VIRAL HAEMORRHAGIC FEVERS

GUIDELINES FOR ACTION IN THE EVENT OF A DELIBERATE RELEASE

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Note: Comments are welcome from healthcare, laboratory and public health professionals, and should be sent to DRcomments@hpa.org.uk. These guidelines may be subject to change as comments are received, so please ensure that you have the latest version available through the HPA website: http://www.hpa.org.uk/deliberate_accidental_releases/biological

For this version of the guidelines changes were made to the following sections of the previous version: 1.2, 1.7, 2.4, 3.5, 4.3.2, 5
1 BACKGROUND
These guidelines are intended for healthcare, laboratory and public health professionals to guide clinical, laboratory and public health action in the event of a deliberate release of the Haemorrhagic Fever group of viruses.

1.1 Introduction
Viral Haemorrhagic Fevers (VHF) are caused by a diverse group of viruses that cause an array of illnesses from relatively mild to rarely severe and life threatening. Viral survival in nature is dependent on the availability of specific natural hosts and this restricts the viruses to where their host species live. Humans are not the natural reservoir for any of these viruses. They become infected by contact with infected hosts or with arthropod vectors. However, under specific circumstances, an infected human can transmit some of the viruses to other humans (person-to-person transmission).

1.1.1 Classification of VHF viruses
Viruses associated with haemorrhagic fever are RNA viruses from four distinct virus families. Although a wide range of viruses are involved, they all share some common characteristics. They all have an RNA genome, and are enveloped. They are transmitted in three ways: by mosquitoes, via ticks, or directly from their host as a zoonosis.

1.1.2 Deliberate release of Haemorrhagic Fever Viruses
In theory, VHF agents can be used as agents of bioterrorist attacks. However, in reality, it is very difficult to create a suitable conduit for transmission of these agents in a weaponised form. Laboratory testing on animal models and epidemiology of the Reston strain (Ebola virus) outbreak in Phillipino imported monkeys, show that some VHF agents can be spread by the airborne route, however to date this has not been seen in any of the human outbreaks studied.

This document focuses on those VHF agents that are known to be readily capable of person-to-person spread. It assumes that even if aerosolisation does occur, it is the following four viruses that can be transmitted by person-to-person spread and could present a risk to public health in the UK. These agents are:

- **Lassa fever** an arenavirus (and related arenaviruses, e.g. Sabia virus from Brazil)
- **Crimean-Congo haemorrhagic fever (CCHF)** a bunyavirus
- **Ebola virus** a filovirus
- **Marburg virus** a filovirus

The threat of infection by these pathogens is considered serious because:

- They can cause severe, rapidly fatal infection.
- Secondary cases may arise from contact with severely ill primary cases.
- The reputation of these diseases is such that they can induce public anxiety and disrupt everyday life in the population.
- Laboratory testing on animal models shows that some agents may be transmitted by aerosol, although this has not been seen in the human outbreaks studied.

1.2 Epidemiology
The agents of these VHF are naturally endemic in different parts of the world, most notably Africa, parts of South America and some rural parts of the Middle East and Eastern Europe. However, environmental conditions in the UK do not support the natural reservoirs or vectors of any of these viruses, thus cases do not occur in the UK except as an imported
disease. Such cases in travellers returning from endemic areas are rare: there have been nine cases of imported VHF (all Lassa fever) since 1980.

Other viruses, such as Rift Valley Fever virus, can cause VHF in humans, but although occasional reports indicate that person-to-person spread has occurred with some of these agents they do not present the same risk to public health.

1.2.1 Person-to-person transmission
All four main VHF viruses are transmitted from person-to-person in the same way: through direct contact with virus-infected body fluids, such as, blood, saliva, vomitus, stools and possibly sweat. Cross infection with multiple-use sharp instruments, such as lancets and needles, is associated with a high infection risk and a high fatality rate. Marburg, Ebola and Lassa virus have been shown to be present in the genital secretions of convalescents several weeks after illness; rare incidents of transmission from convalescent patients to sexual contacts have occurred with both Marburg and Lassa fever.

There is no evidence that close personal contact with a non-febrile, non-symptomatic, infected individual during the incubation period or convalescence results in transmission. Similarly, feverish patients who are well enough to care for themselves have never been shown to transmit infection to contacts in aeroplanes or other public transport or by other casual contact routes. Previous epidemics in Africa have resulted largely from secondary spread to health care workers and family contacts caring for the very ill. Re-use of needles and syringes, inadequate infection control techniques, and unhygienic practices are the major routes for nosocomial transmission among hospital staff and patients. Contact with the body or body fluids of the dead in customary preparation for burial are also a recognised source of infection.

