

# Managing Viral Haemorrhagic Fever in the Emergency Department

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## ABSTRACT

The Emergency Department, regarded as the gateway to healthcare, is frequently the first point of contact for significantly ill patients. Because the initial presentation of a Viral Haemorrhagic Fever (VHF) case is largely non-specific, the role of Emergency Department (ED) staff is pivotal in curtailing a Formidable Epidemic Disease (FED) outbreak. An immediate action plan describing appropriate, safe, effective, yet simple steps to be taken is of utmost value.

This manuscript discusses aspects pertaining to ED preparedness and readiness in the event of a suspected VHF case presentation, including facility readiness in safely receiving a patient, protection of staff and others, decontamination of equipment and personnel, initial steps in containing the disease and prevention of an outbreak.

**Keywords:** Dengue, Ebola, Incident management, Planning, Rift valley fever

## INTRODUCTION

The 2014-2016 Ebola virus outbreak in West Africa accompanied by sporadic outbreaks of other VHF infections worldwide have raised concerns regarding ED preparedness [1,2]. The Emergency Department, often used as the gateway to institutional healthcare, is frequently the first point of contact for ill patients in transit. While the initial presentation of a VHF case is largely non-specific, the role of ED staff is pivotal in the early identification of such a case and the prevention of a FED outbreak.

The 2014 Ebola virus outbreak, which spread across West Africa, is suspected to have originated from an unknown animal vector, which was then transmitted to a Southern Guinean child [1]. From this single index case, there were thousands of infected individuals across Guinea, Sierra Leone, Liberia, and Nigeria. Due to the ease of modern international travel, there have been numerous reported cases of cross-border transmission [3].

Health Care Workers (HCW) and especially emergency care workers have been frequent victims of VHF disease. In 1989, after attending the funeral of his mother in Nigeria, who had reportedly demised from a febrile illness ascribed to malaria, a mechanical engineer returned to his home in Chicago, USA. Two days after returning to Chicago, he was initiated on antibiotic therapy for a suspected streptococcal throat infection at a local clinic. His illness progressed and after two weeks he died. A diagnosis of Lassa haemorrhagic fever was confirmed post-mortem. Of the 102 people he came into contact with since the funeral, a phlebotomist, nurse, doctor and a lab technician were regarded as being at highest risk of acquiring and transmitting the infection, primarily because they had failed to adhere to standard infection control measures [4].

Many of the outbreaks described in the literature have had a significant rate of healthcare worker infection, [5-9]. In many cases when the diagnosis of VHF disease was initially unavailable, due to occupational exposure of healthcare workers, the potential for an outbreak was exacerbated [10-17]. The recent West African Ebola epidemic has taught us many valuable lessons, and highlighted that future efforts should be channelled at preparing HCW and facilities to effectively manage and contain a potential threat [18-20].

In this paper, the authors highlight immediate actions to be taken by ED staff when dealing with a case of suspected VHF. To frame this description, consider the following hypothetical scenario: As the senior emergency doctor on duty, you receive a call from a worried

junior doctor informing you of the expected arrival of a mid-aged male with severe gastrointestinal symptoms. Emergency Medical Service (EMS) personnel, who are an hour away, noted that the patient has been pyrexial for 36 hours, reported several bouts of watery diarrhoea, and when assessed they found that he is moderately hypotensive. The junior doctor tells you that the EMS personnel were unsure about transporting the patient as they are aware of recent outbreaks of viral haemorrhagic fever disease. They were particularly concerned with this case as the patient reported recently returning from visiting a mine in equatorial Africa. The junior confides that neither he know how to safely manage a potential VHF patient nor what to tell the EMS personnel. Are you able to advise him on how to resolve this situation?

In the following sections the authors describe the possible aetiology as well as the clinical findings that may suggest the presence of VHF disease. They propose an approach to safely provide early care, whilst minimising the risk to the healthcare team and preventing a potential FED outbreak.

## Aetiological Agents

Infectious viral agents currently known to cause VHF disease belong to four families: Arenaviridae, Bunyviridae, Filoviridae and Flaviviridae [21]. Since zoonotic vectors are typically the primary host, outbreaks in humans are usually sporadic and irregular [22]. Yellow fever is a notable exception where, in urban environments, humans act as the primary viral reservoirs [16,22].

