Viral haemorrhagic fevers imported into non-endemic countries: risk assessment and management

Barbara Bannister*

Department of Infectious Diseases, Royal Free Hospital, Hampstead, London NW3 2QG, UK

**Background:** Viral haemorrhagic fevers (VHFs) are severe infections capable of causing haemorrhagic disease and fatal multi-organ failure. Crimean-Congo, Marburg, Ebola and Lassa viruses cause both sporadic cases and large epidemics over wide endemic areas.

**Sources of data:** Original articles and reviews identified by PubMed search and personal reading; European and United States national guidance and legislation. World Health Organization information, documents and reports. VHFs cause significant morbidity and mortality in their endemic areas; they can cause healthcare-related infections, and their broad diversity and range are increasingly recognized.

**Areas of controversy:** There is uncertainty about the risks presented by VHFs in non-endemic countries, particularly in healthcare environments. Consensus on the best modes of care and infection control are only slowly emerging.

**Growing points:** With increasing commerce in rural and low-income areas, VHF outbreaks increasingly expand, causing social and economic damage.

**Areas timely for developing research:** New ecologies, viral strains and clinical syndromes are being discovered. There is a great need for rapid diagnostic tests and effective antiviral treatments. Vaccine development programmes are challenged by multiple viral strains and the need for trials in rural communities.

**Keywords:** viral haemorrhagic fevers/disease reservoirs/infection control

**Introduction and history**

Viral haemorrhagic fevers (VHFs) are severe viral infections, which can cause haemorrhage, multi-organ failure and high case-fatality rates in humans. In their endemic areas, they are capable of causing long-lasting and slow burning epidemics, which can interrupt the normal life, commerce or social structure of a community. For most VHFs, there is no fully effective specific treatment or prevention measure.
Some of them are directly transmissible from human to human, and can cause healthcare and laboratory-acquired infections and outbreaks, or wider transmission, in non-endemic countries.\textsuperscript{1}

The risk of healthcare and laboratory-acquired infection in handling rare or newly recognized pathogens is well documented.\textsuperscript{2–4} Transmission to healthcare workers is also reported.\textsuperscript{5,6} Pathogens causing transmissible VHF\textsf{s} are therefore classified internationally at the most dangerous hazard level (category 4), requiring the highest level of laboratory containment (containment level 4 or biosafety level 4).\textsuperscript{7,8} They are grouped together with other dangerous pathogens, some of which may be deliberately released in acts of aggression.\textsuperscript{9,10}

VHF\textsf{s} have been regarded as rare, exotic, but high-profile, diseases since the mid-20th century. However, they have affected human communities for thousands of years. For instance smallpox, though now eradicated, was mentioned in human records around 10,000 years ago.\textsuperscript{11} The first known outbreak was reported in the Egyptian-Hittite war in 1350 BC. Emerging communities in the New World were destroyed by outbreaks related to recent immigrants, and the first American universities were welcomed, as they avoided the risk of young people contracting smallpox while attending European universities.\textsuperscript{12}

Biological attacks were made by providing smallpox-contaminated goods to Native Americans during the ‘French and Indian War’.\textsuperscript{13} After a worldwide vaccination programme, the World Health Assembly declared in 1980 that the world was free of smallpox.

Today’s concerns about VHF\textsf{s} are still reflected in the history of smallpox and its eradication including: widespread anxiety about severe symptoms and high fatality rates; the fear of epidemic or pandemic spread; the occurrence of travel-associated and healthcare-acquired cases and outbreaks; the susceptibility of armies to suffer disabling outbreaks and to carry the disease home; the risk of deliberate release of the pathogen and the importance of highly-organized public health measures in controlling the disease.

**Viral diseases capable of causing haemorrhagic fever**

Nowadays, many viral infections are recognized as able to cause life threatening, diseases, with features such as haemorrhage, jaundice, rash, renal failure or encephalopathy. Many of these are zoonoses; diseases of animals which can be transmitted to humans either directly, or through arthropod vectors and co-hosts (so-called arboviral diseases).

Because these infections have a life cycle involving two, three or more hosts, embedded in various ecologies, they are difficult to eradicate, but can be controlled by interrupting one or more critical points
in their transmission cycle. Energetic measures are usually necessary to contain outbreaks. The endemic range of these infections is constrained by the ecological and climatic requirements of their hosts and vectors, so that they exist mainly in predictable geographical areas. Epidemics in humans are often a sequel to an epizootic or population increase in a key reservoir animal, and tend to occur in human communities as a build-up of sporadic cases with an overlay of household and healthcare-related onward transmission.

Not all diseases that can cause fever and haemorrhage are directly transmissible from human to human. Those which are must be managed by well-organized social distancing, infection control in healthcare settings and safe burial of fatalities, combined with reservoir and vector control.

The International Health Regulations\textsuperscript{14} are designed to protect against the international spread of these dangerous infections.

The continuing expansion in the air transport and travel industries has meant that large sections of the world community now make frequent, long-distance journeys. Leisure travellers and tourists can cross several different countries and ecologies in a short time; business travellers increasingly move between developing economies and high-income countries; families are often dispersed across several countries, including high-risk areas for VHFs and visit between them; exploration for mineral resources, and the building of new transport routes, takes large communities of workers to unfamiliar and sometimes remote territories. Sick people travel to seek high-quality health care. Displaced people migrate, often overland and in adverse circumstances to reach a refuge which may be crowded and have poor sanitary facilities. Any—or many—of these travellers could be exposed to a highly endemic situation, an infectious vector or an infected person or animal. Severe infections are occasionally reported in all of these circumstances, and are sporadically exported along established travel routes to distant countries, where they place great stress on acute medical and public health services.

Additionally, a VHF is a severe illness for the infected individual, and a major concern to their family and community. Families may be harassed by neighbours or pursued by the press and media. They may be subjected to quarantine or other control measures. Communities may be disrupted by necessary, or sometimes ill-founded, control measures. There is significant risk to health care and laboratory workers, and sometimes a risk to the close contacts of a severely ill patient.