These viruses are not airborne, but may be transmitted over short distances of a meter or so by droplets of body fluids from infected patients, if the droplets come into contact with mucous membranes. There is also a potential risk to laboratory workers as small clouds of aerosolised viruses can be released in laboratory accidents, such as breakage of containers within centrifuges.

1.2.2 Infectious dose
The infectious dose of haemorrhagic fever viruses is unknown but is probably low (around 1-10 organisms).

1.2.3 Incubation period
The incubation period varies between 1 and 21 days. The infectivity period depends on viral type and mode of infection.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Disease</th>
<th>Incubation Range (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arenaviridae</td>
<td>Lassa Fever</td>
<td>3-21</td>
</tr>
<tr>
<td>Bunyaviridae</td>
<td>Nairovirus Crimean-Congo Haemorrhagic Fever</td>
<td>1-12</td>
</tr>
<tr>
<td>Filoviridae</td>
<td>Ebola Virus Ebola Haemorrhagic Fever</td>
<td>2-21</td>
</tr>
<tr>
<td></td>
<td>Marburg Virus Marburg Haemorrhagic Fever</td>
<td>3-16</td>
</tr>
</tbody>
</table>
1.2.4 Period of communicability

As a precaution, patients who have clinical symptoms are considered infectious. Lassa virus can continue to be in the blood during early convalescence when the fever has resolved. There are reports of late transmission events (92 days for Marburg) and Lassa fever virus can be shed in urine for several weeks or in semen for months after illness has resolved.

1.3 Clinical features

1.3.1 Lassa fever

The onset of illness is insidious, with fever and shivering accompanied by malaise, headache and generalised aching. Sore throat is a common early symptom. In some cases the tonsils and pharynx may be inflamed with patches of white or yellowish exudate and occasionally small vesicles or shallow ulcers. (Importantly, a similar appearance may be seen in cases of malignant tertian malaria). As the illness progresses the body temperature may rise to 41 ºC with daily fluctuations of 2-3 ºC. The duration and severity of fever is very variable. The average duration is 16 days but extremes of 6-30 days have been reported. A feature of severe attacks is lethargy or prostration disproportionate to the fever. During the second week of illness there may be oedema of the head and neck, encephalopathy, pleural effusion and ascites. Vomiting and diarrhoea may aggravate the effects of renal and circulatory failure. Severe cases develop significant haemorrhage and multi-organ failure with widespread oedema and bleeding into the skin, mucosae and deeper tissues. In non-fatal cases the fever subsides and the patient’s condition improves rapidly although tiredness may persist for several weeks. There is usually a leucopenia early in the course, though a high polymorphonuclear leucocytosis may occur with severe tissue damage. Another common late complication is sensorineural deafness.

1.3.2 Congo-Crimean Haemorrhagic Fever

The illness begins abruptly with fever, chills, malaise, irritability, headache and severe pains in the limbs and loins, followed by anorexia, nausea, vomiting and abdominal pain. Fever is usually continuous but may be remittent and sometimes biphasic, resolving by crisis after 8 days. The face and neck are flushed and oedematous, the conjunctivae and pharynx are injected, and there is oedema of the soft palate. Patients are often depressed and somnolent. In most cases a fine petechial rash begins on the trunk and then covers the entire body. A haemorrhagic exanthem appears on the soft palate and uvula early in the illness and other bleeding manifestations, including severe nose-bleeds, haematemesis and melaena, appear on about the fourth or fifth day in over three-quarters of patients. Leucopenia and severe thrombocytopenia are common. Large ecchymotic areas caused by subcutaneous extra-vasation of blood occur at times. Severe gastric and nasal haemorrhages often lead to death. The liver is enlarged in about half the cases but the respiratory system is unaffected. Involvement of the central nervous system is seen in 10-25% of patients and usually indicates a poor prognosis; features include neck rigidity, excitation and coma. The mortality rate in outbreaks is often as high as 30-50%. Death is usually due to shock, blood loss or intercurrent infection.

1.3.3 Ebola virus

The disease begins with acute fever, diarrhoea, which can be bloody, and vomiting. Headache, nausea, and abdominal pain are common. Conjunctival infection, dysphagia, hiccups, and haemorrhagic symptoms such as epistaxis, gum haemorrhage, haematemesis, melaena, and purpura may further develop. Some patients may also show a maculopapular rash on the trunk at 3-8 days, which is followed by desquamation. Appearance of haemorrhagic manifestations is an indicator of poor prognosis. Dehydration and significant
wasting occur as the disease progresses. At a later stage, there is frequent involvement of the CNS, manifested by somnolence, delirium, or coma. By the second week of illness, the patient will either, markedly improve and convalesce, or will have multi-organ failure and septic shock. Autopsies show panencephalitis, cerebral oedema, and serious renal damage. The case fatality rate ranges from 90% in outbreaks caused by Zaire strain, 50% in those caused by Sudan strain and 0% in Reston strain.

