Clinical Presentation and Care of Patients with Ebola Virus Disease in the China Ebola Treatment Unit, Liberia

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SUMMARY: In order to evaluate the clinical characteristics of confirmed Ebola Virus Disease (EVD) patients admitted to the China Ebola Treatment Unit (China ETU) between January 2015 and March 2015, we retrospectively analyzed clinical symptoms, treatment, and epidemiologic features of 5 patients with confirmed EVD, and reviewed the relevant medical literature. Of these, 3 patients survived, and 2 died. The time interval from the onset of symptoms to the negative PCR test for Ebola virus in the 3 survivors was 14–18 days. All survivors reported direct contact with confirmed EVD patients up to 21 days prior to admission. All patients developed a fever, fatigue, and anorexia. Fever was generally the first symptom to develop, followed by a gastrointestinal phase characterized by vomiting/nausea (3 cases, 60%), diarrhea (3 cases), and abdominal pain (4 cases, 80%). Three patients (60%) reported joint pain, muscle pain, and conjunctival hemorrhage, respectively, and 2 patients (40%) developed a headache. We concluded that strict isolation and interruption of the route of transmission were required for suspected or confirmed EVD patients. The main treatment strategies were supportive care, maintenance of blood volume and electrolyte balance, and the prevention of complications.

INTRODUCTION

Ebola virus disease (EVD) is an acute and severe disease of humans, and it is caused by Ebola viruses. It is often fatal if untreated. Historically, the highest reported mortality rate was up to 90% (1). Since December 2013, the largest and most widespread outbreak of EVD has ravaged West Africa. Genetic similarity across the 2014 samples suggested that this was a typical outbreak resulting from the introduction of the virus into humans from a wild animal reservoir and sustained by human-to-human transmission (2). Signs and symptoms of EVD typically include fever, vomiting, diarrhea, internal or external bleeding, and multiorgan failure. This epidemic of unprecedented scale has already resulted in over 27,443 confirmed, probable, and suspected cases, and 11,207 reported deaths as of June 21, 2015 according to data released by the World Health Organization (WHO) (3). During a 3-month period between January 14 and March 14, 2015, 42 suspected EVD patients were admitted to the Chinese Ebola Treatment Unit (China ETU) in Monrovia, Liberia. Five of these patients were later confirmed positive for EVD. Here, we describe the clinical characteristics of the patients at presentation, the clinical course of EVD, and the outcomes of all patients admitted to the China ETU, as transmission of EBV infection progressed, in order to contribute to a greater understanding of the disease.

MATERIALS AND METHODS

Patients: We performed a retrospective analysis of the medical records of all patients with suspected or confirmed EVD admitted to the China ETU in Monrovia, Liberia, between January 14 and March 14, 2015. Patients were referred if they presented with an illness that met the WHO case definition for EVD.

Planning of the China ETU and training of the medical team: The China ETU in Liberia is a field hospital, installed by the Central Military Commission of China. The medical team consisted of military troops and medical staff from 19 hospitals in China. Military management of the China ETU required that all employees were adhered to a rigid schedule. Human and financial resources were controlled by a single management group. The following departments were planned before the establishment of the ETU: Command, Outpatient Records, Observation, Treatment, Medical Technology Support, Health and Epidemic Prevention, and Logistics Support. The infection prevention and control team was established in Liberia, when its crucial role was recognized. The team was responsible for a range of tasks, including personal prevention training and exercises, and supervision of medical staff. The shortage of supplies in Liberia was anticipated; hence we purchased generators, water purifiers, and routine items, such as tables and cabinets. We established a psychological counseling office and a reading room, and we also organized activities to help reduce psychological stress of our team.
The medical staff originated from 19 hospitals across China, with team members specialized in infectious diseases, respiratory medicine, intensive care, and nursing. All members underwent an infectious disease management training on the treatment and care of Ebola patients provided by the infection specialist within the team. The medical team was also educated on the symptoms, diagnoses, and treatments of other common infectious diseases in Africa.

**Ebola virus (EBOV) diagnosis**: Laboratory confirmation of EVD was made based on the results of real-time reverse-transcription (RT)-PCR assay in an EBOV laboratory established at National Bio-Medical Institute of Liberia. Laboratory staff members used rapid Taqman RT-PCR assays for the detection of EBOV using 5-Carboxyfluorescein (5-FAM) and 3-Carboxytetramethyl rhodamine (3-TAMRA) tagged probes and a portable Smart-Cycler TD (Cepheid, Sunnyvale, CA, USA).

