Viral haemorrhagic fever in returned travellers; a review on clinical symptoms, management, and outbreak prevention

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Abstract - Due to the growing popularity of travel to remote parts of the world, the importation of diseases from abroad is an increasing problem. This induces more need for physicians to develop knowledge on epidemiological characteristics and clinical features of diseases in developing and tropical countries. Most illnesses are treatable and not a threat for the home country. However, a recent case of Marburg viral haemorrhagic fever (VHF) entering the Netherlands demonstrates that rare illnesses, which are initially difficult to recognize and have the potential of inducing an outbreak, can also be imported. The aim of this review is to raise the awareness of clinical symptoms of the four types of VHF containing a high risk of inducing an outbreak; Marburg, Ebola, Lassa, and Crimean Congo VHF. Improved alertness for the symptoms of these diseases probably leads to earlier diagnosis and timely initiation of proper strict isolation measures.

Keywords - Viral Haemorrhagic Fever, Review, Outbreak control, Marburg, Ebola, Lassa, Crimean-Congo

Introduction
The popularity of travel to remote parts of the world that includes close contact with local inhabitants and wildlife, is still growing [1]. Because of this development, it is increasingly important that physicians are knowledgeable on epidemiological characteristics of diseases in developing countries, since the introduction of tropical diseases into the home country of travellers can occur. Most of the common imported diseases are treatable with no risk of causing a life-threatening outbreak in the developed world [2-4]. But a recent imported case of Marburg VHF in the Netherlands demonstrates that rare illnesses, which are initially difficult to recognize and have the potential of inducing an outbreak, can also be imported [5-7].

The majority of returning travellers who are ill and need hospitalization present with fever [4]. In the assessment of these patients, severe diseases that pose a serious public health risk should first be diagnosed or excluded [2]. Important questions for history taking are summarized in Table 1. Concomitant dermatological, neurological, gastrointestinal, or respiratory signs and symptoms may point to a diagnosis. Furthermore, the incubation period, itinerary, geographical and exposure factors need to be considered in order to narrow down the differential diagnosis [4,8]. To help tabulate findings and to provide reasonable differential diagnoses, several flow charts [2,8] and even a website have been developed [9].

In spite of these auxiliary tools, there is often a substantial period between hospital admission and the establishment of a definitive diagnosis. During this “diagnostic window” empirical antimicrobial treatment should already be initiated and the need for hygienic measures should always be evaluated. In the Dutch Marburg VHF case, a considerable risk on horizontal transmission was present, since correct isolation measures were instituted immediately after considering VHF in the differential diagnosis, which only occurred five days after hospital admission. Fortunately, no other cases have occurred and no outbreak has emerged [7].

Only knowledge of endemic features, risk-exposure, and incubation period will lead a physician to consider VHF and commence adequate isolation measures. The aim of this review is to increase knowledge on the clinical symptoms of these diseases which can result in earlier diagnosis and timely initiation of proper isolation measures.

Viral Haemorrhagic Fever
From all viruses able to cause infectious VHF, only three families contain a significant risk for horizontal transmission with a considerable risk of inducing an outbreak: arena-viruses (Lassa, Junin, Machupo, Guanarito and Sabia virus), bunya-viruses (Crimean-Congo virus), and filoviruses (Marburg and Ebola virus) [8,10]. For this reason, only these virus families will be described in more detail here. The most important aspects are summarized in table 2.
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Filovirus haemorrhagic fever
Filoviruses, Ebola virus and Marburg virus, are amongst the most virulent pathogens of humans, causing severe haemorrhagic fever with high case fatality rates. Since the clinical courses of both subtypes overlap to a great extent, without clear distinctive symptoms, the subtypes will be discussed together.

Historical background: The first outbreak of Marburg virus occurred in 1967 in Marburg, Frankfurt, and Belgrade [11]. Thirty-one workers of a vaccine production laboratory, handling Ugandan green monkeys were infected [11]. Since then eight separate occurrences of Marburg haemorrhagic fever have been described worldwide.