1.3.4 Marburg virus
The course of Marburg infection is similar to that of Ebola although Marburg tends to be less severe.

1.4 Mortality
1.4.1 Lassa fever
Approximately 15%-20% of patients hospitalised for Lassa fever die from the illness. However, in endemic countries, probably only about 1% of patients who become infected through contact with the host species Mastomys rodents, die from their disease. The death rates are particularly high for women in the third trimester of pregnancy and their foetuses. The factors affecting disease severity are unknown but there is some suggestion that Nigerian strains cause more severe disease and that route and dose of inoculum may influence pathogenicity.

1.4.2 Congo-Crimean Haemorrhagic Fever
The death rate is often as high as 30-50% in outbreaks.

1.4.3 Ebola virus
Ebola virus outbreaks have shown a wide range of outcomes, from almost 90% mortality in the outbreaks of 1976 and 1995 the in the Democratic Republic of Congo through to 50% in Sudanese outbreaks. The mortality rate is dependent on strain; the Reston strain, identified in imported monkeys from the Philippines, was associated with subclinical infection in the few human cases.

1.4.4 Marburg virus
The Marburg virus outbreak in Germany and Yugoslavia in 1967 had a mortality rate of 28% in primary cases. Other outbreaks, affecting Central Africa in the 1990s and early 2000s have had case fatality rates varying from 40-70%.

1.5 Organism survival
No specific studies have been undertaken, but these are all RNA viruses with lipid envelopes. This renders them relatively susceptible to detergents as well as to low pH environments. Conversely, they are quite stable at neutral pH, especially in the presence of protein.

1.6 Antiviral sensitivity
Ribavirin can be effective if given in the first week of Lassa fever. There is also in vitro evidence that ribavirin is effective against CCHF. No antiviral agent has any effect in Ebola or Marburg haemorrhagic fevers. Convalescent plasma is effective for some arenavirus infections such as Junin (Argentinean Haemorrhagic Fever), but its effectiveness for Lassa fever and Ebola/ Marburg in humans has never been demonstrated.
1.7 **Legal issues**

Currently, if a person is strongly suspected to have VHF, they should be managed by one of the two High Security Infectious Disease Units (HSIDUs) according to the guidelines issued by the Advisory Committee on Dangerous Pathogens (ACDP) on The Management and Control of Viral Haemorrhagic Fevers (HMSO 1996). The Health and Safety Executive can prosecute if there is deviation from these guidelines.

In the event of a deliberate release the numbers of patients will exhaust the current capacity to allow adherence to these strict protocols. Other ways of managing these patients may need to be put in place, for instance, cohort nursing in a dedicated ward. In such a situation, advice and support can be sought from the HSIDUs.

This guideline on bioterrorism has relied extensively on ACDP protocols and **if there is a deliberate release** of VHF agents it should be used **in conjunction** with the ACDP, VHF guidelines. Useful advice on infection control, personal protection and specimen-taking can also be found in the HPA Cardinal Signs and Clinical Tips document: [http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947321070](http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947321070)
2 CLINICAL PROCEDURES

2.1 Diagnosis and Collection of Samples

There are many diseases that have similar presentations to VHF and in case of a deliberate release a high degree of suspicion is needed by clinicians to consider VHF. The most frequent causes of similar illnesses and their distinguishing features are:

- **Malaria** presents with acute fever, headache and sometimes diarrhoea (children). Blood smears must be examined for malaria parasites. Presence of parasites does NOT exclude concurrent viral infection. Antimalarial drugs must be prescribed in an attempt at therapy.

- **Shigellosis and other bacterial enteric infections** are a common initial diagnosis of VHF - presents with diarrhoea, possibly bloody, accompanied by fever, nausea, and sometimes toxaemia, vomiting, cramps, and tenesmus. Stools contain blood and mucous in a typical case. A search for possible sites of bacterial infection, together with cultures and blood smears, should be made. Presence of leucocytosis distinguishes bacterial infections.

- **Typhoid fever** presents with fever, headache, rash, gastrointestinal symptoms, with lymphadenopathy, relative bradycardia, cough and leucopenia and sometimes a sore throat. A therapeutic trial with chloramphenicol or tetracyclines may be indicated. Blood and stool culture can demonstrate causative bacteria.

