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BICHAT GUIDELINES* FOR THE CLINICAL MANAGEMENT OF HAEMORRHAGIC FEVER VIRUSES AND BIOTERRORISM-RELATED HAEMORRHAGIC FEVER VIRUSES

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Haemorrhagic fever viruses (HFVs) are a diverse group of viruses that cause a clinical disease associated with fever and bleeding disorder. HFVs that are associated with a potential biological threat are Ebola and Marburg viruses (Filoviridae), Lassa fever and New World arenaviruses (Machupo, Junin, Guanarito and Sabia viruses) (Arenaviridae), Rift Valley fever (Bunyaviridae) and yellow fever, Omsk haemorrhagic fever, and Kyanasur Forest disease (Flaviviridae). In terms of biological warfare concerning dengue, Crimean-Congo haemorrhagic fever and Hantaviruses, there is not sufficient knowledge to include them as a major biological threat. Dengue virus is the only one of these that cannot be transmitted via aerosol. Crimean-Congo haemorrhagic fever and the agents of haemorrhagic fever with renal syndrome appear difficult to weaponise. Ribavirin is recommended for the treatment and the prophylaxis of the arenaviruses and the bunyaviruses, but is not effective for the other families. All patients must be isolated and receive intensive supportive therapy.

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Introduction

Haemorrhagic fever viruses (HFVs) are a diverse group of viruses that cause a clinical disease associated with fever and bleeding disorder, classically referred to as viral haemorrhagic fever (VHF). The many viruses that are associated with this illness belong to one of four families: Filoviridae, Arenaviridae, Bunyaviridae, and Flaviviridae [1]. The incidence of VHF is strongly associated with the geographic distribution of the viruses (certain areas of Africa, Asia, the Middle East, and South America), various complex biological systems, and seasonal patterns. Most of these viruses have zoonotic life cycles independent of humans (dengue and yellow fever partially excepted). These agents are usually transmitted to humans from animals or arthropod reservoirs via mosquitoes, ticks, or infected animal urine or faeces. The natural reservoirs and vectors of the Ebola and Marburg viruses are still unknown (TABLE 1). Except for Rift Valley fever and the flaviviruses, person-to-person transmission can occur with close contact. This is however not a usual route of transmission. Airborne transmission is possible. Sexual transmission from convalescent
patients has been reported for both filovirus and arenavirus infections. Nosocomial transmission with Machupo, Crimean-Congo haemorrhagic fever, Ebola and Marburg viruses has been documented.

HFV and bioterrorism

Most of the viruses may be transmitted to humans through aerosolisation, although this route of transmission is not common for person-to-person transmission in a typical outbreak setting [2-6]. Nevertheless, transmissions via aerosolisation to laboratory workers have been reported for all the HFVs, including Rift Valley fever and the Flaviviridae. The HFVs have appropriate properties for aerosol weapons [7-9].

Most of these viruses have been studied and developed as biological weapons in the USA and in the former Soviet Union [7]. Yellow fever has been weaponised by North Korea [7]. The Japanese cult Aum Shinrikyo tried unsuccessfully to obtain Ebola virus [7]. Most of the viruses are transmissible by aerosol, and biological weapons have been used with successful infection in non-human primates by aerosolisation. Moreover, HFVs are associated with high morbidity and, in some cases high mortality. And finally, no specific treatment or vaccines exist for these viruses. All these facts underline their possible role as biological warfare agents [7-9].

HFVs that are associated with a potential biological threat are Ebola and Marburg viruses (Filoviridae), Lassa fever and New World arenaviruses (Machupo, Junin, Guanarito and Sabia viruses)(Arenaviridae), Rift Valley fever (Bunyaviridae) and yellow fever, Omsk haemorrhagic fever, and Kyanasur Forest disease (Flaviviridae) (TABLE 1). Most of these viruses have been weaponised [7]. Knowledge, in terms of biological warfare concerning dengue, Crimean-Congo haemorrhagic fever and Hantaviruses is not sufficient to include them as a major biological weapon threat [1]. Dengue virus is the only one that cannot be transmitted via aerosol; moreover it usually causes a mild disease, although in cases of re-infection with different subtypes, haemorrhagic manifestations can occur. Crimean-Congo haemorrhagic fever and the agents of haemorrhagic fever with renal syndrome appear to be difficult to weaponise [7].
When a VHF outbreak in humans is detected in a European country, deliberate release should be suspected.