**Clinical management**: Patients were treated according to protocols established for viral hemorrhagic fever by Medecins sans Frontieres and the WHO urgent interim guidance for case management, endorsed by the Chinese Ministry of Health (4,5). The China ETU comprised 45 doctors and 64 nurses, and included 100 beds. Each patient admitted to the unit was placed in isolation. All patients with symptoms were admitted to the observation ward and were transferred to the treatment ward after laboratory confirmation of EVD. Supervisory system with an intercom was installed by each bed. Pulse oximeter monitors were routinely used to monitor pulse and blood oxygen saturation. Oxygen was supplied if necessary, based on the results. Oral or intravenous rehydration was administered to all treated patients. Antibiotics were administered empirically. Anti-malaria treatment, consisting of dihydroartemisinin and piperaquine phosphate tablets, was performed until the test results proved negative. Symptomatic treatment and treatment of underlying diseases were provided when necessary. Cold compresses were applied to the head, axillary, and inguinal region to alleviate mild fever, and paracetamol was used to treat high temperature. When negative EVD test results were confirmed, the patients were transferred to other facilities, if necessary, or discharged.

**Ethics and biosafety review**: The institutional review board and the ethics committee at the People’s Liberation Army (PLA) General Hospital, and the Liberia Ethics and Scientific Review Committee approved this project. These committees waived the requirement for informed consent during the West African Ebola outbreak. All clinical samples and data were collected for routine patient care and for public health interventions. The institutional biosafety committees at the PLA General Hospital and the Liberia Ethics and Scientific Review Committee reviewed and approved biosafety protocols for this study.

**Data collection and analysis**: Data-collection forms included epidemiologic and demographic data, exposure history, occupation and recent travel, symptoms, date of onset, vital signs at admission, and medical history. The followings were also recorded: complications, treatment, laboratory test results when available, and outcome. The clinical care team collected data from patients who were admitted to the China EVD treatment units. Admission data were reviewed daily by clinicians. Results of descriptive analyses are reported as frequencies, proportions, and arithmetic means and medians.

**RESULTS**

**Patients**: In the China ETU, a total of 42 patients who presented with an illness that met the definition for suspected EVD were tested between January 14 and March 14, 2015, by means of conventional RT-PCR. Five (11.9%) patients had positive results on testing for EBOV. Of these, 4 (80%) were identified by a blood sample. One (20%) patient tested negative although EBOV was detected in the saliva after death of the patient. The patients were aged 32–58 years old. Three (60%) patients of the confirmed EBOV women were discharged after a mean duration of 18 days (Tables 1 and 2). The three patients who survived EVD were discharged after a mean duration of illness of 14–18 days. Discharge occurred when a patient was asymptomatic for at least 48 h and blood samples were negative for EBOV on RT-PCR assay. An overall mortality rate of EBOV positive patient was of 40%.

**Symptoms, vital signs, physical findings**: Data regarding clinical signs and symptoms at the time of presentation were available for all 5 patients. Vital signs were recorded at presentation. All patients were conscious on admission, with a fever and normal or slightly elevated blood pressure except for 1 case whose symptoms were unknown. Although biased by the case definition of EBV, fever, fatigue and loss of appetite were observed in all 5 patients. One patient died following a high fever over 8 days. Another patient deteriorated rapidly with fever complicated by gastrointestinal hemorrhage, and died within 12 h of admission. Fever was relieved in the surviving patients after treatment (Fig. 1). In addition, other symptoms including nausea/vomiting (60% of cases), diarrhea (60%), abdominal pain (80%), joint and muscular pain (60%), and headache (40%), cough and dyspnea were observed in 2 (40%) patients, and conjunctival hemorrhage in 3.
Table 1. Characteristics, vital signs, and time course of clinical progression of 5 patients with confirmed Ebola virus disease (EVD)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49</td>
<td>35</td>
<td>56</td>
<td>32</td>
<td>58</td>
</tr>
<tr>
<td>Gender</td>
<td>W</td>
<td>M</td>
<td>M</td>
<td>W</td>
<td>W</td>
</tr>
<tr>
<td>Exposure history (within 21 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact with suspected or confirmed EVD patient</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Death of family members</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Funeral attendance</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Visit to the infected area</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Vital signs at admission</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>39.0</td>
<td>37.8</td>
<td>37.6</td>
<td>37.2</td>
<td>38.4</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>115</td>
<td>78</td>
<td>91</td>
<td>ND</td>
<td>74</td>
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<td>Respiratory rate (times/min)</td>
<td>30</td>
<td>18</td>
<td>22</td>
<td>ND</td>
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<tr>
<td>Blood pressure (mmHg)</td>
<td>131/98</td>
<td>120/97</td>
<td>130/80</td>
<td>ND</td>
<td>126/78</td>
</tr>
<tr>
<td>Pulse oxymetry oxygen saturation (SPO2, %)</td>
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<td>96</td>
<td>97</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>Consciousness</td>
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<td>Clear</td>
<td>Clear</td>
<td>Clear</td>
<td>Clear</td>
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<td>Known coexisting medical condition</td>
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<td>-</td>
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<tr>
<td>Interval from onset of symptoms (days)</td>
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<td>To hospital admission</td>
<td>7</td>
<td>4</td>
<td>4</td>
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<tr>
<td>To negative PCR</td>
<td>18</td>
<td>14</td>
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<td>14</td>
</tr>
<tr>
<td>To death</td>
<td>-</td>
<td>-</td>
<td>12</td>
<td>5</td>
<td>-</td>
</tr>
</tbody>
</table>