Ebola was discovered in 1976, when a second filovirus was isolated close to the river Ebola in Congo [12,13]. Subsequently, five distinct species were detected: types Zaire, Sudan, Bundibugyo, Reston, and Côte d’Ivoire. Only the types Zaire and Sudan have a high case fatality rate and are associated with outbreaks [12,13].

Virological aspects: The enveloped filovirus genome consists of a single stranded negative-sense RNA, with exceptional length. Transcription leads to seven individual mRNAs that are important for genomic replication and production of glycoproteins [14-16]. Ecology and Epidemiology: Filoviruses circulate in sub-Saharan Africa and occasionally cause outbreaks (Figure 1).

Table 1. Important questions for history taking

<table>
<thead>
<tr>
<th>Travel-related</th>
<th>- Departure and return dates - Countries visited, including stopovers - Urban or rural destination - Climate/season - Type and quality of travel (hotels or camping-sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention measures</td>
<td>- Vaccination - Malaria-prophylaxis - Repellents - Mosquito nets</td>
</tr>
<tr>
<td>Exposure</td>
<td>- Bites Anthropods (mosquito, tick, fly, flea, arachnid) - Reptile (snakes) - Mammal (bats, rodents, dogs, ill animals)</td>
</tr>
<tr>
<td>- Ingestion</td>
<td>untreated water unpasteurized dairy raw or undercooked food (meat, fish, vegetables)</td>
</tr>
<tr>
<td>- Skin contact</td>
<td>Fresh water Sand/dirt/mud</td>
</tr>
<tr>
<td>- Remaining</td>
<td>Sexual contact Contact with ill people</td>
</tr>
<tr>
<td>Symptoms</td>
<td>- Timing and sequence of symptoms - Incubation period - Injuries or illnesses during travel how and where treated (transfusion, injections, sterility of equipment)</td>
</tr>
</tbody>
</table>

Eight separate incidents of Marburg haemorrhagic fever have been described worldwide, including isolated cases and two large outbreaks in Congo and Angola [5,13,17]. Only three cases occurred in returning travellers in South Africa, United States, and the Netherlands [5-7,17]. Outbreaks with Ebola virus have occurred in Zaire, Sudan, Congo, Gabon, and Uganda [12,13,18]. Three cases of Ebola have been reported in returning travellers in Switzerland and South Africa [18].

Most outbreaks are related to contact with infected non-human primates (monkeys) and perhaps herbivores. But the susceptibility of these animals to fatal infection renders it unlikely that they could serve as filovirus reservoir hosts. For decades, the natural reservoir of filoviruses was uncertain. Recently fruit bats have been successfully demonstrated in the cave-dwelling Egyptian fruit bat: Rousettus Aegyptiacus species [19]. Ebola virus could be shown in three different types of fruit bats in the rain forest in central Africa: Hypsignathus monstrosus, Epomops franqueti, and Myonycteris torquata [20-22]. In the Dutch Marburg VHF case, the patient was most likely infected while visiting a Ugandan cave crowded with bats of this Rousettus Aegyptiacus species.

Clinical features: Information concerning the clinical course has been derived from detailed descriptions from the initial Marburg outbreak in Germany and later in Congo [11,14], and from the Ebola outbreak in Kikwit in the Democratic Republic of Congo [23,24].

