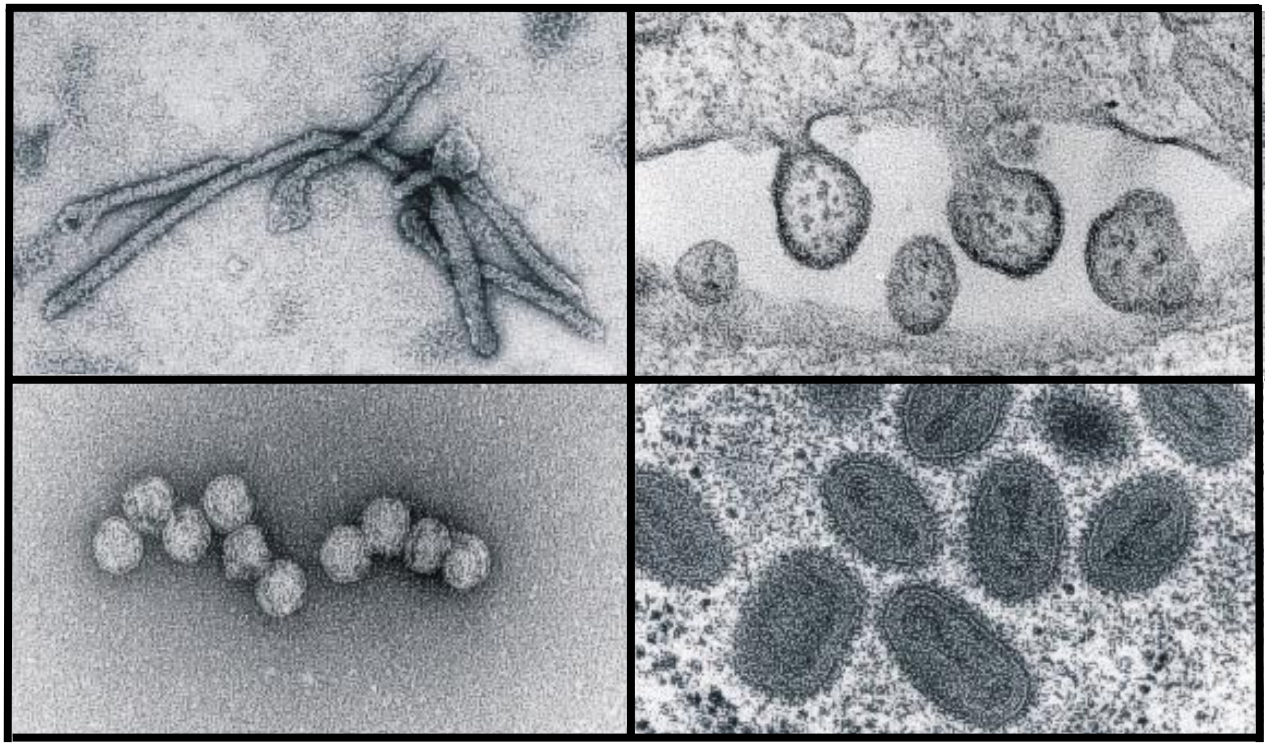
Management and Control of Viral Haemorrhagic Fevers

and other highly contagious viral pathogens



European Network for Diagnostics of Imported Viral Diseases

ENIVD

Scientific Advisory Committee

Management and Control of Viral Haemorrhagic Fevers

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The version is also presented on the ENIVD website: **www.enivd.de**

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Upper left: Ebola right: Lassa
Lower left : Yellow Fever right: Monkeypox

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Management, Control and Surveillance of Viral Haemorrhagic Fevers

Contents

Abbreviations

BSL	Biosafety level (i.e. BSL 1, 2, 3, 4)
CCHF	Crimean-Congo haemorrhagic fever
CMV	Cytomegalovirus
ELISA	Enzyme-linked immunosorbent assay
EBV	Epstein-Barr virus
HF	haemorrhagic fever
HFRS	haemorrhagic fever with renal syndrome
HSID laboratory	high security infectious disease laboratory
HSIDU	high security infectious disease unit
HEPA	high efficiency particulate absorption
IgG	immunoglobulin class G
IgM	immunoglobulin class M
ICU	intensive care unit
NT	neutralisation test
PCR	polymerase chain reaction
UN 6.2 category	Packaging Specification Marking (Figure 3)
VHF	viral haemorrhagic fever
VI	virus isolation
WHO	World Health Organisation

Glossary

endemic	occurring permanently in a particular region or population
hazard	the intrinsic danger associated with the nature of an object or a substance, an activity or, in the context of this guidance, an infectious agent
risk assessment	describing and quantifying the risk associated with a hazard
vector	any agent (living or inanimate) that acts as an intermediate carrier or alternative host for a pathogenic organism and transmits it to a susceptible host
viraemia	the presence of virus in blood
virulence	the degree of pathogenicity of an organism as evidenced by the severity of resulting disease and the organism's ability to invade the host tissues.