Virological characteristics

All HFVs are small RNA viruses with lipid envelopes. Flaviviruses have a positive strand genome, while the others are negatively stranded. Arenaviruses and bunyaviruses contain segmented genomes.

Diseases

Most of the HFVs induce a similar syndrome. The incubation period varies from 1 to 21 days (TABLE 2). Depending on the virus, the disease can progress with respiratory problems, severe bleeding, kidney failure and shock. All HFVs can induce microvascular damage and capillary leak syndrome [10]. The

severity of VHF can range from relatively mild illness to death. Most patients infected with these viruses experience a non-specific febrile illness, without predominant involvement of a single organ system [11].

Filoviruses (Ebola and Marburg)

Ebola and Marburg are native to sub-Saharan Africa. They are thought or suspected to be zoonotic diseases, although their natural animal reservoirs have not been determined.

The Ebola virus was named after the river in Zaire (now the Democratic Republic of the Congo) where it was first discovered in 1976. At least four distinct strains of Ebola have been documented, of which three have been implicated in human infections. Outbreaks of natural disease in Africa may be amplified through secondary transmission associated with hospitals, due to re-use of unsterile needles and lack of appropriate barrier nursing precautions. To date, six known outbreaks of Ebola virus involving humans have been reported in Africa (three in Sudan in 1976, 1979 and 2004, two in Zaire in 1976 and 1995, one in Uganda in 2000-2001 and one in Congo and Gabon in 2002-2003) [12]. Most of the 1200 human cases, with nearly 900 deaths, that have occurred in Africa could be traced to intimate direct contact with infected patients.

Marburg virus was named after the city in Germany where this disease was first diagnosed in 1967 in a laboratory [13]. The source of this first outbreak was green monkeys shipped from Uganda; seven of the 31 infected persons died [13]. Most of the cases of Marburg virus have been reported in laboratory workers in Germany and Yugoslavia who had handled infected monkeys from Africa [13]. Only a small number of cases have been reported in eastern and southern Africa [11].

A total of 23 Marburg and Ebola virus outbreaks causing viral haemorrhagic fever have been reported among humans and monkeys since the first outbreak in Marburg [13].

Following an initial human infection, Ebola and Marburg can be transmitted from person-to-person through close personal contact with blood or body secretions from infected patients. During the last outbreak in Uganda in 2000, 64% of healthcare workers were infected after establishing the isolation wards [12]. Airborne transmission is not suspected to play an important role in person-to-person spread.

Ebola and Marburg viruses cause similar diseases in humans. The clinical and laboratory features are indistinguishable between the two diseases. Following an incubation period of 6 days (range 2-21 days for Ebola, 3-10 days for Marburg), infected persons may abruptly develop non-specific symptoms such as high fever, chills, asthenia, headache, muscle aches, anorexia, conjunctivitis, abdominal pain, nausea, vomiting and diarrhoea, pharyngitis, sore throat and chest pain and an erythematous macular rash [12,14]. After three days of fever, the haemorrhagic manifestations of the disease usually begin. The signs are characterised by haemorrhage (petechia, ecchymoses, conjunctival haemorrhage, gingival bleeding, bleeding from an injection site, frank bleeding from the gastrointestinal tract with melaena, vaginal bleeding, haematemesis, and bleeding from other sites such as internal organs) [15]. Bleeding can occur in 20% of patients and primarily involves the gastrointestinal tract. Patients may die of organ failure and shock. The risk for person-to-person transmission is greatest during late-stage illness. HFV infection has not been reported in contacts whose only exposure was to patients during the incubation period [14]. Ebola virus has been found in the seminal fluid of patients for a period of time after their recovery. Naturally occurring Ebola infections have demonstrated mortality rates of 72%, while Marburg infections carry a 23% mortality rate [16]. Patients with suspected infections should be isolated, and medical staff should focus on minimising the possibility of human-to-human transmission through good nursing techniques and wearing personal protective equipment, such as gowns and gloves.