The incubation time of the Marburg virus ranges from 5 to 12 days [11,25,26] and that of Ebola from 3 to 21 days [27]. The illness starts with a flu-like syndrome: malaise, anorexia, headache, myalgia, lymphadenopathy, and fever with a relative bradycardia. Nausea and vomiting is also seen in the beginning of the illness. Frequent, watery diarrhoea usually follows after one or two days. On days 5 to 7 a characteristic rash develops; first as pinhead dark red papules around the hair follicles on the buttocks, trunk, and upper arm, developing into maculo-papular lesions and later into a more diffuse rash. In more severe cases even a dark erythema can be seen. The rash is often accompanied by scrotal dermatitis and erythematous labia majora. Conjunctivitis develops in almost half of the patients. Furthermore, enanthema, a deep dark colouring of the palate, is seen in Marburg viral infection. In severe cases vascular instability and shock develop, usually 4-5 days after the onset of symptoms and this may be accompanied by diffuse intravascular coagulation. On days 7 and 8, maximal levels of parenchymateous liver enzymes are present, concomitant with a disturbed liver function. Remarkably, elevation of serum bilirubine is frequently absent. From days 6 to 12 a deep thrombocytopenia and leucocytopenia develops. The combination of liver function disturbances, diffuse intravascular coagulation, and thrombocytopenia frequently leads to severe haemorrhagic complications. Contagiousness and mortality are highest at this stage of the illness. Furthermore, mental changes, cough, pleuritic chest pain, elevated amylase, electrolyte disturbances, and paraesthesia, are described. In the convalescent period, arthralgia, parotitis, orchitis with prolonged infectious semen, hearing loss, tinnitus and pericarditis may be present.
Pathogenesis [15,16]: Central in filoviral disease is the rapidly increasing viral burden, which deregulates the innate and adaptive immune response and induces a disproportional inflammatory response. The early infection of dendritic cells, monocytes and macrophages, deregulates the innate immune response. Filoviruses disable at least some of the host interferon pathway and the antigen presenting function of dendritic cells is also disturbed. As a direct result of insufficient production of Interferon α and β and pro-inflammatory cytokines by dendritic cells, an inadequate adaptive immune response is generated. Furthermore, apoptosis of T and B cells, and a generalized failure of specific immune responsiveness are observed, leading to insufficient generation of antibodies. Moreover, a great number of those antibodies is bound and inactivated by freely circulating viral glycoproteins.

As viral load increases, infection spreads to many cells,

Table 2. Main virological aspects

<table>
<thead>
<tr>
<th>FILOVIRUS</th>
<th></th>
<th>ARENA VIRUS</th>
<th>BUNYA VIRUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marburg</td>
<td>- Single strand RNA - Negative sensed - Extremely long 80 nm x 790 nm - Glycoprotein production</td>
<td>- Single strand RNA - Negative sensed - Extremely long 80 nm x 970 nm - Glycoprotein production</td>
<td>- 2 single strand RNA molecules - Ambisensed - 50-300 nm</td>
</tr>
<tr>
<td>Incubation period</td>
<td>5 to 12 days</td>
<td>2 to 21 days, usually 7 days</td>
<td>2 to 21 days, usually 9 days</td>
</tr>
<tr>
<td>Clinical spectrum</td>
<td>Usually fulminant</td>
<td>Zaire, Sudan, Cote d’Ivoire and Bundibugyo types: fulminant Reston: mild/asymptomatic, animal</td>
<td>Mild: 40-90% - Zaire type: 88% - Sudan type: 53% - Reston type: asymptomatic</td>
</tr>
<tr>
<td>Mortality</td>
<td>22-90%, Overall case-fatality rate: 82%</td>
<td>40-90% - Zaire type: 88% - Sudan type: 53% - Reston type: asymptomatic</td>
<td>1-2% - Fulminant: 15-25% - Therapy: 10% mortality reduction</td>
</tr>
<tr>
<td>Reservoir/Vector</td>
<td>Vector: none Reservoir: Egyptian fruit bats</td>
<td>Vector: none Reservoir: several types of fruit bats</td>
<td>Vector: none Reservoir: Rodents (rat) species Mastomys Natalensis</td>
</tr>
<tr>
<td>Transmission</td>
<td>- direct contact with blood/excreta or tissue from infected persons - handling of infected animals (green monkey, bats) - airborne spread cannot be ruled out</td>
<td>- direct contact with blood/excreta or tissue from infected persons - handling of infected animals (chimpanzees, gorillas, cynomolgus monkey, forest antilopes, bats) - airborne spread cannot be ruled out</td>
<td>- direct contact with blood or infected tissues from livestock - tick bite</td>
</tr>
<tr>
<td>Specific risk groups</td>
<td>- health care workers - association with mine workers and cave visits</td>
<td>- health care workers</td>
<td>- Those who live in rural areas with poor sanitation or crowded living conditions, where mastomys are found - Health-care workers</td>
</tr>
<tr>
<td>Therapy</td>
<td>No effective therapy</td>
<td>No effective therapy</td>
<td>Ribavirin: Substantial mortality reduction when started within 6 days after onset of symptoms</td>
</tr>
<tr>
<td>Vaccination</td>
<td>Experimental vaccines only</td>
<td>Experimental vaccines only</td>
<td>Experimental vaccines only</td>
</tr>
</tbody>
</table>
including hepatocytes. Severe illness results from the combined effects of widespread viral induced cytolyses and massive release of pro-inflammatory mediators. This cytokine storm leads to a disproportional systemic inflammatory response with progressive endothelial leakage and disseminated intravascular coagulation. Death follows as a direct result of distributive shock, multi-organ failure, and bleeding complications.