1. Introduction

Through the Ebola epidemics in Zaire, Gabon and Uganda, the Marburg virus outbreak in the Republic of Congo in recent years and the imported Yellow Fever and Lassa cases to Europe we all became aware that dangerous infections could enter Europe in a very short time. Travel is a potent factor in the emergence of infections and the current volume, speed and distance of travel are unprecedented – a problem which has been addressed by the WHO (1, 2). This has increased the risk that persons infected with a number of diseases, including VHF, may occur in Europe. The following guidelines have been drawn up to help the European healthcare systems in there preparing to deal with a suspected case.

While many VHF's were initially considered to be highly communicable between humans, this concept has not been substantiated. Although nosocomial transmission has occurred in areas with endemic disease, accumulated evidence suggests that transmission of these viruses does not commonly occur through casual or remote contact. Several importations to non-endemic countries have occurred without subsequent disease outbreaks. While secondary cases of Marburg, Ebola, Lassa and CCHF have been documented, only few secondary cases following an importation episode have been identified : Lassa fever (Ivory Coast → Germany ;3, 4), Marburg (Zimbabwe → S. Africa; 4a), Ebola (Gabon → S. Africa; 4b)

Body secretions and excretions, blood, semen and tissue specimens from infected patients contain infectious material. It is evident that the risk of infection increases with the clinical progression of the disease. Persons at highest risk of secondary infection are those who are in closest contact with an infected person or her/his body fluids during the period of incubation and acute illness. Such persons include those with close contact with patients, providing direct medical and nursing care, and laboratory workers handling blood, tissues or other specimens (5).

In the table below some of the recently imported suspected and real cases of viral haemorrhagic fevers imported to European countries are listed. This list represents only the known cases which have been brought to public attention.

Table 1: Imported cases of suspected VHF to Europe 1998-2000

Virus	Imported from	Imported to	Time	Reference
Suspected VHF[1]	Gambia	Belgium	11/1998	6
Yellow Fever	Ivory Coast	Germany	08/1999	7
Lassa	Ivory Coast	Germany	01/2000	8, 9
Lassa	Sierra Leone	U K	03/2000	9, 10
Lassa	Nigeria	Germany	03/2000	
Lassa	Sierra Leone	Netherlands	07/2000	11
Suspected VHF[2]	Kenya	Germany	12/2000	

[1] final diagnosis: Malaria, [2] final diagnosis: generalised Herpes (HSV-1)

All imported cases shown in the table resulted in the death of the patient, and raised important issues and questions regarding the protection of clinical personal and tracing contact persons, etc.

All of the involved parties (public health institutions, EC, WHO, hospitals, airline companies, ambulance service, politicians, etc.) obviously require reliable information on the clinical situation and the risk of infection before the media involvement can result in untoward and unnecessary fear. Thus a fast, reliable and a definite information system needs to be established.

This booklet summarises the main points for the management, control and surveillance of viral haemorrhagic fevers (VHF) recommended by the European Network for Diagnostics of "Imported" Viral Diseases (ENIVD) which proposes to the European Parliament and the Council of Europe.

The booklet is designed to assist staff in hospital accident and emergency departments, infectious diseases departments and laboratories who may encounter patients with unexplained febrile illness following a recent stay in countries where viral haemorrhagic fevers are endemic. It provides a brief guide to the initial assessment and management of such cases.

Full local contingency plans will have to be established by the competent local health authorities and this document can be used for reference.

This document is available at the following Internet site: www.enivd.de.

2. The risk to Europe

The term viral haemorrhagic fever (VHF) refers to a group of illnesses caused by five distinct families of viruses (we added the pox virus as an example for other highly contagious pathogens):

Table 2: Agents of Viral Haemorrhagic Fevers

	Mosquito -borne	Tick-borne	Rodent borne	Person –to-person *	BSL ①
Arenaviridae					
Lassa fever (LHF)			●	o	4
Argentine HF(Junin)			●	o	4
Bolivian HF(Machupo)			●	o	4
Brazilian HF(Sabia)			●	o	4
Venezuelan HF (Guanarito)			●	o	4
Bunyaviridae					
Crimean-Congo HF (CCHF)		●	●	o	4
Hantaan*			●	o	3
Rift Valley fever (RVF)	●		②	n	3
Filoviridae					
Ebola (EHF)			③	f	4
Marburg (MHF)			③	f	4
Flaviviridae					
Dengue, Type 1-4	●			n	(3)
Yellow Fever (YF)	●			n	3
Kyasanur Forest fever		●		o	3
Omsk Haemorrhagic fever		●		o	3
Togaviridae					
Chikungunya (CHF)	●			n	3
Poxviridae					
Monkeypox ⑤			④	f	4