Arenaviruses (Lassa fever and New World Arenaviruses)

Six of the 20 known arenaviruses are pathogens for humans; five can cause severe haemorrhagic fever (Junin, Guanarito, Machupo, Sabia and Lassa viruses). The sixth, lymphocytic choriomeningitis virus is associated with neurological manifestations [17].

Lassa fever is most commonly diagnosed in parts of West Africa where it is endemic. The number of Lassa virus infections per year in West Africa is estimated at 100 000 to 300 000, with approximately 5000 deaths. New World arenaviruses cause haemorrhagic fever; most of these viruses are present in South America, specifically in a limited agricultural area of the pampas in Argentina (Junin), in the remote savannas of the Beni province of Bolivia (Machupo), in grasslands and brush in Venezuela (Guanarito), and Brazil (Sabia) [17]. Each virus is associated with either one species or some closely related rodents. These rodents are chronically infected with these viruses and do not develop disease.

Human infection is usually caused by exposure to aerosolised dried excreta, often urine, of infected rodents, either through breathing contaminated dust, consuming contaminated foodstuffs, or by direct contact with abraded or broken skin [18]. These haemorrhagic fevers have occasionally been transmitted person-to-person in healthcare settings and in intimate contacts. In these cases, direct contact with infected body secretions is believed to be a more important route of transmission than aerosol exposure [18].

Following an incubation period of 10 to 14 days (range: 5-18 days), most patients are asymptomatic or develop a mild flu-like illness. The onset of the disease is usually insidious with fever and general malaise over a 2 to 4 day period. In more severe cases, early clinical signs include weakness, retro-orbital pain, joint and lumbar pain, myalgia, headache, pharyngitis, cough and conjunctival injection [17,18]. In the most severe form of the disease, patients can exhibit prostration, abdominal pain, facial and neck oedema, haemorrhage (conjunctival haemorrhages, mucosal bleeding, melaena, haematochezia, haematuria, vaginal bleeding, haematemesis), encephalitis, capillary leak syndrome and shock. Hepatitis is frequent and may be moderately severe in Lassa fever. Pulmonary manifestations can be significant, resulting in rales, pleural and pericardial friction rubs, and adult respiratory distress syndrome in Lassa fever [14]. Haemorrhage and neurological signs are more common in the New World arenaviruses than in Lassa fever: haemorrhage along the gingival margins is characteristic. Neurologic signs may include delirium, confusion, encephalopathy, convulsions and coma. For South American haemorrhagic fever, conjunctival injection, facial flushing, petechial and/or vesicular palatal enanthem and skin petechiae, generalised lymphadenopathy and orthostatic hypotension are common. Lymphopenia, leukopenia and thrombocytopenia are more characteristic and important in the New World arenaviruses than in Lassa fever. Aminotransferase elevations are common only in the case of Lassa fever.

Bleeding, heralded by unremitting high fever, can begin after 5 days of illness, and is followed by dehydration and haemoconcentration, shock syndrome, haemorrhagic manifestations, and cardiovascular collapse. The mortality rate

for hospitalised Lassa patients ranges from 15%-20%, although overall case fatality rates are estimated to be lower (1%-2%). Pregnant women have the highest mortality rate during Lassa infection (16%), and fetal death is common [19]. Long-term sequelae of Lassa infection can include sensorineural deafness. Junin and Machupo have higher reported case fatality rates, ranging from 10%-16% [20].

Bunyaviridae (Rift Valley fever and Crimean-Congo haemorrhagic fever)

Rift Valley fever is usually found in regions of eastern and southern Africa but the virus also exists in most countries of sub-Saharan Africa and in Madagascar. It is a zoonosis that mainly affects domestic animals (cattle, buffalo, sheep, goats, camels) and occasionally humans [8]. Bunya viruses are transmitted by mosquitoes (usually of the genus *Aedes*). Many other mosquito species may transmit the disease. Humans can also get the disease after handling blood or body fluids of infected animals. Infection through aerosolisation has been reported in laboratory workers during work with virus culture or laboratory samples containing the virus.