W, woman; M, man; +, positive; -, negative; ND, no data.

Table 2. Therapies and prognosis of the 5 patients hospitalized for EVD

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Oral</th>
<th>Intravenous</th>
<th>Therapy</th>
<th>Antibiotics</th>
<th>Antimalarials</th>
<th>Oral rehydration salts</th>
<th>Complete nutrition supplement</th>
<th>Multivitamin</th>
<th>Antipyretic and analgesic</th>
<th>Antidiarrheic drug</th>
<th>Glucocorticoid</th>
<th>Others</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Case No.</td>
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<td>2</td>
<td>3</td>
<td>4</td>
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<td></td>
</tr>
<tr>
<td>Hospitalization (days)</td>
<td>22</td>
<td>16</td>
<td>8</td>
<td>1</td>
<td>16</td>
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<td></td>
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<td></td>
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<tr>
<td>Outcome</td>
<td>cure</td>
<td>cure</td>
<td>died</td>
<td>died</td>
<td>cure</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

+, yes; -, no.

(60%) patients. One (20%) patient presented gastrointestinal hemorrhage (Table 3).

Fluid and nutrition management and symptomatic therapy: An oral rehydration solution was administered to all 5 patients, and 1 patient received intravenous fluids including amino acids, glucose, lactated Ringer’s solution, and normal saline. A standard fluid volume of 2,000–3,000 ml was administrated daily, and this was adjusted according to fever, perspiration, diarrhea, and additional sodium and potassium were supplemented if needed. If patients could tolerate oral administration, complete nutrition supplement and/or glucose were administered orally. Complete nutrition supplement is a form of oral nutrition supplement manufactured by the Third Military Hospital, Chongqing, China and consists of 18.4 g protein, 17.5 g fat, and 58.2 g carbon dehydrate per 100 g. Three times a day, 40 g of the supplement was administrated orally. Proper diets were encouraged. Multivitamin supplements were administered to all patients.

During hospitalization, antimalarial and antibacterial drugs were administered to the all patients. Oral
antibacterial drugs, including moxifloxacin and levofloxacin, were administered to 4 patients, while piperacillin/tazobactam was administrated intravenously to 1 patient with suspected lung infection. Acetylcystein and ulinastatin were administered to patients with a cough. Antacids such as omeprazole, were prescribed to prevent stress ulcers. Physical methods or paracetamol compound preparation were used to alleviate fever. In cases of poor response or severe systemic inflammation, dexamethasone (10 mg/day) or methylprednisolone (80 mg/day) were administered.

Mild diarrhea was not treated. In 2 cases of severe diarrhea, berberine and smectite were administered. Sedatives and/or analgesic drugs, such as paracetamol, tramadol hydrochloride, and diazepam were used as required. Oxygen inhalation was used in 2 severe cases. Insulin, dimethylbiguanide, and amlodipine besylate were used in 1 patient with diabetes and hypertension.

Epidemiologic history: All 5 patients confirmed EVD were from Monrovia and its peripheral areas in Liberia, an infected area. Due to the high viral load observed in the body fluids of EVD patients, which causes human-to-human transmission, all contact potentially involving body fluids was recorded. Among them, 3 had contact with confirmed EVD patients up to 21 days preceding hospitalization. One of the 3 patients was a local physician assistant who developed symptoms on day 9 of the isolation period, after contact with a confirmed EVD patient. Of the patients without confirmed contact over the past 21 days, 1 patient reported attendance to the funeral of a relative who died of unknown causes, and another patient reported the death of a family member with suspected EVD 31 days prior to hospitalization (Table 1).