- **Yellow fever and other Flaviviridae** present with haemorrhagic complications. Epidemiological investigation may reveal a pattern of disease transmission by an insect vector. Molecular biological techniques together with virus isolation and serological investigation serves to distinguish these viruses. Confirmed history of previous yellow fever vaccination will rule out yellow fever.

- **Others** - systemic plague, systemic tularemia, viral hepatitis, leptospirosis, rheumatic fever, typhus, and mononucleosis produce signs and symptoms that may be confused with VHF in the early stages of infection.

Note that most of the above diseases are not endemic in UK but may occur if there is an appropriate travel history. In the absence of travel history suspicion should be raised.

2.1.1 Precautions for sampling

Blood specimens should be taken by a doctor or nurse experienced in phlebotomy. Urine samples should only be taken by experienced staff (a 20ml syringe should be used to transfer urine from a bedpan to the specified container).

Protective measures include:

- a protective gown
- a waterproof protective apron
- latex gloves
- particulate filter face mask
- eye protection
- washing hands and exposed skin thoroughly

The following techniques are recommended when obtaining specimens of blood:

- dry cotton wool balls or gauze swabs (not disposable alcohol swabs) should be used to apply pressure to venepuncture wounds
Guidelines for Action in the Event of a Deliberate Release: **Viral Haemorrhagic Fevers**

- use of a vacuum blood sampling system
- specimen tubes should be labelled with patient details before being filled
- use of the most familiar equipment and procedure (unfamiliar procedures are more likely to lead to accidents and spillages)

### 2.1.2 Samples to be taken from acutely ill humans

The emphasis here is to minimise investigations until a diagnosis is confirmed or excluded (see also 3.1 for categorising risk of VHF). The following **specific diagnostic samples** are needed from acutely ill patients:

- **acute phase whole blood** obtained from a patient within 7 days of onset of illness
- **convalescent sera** collected from patients at least 14 days after onset of illness - paired serum samples are ideal, usually collected 7-20 days apart

This does not include other routine blood samples. Chain of evidence documentation should also accompany all specimens; however in larger incidents this would only be required for several of the initial cases. All samples should be identified as High Risk according to local protocols. There is no need to separate acute phase sera from blood clots (a procedure that may significantly increase the risk of accidental infection). The use of sealed sterile dry tubes (Vacutainer® type) is recommended.

Ideally, blood samples should be kept in their original tube and stored at 4°C to allow virus isolation/ PCR. If separate blood samples are collected purely for serological or biochemical purposes they can be frozen. Each collected blood sample must be coded and dated for easy connection with the corresponding record of the case database. The use of labels prepared in advance for both the collection of clinical samples and case report forms is recommended. Refer to section 3.5 and 3.6 for information on reference laboratories and packaging of samples.

### 2.1.3 Post-mortem specimens

Full post-mortem examinations of patients who have died of VHF should not be carried out (see 2.3.4).

### 2.1.4 Samples to be taken from the environment

Environmental sampling is unlikely to provide useful information because the organism dies rapidly outside the body. Expert advice will be provided if required.

### 2.1.5 Transport of samples

Strict procedures should be followed for the transport of samples to the laboratory as outlined in section 3.6. VHFs fall into category A for the purposes of transport. All samples should be transported as per UN602 as described in Appendix 1.2 Transport of infectious substances in Biological agents: Managing the risks in laboratories and healthcare premises Advisory Committee on Dangerous Pathogens (ACDP), Health and Safety Executive May 2005 accessed at: [http://www.advisorybodies.doh.gov.uk/acdp/managingtherisks.pdf](http://www.advisorybodies.doh.gov.uk/acdp/managingtherisks.pdf)

### 2.2 Treatment

Supportive care is essential for patients. Many of deaths attributed to VHF are due to severe dehydration; management of patients should be supportive, with careful maintenance of hydration, and minimal trauma - in particular, injections and parenteral interventions must be kept to a minimum. Replacement of coagulation factors and of platelets may be of value.
Specific treatment with ribavirin may be effective for Lassa fever and CCHF. No specific treatments (antiviral drugs, cytokines or vasoactive agents) have been shown to date to influence the course of the other two main VHF agents (Ebola and Marburg).

2.3 Infection Control Practice

2.3.1 Decontamination of exposed person

The risk of acquiring infection from the contaminated clothing of exposed persons is low. Heavily exposed persons should be instructed to remove outer clothing, which should be double bagged in sealed plastic bags prior to washing according to local infection control policies. They should then be instructed to shower thoroughly with soap and water. An incident specific risk assessment will be required.

2.3.2 Isolation of Patients

Person-to-person spread may occur through exposure to blood or body fluids. Although airborne transmission of these agents appears to be rare the precautionary principle applies. Patients known or strongly suspected to be suffering from a VHF agent should be admitted to a designated High Security Infectious Disease Unit, or to an intermediate isolation facility after consultation with the physician in charge of the patient. In the event of a large-scale event, patients may be cohort isolated in a designated ward.