Major VHFs are therefore listed in Table 1, to give an overview of the range of conditions involved, and where they exist in the world. The VHFs which are transmissible from person to person, or have caused laboratory or healthcare-acquired infections, are indicated in bold type. In this century, outbreaks of these VHFs have been increasingly reported in
Table 1 An overview of viral haemorrhagic fevers.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Causative virus</th>
<th>Non-human host</th>
<th>Vector</th>
<th>Geographical distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue haemorrhagic fever</td>
<td>Dengue viruses serotypes 1–4</td>
<td>None recognized</td>
<td>Various types of Aedes mosquitos</td>
<td>Throughout the tropics, including the Caribbean, Pacific rim and islands; seasonal in northern Australia and Torres Straits</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>YF virus (flavivirus)</td>
<td>Forest-dwelling non-human primates</td>
<td>Aedes mosquitos</td>
<td>Tropical rain forests of Africa and south America</td>
</tr>
<tr>
<td>CCHF</td>
<td>Seven clades of CCHF virus (Bunyavirus)</td>
<td>Small and large animals, including farm animals</td>
<td>Various types of Hyalomma ticks</td>
<td>North-east Europe, north Asia, central and south Africa: virus clades geographically distributed</td>
</tr>
<tr>
<td>Haemorrhagic fever with renal syndrome</td>
<td>Many types of Hantavirus (Bunyavirus)</td>
<td>Ground-dwelling small rodents</td>
<td>None recognized</td>
<td>Canada, north and south America, Scandinavia, continental Europe, north Asia, far East, Korea</td>
</tr>
<tr>
<td>Lassa fever</td>
<td>Highly divergent subtypes of Lassa virus (arenavirus)</td>
<td>Multimammate rat (M. natalensis)</td>
<td>None recognized</td>
<td>Sub-Saharan west Africa from Senegal to Central African Republic</td>
</tr>
<tr>
<td>Lujo virus New World Arenaviruses</td>
<td>Junin</td>
<td>Not known</td>
<td>Not known</td>
<td>Zambia</td>
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<tr>
<td></td>
<td>Machupô</td>
<td>Various small field, bank and harvest mice</td>
<td>Not known</td>
<td>Argentina</td>
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<tr>
<td></td>
<td>Chapare</td>
<td></td>
<td></td>
<td>Bolivia</td>
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<tr>
<td></td>
<td>Sabia</td>
<td></td>
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<td>Bolivia</td>
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<td></td>
<td>Guanarito</td>
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<td>Brazil</td>
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<td>Venezuela</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Infections associated with farming and harvesting</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Zaire (ZEBOV), Sudan (SEBOV), Ivory Coast (CIEBOV), Bundibugyo (related to CIEBOV, discovered in an outbreak in Uganda), Ebola Reston (REBOV, causes severe disease in macaques and possibly pigs: not pathogenic to humans)</td>
</tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Ebola haemorrhagic fever</td>
<td>Various strains of EBOV</td>
<td>Not confirmed, Maybe fruit bats; non-human primates often affected</td>
<td>None recognized: possibly fruit bats</td>
<td></td>
</tr>
<tr>
<td>Marburg haemorrhagic fever</td>
<td>Strains of MARV</td>
<td>Not confirmed</td>
<td>Possibly fruit bats</td>
<td></td>
</tr>
</tbody>
</table>

Some other, rarer VHFs: Chikungunya haemorrhagic fever, an Aedes mosquito-transmitted Alphavirus endemic in Africa and Asia with a reservoir in monkeys; Kyasanur Forest fever, a tick-transmitted flavivirus endemic in north Asia with a reservoir in porcupines and small rodents; Omsk haemorrhagic fever, caused by a tick-transmitted flavivirus endemic in Siberia, with a reservoir in muskrats, but also found in rodents and farm animals, and in contaminated water; Rift Valley fever, an Aedes or Culex mosquito-transmitted bunyavirus endemic in Egypt and sub-Saharan Africa with a reservoir in farm livestock and some large mammals. These diseases are rarely seen in humans, and are only haemorrhagic in a small proportion of cases, but haemorrhagic cases and outbreaks may be recognized associated with epidemics in the reservoir animals (epizootics).
endemic areas. New endemic areas, ecologies and viral strains or species have been discovered, and a small but steady number of cases have been imported into non-endemic countries.

Viral haemorrhagic fevers of concern to non-endemic countries

Four main types of viral haemorrhagic fever fulfil the definition for hazard Group 4 pathogens, are capable of transmission, particularly in healthcare settings, and cause severe diseases with high case-fatality rates. In non-endemic countries they are recognized as needing safe, secure, high-quality medical care with a high level of infection control. This level of care is most effectively delivered by specially trained staff in a designated high-level unit.\(^{15}\)

In countries at risk of the introduction or spread of VHFs, national policies for managing cases focus on those infections which are known to be transmissible from person to person and could therefore cause secondary cases or outbreaks.\(^{16,17}\) These VHFs are: Crimean-Congo haemorrhagic fever (CCHF), the filovirus haemorrhagic fevers (Marburg and Ebola) and Lassa fever.

Pathogenicity of the major VHF viruses

These four diseases are notable for the pathological process by which they cause severe illness and haemorrhage. All four diseases are caused by infection with RNA viruses whose key targets are dendritic cells, mononuclear cells and macrophages of the immune system, and vascular endothelial cells. They can also infect many other cells, including hepatocytes and kidney cells. The pathogenic process has been particularly studied in Ebola virus (EBOV) infection, as this is a very severe disease for which there is no specific prevention or treatment, and for which a number of animal models are available. After a non-specific prodromal illness lasting a variable number of days the disease rapidly progresses to an intense cytokine response, with severe inflammatory tissue damage. There is also a failure of effective immune responses, so that neither viral replication nor the inflammatory process can be controlled.

Two mechanisms in EBOV infections are thought to contribute to disruption of the innate immune response: one is the inhibition by viral protein (VP35) of IFN-regulatory factor 3, a transcription factor necessary for the induction of IFN alpha/beta expression; the other is large-scale ‘bystander’ apoptosis of T-lymphocytes whose normal ability
to inhibit the apoptotic response to major inflammation is therefore disrupted. These processes are represented by severe lymphopaenia and a lack of effective antibody or cell-mediated immune response.\textsuperscript{18–20}

In this situation, the escalating cascade of inflammatory cytokines, notably IFN alpha, IL2, IL10 and TNF alpha, leads to an overwhelming sepsis syndrome and endothelial damage. Direct viral invasion of endothelial cells can also cause cell detachment and death, with a major failure of vascular integrity, further disrupting the control of body fluid compartments and contributing to refractory hypovolaemic shock.

Pathogenetic mechanisms in Marburg virus (MARV) infection are similar to those in Ebola, though there are some differences in the details of how they are achieved.\textsuperscript{21} The role of natural killer cells has also been considered important in defence against both diseases.\textsuperscript{22}

In Lassa fever, although the tendency to shock and haemorrhage is less than with filovirus infections, the virus employs a similar strategy to suppress innate immune responses while stimulating intense inflammatory cytokine release. Very high levels of TNF alpha and IFN gamma, were demonstrated, alongside low levels of IL10, in a Lassa fever patient who died with shock and haemorrhage in Germany.\textsuperscript{23} For all of these viruses, the modulation of the immune response and the inflammatory cascade appear to be initiated by the binding of the virus to the target cell.\textsuperscript{24}

Cytokine activation leading to ‘platelet exhaustion’, together with severe endothelial damage, may explain why an early bleeding tendency in arenavirus and filovirus diseases is not usually due to intravascular coagulation, but may be related to defective platelet activation,\textsuperscript{25,26} though this theory was not supported by \textit{in vivo} investigation.\textsuperscript{27}

In those patients who recover from EBOV infection, and the very few who seroconvert without apparent illness, there is evidence of a very early and intense cell-mediated immune response with sustained levels of IL1b and IL6 in the blood. This response is associated with only a transient increase in proinflammatory cytokines, suggesting that the cytokine escalation has been controlled.\textsuperscript{28}

\section*{Crimean-Congo haemorrhagic fever}

\textit{The CCHF virus}

This virus, genus \textit{Nairovirus} from the family of Bunyaviridae, is an arbovirus whose predominant vectors are ticks of the \textit{Hyalomma} genus (Fig. 1).