[Table/Fig-1] lists viruses known to cause VHF, their endemicity and incubation periods. The old world arenaviruses include Lassa (LASV), Sabia and Lujo viruses which are all characteristically transmitted by rodents [17]. The Bunyviridae include Rift Valley Fever (RVF) and Crimean-Congo Haemorrhagic Fever (CCHF) both of which are arthropod-borne, whereas the hantaviruses, which are transmitted by rodents, are responsible for 2 major syndromes; Haemorrhagic Fever with Renal Syndrome (HFRS) and Hantavirus Pulmonary Syndrome (HPS) [23]. The Flaviviridae include Yellow Fever (YFV) and Dengue Fever (DFV) viruses, both of which are mosquito-borne tropical diseases [24]. The Filoviridae which includes the Ebola (EBOV) and Marburg (MARV) viruses are regarded the deadliest of the VHF viruses and are associated with Ebola Virus Disease and Marburg Virus Disease. The 2014 EBOV epidemic, primarily affecting Guinea, Sierra Leone, and Liberia, has seen approximately 11,300 deaths out of more than 28,000 cases (15,227 were laboratory confirmed), with a reported 40% mortality rate to date [25].

Virus	Disease	Endemic regions	Vector	Incubation period	Associated mortality
<b>Arenaviridae</b>					
Lassa virus	Lassa fever	West Africa	Rodent	5-16 days	±15%
Junin virus	Argentine hemorrhagic fever	Argentine pampas	Rodent	7-14 days	15-30%
Machupo virus	Bolivian hemorrhagic fever	Beni province, Bolivia	Rodent	9-15 days	25-35% [76]
Sabia virus	Brazilian hemorrhagic fever	Rural São Paulo, Brazil	Rodent	7-14 days	15-30%
Guanarito virus	Venezuelan hemorrhagic fever	Portuguesa state, Venezuela	Rodent	7-14 days	15-30%
<b>Bunyaviridae</b>					
Phlebovirus	Rift Valley fever	Sub-Saharan Africa	Mosquito and slaughter of infected livestock	2-5 days	±50%
Nairovirus	Crimean-Congo HF	Eastern Europe, Asia, Africa	Tick and aerosol transmission	3-12 days	15-30%
Hantavirus	Hemorrhagic fever with renal syndrome, Hantavirus pulmonary syndrome	Worldwide	Rodent	9-35 days	5-15%
<b>Filoviridae</b>					
Marburg virus	Marburg	Africa	Fruitbat/African Green Monkey	2-16 days	25-90%
Ebola virus	Ebola	Africa	Fruitbat/African Green Monkey	2-16 days	25-90%
<b>Flaviviridae</b>					
Yellow fever virus	Yellow fever	Tropical Africa, South America	Mosquito	3-6 days	20%
Dengue virus	Dengue	Asia, Americas, Africa	Mosquito	1-7 days for Dengue Fever, severe	<1%

**[Table/Fig-1]:** Distinctive characteristics of VHF viruses.

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Although VHF viruses are endemic in specific regions [Table/Fig-1], one should not rule out a VHF infection based on a negative travel history, as the potential for horizontal transmission is evident [17,26]. Recent travel to a VHF endemic region should be considered a 'rule in' rather than a 'rule out' criterion, that is to say if the travel history is significant it should increase suspicion of exposure however its absence should does not eliminate the possibility of exposure to one of the aforementioned agents.

### Clinical Presentation

Potential VHF infected patients may present to the ED as a self-referral, a referral from a primary healthcare centre or an EMS transfer from home or another facility [1,27]. Due to the lack of specific early signs and symptoms, VHF is often missed on first contact [28]. The typical first presentation is characterised by a fever of indeterminate origin, associated pharyngitis and/or conjunctivitis, malaise, myalgia, gastrointestinal disturbances, as well as a history of travel to a VHF endemic region or contact with an individual with a similar history and clinical presentation without a reliable diagnosis.