The incubation period varies from 2 to 6 days. The initial clinical manifestation is a biphasic fever, the first bout lasting 4 days. After 1 or 2 days without fever, the second fever spike occurs lasting 2 to 4 days. Usually the illness is mild and associated with fever and liver abnormalities but in severe cases, haemorrhagic encephalitis and retinitis can occur [21]. Less than 1% of patients develop haemorrhagic fever syndrome 2 to 4 days after the onset of the illness. Clinical features are the same as those observed in other VHF (epistaxis, haematemesis, melaena, and gastrointestinal haemorrhage). Patients usually recover within two days to one week after onset of illness. Retinitis and meningoencephalitis are usually observed 1 to 3 weeks after the onset of the disease. In 1% to 10% of cases, patients may have vision loss when the lesions are in the macula. The mortality rate for patients with Rift Valley fever is close to 1%, death mainly occurring in patients with haemorrhagic manifestations [21].

Crimean-Congo haemorrhagic fever (CCHF) is endemic in Africa, Europe and Asia. During 2001, cases or outbreaks were recorded in Kosovo, Albania, Iran, Pakistan, and South Africa. It is a tickborne disease and is associated with a high mortality rate in humans. Nosocomial infections have been reported in laboratory workers. The CCHF virus may infect a wide range of domestic and wild animals.

Human infection is acquired through direct contact with blood or other infected tissues from livestock during this time, or from a tick bite. The incubation period is 1 to 3 days (maximum 9 days). Onset of symptoms is abrupt with fever, myalgia, dizziness, neck pain and stiffness, backache, headache, sore eyes and photophobia, nausea, vomiting, diarrhoea and abdominal pain. Over the next few days, the patient may experience sharp mood swings, and may become confused and aggressive. After 2 to 4 days, sleepiness, depression and lassitude may replace the agitation, and the abdominal pain may localise to the right upper quadrant, with hepatomegaly. Other clinical signs include tachycardia, lymphadenopathy, and a petechial rash or ecchymoses, both on mucosal surfaces and on the skin. Haemorrhagic symptoms include melaena, haematuria, epistaxis and bleeding from the gums. A hepatitis is usually present. Multi-organ failure with hepatorenal and pulmonary failure may develop after the fifth day of illness. The mortality rate is close to 30%.

Treatment includes supportive therapy and ribavirin. Treatment with immune plasma from recovered patients has not proved efficacious.

Flaviviridae (yellow fever, Omsk haemorrhagic fever, and Kyanasur Forest disease)

Yellow fever is transmitted by mosquitoes. Yellow fever shares many of the clinical manifestations observed in other VHFs. However, severe hepatic involvement is characteristic. After an incubation period of 3 to 6 days, the onset of the illness is abrupt with fever, headache, generalised malaise, weakness, lumbosacral pain, bradycardia, nausea, and vomiting. This period lasts 3 days and is followed by a remission lasting 24 hours. Then, intoxication, which can progress to death 7 to 10 days after presentation, appears. Symptoms and signs include jaundice, albuminuria, oliguria, cardiovascular instability, and haemorrhage [8]. The mortality rate for patients with severe yellow fever is almost 50%.

Omsk haemorrhagic fever and Kyanasur Forest disease are transmitted to humans by ticks, but aerosol transmission is also possible. The incubation period for these two diseases is 3 to 8 days. For Kyanasur Forest disease the onset is abrupt with fever, headache, severe myalgias, diarrhoea, vomiting, severe prostration, conjunctival injection, photophobia, cervical and axillary adenopathy, and more rarely splenomegaly or hepatosplenomegaly. Papulovesicular lesions involving the soft palate are frequent. Pulmonary manifestations are also frequent during the first stage of the illness. The second stage of the illness is associated with neurological involvement. Haemorrhagic manifestations are those observed with other VHFs. The mortality rate is 5% to 10%. Manifestations of Omsk haemorrhagic fever are similar [8].

