeding into skin (purpura), bleeding into eyes and urine within and around Abuja from 9th February 2014 to 2nd April 2014. We reviewed the hospital records of the index case and re-tested stored blood samples. We searched actively for contacts with the index case in hospitals where she was treated before her demise. Hospital staff were line listed at the various hospitals. We confirmed one death (index case) a 15 year old female who died on 15th March 2014. Serum sample tested positive for Dengue virus serotypes 1,2,3 and 4 using ELISA and PCR. We implemented VHF detection, management and reporting for health professionals in the country. We recommended sero-surveillance and entomological surveys be done to determine the prevalence of Dengue virus and its vector in Abuja and Nasarawa state. Dengue and other VHFs are emerging diseases that can easily be missed or misdiagnosed in early stages. Equipping laboratories and improving surveillance can help in early detection, management and epidemic aversion.

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Introduction

VHFs refer to a group of illnesses that are caused by several distinct families of viruses: arenaviruses, filoviruses, bunyaviruses and flaviviruses [1]. The term is used to describe a severe multisystem syndrome; characteristically, the overall vascular system is damaged, and the body´s ability to regulate itself is impaired [1]. These viruses share a number of features: they are all enveloped RNA viruses, their survival is dependent on an animal or insect host (natural reservoir), the viruses are geographically restricted to the areas where their host species live, humans are not the natural reservoir but are infected when they come into contact with infected hosts and after the accidental transmission from the animal host, humans can transmit the virus to one another, outbreaks occur sporadically and irregularly and with a few exceptions, there is no cure or established drug treatment for VHFs [1, 2] (Figure 1). Lassa fever is endemic in parts of West Africa; it is responsible for an estimated 100,000 - 300,000 infections annually, with 5,000 deaths [3]. Approximately 150,000 to 200,000 cases of Hantavirus hemorrhagic fever with renal syndrome are hospitalized each year worldwide, with most of the cases occurring in the developing countries [4]. Ebola virus is a febrile, rapidly fatal hemorrhagic illness; a recent widespread outbreak involving several African countries including Nigeria has been ongoing since 2014. Caregivers who work both at home and in hospitals are at greatest risk for exposure [5] as outbreaks appear to propagate in hospital settings. Yellow fever and dengue fever (DENV) viruses are the most well known flaviviruses; both are arthropod-borne. The yellow fever burden in Africa was estimated for the year 2013 as 130,000 cases with fever including 78,000 deaths, taking into account the level of vaccination coverage [6]. A study in Nigeria showed that the prevalence of immunity was 38% for DENV-1 infection, 45% for DENV-2 infection. This study also showed an increase in prevalence of antibodies against DENV with age, which suggests endemic infection [7]. The surveillance goal for VHF is early detection of cases and outbreaks, rapid investigation of all suspected cases with contact tracing, and early laboratory verification of the aetiology of all suspected cases [8]. But during epidemics, most infected patients do not show haemorrhagic symptoms [8]; symptoms are usually nonspecific and may include fever, headache, myalgia, etc and this makes early diagnosis difficult without appropriate blood assays. In regions to which malaria is endemic, >70% of febrile illnesses are treated as presumptive malaria, often without proper medical examination and laboratory diagnosis [9]. Under these prevailing practices, there is a real potential of misdiagnosing other febrile illnesses as malaria. Although vaccines have been developed for some of these viruses and Ribavirin is considered helpful if given early in the course of Lassa fever infection, clinical management of VHF is still primarily supportive [8]. To implement timely public health measures, early diagnosis is a necessity. But low detection rates of VHF persist in potentially endemic regions such as Nigeria due to clinical oversight and lack of appropriate diagnostic facilities.