Gastrointestinal Tract (GIT) signs are very common in patients with EBOV or MARV infection [29,30]. Occasionally the typical, non-specific, presentation described above may also be accompanied by petechia, haemorrhagic contusions or a purpuric rash indicating a haemorrhagic manifestation. These dermatological signs should prompt the first medical practitioner to conduct an immediate risk assessment of the likelihood of a VHF infection as they are unusual signs in leptospirosis, influenza, malaria or typhoid infection [31].

Viruses responsible for VHF tend to have an affinity for the vascular system, with the primary pathophysiology relating to increased vascular permeability secondary to release of chemokines, pro-inflammatory cytokines and other mediators of the Systemic Inflammatory Response (SIRS) cascade [32]. An overwhelming SIRS may culminate with cellular dysfunction and ultimately multiple organ dysfunction and death [27]. Severity is determined by viral type, viral load, route of exposure and host immune response. Despite the VHF moniker very few patients present with haemorrhagic signs. In a meta-analysis of 4867 patients from the Central Africa and West Africa EVD outbreaks, conjunctival bleeding was present in only 33.6% of cases, nasal bleeding in 8.7% and gingival bleeding in 21.1% [33].

With progression, patients may manifest with mucous membrane haemorrhage, hypotension, shock, and circulatory collapse. Hepatic involvement, disseminated intravascular coagulopathy, and megakaryocyte injury are responsible for haemorrhagic manifestations [27,34-36]. Further progression results in multisystem organ failure affecting the hematopoietic, neurologic, and pulmonary systems. Hepatic involvement is more commonly seen in patients infected with RVF, CCHF, EBOV, MARV, and YF, whereas oliguric renal failure is seen in patients with HFVS and is also seen in individuals with intravascular volume depletion associated with progression of most other VHF viral illnesses. Bleeding complications are more common with the South American arenaviruses, CCHF, Ebola and Marburg viruses. Febrile exanthema, leucopenia, neutropenia, and thrombopenia are commonly seen with dengue fever [37]. Severe dengue infection manifests with markedly increased vascular permeability and shock [29,35]. The presence of retrosternal chest pain, a non-productive cough and proteinuria should prompt an investigation for the presence of Lassa virus [38-40].

### Immediate Action Plan

Due to the broad differential diagnoses, relatively non-specific initial presentation and sporadic incidence of VHF, making a clinical diagnosis at the early phase of the disease can be a challenging task. Therefore, ED staff are required to maintain a high index of suspicion, especially when receiving patients with typical presenting features and a history of exposure or recent (<21 days) travel to an endemic region [21,40]. In this section, the authors propose a strategy to deal with the unexpected arrival of a potential VHF case to the ED.

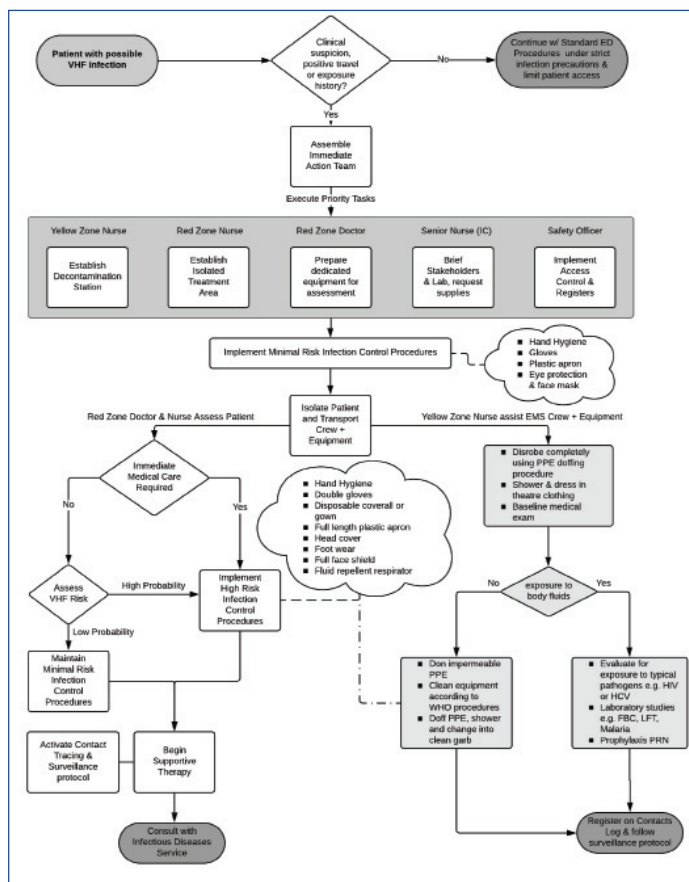
The Immediate Action Plan (IAP) describes the minimum essential steps in managing a patient who may have a VHF infection. The IAP [Table/Fig-2] uses the fewest personnel to implement the WHO recommended isolation precautions and attempts to implement a rational approach based on the likelihood of a VHF infection. In general, all actions should be undertaken but the order of the actions will be largely determined by the treating clinician's assessment of the likelihood of VHF infection as well as local circumstances.