Diagnosis

Case definitions are listed in Table 3.

VHF must be suspected in any patient presenting with a severe illness and evidence of vascular involvement who has travelled to an area where the virus is endemic or when a biological warfare threat is suspected [9]. With the exception of Lassa fever, thrombocytopenia is usual, although not usually of sufficient severity to account independently for haemorrhagic manifestations. Leukopenia characterises most of the VHFs (except in some cases of Lassa fever, in which leukocytosis may be present). Proteinuria is also frequent. Elevation of liver enzymes is usual. Jaundice is typical in yellow fever and Rift Valley fever [7]. Disseminated intravascular coagulation has been reported occasionally in many of the VHFs, but this symptom is not regarded as a characteristic sign for any of them.

Methods of diagnosis include viral isolation, and antibody detection including IgM by using enzyme-linked immunoabsorbent assay (ELISA). Antigen-capture can be used for detection of virus antigens. RT-PCR is widely used to detect the genome of the viruses in fluids and tissues (TABLE 3). Handling of samples and viral cultures must be performed in a biosafety level-4 laboratory [7].

Treatment

Ribavirin is recommended for the treatment and the prophylaxis of the arenaviruses and the bunyaviruses [11,22,23] (TABLE 4). It should be noted that men and women who take ribavirin for prophylaxis should avoid conception for six months after taking it because of ribavirin's teratogenic effects. For the other families, this antiviral is not effective. This drug is effective against hepatitis C virus, respiratory syncitial virus, Congo-Crimean haemorrhagic fever, hantavirus and arenaviruses. Ribavirin is teratogenic in experimental animals [11]. Its use may be contraindicated in pregnant women; however, given the seriousness of the disease, ribavirin must be considered. Ribavirin has been shown to be effective in early-stage

arenavirus infections, particularly Lassa virus. Intravenous ribavirin should be administered within 6 days of illness onset as follows: 30 mg/kg loading dose, followed by 15 mg/kg 4 times a day for 4 days, then 8 mg/kg 3 times a day for 6 days (TABLE 3). Specific immune plasma given within 8 days of illness onset has been effective in treating Junin virus infection. Finally, Interferon-alpha has shown protective activity in animal models, mainly against Rift Valley virus. This activity is limited to very early stages, following viral infection. Combination therapy with ribavirin may enhance protection but data for humans are lacking [22].

When a patient presents with a VHF syndrome but the aetiologic agent has not yet been determined, physicians should consider instituting ribavirin therapy while awaiting confirmation of the diagnosis. In any case, patients must be isolated and receive intensive supportive therapy.

Currently there is no licensed vaccine to protect against VHFs, with the exception of yellow fever, although a number of candidate vaccines are in clinical trials (TABLE 5) [23,24]. An experimental vaccine for Junin may be available under an Investigational New Drug licence, although the FDA has not approved it for general use. This vaccine has also been shown to be protective against Machupo virus in experimental animal models. An inactivated vaccine against Rift Valley fever has been developed for human use, but is not licensed or commercialised.

Ribavirin prophylaxis should be considered for high-risk contacts of Lassa, Junin, and Machupo patients using 500mg po qid for 7 days. High-risk contacts would be defined as persons with mucous membrane contact (sexual intercourse or kissing) with a VHF patient, direct contact with blood or other body fluids from a VHF patient, or persons exposed to such fluids through laboratory procedures.

Conclusions

Even if data are lacking, most of the HFVs must be considered as a serious potential biological weapon (Ebola, Marburg, Lassa fever, New World arenaviruses, Rift Valley fever, yellow fever, Omsk haemorrhagic fever, and Kyanasur Forest disease). Most of these viruses have been studied and developed as biological weapons in many countries. Aerosolisation of these viruses can be associated with significant morbidity and mortality in the exposed population: transmission from person-to-person can amplify disease outbreaks. Moreover, specific treatment and vaccines are lacking for most of them.