Outbreak setting: a newspaper article published on 26th March 2014 documented the death of a 15 year old female student in a private university in Nasarawa, who died from an unknown Viral Haemorrhagic Fever (VHF) suspected to be Ebola. The patient was reported to have visited several hospitals before her demise. This newspaper article was against a background of an Ebola scare in West Africa following a confirmed Ebola outbreak in Guinea; as at 25th March 2014, 103 cases have been reported with 66 deaths (4 of whom are health care workers) and 15 have been laboratory confirmed. An official from the Federal Capital Territory (F.C.T.) Public Health Office has also given out unconfirmed and unauthorized reports to the media through an interview, stating that the case died from Ebola; this led to public scare and the parents of the deceased were upset on receiving such news from the media as the laboratory results had not yet been communicated to them. We investigated the outbreak from 28th March - 4th April 2014 with the following objectives: to describe magnitude of the outbreak and confirm the diagnosis through laboratory testing; to conduct contact tracing in Abuja and Nasarawa states; to proffer recommendations to the State Ministry of Health and State Epidemiologist on how to improve Viral Hemorrhagic Fever surveillance in health facilities and in the community.

Patient and observation

An alert of a possible outbreak of any of the viral haemorrhagic fevers especially Ebola was sent by the Federal Ministry of Health on the 24th March 2014 to all state epidemiologists to alert health workers in their state. We defined a suspected a case of viral haemorrhagic fever as any person with onset of fever and no response to usual causes of fever and at least one of the following signs; bloody diarrhoea, bleeding from gums, bleeding into skin (purpura), bleeding into eyes and urine, within and around Abuja from 9th February 2014 to 2nd April 2014 [8]. A confirmed case

is a suspected case with laboratory confirmation (positive IgM antibody or viral isolation) or epidemiologically linked to confirmed cases within the same time frame. Family members were also contacted to watch out for any signs and symptoms of VHF and if any to contact any of the investigators.

We collected information from the 3 hospitals visited by the deceased; 2 in Abuja and 1 in Edo State, before her demise. We searched actively for contacts with the index case in all the hospitals and staff members were line listed. Her case notes in the 3 hospitals were also reviewed to determine the clinical symptoms and line of management. Aliquots of the patient's blood and urine were taken and investigations conducted at 2 reference laboratories in Nigeria. Blood samples of the case's close relatives were also taken to confirm any of the viral haemorrhagic fevers.

Her first visit was to a private hospital in Abuja was on the 7th of March, 2014. She presented with malaise and was given some medications, but no laboratory investigations were conducted. At the second visit on the 10th of March, 2014, she presented with haemorrhagic symptoms; temperature was 39.0°C, pulse rate 120bpm. Laboratory investigations demonstrated leucopenia (2.6 x 10^9/L) and mild anaemia (29.3%). Erythrocyte Sedimentation Rate (ESR) was high (93mm/hr). Due to the new symptoms noticed, she was referred to a teaching hospital in Abuja. That same day, she presented at the paediatric department of the teaching hospital with a history of generalized joint pain of 1 week but no joint swelling. The pain was severe enough to prevent normal daily activities. She also complained of high grade and intermittent fever for 5 days, non-productive cough for 5 days with no associated difficulty in breathing or chest pain, non-projectile vomiting of 2 days duration with associated anorexia and passage of bloody urine. There was also nasal bleeding lasting for a day; bilateral, spontaneous and continuous. She was a known peptic ulcer disease patient and denied any history of recent travel outside the country or regular environment (home, school) or contact with rodents. On examination, she was moderately pale, febrile (39.6°C) and anicteric; no petechial rash i.e. submucosal bleeding was noticed on the lips. There were no significant findings on examination of other systems.

Anaemia (28%), leucopenia (3.3 x 10^9/L) and thrombocytopenia (29 x 10^9/L) were demonstrated; blood was detected in the urine. Prothrombin time and Partial Thromboplastin Time in Kaolin (PTTK) were prolonged while the International Normalized Ratio (INR) was normal. An assessment of Viral Haemorrhagic Fever (VHF) with septicaemia was made. Supportive care was instituted: blood transfusion with one pint, intravenous antibiotics, intravenous fluids and antimalarials were given. She was referred to the VHF management centre on the 12thof March, 2014 in Edo State, Nigeria. At this center, she was also transfused with one pint and other supportive care was continued. She died on the 15th of March, 2014 (Figure 2).