2.3.3 Cleaning and waste disposal

Normal procedures for standard isolation are appropriate. Contaminated environmental surfaces should be cleaned with hypochlorite solution (5000ppm available chlorine).

2.3.4 Post-mortem

Autopsy

The risk of acquiring a VHF agent following contact with the body of a person who has died from the disease is moderate to high, because person-to-person transmission occurs via blood and body fluids and there is evidence of autopsy transmission.

Autopsy examinations should not be performed if VHF is suspected, as all the body fluids in a patient who has died of VHF will have large numbers of virus present and there is documented evidence of transmission during autopsy. If an autopsy is necessary expert advice must be sought from the HPA. The Pathologist must be informed of the known or suspected diagnosis. Precautions for post-mortem examinations on patients infected with Containment Level 4 organisms are appropriate. Instruments should be autoclaved.

Body preparation procedures should not be undertaken and the coffin should not be opened. Cremation is the preferred method for disposal of the deceased. Embalming of bodies must not take place because the body fluids will have large numbers of haemorrhagic fever viruses present and therefore the process of embalming exposes the embalmer to unacceptably high risk.

Pacemaker removal

Pacemaker removal is permitted provided personnel take appropriate precautions. PPE should include a full length fluid-impermeable gown, apron, hair cover, overshoes, correctly fitting FFP3 mask, suitable eye protection, and disposable gloves. Pacemaker should be treated with hypochlorite solution (10,000ppm available chlorine), bagged and disposed of appropriately (not by incineration).
2.4 Prophylactic treatment for persons exposed to VHF - specific to Lassa fever (only evidence)

The level of prophylaxis provided depends on the assessment of the situation and ascertainment of the level of risk. Below is a guide to categorising exposed people to various risk groups depending on exposure.

For contacts that fit category 3 description, ribavirin should be administered prophylactically. Also, all those in category 2 or 3 should be actively followed up for development of fever for 21 days; however, those in category 2 do not need prophylactic ribavirin. Contacts in category 1 need to be identified and made aware of possible signs and symptoms of VHF but no active follow up is needed. The active follow up should be organised locally by the CCDC at the local Health Protection Unit and co-ordinated by HPA Colindale.

<table>
<thead>
<tr>
<th>Contact</th>
<th>Risk Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casual</td>
<td>1</td>
<td>No direct contact with patient or with bodily fluids or specimens. Shared the same public space as a case.</td>
</tr>
<tr>
<td>Close</td>
<td>2</td>
<td>Direct contact with the patient but did not handle blood/bodily fluids or wore adequate protective clothing for the task.</td>
</tr>
<tr>
<td>Unprotected</td>
<td>3</td>
<td>Unprotected exposure of skin or mucous membranes to blood or bodily fluids or unprotected handling of specimens.</td>
</tr>
</tbody>
</table>

2.4.1 Immunisation

Currently, there are no vaccines available for the management of pre-exposure or post-exposure to VHF.

2.4.2 Decontamination of exposed persons

The risk of acquiring infection from contaminated clothing of exposed persons is low. Heavily exposed persons should be instructed to remove outer clothing, which is placed in sealed plastic bags prior to autoclaving or washing according to local infection control policies.

2.5 Environmental decontamination

The risk of acquiring infection from contaminated environmental surfaces is extremely low. Drying and exposure to sunlight will kill the organisms. Environmental decontamination is not recommended, except for highly localised contamination like vomitus or blood spillages in the laboratory or the ward. If such a situation arises, standard disinfectants like strong hypochlorite solution containing 5000 ppm of available chlorine should be used according to local policies.

2.6 Protection of frontline workers

This includes all emergency staff involved in management at the scene of a release, and healthcare staff involved in the care of patients.
2.6.1 **Protective clothing**

The release of VHF agents will create an **exposed zone** that presents a high risk of inhaling the agent. Any personnel entering this zone should wear a biologically-resistant suit with outer gloves and boots (for example a CR1, PRPS or gas-tight suit), and a correctly fitting high-efficacy particulate respirator FFP3 standard AT ALL TIMES.

Healthcare workers will not normally be asked to enter this exposed zone, but may be called into it to treat casualties, for example if an explosive device has accompanied the release of biological agent. In this case the appropriate protective clothing should be worn.

Exposed persons will normally be moved from the exposed zone, through decontamination, and into a place of safety (see section 4.3.1) for medical assessment. Frontline workers involved in decontamination, and others who have who have any contact with contaminated clothing and fomites should observe complete universal precautions (full personal protective equipment (PPE) includes: gloves, gown, boots, head cover, dust-mist (FFP3) respirator mask, eye protection). Healthcare workers who attend exposed persons after decontamination has been completed need observe Universal Precautions only.