### Assembling the Team

Based on experience gained largely from epidemics in West Africa, implementation of an incident management system is crucial in controlling an outbreak [41]. The IAP defines the initial tasks to be completed by each team member.

Ongoing responsibilities of the incident commander relate to the overall control of the immediate action plan [Table/Fig-2] and acting

as the sole point of contact for all stakeholders (both internal and external). All stakeholders including the hospital infection control team, laboratory staff, hospital management and regional health authorities must be contacted as soon as the probability of a VHF infection is determined to be high [42].



**[Table/Fig-2]:** VHF Immediate Action Plan.

WHO: World health organisation; FBC: Full blood count; LFT: Liver function test; PRN: as required

The primary role of the incident commander is to ensure the safety of all involved whilst balancing the administration of appropriate care to the patient and minimising the impact on the operation and function of the rest facility [2]. It is suggested that this role should not be performed by a doctor, as they may be more effectively utilised in seeing either the patient under consideration or the other ED patients. In addition, nursing staff are often more aware of the facilities management model and how to contact various stakeholders. Nonetheless, local conditions will dictate who is delegated as the Incident Commander (IC) but the key responsibility to ensure effective and efficient communication between all parties remains paramount as a breakdown in communication is often cited as the root cause in medical safety incidents [43].

An ideal nursing team would comprise of at least one registered nurse (IC) and two enrolled nurses. Due to the high workload and time-consuming donning and doffing of Personal Protective Equipment (PPE), a nursing team should be solely allocated to the care of the patient in question and they should be rotated as necessary [2]. The Red Zone Nurse (RZN), will assist the Red Zone Doctor (RZD) in assessing and stabilising the patient in the isolated treatment area. Another nurse, the Yellow Zone Nurse (YZN), manages the staging area, ensuring that appropriate PPE is used and that it is removed and disposed of safely upon leaving the Red Zone. The YZN will also ensure the EMS crew that attended the patient is appropriately decontaminated, evaluated for exposure and registered in the Contact Register for surveillance.

A Safety Officer (SO), ideally a member of the nursing staff with a thorough understanding of infection control principles must be present at all times to ensure adherence to infection control and safe working procedures [44]. However, in resource constrained

settings it is reasonable to train a non-medically qualified individual to fulfil this role. The use of checklists and training aids, such as those published by the CDC (<https://www.cdc.gov/hf/ebola/hcp/ppe-training/index.html>), are highly recommended to ensure compliance with best practice [45].

The SO is tasked with ensuring that only pre-designated medical personnel who have signed the Contact Register are allowed access to the isolation area [46,47] and that personal protective measures are stringently adhered to at all times including the donning of PPE [48,49]. The SO is also tasked to compile and maintain a register of potentially exposed persons and equipment including individuals that were in contact with the patient prior to arrival at the first point of care [22,50]. Names, date of exposure, contact telephone numbers and a description of contact with the patient must be included in the Contact Register.

Directions on how to safely decontaminate EMS equipment will be provided by the SO. Once decontamination of equipment is complete, the personnel decontamination process should be repeated [51].