Various species of these ticks are widely distributed across Africa, the Middle East, eastern Europe, Asia and the Far East. The main
reservoirs for the disease are livestock, including cattle, goats, sheep and other animals, as well as wild animals and smaller rodents. In South Africa, ostriches have been shown to suffer asymptomatic viremia and to carry infected ticks.\(^{29}\) The virus has recently also been identified in smaller birds.\(^{30}\)

The *Bunyaviridae* are characterized by a single strand, negative-sense, segmented, RNA genome which exists as three sections: S (small), M (medium) and L (large). There is a great variation between strains, mainly based on mutations, though reassortment between viruses does occur more rarely, most often within the M segment.

Investigation of the gene segments and their peptide products identifies seven main clades of the CCHF virus, which tend to group to the distribution of the disease in various parts of the world (Fig. 2).\(^{31}\) Outliers to this pattern, suggest that some virus strains have been transported over long distances, either by human migration or, possibly by migrating hosts.\(^{52}\)

The different virus strains exhibit differences in the clinical disease, which they cause. For example: recently described cases in south western Bulgaria suffered predominantly pulmonary haemorrhage, rather than the major gastrointestinal haemorrhage commonly seen in

Fig. 1 Adult *Hyalomma* tick.
eastern Bulgarian cases, but similar to a case in nearby Greece. Strains of CCHF virus circulating in Pakistan tend to be more virulent than those in Europe and Africa, and often cause the high fatality rates.

The importance of CCHF

CCHF is a relatively common infection in endemic areas. It has become more common in the last decade, partly because of increased vector and viral activity, which may be climate related. It is increasingly reported from eastern European countries. Annual outbreaks affect farming communities in Turkey, with well over 3000 cases reported from 2005 onwards and an overall case fatality rate of around 5%. Case series describe the tendency for index cases to have removed ticks from animals, or suffered tick bites, while secondary cases are reported in family members. A serosurvey of two affected areas of Turkey showed that 12.5% of the population possessed IgG antibodies to CCHF virus. Most were farmers in the 40s–60s age group. Epidemics have also occurred in Albania, Iran and neighbouring countries of the Middle East.
In all endemic countries, healthcare workers have been infected when caring for patients. Military personnel may be at risk if they live or work in basic accommodation in endemic areas. In September 2009 a US soldier died of CCHF after sustaining a tick bite while serving in Afghanistan.

**Clinical and pathological features of CCHF**

CCHF has a shorter clinical course than the other VHFs, but is unique in causing early-onset and extremely severe haemorrhage.

The incubation period is usually 2 or 3 days after infection by tick bite (range one to nine days), but around 5 or 6 days after exposure to infected blood or tissue. The maximum incubation period for any route is 13 days. Infection by blood and tissue exposure is thought to result in more severe disease, but this is a largely anecdotal observation.

The onset of illness is usually abrupt, with high fever, severe muscle and joint pains, headache, lower back pain and prostration. Eye pain, photophobia, sore throat and vomiting may occur, and lymphadenopathy is sometimes reported. In some cases, severe abdominal pain, often with diarrhoea, leads to misguided surgical intervention.

Haemorrhagic features often begin 3 or 4 days after the onset of illness, and are seen in around 70% of cases. Bleeding appears first as petechial lesions on the skin and buccal mucosa, and as oozing from venepuncture sites. This milder degree of bleeding has a less severe prognosis than major haemorrhage, but can still carry a case fatality rate of up to 70%. Bleeding from the gums is common.

More severe cases develop severe gastrointestinal bleeding, with uncontrollable haematemesis and severe bloody diarrhoea. In some cases exsanguinating epistaxis occurs. These features are usually accompanied by bruising and sometimes by the formation of blood-filled bullae in the skin (Fig. 3). Pulmonary haemorrhage may also occur. The features of disseminated intravascular coagulopathy can develop quickly, and severely affected patients require treatment for platelet deficiency, disseminated intravascular coagulation (DIC) and massive haemorrhage.

If the bleeding can be managed, patients may begin to recover after 5–7 days. Later features of the disease include hepatic dysfunction, renal failure, pleural effusions, acute respiratory distress syndrome or multi-organ failure, and are often accompanied by DIC. In fatal cases, death usually occurs at around 9 or 10 days of illness.

Patients who recover have a prolonged convalescence. They may suffer from hair loss, poor concentration and reduced acuity of hearing, but these sequelae are rarely permanent.

The relatively high prevalence of seropositivity suggests that milder illness occurs in populations living and working in endemic areas.
**Differential diagnosis**

The features of CCHF can be similar to those of other infections, which occur in farming and rural areas. These include severe leptospirosis, haemorrhagic fever with renal syndrome and rickettsial infections. Malaria or plague must be excluded for patients in the relevant endemic areas, as they can be life threatening without early treatment. Meningococcal bacteraemic disease must always be considered.

Unrecognized CCHF cases have also been interpreted as autoimmune thrombocytopaenia, thrombotic thrombocytopaenic purpura or bone marrow malignancy. Many of the alternative diagnoses are more common than CCHF, even in CCHF-endemic areas. It is therefore important to obtain and store clinical specimens for laboratory testing under safe containment conditions, and to treat empirically for likely alternative diagnoses, while awaiting the results of diagnostic tests.

**Laboratory findings**

Blood tests initially suggest an acute viral infection with leukopenia, raised inflammatory indices and sometimes a modest rise in transaminase levels. Sudden and marked escalation of the aspartate transaminase (AST) level to the high hundreds, and a rapid fall in platelet count to well below $30 \times 10^3$/l are important warning signs of progression of the illness. Severe tissue damage may be accompanied by a rise in the neutrophil count.

Laboratory markers of an adverse outcome were described for South African cases as: WBC $>10,000$/mm$^3$; platelet count $20 \times 10^3$/cu mm, AST $>200$ U/l; ALT $>150$ U/l; APTT $>60$ s, and fibrinogen $<110$ mg/dl. There is a high viraemia at the onset of illness. During outbreaks in Kosovo, this was shown to correlate with the severity and
prognosis of the disease. Viraemias as high as $8 \times 10^{10}$ copies were seen in fatal cases. Levels of 1000- to 10 000-fold less were associated with moderate severities of illness and a high rate of recovery. Even in fatal cases, the viraemia tended to decline over time. The duration of viraemia varied from 8 to 23 days, but no cases of persistent viraemia were found.\(^{42}\) Fatal cases often show no evidence of IgM or IgG antibody development. Even in some severe cases who recovered from the infection, there was no evidence by ELISA of antibody production.