* Person-to-person spread : n= none; o = occasional; f = frequent

① Biosafety level
② Domestic animals
③ Unknown reservoir and source
④ Squirrel, monkey
⑤ Does not classify as VHF

Each of these families share a number of common features:

With the exception of Monkeypox (dsDNA) they are all RNA viruses with a lipid envelope, their survival is dependent on an animal or insect host and they are geographically restricted to the areas where their host species live. Humans are not the natural reservoir

for any of these viruses and human cases occur sporadically. They can cause severe life-threatening diseases with high mortality.

Most of these viruses are endemic in a number of parts of the world: most notably Africa, parts of South America and some rural parts of the Middle East and Eastern Europe. Moreover, environmental conditions for the maintenance of these pathogens may be present in parts of Europe. Since cases of VHF are occasionally imported into Europe, there is a risk of secondary infection, particularly among hospital and laboratory staff. Accidental inoculation may result from needle sticks or contamination of broken skin or mucous membranes by infected blood or body fluids. Strict infection control precautions are required to protect those who may be exposed.

In addition there is the constant albeit very low risk of import of the reservoir and vector, and particularly for mosquito-borne diseases (Dengue, Yellow fewer, Rift Valley fever, West Nile fever, malaria) to European countries, which could cause occasional outbreaks. It should be noted that parts of Europe are already endemic for hantavirus infections, Crimean-Congo HF, and West Nile virus which qualify as VHF pathogens. Consideration should be given to the possibility of importation of both reservoir animals and vectors of other VHF viruses.

3. Viral haemorrhagic fever viruses

A brief description of the most important VHFs and pathogens to be considered for differential diagnosis.
For further details see appendix B or http://www.enivd.de → Management → fact sheets

3.1. Ebola fever

Ebola was first recognised in 1976 in the Democratic Republic of Congo. It is a severe, often fatal disease in humans and non-human primates. Ebola typically appears in sporadic outbreaks usually within a health-care setting. The exact location, origin and natural reservoir, and the endemic region of Ebola remain unknown as well as is the exact mode of transmission to humans but researchers believe that the virus is zoonotic, native to the African continent. Ebola–Reston however is originated in the Philippines.

Confirmed cases of Ebola have been reported in the Democratic Republic of the Congo, Gabon, Sudan, Uganda and the Ivory Coast. In 1976 a laboratory worker in the UK became ill as a result of a needle stick injury.
Mortality is high. The mortality rate in outbreaks in Africa ranges from 40% up to 80 % depending on the strain involved and other factors.

If a case presented in Europe, nosocomial transmission is most likely to occur through either direct or indirect contact with the blood and/or secretions of an infected patient. The Reston strain appears not to be pathogenic, and airborne transmission appears not to occur during outbreaks of the human pathogen strains Zaire and Sudan.

Conjunctivitis, petechiae and in the case of filovirus infections (Marburg and Ebola) a morbilliform skin rash appear later and are suggestive of VHF. These symptoms do not occur until the second week of infection by which time a reasonable suspicion of VHF should exist in the presence of a compatible travel history, the absence of a history strongly suggestive of other illnesses and at least two negative blood smears for malaria.

3.2. Marburg fever

Marburg virus was first recognised in 1967 when outbreaks of haemorrhagic fever occurred simultaneously in Marburg and Frankfurt in Germany and in Belgrade in the former Yugoslavia. The virus had arrived with imported monkeys from Uganda. The next case did not occur until 1975 in Johannesburg and the patient had most likely been exposed while travelling in Zimbabwe. A travelling companion and a nurse were subsequently infected. In 1980 there were two further cases, one in Western Kenya and the secondary in Nairobi. In 1987 another case was reported in an individual who had travelled extensively in Kenya. A total of 39 people were infected by contact to imported African green monkeys or secondary infection.

Marburg virus is endemic in Durba region part of DR of Congo and also appears in parts of Uganda, Western Kenya and perhaps Zimbabwe. As with Ebola the animal reservoirs for Marburg virus remain unknown. Also the route of transmission from animals to humans is unknown.

If a case were to occur in Europe those most at risk would be hospital staff and also family members or other individuals who had cared for the patient prior to their diagnosis.