### Staff Briefing

Following the appointment of a dedicated team, checklists of responsibilities for each member should be issued. In the team briefing, the incident commander should provide the team with the latest information regarding the patient as well as briefly explaining each member's role and the chain of command within the hospital incident command system [52,53]. The team should then be left to execute their priority tasks before assembling in the staging area once again prior to the arrival of the patient. Staff members who are not allocated to the care of the patient under consideration should be briefed on the situation and clearly instructed to refrain from direct involvement in the operation. Unnecessary involvement with the operation may increase the pool of potentially exposed persons, detracts from administering care to other patients and diminish the effective chain of command [54].

A senior laboratory staff member should be appointed to liaise with the incident commander and laboratory staff to ensure that samples are appropriately handled, laboratory infection control procedures adhered to, testing prioritised and results made expediently available [22]. In addition, house-keeping/laundry services should be briefed, and appropriate precautions implemented [55].

### Receiving the Patient and Decontamination Procedures

The two nursing team members, as well as the safety officer, should receive the patient and transport team. Only the RZN should approach the bedside of the patient and should wear the minimum risk PPE ensemble unless the stretcher or linen has been soiled with bodily fluids or the patient is vomiting. In this scenario, the high-risk PPE ensemble should be donned before approaching the patient.

The YZN must wear the full minimum risk PPE ensemble and is responsible for providing any equipment or consumables needed by the RZN. The YZN will also ensure doors are opened as the stretcher is pushed towards the isolation room. Neither the RZN, nor the EMS crew, should touch any furniture, appliances or work surfaces. The SO, who is attired in the minimum risk PPE ensemble, will ensure that the route remains secured from inadvertent access and that any contaminated material is immediately treated with a sodium hypochlorite solution [17,55].

Local emergency services and waste management contractors with Hazardous Materials training may need to be mobilised to assist with decontamination of EMS equipment and vehicles [56,57]. A demarcated decontamination station in an isolated area with good ventilation should be established for donning and doffing of protective clothing and holding contaminated equipment and linen [58]. The decontamination team is tasked to receive the transport vehicle and assist with decontamination procedures. After handing

over the patient and prior to leaving the facility, the transport crew must remove all clothing, take a shower and wear clean clothing or surgical scrubs. Details of the transport crew must be entered in the Contact Register to allow for subsequent monitoring [50].

### Isolation Procedures and Access

In an emergency situation, any fully enclosed room or tent away from other patients can serve as an isolation room (Red Zone) until confirmation or exclusion of a diagnosis [59]. The area must be sizable enough to accommodate a nursing station and have a toilet. It is often suggested that the area ventilation settings should be set to negative pressure mode if possible, to prevent dissemination of the virus. However, consider that most VHF organisms are not spread through the air and that droplet isolation is sufficient for EVD and MVD [17]. A review of Secondary Attack Rates (a measure of transmissibility) in Ebola outbreaks between 1976 and 2014 suggests transmission without direct physical contact, even amongst those sharing a household, is approximately 0.8% whereas for those providing home nursing care it may be as high as 48% [60]. Prevention of direct patient contact, or contaminated surfaces, is thus the most important aspect in isolating these cases.

An area for donning PPE and removing contaminated clothing should also be demarcated in this area (Yellow Zone). There must be a means of two-way communication between the nursing station within the isolation area and the general nursing station outside the isolation area [61].

Restricted access and contact isolation signage must be displayed at each access point. To reduce exposure hazards, minimal furniture, and other items should be kept in the patient's room and all clothing products such as linen, fluid absorbent pillows or mattresses and textile privacy curtains should be removed [55]. Considerable attention should be given to the management of infectious waste which may be considerable in an unstable patient. Purpose designed, sealable 60 litre or UN Category A Medical Waste drums must be utilised and thereafter, externally decontaminated and carefully transported to certified hazardous medical waste disposal facilities [62].