For healthcare workers involved in the management of hospitalised patients with all forms of VHF strict protocols in accordance with ACDP publication on management of VHF should be adhered to (ACDP, HMSO 1996). If such facilities have been exhausted, HPA Colindale should be contacted for advice on the sufficient level of protection that should be used.

In addition frontline workers involved at the scene of a release, and healthcare workers and mortuary staff involved in the management of VHF cases should be advised to seek urgent medical attention should they develop a febrile illness.

2.7 **Patient, visitor and public information**

Fact sheets have been prepared for distribution in the event of an incident.
3 LABORATORY PROCEDURES

3.1 Risk assessment

Lassa, Ebola, Marburg and CCHF are hazard group 4 pathogens, and should thus be covered by existing risk assessments for handling such organisms in diagnostic laboratories. These facilities are available at both HPA Colindale and HPA Porton, where all specimens must be sent for diagnosis.

It is recognised that in the event of a covert deliberate release specimens from the first unsuspected cases might be examined in regional laboratories before the diagnosis is known. If VHF is not suspected, routine investigation will inevitably be done in local laboratories. If VHF is suspected, then the level of exposure of the patient should be categorised based the risk categories shown below.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum Risk</td>
<td>Febrile patients who have been in contact with a known or suspected source of VHF but in whom the onset of illness was definitely more than 21 days after their last contact with any potential source of infection</td>
</tr>
</tbody>
</table>
| Moderate Risk | Febrile patients who
- were adjacent to an exposed zone in the 21 days prior to onset of an illness which has similar signs and symptoms as VHF or
- Lived in or stayed in a house for more than 4 hours where there were ill, feverish persons known or strongly suspected to have a VHF |
| High Risk     | Febrile patients who
- Have been in the exposed zone or
- Took part in nursing or caring for ill feverish patients who had or suspected to have VHF or
- Had contact with the body fluids, tissue or the dead body of such patients or
- Were previously categorised as moderate risk, but who have developed organ failure and / or haemorrhage |

For minimum risk patients, key investigations such as malaria film can be done in a Containment Level 2 laboratory with eye and face protection. For those in moderate risk group, investigations such as malaria can be undertaken in a Class 1 microbiological safety cabinet in Containment Level 3 laboratory. If VHF cannot be ruled out, any further investigation should be done in a Containment Level 4 (CL4) laboratory.

All investigations for patients in high-risk category should be undertaken in a CL4 laboratory currently located at either HPA Colindale or HPA Porton. If the capacity of CL4 laboratories for routine investigations (not direct viral investigations) is exhausted, then after appropriate risk assessment and discussion with HPA Colindale or HPA Porton automated blood counting machines and chemistry analysers may have to be used as long as they are designated for this purpose and work in a closed system (see ACDP, HMSO 1996 for further details).
In exceptional circumstances such as deliberate release the numbers of cases may quickly exhaust the available facilities. In these situations patients will have to be nursed in cohort isolation in a designated ward and patient support laboratory investigations carried out using closed system blood analysers. If specimen handling for these purposes could produce an aerosol e.g. in blood cross matching then these procedures must be carried out in a CL3 laboratory using a Class I or Class III microbiological safety cabinet. In no circumstances should any procedures that may lead to propagation of the viruses be carried out, these specimens must be referred to the reference laboratories.

3.1.1 Receipt of samples
Samples should be labelled as High Risk by the submitting staff and discussed with the receiving laboratory. Samples should be handled according to local protocols for such samples. Chain-of-evidence documentation should accompany specimens. In larger incidents, this would only be required for several of the initial cases.

3.2 Isolation and identification
These viruses can be cultured in vero E6 cells but this should only be attempted in a Containment Level 4 laboratory. RT-PCR tests have been described for all four viruses and this is the first line diagnostic test. Identification of virus is on the basis of specific amplification and sequencing. The laboratory must be warned in advance that samples are being submitted.

3.3 Confirmation
Serological confirmation is possible by IF or ELISA but antibodies may not be detectable when the patient first presents. Acute and convalescent sera should be sent to the Reference Laboratory for testing. The laboratory must be warned in advance that sera are being submitted.