Pathological studies have shown that viral antigens are mostly concentrated in mononuclear cells, phagocytes, endothelial cells and hepatocytes. This correlates with the tendency of CCHF virus to inhibit the immune response, and to cause severe bleeding. The finding of viruses in hepatocytes is in keeping with the production of focal or general necrotic lesions in the liver.\(^{41}\)

**Diagnosis of CCHF**

Until recently, the rapid diagnosis of CCHF was based on antigen detection using ELISA techniques to detect nucleoproteins, IgM antibody detection and viral culture.

Antigen detection is most reliable in the first 5–7 days of illness when the viral load is high. Although it is a useful rapid test if positive, it is relatively insensitive and cannot detect virus levels of less than around 2–2.5 log TCID\(_{50}\) in blood. IgM antibody detection is not entirely reliable, as the appearance of the antibodies may be transient and patients with severe disease tend to produce antibodies very late, or not at all.

Reverse transcription polymerase chain reaction (RT-PCR)-based tests, for RNA genome detection, are now established as the most reliable rapid diagnostic tests. The tests are carried out using sequestrine-anticoagulated whole-blood samples. Using ‘real-time’ systems, a positive result can be obtained on the same day or overnight in many cases. The tests are sufficiently sensitive to remain effective as viral titres in the blood fall in the second week of illness. They are also highly specific, so that the diagnosis can usually be excluded by a negative test. The main difficulty with PCR tests is that they can give false-negative results if the gene sequences used to detect the infecting virus are significantly different from the targets of the detection system. This is rare with CCHF.

It is also possible to detect virus in saliva or urine. A recent study suggests that titres in blood and in other body fluids are similar in most patients.\(^{43}\) Viral culture remains the ‘gold standard’ diagnostic test, as it permits the detection of almost all strains of the virus, at the same time providing material for investigation of viral components other than the genome.
Treatment of CCHF

Early diagnosis and supportive treatment significantly improve the outcome for CCHF patients. Resuscitation and adequate haemodynamic support is potentially life saving at this early stage. Vigorous management of severe or massive bleeding is necessary with red-cell and platelet transfusions, fresh frozen plasma and calcium replacement.

The nucleoside drug ribavirin strongly inhibits viral replication in cell cultures.44 There is widespread expert opinion that ribavirin is effective in treating CCHF, though not all case series have confirmed this.45 High-quality studies of ribavirin’s effectiveness are not available partly because of the unpredictable occurrence of cases. Most of the studies have been based on the use of oral ribavirin treatment, which may not be the optimal route of administration in severely ill patients. Also, in the absence of any other effective agent, it would be considered unethical to withhold ribavirin for the purposes of controlling a study.

A recent study in Iran showed a strongly significant correlation between early oral ribavirin treatment and both the absence of haemorrhage and the likelihood of survival.46 Even in this case series, the fatality rate was 16 of 63 cases.

In most Western countries, treatment with intravenous ribavirin would be preferred. A widely accepted regimen for the treatment of VHF is given in Box 1:

Box 1: recommended dosage regimens for treating CCHF or Lassa fever with ribavirin

**Intravenous regimen (preferred)**

- **Loading dose:** 33 mg/kg by infusion in normal saline
- **Continuation dose:** begin 6 h after loading dose and give 16 mg/kg 6 h for four days
- **Completion dosing:** 8 mg/kg 8 h for a further six days

**Oral regimen (commence if intravenous ribavirin is not available)**

- **Loading dose:** 2 g
- **Continuation dose:** begin 6 h after loading dose and give 1 g 6 h for four days
- **Completion dosing:** 0.5 g 6 h for a further six days

**Observe for adverse reactions:**

- Nausea, sleeplessness, intrusive dreams
- Dose-related haemolytic anaemia, which may require blood replacement
- Jaundice, transaminitaemia, rare pancreatitis

Ribavirin causes dose-dependent haemolytic anaemia, which may require transfusion. Patients who have recovered from CCHF should be
monitored for iron and folate deficiency, and will often require replacement of haematinics to aid recovery.

Prevention and control

In endemic areas, convalescent plasma with high antibody titres, may be used as post-exposure prophylaxis in household members or healthcare workers caring for infectious cases. Its effectiveness is unknown, and no trials have been carried out.47

There is no available licensed vaccine for the prevention of CCHF, though an inactivated mouse brain-based vaccine has been used in some countries. There is currently a sustained effort to employ reverse genetics to generate virus proteins of interest for vaccine development.48 This is a technique, used for a range of RNA viruses, by which viral RNA is transcribed into DNA, which can then be inserted into plasmids to generate the protein for which the RNA originally coded.49 It has the advantage that the handling of whole, infectious virus is not necessary to produce purified proteins, so that individual proteins can be manufactured at biosafety level 2 (the level at which diagnostic procedures for most human pathogens is carried out).

EBOV and Marburg haemorrhagic fevers (filovirus infections)

EBOV and MARV

These viruses are unique among human pathogens. They are filamentous, single-stranded, negative-sense RNA viruses. Marburg disease was discovered in 1967, originating from infected monkeys imported from Uganda into Germany and former Yugoslavia.1 The filamentous virus was easily identified in the blood and tissues of the patients.50

As only a few sporadic cases and small outbreaks were reported in the next 10 years, MARV infection was considered to be rare and sporadic. However, in this century substantial outbreaks have occurred in the Democratic Republic of the Congo51,52 and Uganda.53 A large, prolonged epidemic in Angola caused over 200 deaths, including staff working in the affected hospital.54

Individual cases of imported Marburg disease have been recognized in Sweden and the Netherlands. A case in the USA occurred in 2008, in a person who had visited Uganda, including the same cave, popular with tourists that was visited by the Swedish case.55 It was diagnosed only after the patient recovered from a severe and debilitating illness. A late blood test showed the presence of IgG antibodies. Ebola
haemorrhagic fever was recognized when two large outbreaks, both centred on hospitals, occurred in 1976, first in Sudan and soon afterwards in a nearby part of Zaire, now the Democratic Republic of the Congo (DRC). The outbreaks were probably amplified by inefficient sterilization of re-used needles and by other routes of hospital transmission. The very high case-fatality rates of 70–85%, and transmission within the hospital setting, led to plans in many countries to manage imported cases of VHF with very stringent infection control.

Large numbers of Ebola cases were not reported again until 1994 and 1995, when large outbreaks occurred in Uganda and the DRC. Frequent large outbreaks have since been reported from Gabon, Congo, DRC and Uganda. A fatal hospital-acquired case occurred in Johannesburg, in a nurse who cared for a doctor infected in one of the Gabon outbreaks.

EBOV is genetically and phenotypically similar to MARV, but the viruses are distinct (Fig. 4), with little or no natural cross-immunogenicity between them.

The Ivory Coast strain of EBOV was identified from a single case in 1994, in a scientist who had examined a dead chimpanzee. An epidemic of a new strain of EBOV, now named the Bundibugyo strain, occurred in Rural western Uganda in 2007. The resulting illness has a low case-fatality rate (25%) and no haemorrhagic features. This virus is closely related to the Ivory Coast strain.