**Diagnostic work-up and definitive diagnosis**: The diagnosis can be confirmed by viral RNA detection using PCR. Several reference laboratories in Europe are able to perform diagnostics [28]. Preferably serum or plasma samples taken at different time points are transported to the laboratory. As infection may involve virus variants, reference laboratories will use PCR that targets different parts of the viral genome. Patients with a fatal course of VHF due to any type of virus, do not usually develop a measurable antibody response. As such, serologic testing is inappropriate for reliable exclusion. Serological diagnosis by detection of specific IgM and IgG antibodies can be used in later stages of the disease, if antibody response has mounted [29].

**Treatment and prognosis**: Filovirus haemorrhagic fever outbreaks are associated with a high case fatality rate: Marburg virus, 82% [5,27,30], Ebola Zaire strain, 80 % [13,18,27], Ebola Sudan strain, 50 % [13,18,27]. There is no effective antiviral drug against the filoviruses. Other possible strategies, such as the administration of convalescent serum/whole blood, poly- or monoclonal antibodies, interferon α, or recombinant interferon, or extracorporeal blood treatment with haemosorbents or dialysis, have not been proven successful either [27].

**Prevention**: Because filoviruses contain all properties of a potential biological weapon, much effort has been put into the development of a vaccine. So far, only the use of a recombinant vesicular stomatitis virus (VSV) vector based vaccine has been proven effective in non-human primates. Since intentional exposure of people to filoviral infection would be too dangerous,
Although the illness has been known for its outbreaks and cases in returned travellers, only this virus will be discussed.

Historical background: Although the illness has been known since 1950, Lassa virus was not identified until 1969 when two missionary nurses died from it in the town of Lassa in the Yedseram river valley in Nigeria [18,33,34]. Since then several outbreaks and recurrent infections have been reported in West Africa [35-37].

Virological aspects: Lassa virus is an enveloped, single-stranded, bisegmented RNA virus belonging to the family of arena viruses. The virus consists of a small and large RNA segment, encoding the viral glycoprotein precursor protein, the nucleoprotein and the Zinc-binding protein [36]. Four Lassa virus strains have been identified: Josiah strain (originating from Sierra Leone), Nigeria strain and LP strain (both originating from West Africa) and the AV-strain, closely related to the Josiah strain (imported into Germany by a traveller after visiting Ghana, Cote d’Ivoire, and Burkina Faso) [36].

Ecology and epidemiology: Lassa-fever is endemic in West Africa (figure 1). The prevalence of antibodies to the virus in the population ranges from 4-55% [37]. Several outbreaks and recurrent infections have occurred in West Africa [35-37] and 22 cases have been reported in returned travellers in the United States (5), United Kingdom (10), Canada (1), Germany (3), the Netherlands (2), and Japan (1) [37-43]. The virus is carried by rodents of the Mastomys natalensis species complex, which are distributed all over West, Central, and East Africa, mostly in rural areas. Infected rodents are asymptomatic and remain carriers for life, excreting the virus in urine, saliva, respiratory tract and in blood [36]. Humans become infected by contact with infected rodent excreta, or by contact with infected animal blood while preparing food [36,37]. Person-to-person transmission can occur through contact with infected blood, bloody excreta, sexual intercourse and contaminated medical equipment [42].