Clinical course: The clinical course of the 5 EVD patients was characterized as follows. Early-stage fever typically developed over the first 1-3 days after the onset of the symptoms, accompanied by fatigue and joint pain. Gastrointestinal manifestations appeared on days 1-4 and largely consisted of abdominal pain, anorexia, nausea, vomiting, and diarrhea, accompanied by sustained fever, weakness, headache, conjunctival congestion, and chest and joint pain. Of 5 patients, 2 experienced shock, on day 5 and day 11 after the onset of the disease, respectively. This manifested as coma, tachycardia, rapid pulse, oliguria, and tachypnea. The recovery phase began 10–15 days after the onset of EVD, with gradual resolution of fever, restoration of gastrointestinal function, and increased oral intake.

DISCUSSION

EVD is a severe and often fatal disease caused by negative-sense single-stranded RNA viruses classified by the International Committee on Taxonomy of Viruses as belonging to the genus *Ebolavirus* of the Filoviridae family (6,7). West Africa is currently witnessing the most extensive EBOV outbreak recorded to date. The origin of the virus has been attributed to a zoonotic transmission from a bat to a 2-year-old boy in December 2013 (3). Ebola virus is transmitted by direct contact with body fluids, such as blood, urine, sweat, vomitus, semen, and breast milk, with an incubation period of 1–21 days, 5–9 days on average (6,8–11). Currently, there is no evidence of transmission during the incubation period. Animal models for Ebola transmission have indicated possible mucosal infection without direct contact, however, airborne transmission of Ebola remains unsupported clinically (12). In the current study all patients were from infected areas of Liberia, and reported possible contact with EVD patients. The incubation periods were consistent with previous reports and similar to those reported in previous outbreaks of EVD. Therefore, all contacts must be managed, if symptomatic, in the ETU and if non-symptomatic, in the community, as one of the central purposes of the ETU has historically been to isolate infected persons early in the course of disease in order to break the chain of transmission (6,13). Nosocomial transmission should be prevented by sufficient training and proper application of personal protective equipment.

Early symptoms of EVD are non-specific, including fever, malaise, fatigue, and muscle pain, and in some cases, headache, chest pain, rashes, and conjunctival congestion (14–17). In the late phase of the disease, secondary sepsis and hemorrhagic symptoms can develop (7,18,19). The fever persists, and by day 3–5 of the illness, gastrointestinal symptoms typically begin, with epigastric pain, nausea, vomiting, and diarrhea.

In the current outbreak of EVD, abrupt onset of symptoms, characterized by fever, general malaise, weakness, and anorexia was commonly observed (16), particularly, in the 2 patients that died of EVD. Although subconjunctival hemorrhage was observed in 3 cases (60%), severe hemorrhagic symptoms were uncommon (1 case), consistent with other reports (8,20). As highlighted by Kortepeter, et al. (18), the rarely documented hemorrhagic symptoms were inconsistent with the earlier name for the disease, Ebola hemorrhagic fever, leading to the adoption of the current name of EVD by the WHO. In the present study, gastrointestinal symptoms were common. By the time the cases had been detected, the patients had developed nausea, vomiting, and diarrhea, particularly, in the 2 patients that died of EVD. The WHO Ebola Response Team reported that 66%, 68%, and 44% of confirmed EVD patients presented with diarrhea, vomiting, and abdominal pain, respectively (8), and severe diarrhea appeared to be associated with increased mortality. This is consistent with our observations.

Ebola viruses are identified as biosafety level 4 pathogens and Centers for Disease Control and Prevention (CDC) Category A agents of bioterrorism. While monoclonal antibody-based therapies with passive immunization appear promising in changing the paradigm of EVD treatment, to date, there are no approved therapies or vaccines available to treat these infections (21–23). Therefore, current treatment remains supportive and symptomatic, including fluid and blood pressure management, electrolyte and acid-base homeostasis, oxygen saturation maintenance, and prevention of secondary complications, such as sepsis. Following EBOV entry, rapid activation of dendritic cell and macrophages triggers massive release of pro-inflammation cytokines and subsequent nitric oxide-induced vasodilation and vascular leakage, causing a drop in the effective circulating blood volume, apoptosis of lympho-
cytes, and eventually aggravation of tissue damage (15). The inflammation cascade is thus activated (19). Therefore, the primary aim of treatment is to limit or alleviate the systemic inflammatory response, prevent complications, and facilitate recovery (15,24,25). Despite the lack of specific treatment, proper strategies should include inhibition of virus replication and limiting progression of the disease to gain sufficient time for the immune system to finally eliminate the infection (24).