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* **BICHAT**, the European Commission's Task Force on Biological and Chemical Agent Threats, has developed this set of guidelines that may be the basis of national authorities' guidance, and may also be used directly by clinicians, general practitioners and specialists when confronted with patients infected by agents that may be due to deliberate release of biological agents. Ref. Bossi P, Van Loock F, Tegnell A, Gouvras G. Bichat clinical guidelines for bioterrorist agents. *Euro Surveill.* 2004; 9(12)

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Editorial note: *These clinical guidelines were reviewed by the Task Force and by two experts designated by each Member State of the European Union. This review was completed at the end of February 2003. The revised guidelines were submitted to the Health Security Committee which approved them in April 2003 and agreed their publication in a widely disseminated journal so as to allow access to as large an audience as possible. The editorial process of Eurosurveillance also introduced modifications that improved the contents of these guidelines.*

TABLE 1

HFVs that could be involved in biological warfare

Family	Virus	Disease	Vector in nature
Filoviridae	Ebola	Ebola haemorrhagic fever	Unknown
	Marburg	Marburg haemorrhagic fever	Unknown
Arenaviridae	Lassa	Lassa fever	Rodent
	Machupo	Bolivian haemorrhagic fever	Rodent
	Junin	Argentine haemorrhagic fever	Rodent
	Guanarito	Venezuelan haemorrhagic fever	Rodent
	Sabia	Brazilian haemorrhagic fever	Rodent
Bunyaviridae	Rift Valley fever	Rift Valley fever	Mosquito
	Crimean-Congo haemorrhagic fever	Crimean-Congo haemorrhagic fever	Tick
Flaviviridae	Yellow fever	Yellow fever	Mosquito
	Omsk haemorrhagic fever	Omsk haemorrhagic fever	Tick
	Kyanasur Forest disease	Kyanasur Forest disease	Tick

TABLE 2

Summary of clinical description of HFV

Virus	Incubation (days)	Clinical feature	Mortality (%)
Ebola	2-21	Onset abrupt: high fever, chills, asthenia, headache, muscle aches, anorexia, conjunctivitis, abdominal pain, nausea, vomiting, diarrhoea, pharyngitis, sore throat, chest pain and erythematous macular rash. After 3 days, prostration, haemorrhagic manifestations (petechia, ecchymosis, conjunctival haemorrhage, gingival bleeding, bleeding from injection site, frank bleeding from gastrointestinal tract with melaena, vaginal bleeding, haematemesis, and bleeding from other sites such as internal organs). Patients may die of organ failure and shock.	72
Marburg	3-10	Idem Ebola	23
Lassa fever	10 -14	Usually asymptomatic or mild illness. The onset of the disease is insidious with fever and general malaise over a 2- to 4-day period. In more severe cases; weakness, retroorbital pain, joint and lumbar pain, myalgia, headache, pharyngitis, cough and conjunctival injection. In the most severe form of the disease; prostration, abdominal pain, facial and neck oedema, haemorrhages (conjunctival haemorrhages, mucosal bleeding, melaena, haematochezia, haematuria, vaginal bleeding, haematemesis), encephalitis, capillary leak syndrome and shock. Hepatitis is frequent. Pulmonary manifestations can be significant with ARDS. Long-term sequelae of Lassa infection; sensorineural deafness.	15-20
New World Arenaviruses	7-14	Idem Lassa fever Haemorrhage, and neurological signs are more common: haemorrhage along the gingival margins is characteristic. Neurologic signs may include delirium, confusion, encephalopathy, convulsions and coma. Conjunctival injection, facial flushing, petechial and/or vesicular palatal enanthem and skin petechiae, generalised lymphadenopathy and orthostatic hypotension are common.	10-16
Rift Valley fever	3-6	The initial clinical manifestations are a biphasic fever, the first bout lasting 4 days. After 1 or 2 days without fever, the second fever spike occurs lasting for 2 to 4 days. Usually, the illness is mild and associated with fever and liver abnormalities. In severe cases, haemorrhage (<1%), encephalitis (1%) and retinitis (10%).	1
Crimean-Congo haemorrhagic fever	1-3	Onset of symptoms is abrupt with fever, myalgia, dizziness, neck pain and stiffness, backache, headache, sore eyes and photophobia, nausea, vomiting, diarrhoea and abdominal pain. The patient may experience sharp mood swings, and may become confused and aggressive. After 2 to 4 days, sleepiness, depression and lassitude may replace the agitation, and the abdominal pain may localise to the right upper quadrant, with hepatomegaly. Other clinical signs include tachycardia, lymphadenopathy, and a petechial rash or ecchymoses, both on mucosal surfaces and on the skin. Haemorrhagic symptoms include melaena, haematuria, epistaxis and bleeding from the gums. A hepatitis is usually present. Multiorgan failure with hepatorenal and pulmonary failures may develop after the fifth day of illness.	30
Yellow fever	3-6	The onset of the illness is abrupt with fever, headache, generalised malaise, weakness, lumbosacral pain, bradycardia, nausea, and vomiting. This period lasts 3 days and is followed by a remission lasting 24 hours. Then, intoxication, which can progress to death 7 to 10 days after presentation, appears. Symptoms include jaundice, scleral icterus, albuminuria, oliguria, cardiovascular instability, and haemorrhagic manifestations.	20-50
Omsk haemorrhagic fever	3-8	The onset is abrupt with fever, headache, severe myalgias, diarrhoea, vomiting, severe prostration, conjunctival suffusion, photophobia, cervical and axillary adenopathy, and more rarely splenomegaly or hepatosplenomegaly. Papulovesicular lesions involving the soft palate are frequent. Pulmonary manifestations are also frequent during the first stage of the illness. The second stage of the illness is associated with neurological involvement. Haemorrhagic manifestations are those observed with other VHFs.	0.5-10
Kyasanur Forest fever	3-8	Idem Omsk haemorrhagic fever	3-10