Clinical features: In the majority of cases the course of disease is almost asymptomatic and subclinical, although excreta must be considered contagious [10]. Only 10% of the cases develop a severe illness [35,37]. The incubation period is 3 to 21 days [36-37]. The initial symptoms consist of high fever, headache, rigors, myalgia and malaise. Other signs are nausea, vomiting, abdominal pain, especially around the liver, and pleuritic pain. Furthermore, oral ulceration with white/yellowish exudates or bleeding gums can be present. Proteinuria can also develop as a sign of kidney inflammation. Less than one third of the patients present with bleeding, but this is associated with a significantly higher risk of death [35-37,42]. Due to the proteinuria and capillary leakage, severe cases progress to facial oedema, pleural effusion and finally shock, seizures, tremors, disorientation and coma. During convalescence, pericarditis, aseptic meningitis, hair loss, and cerebellar ataxia may develop. Furthermore, temporary or permanent deafness occurs in 30% of patients [35-37,42].

Pathogenesis [44]: Since arena virus infection usually develops after inhalation of infected material, the initial replication takes place in the lungs and mediastinal lymph nodes. Thereafter the spread to other organs takes place, resulting in inflammation. Furthermore, macrophages are infected which leads to the excretion of cytokines and chemokines and the initiation of an inflammatory response. Due to this response, capillary leakage develops but is also a result of direct infection of endothelial cells. Little organ necrosis is present at autopsy, except for lymph nodes and lymphoid follicles in the spleen, which might explain a part of the deficient immune response.

Diagnostic work-up and definitive diagnosis: A rapid and reliable diagnostic tool is the detection of viral RNA in blood by a RT-PCR [8]. IgM antibodies are usually detectable from day nine of illness. Serological testing is not suitable for early diagnosis as such.

Treatment and Prognosis: Some studies indicate that 300,000 to 500,000 cases of Lassa fever and 5,000 deaths occur yearly across West Africa [35]. The overall case fatality rate is 1%
up to 15% among hospitalized patients. Especially pregnant women and neonates are at risk for developing a serious course of disease and death, probably due to the suboptimal cellular response needed as a defence against this virus [10]. Death usually occurs within 14 days of onset. Although standardized clinical trials are lacking, a 10-day intravenous treatment with ribavirin is commonly advised. From patient-population based studies, it can be concluded that ribavirin is most effective when given in the first 6 days of illness. In severe cases, mortality reduction is described (25% to 5%) [36,37,42,45]. Moreover, it might also be effective as post-exposure prophylaxis [45].

Prevention: Primary transmission of Lassa virus from the reservoir to humans in endemic areas can be prevented by reducing contacts with Mastomys rodents by storing food in rodent proof containers, promoting good “community hygiene”, and discontinuing the use of these rodents as food source [42]. Human-to-human transmission should be prevented by general isolation measures. Up to now, several vaccines have been tested in primates, but no vaccine is available for humans [36].

Bunya virus haemorrhagic fever - Crimean-Congo virus

Historical background: The description from a 12th century physician of a Tajikistan patient with haematuria, bloody stools, haematemesis, haemoptysis, bleeding gums, and blood in the free abdominal space, caused by a tough and small arthropod, related to a louse or tick, is probably the first known case of Crimean-Congo Haemorrhagic Fever (CCHF) [46,47]. It became a clinical entity in World War II, when approximately 200 Russian soldiers were infected while assisting local farmers in the Crimea with their work. The recognition, that this virus was identical to an African strain of the “Congo-virus”, led to the renaming of these viruses to CCHF-virus [47-49].