The ecological niches associated with filovirus infections have now been well described, and are useful indicators of likely areas where exposure is a significant risk (Fig. 5).
Ebola reston virus

In 1989 monkeys imported to the USA from the Philippines suffered from a haemorrhagic fever while in a quarantine facility. They were found to be infected with an EBOV, which was named Ebola Reston or REBOV. Some healthy staff who had close contact with the monkeys were seropositive when tested, but had suffered no clinical illness. Monkeys had been infected at an animal holding centre in the Philippines, and often died of the disease. In early 2009, REBOV was also identified in sick pigs in the Philippines, and some farm workers were also seropositive. There is little evidence that REBOV causes a distinct illness in pigs. The World Health Organization confirmed that no infected human had suffered a clinical disease, but warned that the effect of infection in susceptibles, such as immunosuppressed or pregnant individuals, is not known.

The reservoirs of filovirus infections are now beginning to be identified. Cases of Marburg infection have been associated with caves in Kenya and Uganda, and also with mines. The original Ebola outbreaks centred around cotton factories where bats inhabited the roofs. Particularly for Ebola, contact with sick forest primates was a recognized feature of several index cases, but there was no serological evidence that primates were commonly infected or seropositive.

After many studies of various animals, Egyptian fruit bats in Kitaka cave, in Uganda were tested as part of the investigation of a nearby Marburg outbreak. Five percent of the bats had virus-specific antibodies in their blood, and viruses were isolated from their tissues. A larger and more widespread survey showed the presence of antibodies to both ZEBOV and MARV in Gabonese bat populations. Monkeys affected by REBOV in the Philippines were housed in an area where

Fig. 5 Ecological niches: C: EBOV; D: MARV Source: Towner JS, Townsend A, Peterson et al. EID 2004; 10: 40–47
fruit bats roosted. Fruit bats excrete viruses in their urine and saliva. Partly eaten fruit, which is heavily contaminated, often falls from trees and is eaten by other animals, including pigs on farms where bats roost in fruit trees above the pig pens.

Clinical features of Marburg and Ebola infection

The clinical features of these two infections are similar, and have been well documented both in endemic areas and in hospital practice.\textsuperscript{55,66} The incubation period is usually between 3 and 9 days, but can be as long as 16 or 17 days. There is little evidence that asymptomatic infection occurs.\textsuperscript{67} The onset of illness is abrupt, with fever, conjunctival injection, headache, general muscle and joint aches, anorexia and nausea. Abdominal pain is common and may lead to erroneous surgical investigation or diagnosis.\textsuperscript{57} Many patients have diarrhoea, which may or may not be bloodstained, beginning between the first and fourth day. At this stage, they may not appear to be severely ill. A maculopapular rash is a common finding. In Marburg infection, it may be confined to the arms and upper torso but, in both Marburg and Ebola, it can become generalized, and may include a petechial element.

After 3 or 4 days, patients tend to deteriorate suddenly, becoming exhausted, with worsening diarrhoea and vomiting. Rigors are common. The blood pressure and peripheral oxygen saturation levels fall and confusion is common. Not all patients have major haemorrhagic features, though these are relatively common in very severe or terminal disease, especially with Ebola infection.

After 7 or 8 days, shock, oliguria, organ failures and increasing oedema occur and often mark the beginning of a terminal decline leading to death. Haemorrhagic manifestations often take the form of bloodstained diarrhoea, nosebleeds, petechiae, bruising or haematemeses, but are not usually as early or as extreme as in CCHF. Mucosal candidiasis is common, perhaps related to inhibition of immune responses, or to ongoing antibiotic treatment.

Patients who recover become gradually afebrile and less confused from around the 10th day of illness, but often remain debilitated for some weeks or months with anaemia and complaints of poor concentration. Long-term sequelae have not been described.

The case-fatality rate varies with the infecting filovirus strain: from around 25 to 40\% for Marburg infection, 50–70\% for Ebola Sudan and 80–90\% for Ebola Zaire. The first recognized outbreak of Ebola Bundibugyo had a case-fatality rate of 25\%.
Laboratory findings

Leucopenia is seen in both early and late disease. Total white cell counts of 1–4 × 10^9/l are common. However, the haemoglobin, platelet count and coagulation indices are often stable for up to a week, after which a variable degree of thrombocytopenia usually occurs.

Characteristically there is a large rise in AST levels between 1200 and 10 000 U/l. Alanine transaminase (ALT) levels are much less elevated, suggesting that the AST originates from widespread cellular damage rather than from the liver alone. Other common features include large elevations of creatine kinase (CK), suggesting myositis, raised creatinine levels and, in severe or late disease, evidence of intravascular coagulopathy.

Virus titres in the blood are very high. Virus persists in the blood throughout the illness and sometimes for several days into convalescence, even in the presence of significant antibody titres. Very low levels of virus can be detected in early convalescence by nested RT-PCR methods, but there is little evidence that these levels constitute a risk of transmission of the infection.

In some body fluids, such as semen, EBOV has been detected for up to 3 months after recovery from the acute illness. MARV has been recovered from the aqueous fluid of an inflamed eye after a similar period.

The antibody response to filovirus infections is variable in onset and degree. Many patients will begin to develop antibodies, detectable by ELISA techniques, after anything from 3 to 14 days. Those who develop antibodies in the first few days of illness tend to be among the survivors. However, antibody is not the major factor in terminating viral activity, which may persist for weeks after high levels of total antibody are reached. Furthermore, it is known that fatalities still occur in patients who develop significant antibody levels in the blood. Early antibody development is more likely a marker of an immune response, which has occurred despite the inhibiting effect of the severe viral infection.

Diagnosis of filovirus infections

Rapid methods for the diagnosis of filovirus infections include antigen detection, IgM detection and RT-PCR tests.

Antigen detection employs monoclonal antibodies in antigen-capture ELISA systems, to detect nucleoprotein, surface glycoproteins or VP40. It is sensitive, and can be used in early disease when viraemia is high and antibodies have not yet developed. It is also useful in detecting virus in tissues, including post-mortem materials. Antibodies raised
against recombinant viral proteins are not completely strain-specific and can therefore detect viruses of more than one strain.

Immunofluorescence tests to detect IgM antibodies are sensitive, but can be affected by high levels of antibodies to, for instance, malaria. ELISA methods are more sensitive and less prone to false-positive and false-negative results. Antibody detection methods have the disadvantage that antibodies are not present at detectable levels in early disease, or in patients with very severe disease. In patients who recover, IgG antibodies are detectable for several years, at least.

Reverse transcription PCR tests to detect sequences for conserved genes are sensitive, but can occasionally fail if the infecting filovirus does not closely match the oligonucleotide primers used in the detection system. A range of primers may be needed to be sure that a positive diagnosis is not missed. Real-time RT-PCR has been used to detect MARV RNA extracted from formalin-fixed tissues.

Detection of virus in cell culture is not as rapid as antibody and RT-PCR tests, but viruses grow easily on many standard types of cell and produce a cytopathic effect. Culture is less necessary now that rapid genome sequencing methods are available to identify strains of viruses, but it is still the gold standard for virus detection, and necessary for research, including for vaccine development. It is hazardous, owing to the high pathogenicity of the viruses, and must only be carried out in accredited BSL4 facilities.