Malaria parasite test, urinalysis, full blood count, serum antibody and antigen tests for Lassa, Ebola, Dengue, Tick borne encephalitis, West Nile and Japanese encephalitis viruses were also conducted at the health facility in Edo state. Enzyme-linked immunosorbent assay (ELISA) test detected IgM antibodies to DENV serotypes 1, 2, 3 and 4 in the blood samples and this was confirmed with the aid of Polymerase Chain Reaction (PCR) test at another referral laboratory in Lagos, which detected DENV antigens. No other case of viral haemorrhagic was documented at Abuja or Nasarawa during the period.

Discussion

Dengue fever is commoner in children aged 10-19 years in Northern Nigeria [10], congruent with the patient's age. A higher prevalence of Dengue infection has also been demonstrated in females [10] but a male preponderance was noticed in a study conducted in North-central part of Nigeria [11]. A study in Nigeria determined that immunity in adults to the virus was significantly higher than in children younger than 20 years [7], this might have increased her vulnerability and eventual succumbing to the disease. The patients' symptoms suggest internal haemorrhage; its risk of occurrence increases as age increases [12] and thrombocytopenia is the commonest laboratory finding [13]. The patient's diagnosis of associated septicemia is also comparable to a study which indicated that patients with DHF often have dual infections such as bacteraemia [14]. The deceased was positive for the 4 serotypes; two or more separate attacks of the four different serotypes of the dengue virus is more likely to cause

Dengue Hemorrhagic Fever (DHF) [15] and other life-threatening complications [16]. All serotypes of DENV have been demonstrated in Nigeria [7, 10] even though endemicity for each serotype is still poorly documented. This case might have been missed if it was not published in a newspaper. Dengue and VHF surveillance in Nigeria is low and this is affected by the lack of routine laboratory diagnosis [17] and the index of suspicion for Dengue and VHF is low in most health facilities [18]. This investigation depicts the difficulties encountered in differentiating VHFs from other febrile illnesses based solely on clinical characteristics without performing laboratory tests. A successful clinical outcome requires efficient and early diagnosis of cases provided by accurate differential diagnosis, rapid laboratory assessment/confirmation, and early response to severe disease [19]. Sample collection limitations, time and labour intensive methods of diagnosis, the need for laboratories at bio-safety level 3, professional training of the personnel are some of the requirements limit the routine use VHF diagnostic tools, especially in developing countries [18]. The limitation of this investigation was that an entomological study was not carried to determine the prevalence of Aedes aegypti in areas at risk though, geographical boundaries of the vector has been established worldwide [20]. Her close relatives declined screening for Dengue virus infection; this would have given an insight on the prevalence of the serotypes amongst close contacts. The following public health actions were conducted: the public was informed promptly on the cause of the VHF and precautionary measures taken so far. Furthermore, the team provided the hospitals visited by the case in Abuja, with IEC materials on "Infection Control in Screening Ebola Suspected Cases and Contacts in Health Facility Entry Clinics" and "General Information on Viral Haemorrhagic Fever". Also, trainings were conducted for hospital workers on the "Diagnosis and Management of VHFs" in the six geopolitical zones in the country.

It was recommended that sero-surveillance of blood banks for Dengue virus be conducted in Abuja and Nasarawa state, that the Arbovirus laboratory in Nigeria conduct and publish an entomological survey of Aedes aegypti in the country and that the Federal Ministry of Health liaise with laboratory companies to develop an IgM antigen ELISA rapid test kit for Dengue, Lassa and Ebola viruses. It was also recommended that active surveillance be intensified at all ports of entry into the country in the face of the threat of other VHF via laboratory screening of suspected case and the health facilities visited by the case construct isolation ward. Furthermore, we advocated that VHF specific personal protective equipment (PPE) be made readily available at all health facilities in the country, that health facility surveillance and reporting of VHF suspects be intensified, that access to case definitions for VHFs and protective equipment be improved and that community awareness on VHF prevention and reporting be increased.

Conclusion

Dengue and other VHFs are emerging diseases that can easily be missed or misdiagnosed in early stages. Equipping laboratories and improving surveillance can help in early detection, management and epidemic aversion.

Competing interests

The authors declare no competing interest.