TABLE 3

Laboratory criteria for diagnosis and case definition

Laboratory criteria for diagnosis
Positive virus isolation Positive skin biopsy (immunohistochemistry for Ebola/Marburg viruses, Lassa fever virus) Detection of specific viral nucleic acid sequences Positive serology, which may appear late in the course of the disease
Case definition of suspected and confirmed cases of VHF
Possible: Not applicable **Probable**: A clinically compatible case with an epidemiological link **Confirmed**: A clinically compatible case that is laboratory confirmed
Case definition of a suspected deliberate release of VHF
- ≥1 confirmed case in Europe which is not an imported case

Source: [25,26]

TABLE 4

Recommendations for treatment and post-exposure prophylaxis of VHF

	Treatment of suspected or confirmed clinical cases of VHF 10 days	**Post-exposure prophylaxis (7 days)**
Adults (including pregrant women) It is recommended, when possible, to stop breastfeeding.	Ribavirin IV; Initial dose of 2g followed by 1g every 6 hours for 4 days, followed by 0.5g every 8 hours for 6 days **Or** Initial dose of 30 mg/kg followed by 15 mg/kg every 6 hours for 4 days, followed by 7.5 mg/kg every 8 hours for 6 days. **Or** Ribavirin per (os): 2 g orally (loading dose) followed by 4 g/day in 4 divided doses for 4 days followed by 2 g/day for 6 days	Ribavirin: 2 g/day orally in 4 divided doses.
Children	No recommendations can be given	No recommendations can be given

Source: [23]

TABLE 5

Status of vaccine development against HFV in 2002

Virus	**Vaccine candidate**	**Development stage**
Ebola	Recombinant sub-unit Replicons	Pre-clinical Pre-clinical
Marburg	Not mentioned	
Lassa fever	Not mentioned	
New World arenaviruses	Not mentioned	
Rift Valley fever	Inactivated Live, attenuated	Phase II Phase I
Yellow fever	Live-attenuated (17D strain) Infectious clone	Licensed Pre-clinical
Omsk haemorrhagic fever	Not mentioned	
Kyasanur Forest fever	Not mentioned	

Source: [24]