### Treatment, prevention and control of filovirus infections

A wide range of treatments for filovirus infection have been tested, including interferons, specific immunoglobulins, prostacyclins and antiviral drugs. None of these have produced a significant effect on the course of the disease.

The recent discovery that fruit bats may be the reservoir of filoviruses offers a new opportunity to control human exposure to infection. However, this may not be practicable in all rural tropical areas. The search for a vaccine against either MARV or EBOV or both pathogens has been vigorous and innovative.

Various live-attenuated vaccine constructs have been investigated, including poxviruses, adenoviruses human paramyxoviruses and vesicular stomatitis virus (VSV). The VSV-based vaccine is of particular interest as VSV is not a natural human pathogen, but efficiently carries the Ebola viral glycoprotein gene into human cells. The VSV vaccine produces modest levels of antibodies, which protect immunized animals from high viral exposures.
It has also provided post-exposure protection in non-human pri-mates,\textsuperscript{71} and a trial preparation was given to a scientist who suffered a needlestick with an Ebola-contaminated needle at the Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany. The scientist remained well.\textsuperscript{72}

Prototype vaccines have also been developed using insect cells to generate glycoproteins and VP40 of MARV and EBOV, which bud from the host cells as filamentous, virus-like particles. Used as a vaccine, these produce high levels of neutralizing antibodies, which protect mice against lethal viral challenge.\textsuperscript{73}

**Lassa fever and other arenavirus infections**

Lassa fever was first identified in 1969 in cases from Lassa in Northern Nigeria. A number of local healthcare workers became infected and a sick American nurse was repatriated to the USA, where she recovered. A senior professor in the USA identified the causative virus, but he and another laboratory worker were infected by it.

A large number of related viruses has now been identified in both the Old World and the New World countries of South America, and has been named the Arenavirus family. As more has been learned about these viruses, transmission from human to human is now known to be uncommon, but the viruses remain classified as hazard category 4, because they can cause severe disease for which there is not a reliable treatment.

**The arenaviruses pathogenic to humans**

Arenaviruses are enveloped viruses with a single-stranded, negative sense RNA genome. The genome has two fragments, small and large (S and L). The most studied gene, coding for nucleoprotein, resides in the S segment, and formed the basis of most earlier taxonomies of Lassa and other viruses.

**Old World Arenaviruses**

Investigations of potential animal reservoirs were conducted in Nigeria, Sierra Leone and Liberia. The multimammate mouse, *Mastomys natalensis* was found to excrete the virus, and to support asymptomatic neonatal infection. No other rodent species has been shown to act as a reservoir of Lassa virus.

It is been estimated from reported outbreaks and serosurveys that 100 000–500 000 human cases of Lassa fever occur each year in West...
Africa. Many are probably subclinical or mild, but up to 20% of cases are severe. Lassa fever is a common reason for admission to hospital with non-malaria fever in endemic areas.

Two serotypes of Lassa virus were initially recognized: Nigeria, and Josiah (from Sierra Leone). Non-pathogenic arenaviruses, (Ippy, and Mobala) were discovered in various other African regions, with reservoirs in other rodents. Mopeia virus, also not pathogenic for humans, has a reservoir in *M. natalensis*. Using all available data on virus cases and reservoirs in Nigeria, Sierra Leone, Liberia and Guinea, an ecological distribution map (Fig. 6) confirmed that Lassa virus is expected to occur throughout West Africa.

In 2000, a new strain of Lassa virus was recovered from a fatal case imported to Germany after exposure in Cote D’Ivoire, Ghana and Burkina Faso. Based on genome structure, Lassa virus strains are highly divergent, and appear to be quasi-species (Fig. 7). There is corresponding immunological strain specificity. This means that antibody-based diagnostic tests and serosurveys must take account of strain variation, and avoid using poorly matched strains. It has also implications for the development of a widely applicable vaccine.

In 2008 a safari-tour worker, living in Zambia, died of a feverish illness after repatriation to a clinic in Johannesburg. Three fatal secondary cases and a tertiary case occurred in exposed health care and

Fig. 6 Risk maps of Lassa fever in West Africa. Source: Fichet-Calvet E, Rogers DJ, PLoS Negl. Trop Dis 2009;3(3):388. doi:10.1371/journal.pntd.0000388
hospital staff. A new arenavirus was identified in tissue and serum from the cases, and characterized by PCR analysis and sequencing. This new arenavirus has been named Lujo virus.⁶

In the New World, seasonal outbreaks of haemorrhagic fever have been described in Argentina. Harvest mice harbour the causative Junin virus and infect farmers at harvest time. Similar viruses are found in Bolivia (Machupo virus), Brazil (Sabia virus) and Venezuela (Guanarito virus). As recently as 2008, a new arenavirus now known as Chapare virus, was recognized in a patient from a cluster of cases in Bolivia.⁷,⁸ New World Arenaviruses are not thought to cause human to human transmission, Sabia virus has been transmitted through accidental aerosol generation in the laboratory.³,⁴

The populations affected by New World Arenaviruses are not often likely to travel internationally, so that importation of these infections to other countries is exceptionally rare. Although some of them have caused single infections after laboratory accidents, and may have caused small local outbreaks, they are mentioned here for completeness rather than because of the risk of international spread.
Clinical features of Lassa fever

Lassa fever has been extensively studied, both in its endemic areas and in countries to which it has been imported. Hospital cases have around a 15% case-fatality rate. While most described cases are in adults, children and babies can be affected and may suffer fatal infections characterized by shock and massive tissue swelling: ‘swollen baby syndrome’.

The incubation period for most cases is 3–10 days, but with a maximum of around 18 days. The illness tends to occur in three phases.

The first phase evolves slowly as a moderately severe acute viral syndrome, with sustained high fever, anorexia, often headache, pharyngitis, sometimes exudative or ulcerative tonsillitis, and muscle and joint aches. The white cell count is low or normal, the C-reactive protein level is moderately elevated and other blood tests, including coagulation tests, are usually normal. The patient does not appear severely ill. Tests and treatment for malaria are usually conducted. Other differential diagnoses include influenza, dengue, rickettsial infections, typhoid fever and community-acquired urinary tract infection or tonsillitis. Many patients receive empirical antibiotic treatment.

The second phase develops after 7 or 8 days, when more distinct features of Lassa fever begin to appear. Half or more of patients develop a doughy swelling of the neck and lower face, which does not pit on pressure, and which is a useful warning sign of the likely diagnosis. Nosebleeds and microscopic haematuria are common, but are not always precursors of more major haemorrhagic features. A slight drop in the blood pressure is often seen, and the peripheral oxygen saturation may fall to below 95%. The AST level begins to rise and may eventually reach a peak of 1–2000 U/l. The ALT does not rise so much, so that around a 10:1 AST:ALT ratio is common. The platelet count usually falls slightly. Pancreatic lipase and muscle enzyme levels may also rise.