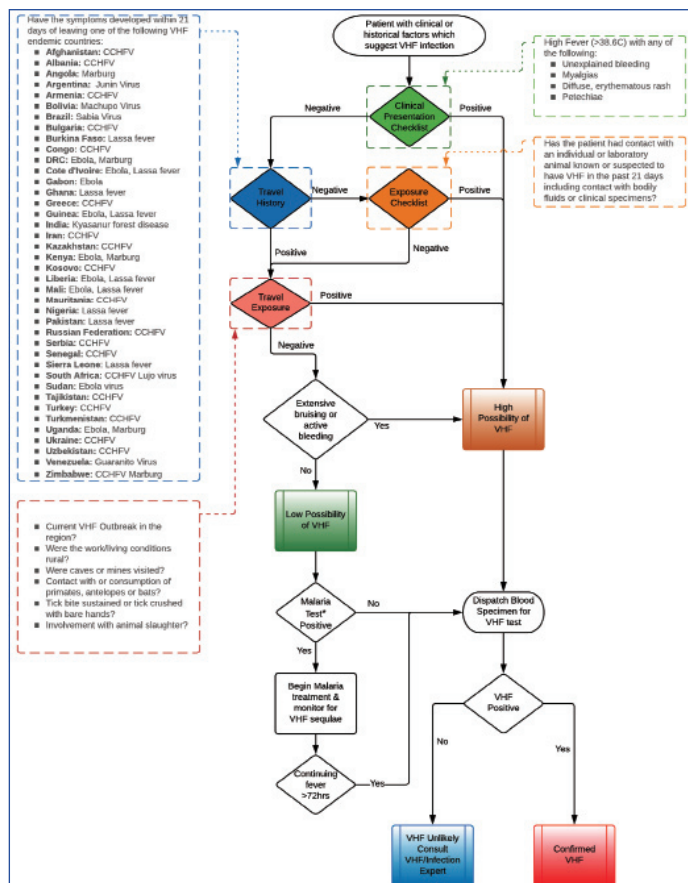
### Laboratory

Laboratory samples must not be delivered via a pneumatic tube system but rather hand delivered whilst ensuring that ED-based as well as central laboratory staff are informed of the probability of VHF [63]. Specimens should be double bagged and placed in a sealed, hard-cased plastic receptacle [1]. Closed shoes with overshoes or boots, gloves, disposable impermeable gowns, eye protection or face shields and particulate respirators (e.g., FFP2) or Powered Air Purifying Respirators (PAPR) must be donned by laboratory staff prior to performing centrifugal or other aerosol generating procedures [47].

### Screening Procedure and Risk Determination

Upon presentation, a clinical VHF risk assessment should be carried out [1,64]. [Table/Fig-3] provides a summary of the VHF assessment process that may be utilised to assign the patient to one of four VHF categories. If the patient is too unwell for the VHF assessment to be completed, then it should be assumed that the patient is at high risk for a VHF infection and appropriate precautions taken, these are listed in [Table/Fig-2].

**Improbable VHF infection:** Any presentation with fever beginning more than 21 days after returning from an endemic region or from an exposure event makes the diagnosis of VHF unlikely. The healthcare practitioner should consider other causes of fever in this instance such as non-VHF arboviruses, influenza-like illness, helminths and parasites, sepsis, malaria or HIV seroconversion. The use of standard infection control precautions is sufficient in this scenario.



**Low probability of VHF infection:** In patients presenting with fever within 21 days of travel to an endemic region with a reliable history with no mention of exposure to an infected individual/animal, funeral attendance or healthcare work, there is a low probability of EVD infection (NLR 0.9 [95% CI: 0.9-1.0]; PLR 1.0 [95% CI: 1.0-1.1]) [65]. The likelihood of an EVD infection is further diminished in the absence of diarrhoea, anorexia, myalgia and dysphagia [66].

Malaria and other tropical illnesses should be considered as part of the workup. Patient observation and strict infection control practices must be continued in the interim. In addition to standard precautions fluid repellent surgical facemasks, eye-shield or goggles, disposable cover gowns and plastic aprons should be used (Minimal Risk Infection Control Procedures), if droplet producing procedures are performed. If the PPE becomes visibly soiled, decontamination with a bleach solution or disinfecting wipe should be performed before doffing and disposal. The patient should also wear an appropriate facemask, avoid making contact with other patients and practice respiratory hygiene and cough etiquette [1,64,67].