3.4 Waste disposal
Waste should be disposed of according to local procedures for Containment Level 4 Laboratory.

3.5 Reference laboratories
Samples should be packed and labelled according to current regulations for Hazard group 4 pathogens (see section 3.6) and the Reference Laboratory should be notified when samples are despatched. All specimens, including sera, should be sent to HPA Colindale and HPA Porton:

Dr David Brown or Dr Robin Gopal
HPA Colindale, Viral Zoonosis Unit
Enteric, Respiratory and Neurological Virus Laboratory,
61 Colindale Avenue, London. NW9 5HT
Tel (+44) 020 8327 3117 or (+44) 020 8200 4400 (24hour)
For further information on ERNV and referral of specimens and samples: http://www.hpa.org.uk/ProductsServices/InfectiousDiseases/LaboratoriesAndReferenceFacilities/VirusReferenceDepartment/ViralZoonosesUnit/
3.6 Transportation of samples with high suspicion of VHF agents

Strict procedures apply for transport of samples to the laboratory. Biological agents or materials that contain or may contain them are allocated to UN Division 6.2 – infectious substances. Infectious substances are divided into Category A or Category B. Full details are given in Appendix 1.2 Transport of infectious substances in Biological agents: Managing the risks in laboratories and healthcare premises. ACDP HSE May 2005, available at http://www.advisorybodies.doh.gov.uk/acdp/managingtherisks.pdf and in the Department of Health’s guidance, available at http://www.dh.gov.uk/assetRoot/04/11/48/13/04114813.pdf

VHF agents are Category A infectious substances capable of causing disease in humans or animals and is therefore assigned to UN2814 and are therefore assigned to UN 2814 and must be packaged in accordance with UN Packaging instructions PI620 (road/rail)/ PI602 (air). P620 and P602 are identical specifications but given different codes in ADR and ICAO regulations respectively (for full description of PI see http://www.unece.org/). Category A transfers should be individually requested through an approved courier. The service will be a next day, tracked door-to-door delivery, which must be signed for at collection and receipt. The current HPA courier arrangements can be seen at: http://www.hpa.org.uk/infections/topics_az/deliberate_release/pdf/HPA%20courier%20arrangements.pdf

Packaging must meet with UN performance requirements i.e. UN-type approved packaging for Division 6.2 substances. The packaging should consist of an inner package (watertight receptacle, watertight secondary packaging, an absorbent material in sufficient quantity to absorb the entire contents placed between the receptacle and the secondary packaging) and a rigid outer package of adequate strength for capacity, mass and intended use. Packages should be marked with the proper shipping name (i.e. “Infectious substance affecting humans” UN 2814), and the appropriate warning label (i.e. the danger sign for infectious substances).

The following procedures should be adopted for the transport of all specimens. These apply within hospitals and laboratories as well as for specimens sent to the reference laboratory:

- The primary container should be screwed tight, labelled and placed in an intact plastic bag.
- A ‘High Risk’ label should be affixed to both specimen and request form. The latter should include any other relevant information and include adequate clinical details to indicate level of suspicion.
- Under no circumstances should the request form be placed in the same bag as the specimen.
- The bag should be sealed, using tape or heat sealer. Pins, staples and metal clips should not be used. A separate bag should be used for each specimen.
- Each specimen must then be placed in a leak-proof secondary container with sufficient absorbent material to absorb all the contents should leakage occur.
• Each specimen must be packaged individually - i.e. three specimens, three separate packages.
• The secondary container should be externally disinfected by wiping with hypochlorite (1,000ppm available chlorine).

3.6.1 Samples sent to the reference laboratory
Samples should be transported according to local arrangements for High Risk specimens. Precautions should include:
• Secondary containers should be placed within a final outer tertiary packaging.
• This packaging must comply with the UN-type approved packaging for the transport of infectious substances.
• The package should be certified to this standard and carry the appropriate UN certification numbers on the tertiary packaging along with the following information:
  1. BIOHAZARD – danger of infection symbol Class UN 6.2.
  2. Instructions not to open if found.
  3. Telephone number of a responsible person e.g. Consultant Microbiologist, Laboratory Manager.
• The container should be transported by an approved courier (see link to HPA courier arrangements above), without delay, directly to the reference laboratory.

3.6.2 Samples sent within hospitals and laboratories
• Secondary containers should be placed in a good quality box, which is well taped up and clearly labelled “Pathological Specimen – Open only in Laboratory”.
• Specimens should be transported by hand by a responsible person using the above packaging.
• Vacuum-tube systems should not be used for transportation of specimens within hospitals or laboratories.
• Extra care should be taken to ensure that laboratory records are kept to a high standard.
4. PUBLIC HEALTH PROCEDURES

4.1 Surveillance and detection of deliberate releases of VHF agents
A deliberate release may be overt and associated with an announcement or covert, where suspicion will not arise until the first cases have been diagnosed.