Virological aspects: the CCHF-virus is a member of the nairovirus genus of the family bunya viridae. The virus is an enveloped particle with a single-stranded RNA genome of negative polarity, encoding for four structural proteins; the RNA polymerase, two types of glycoproteins and the nucleocapsid [50].

Ecology and Epidemiology: The virus is transmitted by the Hyalomma genus ticks. The virus circulates in nature unnoticed in an enzootic tick-vertebrate-tick cycle, including cattle, goats, sheep, hares and even domestic dogs [47]. Although birds seem to be refractory to the infection [47,50], ostriches from the commercial ostrich meat industry in South Africa were able to become infected and even cause an outbreak under workers of an ostrich abattoir [51]. The distribution of CCHF in more than 30 countries in Africa, Asia, Southeast Europe, and the Middle East (figure 1), coincides with the global distribution of the ticks [47,50]. Climate changes might be an additional factor of the increased incidence of tick-borne diseases in many parts of Europe over the past two decades. At present, Bulgaria, Greece, Turkey, Albania, Serbia, Bosnia, Croatia and parts of Russia are part of the natural habitat of this Hyalomma genus tick [50]. So far, several tick-borne outbreaks have occurred in these countries, but no imported cases have been described in the Netherlands [50].

Clinical features: Humans are the only known host of CCHF virus in which disease is manifested. A subclinical course has been described [52], but the majority of infections lead to a severe clinical picture. The typical course of CCHF has four distinct phases: incubation, pre-haemorrhagic, haemorrhagic, and convalescence period [47,50,53]. The incubation time is usually 3 to 7 days, but can differ depending on viral dose and route of transmission [47,50]. The pre-haemorrhagic period usually lasts for approximately 3 days and is characterized by a sudden onset of high fever, headache, dizziness, photophobia and myalgia. Furthermore, hyperaemia of head, neck and chest, and conjunctivitis are present. The haemorrhagic period is short, develops rapidly and usually starts on day 3 to 6. Haemorrhagic manifestations can range from petechiae to large areas of ecchymosis and often appear on the mucous membranes and skin. But vaginal, gingival, gastro-intestinal and abdominal bleeding - and in severe cases cerebral haemorrhage - have also been reported [47,50]. There is usually some evidence of hepatitis as well. Multi-organ failure may develop after the fifth day of illness. In survivors, the convalescence period starts at day 10 to 20 and is characterized by generalized weakness and complete loss of hair. Additional sequelae can include polyneuritis, headache, poor appetite, poor vision, hearing loss, memory loss, and heavy breathing. These symptoms are mostly reversible, but can last for more than a year.

Pathogenesis [47]: After local viral replication, the virus spreads through the body via blood and the lymphatic system. Common target cells are phagocytes, endothelial cells, and hepatic cells. The production of viral factors, direct infection of endothelial cells, and the hosts’ inflammatory response can cause endothelial activation and dysfunction, resulting in haemostatic failure by activation of the intrinsic coagulation cascade and disseminated intravascular coagulation. The development of disseminated intravascular coagulopathy early in the disease is an unfavourable sign for the prognosis. Viral replication in the liver causes focal or global hepatic necrosis and reactive haemophagocytosis causes leucocytopenia, leading to susceptibility to secondary infections.

Diagnostic work-up and definite diagnosis: Analogous to the other VHF, the best way to detect CCHF viral genome in blood is by the use of PCR. IgG and IgM antibodies may be detected in serum by ELISA from approximately day six of the illness [54].

Treatment and Prognosis: With conventional supportive therapy, the mean mortality is 30% to 50%. Animal studies and case reports suggest efficacy from a 10-day treatment with intravenous ribavirin [55-57]. The value of immune plasma from recovered patients for therapeutic purposes has not been demonstrated, although it has been employed on several occasions [58].