A previous study enrolled 581 EVD subjects and revealed that, on average, patients were admitted 3 or 4 days after the onset of symptoms, while the inpatients who died usually did so within 3 or 4 days after admission; survivors were generally hospitalized for approximately 2 weeks (26). In our study, patients were admitted 4–7 days after the onset of the symptoms, and duration of hospitalization of survivors was 16–22 days. The time lag between presentation of symptoms and admission was relatively long, particularly in patient 1, who had been contact with an EVD patient and was admitted 7 days after the presentation of the symptoms. We did not have specific data on the reason of the delayed admission, but we assume this was due to the reluctance of the patient to seek medical help, and the delay in the confirmation of her contact.

The survivors were discharged after testing negative for the Ebola virus, which occurred 14–18 days after the onset of symptoms. In resource-limited areas, such as Liberia, with poor healthcare infrastructure, the cornerstone of treatment was oral or intravenous rehydration, maintenance of electrolyte and acid-base homeostasis, and maintenance of arterial blood pressure, as well as other symptomatic and supportive treatment, involving antipyretics, analgesics, and antibiotics were guaranteed. At the same time, intense surveillance of blood pressure, pulse, oxygen saturation, and vital signs was of paramount importance to make necessary adjustment to the protocol. In our ETU, constant monitoring of arterial blood pressure, oxygen saturation, and heart rate, were implemented, and treatment including oxygen inhalation, venous transfusion, physical cooling and/or antipyretics, and antibiotics were also available.

In EVD patients, fluid management was crucial, due to frequent intravascular volume depletion and electrolyte abnormalities (16,17,22). For patients with potential hypovolemia, capable of self-care, oral rehydration solution was administered, with antiemetics and anti-diarrheal drugs if required, to mitigate the massive fluid loss through the gastro-intestinal tract and to prevent hypovolemia. In the present study, all confirmed EVD patients received oral rehydration, and satisfactory effects were achieved in all but 1 patient who was in an extremely critical condition on admission and died soon afterwards. In patients with severe diarrhea and/or vomiting, substantial intravascular volume depletion and severe electrolyte abnormalities are likely to develop; hence intravenous rehydration may be essential.

However, in all medical institutions established in West Africa, including the China ETU, healthcare workers must endure extremely hot weather while wearing several layers of personal protective equipment. Direct contact with patients would be thus very limited (every 1–2 h). At the same time, intravenous rehydration was limited by difficulties with the establishment and maintenance of venous access and by the risks of infected fluids and needles. Furthermore, surveillance of arterial blood gases, biochemical indexes, and abdominal ultrasound exams, all proved beneficial in the management of EVD patients (24). For cases with severe complications, intensive care would also significantly improve prognosis (27). This is consistent with reports that a number of critically ill patients eventually survived following transfer to developed countries where therapies, such as mechanical ventilation and blood purification, were available (15,16,24). However, the effect of treatment on site remained relatively poor (28), largely due to the high infectiousness of EVD, and the unavailability of intensive monitoring and laboratory examinations.

Safe and effective organization and management measures were essential to achieve the objective of fighting EVD in Liberia, as well as preventing infection within the team. Before undertaking any clinical work, each employee took a training course that included basic Ebola knowledge, the process of engaging Ebola patients, the use of isolation methods, and the supervision of each other. Medical staffs were required to use the following personal protective equipment before direct contact with patients: protective clothing, masks, hats, gloves, eye shields, face shields, and rubber boots. Two employees worked together to take isolation gowns. The engaging processes were monitored by nurses on duty in the monitoring room, and warnings would be given if necessary. Despite the high level of contact, no member of our medical team became infected with Ebola.

Liberia is a country that lacks healthcare, education, and medical facilities. As a result, the population suffers from a lack of awareness of disinfection and isolation procedures. Our medical team visited and evaluated schools, factories, and other facilities. It also promoted and supervised disinfection and measures taken to protect these facilities to reduce the risk of Ebola transmission. Furthermore, our team aimed to enhance public health awareness and improve disinfection and isolation procedures by hosting training courses on Ebola prevention and control for local clinicians and educators. We taught them proper hand-washing techniques and usage of disinfectant. The EBV mortality rates could be reduced through improved understanding of the pathogenesis, clinical manifestations, and treatment strategies combined with the development of more specific treatment.

Conflict of interest None to declare.

REFERENCES