Even a single confirmed case of VHF must be regarded with a high index of suspicion of deliberate release. This suspicion also applies to cases that occur in people who have returned from endemic areas. All infections should be investigated to ascertain that they have not occurred due to deliberate release of VHF agents.

In addition, a deliberate release should be considered in the event of two or more suspected cases of VHF that are linked in time and place. Expert advice will be provided in order to confirm the occurrence of a covert release and assist with epidemiological investigations to define an exposed zone in time and space.

4.2 Case definition

4.2.1 Suspected cases
Clinicians should be alert to the possibility of cases of VHF. Any previously healthy patient with sudden onset of Pyrexia of Unknown Origin (PUO) and pathognomonic signs of facial oedema and haemorrhage should arouse suspicion and be immediately reported to the local Consultant in Communicable Disease Control.

In the event of a suspected deliberate release of VHF agents, a higher index of clinical suspicion should be maintained and the diagnosis considered if the symptoms outlined below present at medical services, especially if they arise in people who have been within or in close proximity to the exposed zone. Obviously the level of suspicion depends on clinical symptoms and the circumstances, but if a case is suspected, microbiological investigations should be sent to eliminate or confirm the diagnosis.

VHF syndrome can be described as an acute febrile illness characterised by malaise, prostration, generalised signs of increased vascular permeability and abnormalities of circulatory regulation. Bleeding manifestations often occur, especially in the more severely ill patients. Bleeding is a poor prognostic factor but death may not be due to a massive loss of blood volume.

4.2.2 Confirmed case
A confirmed case is a case that clinically fits the criteria for VHF and is supported by laboratory investigations, which include culture, PCR, or specific serological testing.

4.3 Public Health Action

4.3.1 Procedure for handling exposed persons at the scene of an overt release
Some of them will still be at the scene when emergency services respond to the incident. This group will be decontaminated and then referred to health workers at a nearby place of safety for assessment (this is a clinical area just outside the exposed zone and within the cordon that will be established at the scene of the incident). Others will have left the scene before emergency services arrive and will be identified later when they approach GPs and A&E departments after details of the incident have been made public. Procedures need to ensure that these individuals are identified for monitoring.
4.3.2 **Follow-up of exposed persons**
After an overt release, all exposed persons will be moved to a place of safety. They will be categorised based on the categories shown in the table in section 2.4 and those in category 3 will be offered prophylaxis with ribavirin. Others will either be actively followed up or will be offered advice on the possible symptoms that may develop. The level of involvement by the health professionals depends on the category that the exposed people fit in to.

4.3.3 **Case finding**
If cases of VHF arise and a covert release is suspected, health services should be contacted to raise awareness of the possibility of the further cases and determine whether any others might already have presented. This should follow the usual chain of command of CCDC, RE and HPA Colindale.

4.4 **Epidemiological investigation**
If a case is strongly suspected or confirmed, the CCDC at the local HPU and HPA Colindale (020 8200 6868, 24 hours) should be notified **immediately**. If cases arise due to a covert release, or following an overt release but in people who have not been present in the exposed zone, it is important to collect some epidemiological details in addition to a basic set of personal details. This is in order to define or redefine the exposed zone and aid identification of others at risk of infection. Details should be as thorough as possible, whilst recognising that in the event of a large release with multiple exposed persons or cases, it may not be possible to collect comprehensive information from everyone.

The aim of epidemiological investigations may be:
- Following a covert release, to assist definition and ongoing review of the temporal and spatial parameters of the exposed zone so that post exposure prophylaxis can be distributed appropriately.
- Following an overt release, to guide review of the exposed zone if cases arise in persons who were not present within it.

4.4.1 **Epidemiological sampling**
There is no rapid test that can be offered to inform asymptomatic people who suspect they have been exposed whether or not they have been infected.

Collection of acute and convalescent sera from asymptomatic people who have been exposed to a release, or who fit the definition of contacts of VHF cases may provide useful epidemiological data and information about the efficacy of prophylaxis. Obviously the practicalities of this depend on the scale of the incident.
5. LIST OF NATIONAL SPECIALISTS

Clinical expert advice

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Out of hours contact details are held at HPA Colindale by the 24 hr on call duty doctor;
Tel: (+44) 020 8200 6868 or (+44) 020 8200 4400
6. BIBLIOGRAPHY

6.1 General Reviews

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2 Centre for infectious disease research and policy (CIDRAP) University of Minnesota. Viral Hemorrhagic Fever (VHF): Current, comprehensive information on pathogenesis, microbiology, epidemiology, diagnosis, treatment, and prophylaxis. (Last updated March 1, 2007). http://www.cidrap.umn.edu/cidrap/content/bt/vhf/biofacts/vhffactsheet.html


6.2 References