While the case fatality rate was initially thought to be significantly lower than that of Ebola, analysis of recent outbreaks in the Democratic Republic of Congo have shown that this is also greater than 70%. Recovery from Marburg can be long and known sequelae include orchitis, recurrent hepatitis, transverse myelitis and uveitis.

3.3. Lassa fever

Lassa Fever is an acute viral illness that occurs in West Africa. The illness was first reported in 1969 when two missionary nurses died in Nigeria. Lassa Fever is endemic in parts of West Africa including Guinea, Liberia, Sierra Leone and Nigeria. The reservoir of Lassa virus is the multimammate rat.

Humans can be infected in several ways. Rats shed the virus in urine and droppings and therefore primary transmission is likely to be through direct contact with these materials. Infection can also occur following airborne transmission. Secondary transmission can also occur through person to person contact. In Europe such secondary transmission is most likely to occur in a healthcare setting by either contact with the virus in blood, tissue or secretions of a case or by breathing in airborne particles which the patient can produce by coughing. It is the potential transmission by aerosol that makes Lassa particularly dangerous.

Approximately 15-20% of patients hospitalised for Lassa fever die. The death rates are particularly high for women in the third trimester of pregnancy and for foetuses, about 95% of which die in the uterus of infected expectant mothers. Following recovery the most common complication is deafness which occurs in approximately 33% of cases.

3.4. Crimean-Congo haemorrhagic fever

Crimean-Congo Haemorrhagic Fever (CCHF) was first described in the Crimea in 1944. In 1969 it was recognised that the virus causing Crimean haemorrhagic fever was the same as that responsible for an illness identified in 1956 in the Congo, hence the linkage of the two names.

CCHF is transmitted by tick bite and caused by a virus which is widespread in East and West Africa, Central Asia and the former USSR. More recently, CCHF or antibody to it, has been detected in Dubai, Iraq, South Africa, Pakistan, Greece, Turkey, Albania, Afghanistan, and India.

CCHF is a severe illness in humans with a high mortality but fortunately human illness occurs infrequently. Animal infection is more common. Animals become infected with CCHF from the bite of infected ticks. Humans who become infected usually do so from direct contact with blood or other tissues from infected animals or directly from a tick bite. The majority of cases have occurred in those involved with the livestock industry such as agricultural workers, slaughterhouse workers and vets.

3.5. Rift Valley fever

The natural range of Rift Valley fever virus (RVF) is confined to sub-Saharan Africa, but the virus has recently been found in Madagascar and South Arabian countries and has been introduced into Egypt twice, with extensive epidemics occurring on both occasions (1977 to 1979 and 1993 to 1995).

This mosquito-borne virus is a pathogen of domestic animals such as sheep, cattle, and goats. It is maintained in nature by transovarial transmission in floodwater *Aedes* mosquitoes and presumably in a vertebrate amplifier. Epizootics and epidemics occur when sheep or cattle become infected during particularly heavy rains; developing high-level viraemia, these animals infect many different species of mosquitoes. Remote sensing via satellite can detect the ecological changes associated with high rainfall that predict the likelihood of Rift Valley fever transmission; it can also detect the special depressions from which the floodwater *Aedes* mosquito vectors emerge. In addition, the virus is infectious when transmitted by contact with blood or aerosols from domestic animals or their abortuses. The slaughtered meat is not infectious.

Rift Valley fever virus is unusual in that it causes at least four different clinical syndromes. Most infections are manifested as the febrile-myalgic syndrome. A small proportion result in VHF with especially prominent liver involvement. Perhaps 10 percent of otherwise mild infections lead to retinal vasculitis; funduscopic examination reveals oedema, haemorrhages, and infarction, and some patients permanently lose partial vision. A small proportion of cases (less than 1 in 200) are followed by typical viral encephalitis. One of the complicated syndromes does not appear to predispose to another. Neither person-to-person nor nosocomial transmission has been documented until now.

3.6. Yellow fever

Yellow fever (YF) occurs in two forms. In urban yellow fever, the virus is transmitted by the bite of an *Aedes aegypti* mosquito infected 2 weeks previously by feeding on a viraemic patient. In jungle (sylvatic) yellow fever, the virus is transmitted by other forest canopy mosquitoes that acquire the virus from wild primates. Yellow fever is endemic in Central Africa and areas of South and Central America.

Yellow fever is an acute flavivirus infection of variable severity, characterised by sudden onset, fever, a relatively slow pulse, and headache. Diagnosis is confirmed by isolation of the virus from the blood, by a rising antibody titre, or at autopsy by the characteristic midzonal liver cell necrosis. Needle biopsy of the liver during illness is contraindicated by the risk of haemorrhage.