Laboratory results that demonstrate elevated blood urea nitrogen; creatinine and generalised transaminitis are common to malaria and VHF infections [30]. The combination of leucopenia, transaminitis and thrombocytopenia has been documented in EBOV and CCHF [31]. Since patients may have both a VHF and malaria infection, VHF should remain on the list of possible diagnoses until the patient has fully recovered. If a definitive assessment is necessary, the current practice is to utilise Reverse Transcription Polymerase Chain Reaction (RT-PCR) methods to detect the presence of most VHF organisms [68].

**High probability VHF infection:** These patients present with a fever within the 21-day incubation window and fulfill the exposure screening criteria and/or the symptomatic screening criteria. If not already done, immediate isolation precautions should be taken, High-Risk Infection Control Procedures should be implemented and the case discussed with the facility's infection control team.

The procedure for donning and doffing High-Risk PPE has been well described [69]. Laboratory samples are classified as Category

A infectious substances and must be transported in accordance with local regulations regarding IATA Hazard Class 6.2 materials, typically requiring a rigid outer container, and marked as such [63].

**Confirmed VHF infection:** Upon confirmation of VHF, a larger VHF incident control team must be mobilised, with additional efforts primarily aimed at containing the disease, performing risk assessment and surveillance of contacts [1]. Consideration should be given to the transfer of the patient to a purpose-built isolation unit if available. The transfer should be undertaken by ED staff clad in appropriate PPE who has already been involved in the care of the patient. An oxygen tent must be placed over the patient's face and pathways cleared and cordoned off ahead of the patient transfer. In the event of contamination of pathways with vomit, diarrhoea, blood or other body secretions, the area must be kept clear by security until cleaning and disinfection have taken place by staff dressed appropriately with PPE. The additional risk of moving the patient should be weighed against the risk of treating the patient in situ. In the event of the patient demising, liaison with mortuary staff for appropriate handling of the body is necessary.

### Initiating Supportive Therapy

The management of suspected VHF is largely supportive. The use of oral and parenteral rehydration therapy as well as analgesia and antibiotics has been strongly advised by a large evidence-based review on the treatment of EBOV [70]. Consideration should also be given to antipyretics other than non-steroid anti-inflammatory agents, oxygen, anticonvulsant therapy, antimalarial therapy and blood replacement products. The level of PPE used may need to be increased for specific droplet generating procedures and procedures such as intramuscular injections; Continuous Positive Pressure Ventilation (CPAP), sputum generation or intubation should be avoided as they are associated with greater nosocomial infection risk.

VHF pathogens are generally resistant to specific antiviral therapies with exception of Lassa and CCHF viruses which may respond to the early administration of parenteral ribavirin [7,21]. In general, therapy is aimed at organ support in the hope that the patient's immune response and antibody production overcomes organism virulence prior to the development of multiple organ failure [71,72]. Although no large-scale human studies have been conducted, there is anecdotal experience emanating from the current EVD outbreak that supports the administration of convalescent plasma from individuals that have recovered from EVD infection [73].

With regard to vaccination, YF vaccines have been in use since the 1930's [75] and a vaccine targeting Dengue haemorrhagic fever has recently (2015) been approved for use in the Philippines [75]. Although not currently available, large international studies investigating the safety of vaccines targeting EBOV are currently underway [76]. Two candidate vaccines targeting Lassa fever have proven to be effective in animal models and are expected to enter clinical trials soon [77,78].

### CONCLUSION

Emergency medical workers play a pivotal role in providing early warning of a potential outbreak as well as spearheading the response when additional cases emerge. Despite the low incidence of patients presenting with a high probability of VHF, all healthcare practitioners must maintain a high level of vigilance and a low threshold to initiate the immediate action plan. It is not the transmissibility of the diseases mentioned here that make them so dangerous but rather that they are novel and difficult to diagnose in the early stages. Therefore, preventing another outbreak of the scale seen in West Africa from 2014 will depend on the effectiveness of efforts made to strengthen the local health systems. By developing a pool of healthcare workers skilled in infection control, educated in surveillance techniques and priorities, and able to communicate their findings to authorities as well as community leaders FED may be

more rapidly detected and confined. Implementation of immediate action plans is a cost effective method to support HCWs in the use of infection control techniques which are imperative in limiting the extent of a FED outbreak. This practical approach will ensure robust and safe clinical management of the patient whilst safeguarding the well-being of the healthcare professional and public.

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