Prevention: An inactivated mouse-brain preparation vaccine has been tried in volunteers leading to adequate antibody formation in 96.6% [59]. Former use in medical workers and military personnel might have reduced the number of cases and the case fatality rate, but studies were limited in time and confined to a few areas [50].
Outbreak control

Risk-assessment: Since VHF-viruses are highly contagious diseases with a high case fatality rate, consequences for the population are huge when insufficient isolation measures are instituted. The person’s medical history is the key tool when making a risk assessment, see table 1 [8]. When a patient presents with fever within the incubation period (3-21 days) after visiting endemic areas (figure 1) and with risk contacts (table 2), without any other proven diagnosis, VHF should be considered. Although contagiousness is highest in the haemorrhagic phase, transmission is also possible in the non-haemorrhagic symptomatic stage and in the convalescence period. For this reason, strict isolation measures should be initiated while awaiting diagnostic laboratory results (figure 2). Because of the infrequency of VHF infection in industrialized countries, more common pathogens should also be treated or ruled out as well [60].

Isolation indications [8,61-63]: If the clinical condition of a returned traveller with fever, who is suspected of VHF, requires admission to an intensive care unit, he/she usually belongs to the high risk category. A high risk patient is defined as a patient who is highly suspected of having VHF and one out of four of the following symptoms: manifest bleeding, pulmonary lesions, productive or non-productive cough, vomiting or diarrhoea. In this high risk patient category, strict isolation measures should be instituted and transfer to another hospital is undesirable, but special protocols are available if transport is necessary [61-63].

Strict isolation measures [61-63]:
- A negative air pressure room must be used with an adjoining anteroom serving as its only entrance. Hand-washing facilities, containers and decontaminating solution should be available in the anteroom.
- Strict barrier nursing techniques should be in place. All persons entering the room should wear disposable gloves, gowns, eye protection, FFP2 masks, and shoe covers. Dressing and undressing should follow a specific protocol, followed by disinfection of the hands with a 70% alcohol solution.
- Protocolized waste handling must be in place. All waste should be collected in rigid plastic containers, that can be sponged on the outside. The container should be autoclaved, incinerated, or otherwise safely discarded.
- Protocolized handling of blood specimens must be enforced. Laboratory tests should be kept to the minimum. All specimens should be collected in unbreakable material and be double-packed in leak-proof boxes, according to the triple packaging principle. Pneumatic channels should not be used for transport. Before handling the blood specimens in general laboratories, inactivation of the virus should take place in a C-II laboratory with a biosafety level III. A full blood smear for malaria, blood cultures and virus isolation should only be attempted at biosafety level IV laboratories, which can be found at the ENIVD-website [28].
- Exceptional handling of the corpse in case of death must take place. According to an order described in detail, the corpse should be double-body-bagged. Only after the outer body bag has been disinfected, can the corpse be transported out of the room and be cremated, without any further opening of the bags.

Management of patient-contacts [7]: A contact is defined as a person who has been exposed to an infected person or to an infected person’s secretion, excretion, or tissues within 3 weeks of the patient’s onset of illness. In order to prohibit further spread of VHF, all contacts of the index patient should be placed under surveillance for three weeks after the last contact. The surveillance consists of temperature measuring twice daily and reporting any fever or other symptom of disease to the public health officer responsible for surveillance. Should fever or other symptoms occur, then immediate isolation and treatment as a VHF patient should follow [7]. Convalescent patients and their contacts should be warned about the possibility of ongoing excretion of virus in semen, as demonstrated with Marburg and Ebola [11,61,62], as well as in urine, as this has occurred incidentally with Lassa virus [61,62]. Abstinence should be advised until genital fluids have been proven free of virus.

Conclusion

The occurrence of VHF in returning travellers is still exceedingly rare, but due to increasing travel to endemic areas, awareness of these diseases is important. Although initial symptoms are non-specific, VHF should be considered when a traveller to endemic areas presents with fever within the incubation period - especially when the history is positive for risk-contact. This enables isolation measures to be instituted on time and a possible outbreak with high impact on the population can be prevented. This is especially relevant for cases of Marburg haemorrhagic fever and Ebola haemorrhagic fever as these are known for high case-fatality rates, since no treatment or vaccination is available.
References