At this stage, encephalopathy can occur causing confusion or altered consciousness. Signs of cerebral irritation may include seizures and neurological signs such as upgoing plantar responses; sensorineural deafness develops in 5–30% of hospital cases, and is usually irreversible.

The third phase begins after 10–12 days, with a rapid decline in blood pressure and oxygen saturations, marking the onset of shock. Patients may develop a sepsis syndrome, but significant haemorrhage occurs in only about 17% of patients. Severe haemorrhage is a marker of a potentially fatal outcome. In severe cases, renal failure and ARDS are common; endothelial integrity is lost; fluid accumulates in extracellular compartments, including the pleural and peritoneal cavities, and death follows due to multiorgan failure and haemodynamic collapse. The course of fatal disease is often between 2 and 3 weeks.
Patients can begin to recover at any stage of the illness. The convalescent process is often prolonged, with slow resolution of exhaustion, poor concentration or frank depression.

**Important laboratory findings**

Poor prognostic factors include transaminase levels above 400–500 U/l, very high lactate dehydrogenase (LDH) levels, a high viral load (10⁷–10⁸ genome copies/ml), severe haemorrhagic features and failure to develop a detectable antibody response after 8–10 days. The AST and LDH levels may fall back to near normal levels 2–3 days after peaking, but this does not indicate an improvement in prognosis if the fever and other features have not also improved. Viruses can be detected in blood, respiratory secretions, faeces and urine throughout the active illness and into convalescence. A declining viraemia can be demonstrated for 1 or more weeks after the end of the fever. Viral RNA may be detectable for 3 or more weeks in urine and for much longer in semen. One surviving patient had detectable viruria for 70 days after the onset of her illness. The persistence of virus may be related to the very late development of neutralizing antibodies to arenaviruses in primates of all species, and particularly to Lassa infection in humans, where it may be 3 months or more before they appear.

**Treatment and prevention of Lassa fever and other arenavirus infections**

**Antiviral treatments**

The current treatment of choice for Lassa fever is intravenous ribavirin (see Box 1). A large study with retrospective controls showed that ribavirin treatment significantly improved the outcome of severe Lassa fever if dosing was begun before the eighth day of illness. This treatment did not make a significant difference to the level or persistence of viraemia, or to the occurrence of viruria during convalescence. Early treatment of humans infected with other arenaviruses has apparently aborted the development of severe illness.

Ribavirin is relatively toxic. It is concentrated in red blood cells and causes haemolysis, and it may contribute to liver and pancreatic dysfunction during illness. It is an unpleasant drug to take orally, as it causes debilitating malaise as well as more specific unwanted effects. Recent work with a novel, broad spectrum, pyrazine-derived antiviral drug, T-705 (favipiravir), suggests that it can be as effective as ribavirin in treating arenavirus infections in animals, and is significantly less toxic. However T-705 did not reach effective blood levels if treatment was delayed after early infection.
Post-exposure prophylaxis of Lassa fever
Oral ribavirin has been extensively used for post-exposure prophylaxis, but evidence for its effectiveness in humans is anecdotal, as no studies have been performed. Work with arenavirus exposure in primates suggests that it is likely to be effective, but the recommended dosage (1 g twice daily or 600 mg three or four times daily for 10 days), is difficult to tolerate. It is only recommended for high-risk exposures.

Immunotherapy
Symptomatic Junin virus infection can be treated effectively with immune plasma containing high-titre neutralizing antibodies. This treatment greatly reduced the number of fatal cases before specific antiviral therapy was available though, unlike antiviral treatment, it did not prevent the occurrence of reversible encephalopathy.

Prevention using vaccines
An investigational live-attenuated vaccine for Junin virus was used in Argentina, but is now no longer produced. No effective Lassa vaccine is yet available. Many candidates have been developed, based on viral proteins, or constructs using paramyxoviruses, adenoviruses, vesicular stomatitis viruses and others. Their potential effectiveness is limited by the wide strain variation between Lassa viruses, and difficulty in developing a strategy for their effective use in at-risk populations.

Safe management of viral haemorrhagic fevers
Understanding the challenge of managing VHF patients
It may be difficult to recognize VHF’s from their clinical features in the first 3 to 7 days of the illness because they all present with similar, influenza-like syndromes. These features are also seen at the onset of other, more common severe infections such as malaria, dengue, meningococcal bacteraemia, enteric fevers, gram-positive and negative bacteraemias, rickettsial infections, legionelloses and influenza itself. As a VHF illness progresses, other differential diagnoses include thrombotic thrombocytopenic purpura, other immunological disorders, myelodysplastic syndromes and leukaemias. Acute abdominal pain, with or without diarrhoea, may be (inappropriately) investigated by invasive or surgical procedures.

As patients progress to high dependency or intensive care, bleeding and discharge of highly infectious body fluids becomes more likely and procedures such as endoscopy or plasma exchange may be carried out.
The risk of exposing healthcare workers and laboratory staff therefore increases.

Casual or household contact, or sharing public transport, with a feverish, ambulant or self-caring patient has not been shown to carry any risk of infection. When patients develop significant haemorrhagic features, percutaneous exposure, mucosal splash with infected fluids, or inadvertent ingestion become more likely. With today’s control of infection protocols, healthcare-associated transmission is rare and ‘standard’ personal protective measures permit high-quality care of cases in endemic areas. However, managing unsuspected cases without effective protective measures still gives rise to secondary cases, even in well-equipped hospital settings.

Aerosol transmission of the VHF viruses has not been confirmed outside the laboratory or animal management setting, and did not seem to occur in households of severely ill patients in the very large Ebola outbreak in Kikwit, in 1995. Laboratory transmissions have mainly been caused by needlestick injuries when handling small animals such as mice, or through inadvertent close contact with accidentally generated aerosols.

Key in managing VHFs is the need to provide specific treatment, when available, as early as possible, as delays greatly reduce the benefit which can be gained. Because it is so difficult to predict the prognosis during the early stages of illness, it is also important to manage all patients as though they may quickly develop shock or haemorrhage. Nowadays, the availability of rapid antigen-detection tests and PCR-based diagnosis mean that treatment can be started, and modified within 24 h, when the diagnosis is confirmed or excluded.

Failure to act if the diagnosis is a possibility may deprive the patient of life-saving treatment and put healthcare workers at risk of exposure. Most cases will NOT have a VHF, but will benefit greatly from early exclusion of the diagnosis.

The first response: make the patient and the contacts safe

Consider the possibility of the diagnosis in a sick traveller from an endemic country, who has no clear features of an alternative diagnosis (e.g. cough and physical signs in the chest) and: (a) put the patient in a separate room, cubicle or resuscitation area; (b) use available personal protective equipment (water repellent gown and/or apron, disposable gloves, surgical face mask and wrap-around eye-protection); (c) have appropriate sharp containers and clinical waste containers nearby for direct disposal of used equipment.
Manage the patient’s immediate needs: (i) fluid resuscitation if needed; (ii) urgent blood examination for malaria; (iii) blood for auto-analyser-based full blood count, clinical chemistry and blood cultures; (iv) necessary X-ray or other imaging using blood-wound-stool-urine precautions according to local protocols; (e) empirical antibiotic treatment if indicated.