Authors' contributions

Abiodun Oladejo, Olaolu Moses Aderinola, Musa Muhammda Abdullahi, Whenayon Simeon Ajisegiri, Abimbola Folakemi Aman-Oloniyo, Ejoh Ojong Ojong, Samuel Sha'aibu, Patrick Nguku, Peter Nsubuga, Adebola Olayinka, Akin Oyemakinde, Abdulsalami Nasidi made substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data for the work; revising it critically for important intellectual content; final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and agreed

to the final version of this manuscript and have equally contributed to its content and to the management of the case. All authors have read and agreed to the final version of this manuscript and have equally contributed to its content and to the management of the case.

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Figures

Figure 1: Map of africa depicting the geographical distribution of some viral hemorrhagic fevers

Figure 2: Timeline of events and outbreak investigation

Figure 3: Geographic representation of states at risk of the suspected Viral Hemorrhagic outbreak in Abuja, Nasarawa and Edo states, Nigeria, 2014

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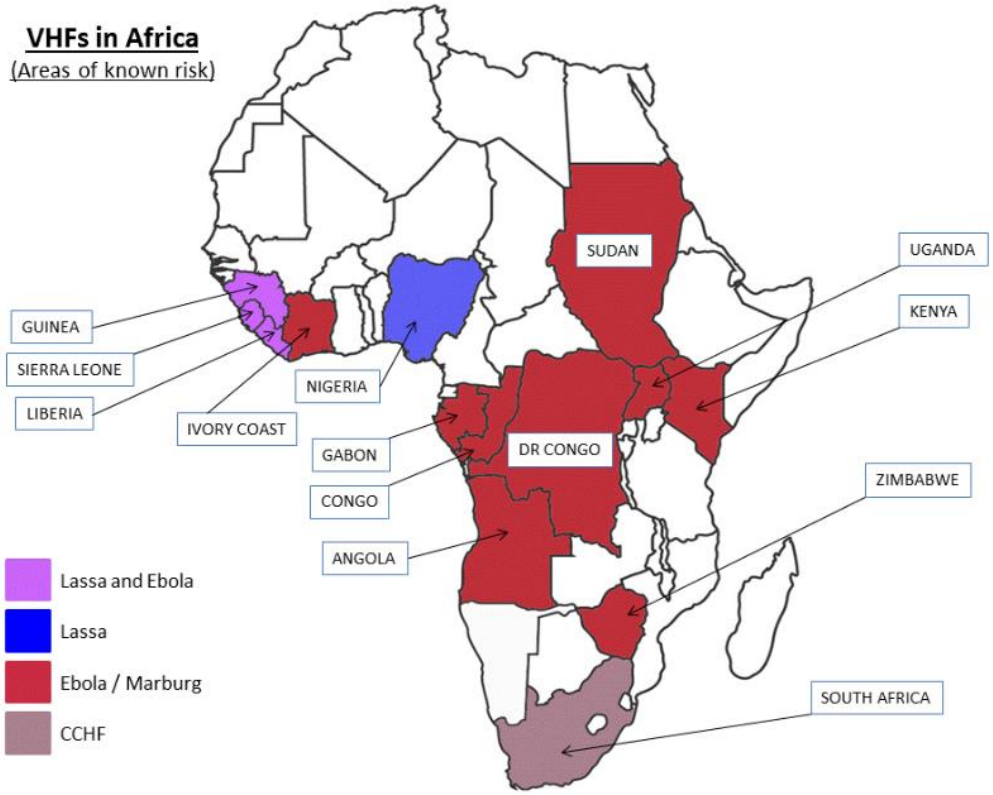

Figure 1: Map of Africa depicting the geographical distribution of some viral hemorrhagic fevers