Tell the local infection specialist and infection control team and: (i) get help in obtaining detailed epidemiological information to begin the risk assessment; (ii) get help in discussing specific diagnostic tests with the reference laboratory experts (who will also advise on additional tests for alternative tropical disease diagnosis); (iii) get help to obtain first doses of intravenous ribavirin, if indicated.

Work with local and reference experts to: (i) make the necessary risk assessments (see below) and (ii) prepare to transfer the patient to a specialist unit, if necessary.

Risk assessments: important factors in diagnosis and safe management

There are two key stages in making a risk assessment:

- estimating the risk that the patient has been exposed and may have a VHF;
- deciding on the level of risk that the patient poses for healthcare workers and other contacts.

Estimating the risk of a VHF diagnosis

Epidemiological factors

In many cases, simply considering the incubation period can avoid the need for further action. If the interval between the last possible exposure and the onset of fever exceed the incubation period, the diagnosis can be excluded. For arenavirus and filovirus infections, a cut-off of 21 days is appropriate; for CCHF, the appropriate period is 13 days.

Exposure to an endemic area should be considered in detail. Simply being in a country such as Nigeria, where a VHF exists, does not carry a risk of exposure. Exposure does not occur in cities or in well maintained modern hotels. Travel by air, and by road without stops for rural excursions, is safe. High-risk factors which are typical in the histories of cases, can be recognized (Table 2). Patients should be asked directly if any of these factors apply to them.

Clinical signs

Clinical pointers to a VHF diagnosis are few, and it is important to realize that patients with VHF illnesses may not look severely ill, or manifest
significant bleeding until features of severe disease begin to develop. Warning signs may include: failure to improve on antimalarial and/or antibiotic treatment for a preliminary diagnosis; failure of ‘dengue’ fever to improve after 7 days or more; rapid escalation of AST or LDH levels; a rapid fall in the platelet count and the onset of epistaxis or bloody diarrhoea.

**Estimating the risk to healthcare workers**

Applying the knowledge and principles above permits the safe assessment and initial management of a potential VHF case. However, expert infection control and healthcare worker safety, over a possibly prolonged admission, are much easier to maintain an appropriate facilities where sufficient staff are securely trained. It is a great advantage if laboratory, imaging and intensive care staff are included in training and operational policy. Appropriate ventilation, engineering and waste-management facilities are also important, and need trained staff to support them. Many countries therefore maintain specified units with

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<th>Table 2 Epidemiological risks for VHFs.</th>
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<td><strong>CCHF</strong></td>
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internationally recognized facilities for the management of high-risk diseases.\textsuperscript{28} Healthcare workers, including paramedics, clinic, ward and emergency department receptionists, nurses, doctors and students, are often seriously concerned about risks to their own health when a VHF patient has been identified in their work area. The risks to most contacts are low, but a few with higher risks will require support and, possibly, active management. There is no internationally agreed protocol for these risk assessments, but Table 3 gives a summary of the kinds of risks which are recognized, and the usual level of response which is considered reasonable (Table 3). Family members, work and school contacts may also be concerned. Those not involved with the medical care teams should be advised by the local Health Protection or Public Health officers, who will be responsible for the safety of household and community contacts.

\textit{International health regulations and public interests}

The recently updated International Health Regulations\textsuperscript{14} require the responsible body for a Nation to report all cases and outbreaks of internationally significant diseases without delay to the World Health Organization. This allows the WHO to collate data about the situation and to judge whether assistance or intervention is required either in the reporting country or in the place where the infection probably originated. A case in one country may indicate the presence of an outbreak or incident in another, or may be one of a number of people exposed to the same risk.\textsuperscript{55} Doctors who recognize or care for a case should first inform their own hospital service, and then ensure that notification of the case is passed to the responsible health protection bodies to be reported onwards.

The report of a case usually results in a large burden of communication and information exchange, for which the local health protection team, the hospital press and communications team, and the doctors themselves should be prepared. The confidentiality of the patient and their family is of paramount importance. Doctors should therefore be guided by their hospital communication teams, and should not seek to make independent statements.

While caring for a suspected viral haemorrhagic fever case is challenging and demanding, it provides a rich experience in team working. It also gives an insight into how high-level public health responses are made. The information in this review should give confidence to first responders. Understanding the diseases, and the appropriate infection control precautions, will help them to make a methodical, safe and...
### Table 3 Managing risk from suspected VHF cases assessments and responses in healthcare facilities.

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<th>Type of risk</th>
<th>Risk level</th>
<th>Specific measures for worker</th>
<th>Infection control for patient</th>
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<td>Casual contact, receptionist tasks, sharing a sitting area or public transport with a feverish ambulant, self-caring patient, taking temperature and blood pressure observations.</td>
<td>None recognized</td>
<td>None required</td>
<td>Single room isolation; standard personal protective equipment (PPE); prepare for transfer to specialist unit if rapid VHF test results are positive As above</td>
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<td>Close face-to-face contact with a feverish ambulant or self-caring patient, taking or examining diagnostic specimens</td>
<td>Low</td>
<td>Healthcare worker should report the onset of fever, if within the incubation period, and have a full clinical review, other community-acquired infections should be considered</td>
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<tr>
<td>Caring, taking diagnostic specimens or having close face-to-face contact, without appropriate PPE, with a patient who is coughing or vomiting, has nosebleeds, or who has diarrhoea</td>
<td>Moderate</td>
<td>Healthcare worker should check their temperature each day, and to report any elevation above 38°C, and should have a full clinical review: with consideration of early diagnostic testing for the VHF.</td>
<td>Single room isolation; negative pressure or airflow ventilation to dilute droplets; standard PPE with face and eye protection; expect to transfer to specialist unit (may wait for VHF test results, discuss with specialist)</td>
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<tr>
<td>Percutaneous, needlestick or mucosal exposure to virus-contaminated blood, body fluids, tissues or laboratory specimens in a severely ill or known positive patient; accidental aerosol exposure in a laboratory setting.</td>
<td>High</td>
<td>Do baseline blood tests and VHF tests; for CCHF, consider post-exposure treatment with immune plasma or oral ribavirin; for Lassa fever, consider post-exposure prophylaxis with oral ribavirin.</td>
<td>Send specimens for VHF diagnostic tests immediately; patient should be transferred without waiting for results, to a specialist unit; discuss with specialist unit whether to commence antiviral treatment, and treat for malaria or bacterial infections.</td>
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For moderate and high risk VHF exposures healthcare worker should report temperature daily to the appropriate safety officer (extend the reporting period to 4 weeks if post-exposure prophylaxis is given). If fever develops, do diagnostic tests, admit to specialist unit and commence treatment, if appropriate, until the result is known.
effective approach to the problem. Ensuring timely recognition of the illness and early provision of care, while more common and sometimes equally severe differential diagnoses are not forgotten, will offer the best chance of a good outcome.

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