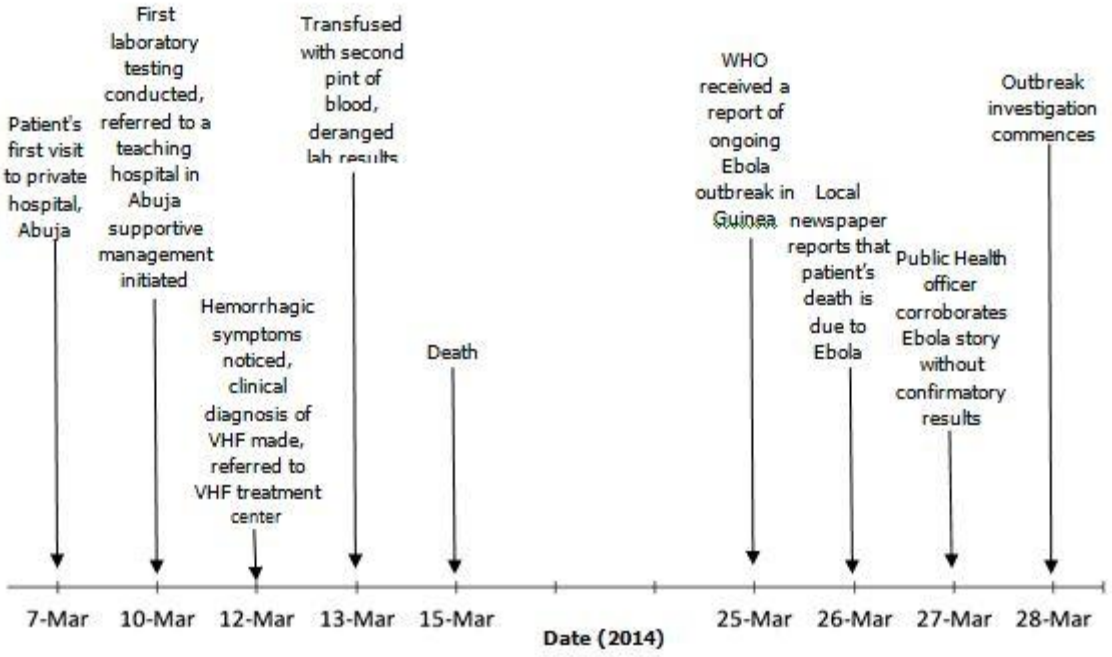

Figure 2: Timeline of events and outbreak investigation

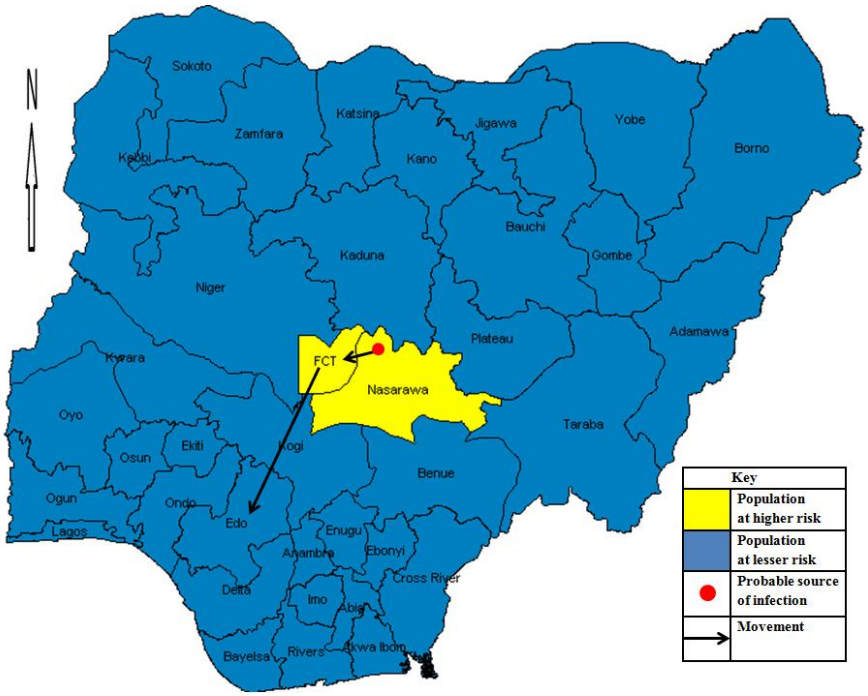

Figure 3: Geographic representation of states at risk of the suspected Viral Hemorrhagic outbreak in Abuja, Nasarawa and Edo states, Nigeria, 2014