Supportive treatment is directed toward alleviating major symptoms. Complete bed rest and nursing care are important. Correction of fluid and electrolyte imbalance is imperative.

3.7. Dengue fever (DHF), Dengue Haemorrhagic Fever (DHS) and Dengue Shock Syndrome (DSS)

Dengue is endemic throughout the tropics and subtropics; outbreaks have occurred since 1969 in the Caribbean, including Puerto Rico and the U.S. Virgin Islands. Imported cases have also been documented in tourists returning from Tahiti. The causative agent, a flavivirus with four distinct serogroups, is transmitted by the bite of *Aedes* mosquitoes.

Dengue fever (Breakbone or Dandy Fever) is an acute febrile disease of sudden onset with headache, fever, prostration, severe joint and muscle pain, lymphadenopathy, and a rash that appears with a second temperature rise after an afebrile period.

After an incubation period of 3 to 15 (usually 5 to 8) days, onset is abrupt with chills, headache, retro-orbital pain on moving the eyes, lumbar backache, and severe prostration.

In dengue haemorrhagic fever (DHF), the degree of hemoconcentration, dehydration, and electrolyte imbalance must be evaluated immediately and monitored closely for the first few days, since shock (DSS) may occur or recur precipitously.

3.8. Haemorrhagic fever with renal syndrome

Because of their world-wide occurrence, additional consideration should be given to infections with hantaviruses. Classic HFRS (also referred as Korean haemorrhagic fever or epidemic haemorrhagic fever) has a severe course which progresses sequentially from fever through haemorrhage, shock, renal failure and polyuria. This clinical form of HFRS is widely distributed in China, the Korean peninsula and the Far Eastern Russia. Severe disease also is found in some Balkan states, including Bosnia, Serbia and Greece.

However, the Scandinavian and most European virus strains carried by bank voles usually produce a milder disease (referred to as nephropathia epidemica) with prominent fever, myalgia, abdominal pain and oliguria but usually without shock or severe haemorrhagic manifestations.

Hantavirus Pulmonary Syndrome, another hantaviral disease, recently recognised in the Americas, lacks haemorrhagic manifestations but nevertheless carries a very high mortality due to its rapidly progressive and severe capillary leak which presents as “Adult Respiratory Distress Syndrome”.

Phase III efficacy trials have indicates that parenteral ribavirin reduces both morbidity and mortality in HFRS. Treatment was effective if begun within the first 4 days of fever and was continued for 7 days total.

3.9. Chikungunya haemorrhagic fever

In 1952-1953 between July and March, the disease broke out in southern Tanganyika, where 60.000 cases were diagnosed and the virus was isolated for the first time. After the Tanganyika epidemic, outbreaks occurred in 1958 and 1962-1964 in Thailand, 1962 in Zimbabwe, 1964 in India, 1966 in Vietnam, 1969 in Nigeria, 1956 and 1975-1976 in South-Africa, 1982 in Uganda and 1983 in Indonesia. It is likely that the disease in the

form of small outbreaks frequently goes unrecognised; at least antibody is prevalent in man throughout much of Africa and Asia.

An incubation period of 22 hours was documented in a laboratory infection following the bite of *Aedes africanus*, but is usually between 3 and 12 days. The disease has abrupt onset with high fever, myalgia and sudden intense pain in one or more joints. Other signs and symptoms include headache, sometimes nausea and vomiting, coryza, lymphadenitis and conjunctivitis, photophobia and pain behind the eyes. Rash develops on the second to fifth days after onset and is maculopapular, occasionally with petechiae and rarely with more severe bleeding. The acute disease lasts 3 to 10 days, but convalescence may include prolonged joint swelling and pain lasting weeks or months.

3.10. Monkeypox

Monkeypox was first identified in primates in 1959. Recent studies indicate that squirrels (*Funisciurus, Heliosciurus*) and rodents are the host and reservoir of the monkeypox virus. The majority of human infections are attributable to contact with infected animals.* Reports of human monkeypox from 1970 to 1986 revealed 404 cases, mainly in children under age 16, in West and Central African countries (DR Congo, Côte d'Ivoire, Sierra Leone, Cameroon, Central African Republic, Liberia, Nigeria). Of these, 95% of the cases were identified during WHO intensified surveillance from 1981-86 in DR Congo. 67% Of the cases were seen during the rash stage and later verified by virus isolation. 32% were seen soon after disease onset and were verified clinically and by detection of specific antibodies in serum; 10% were corroborated by examination of epidemiological and clinical data. Vaccination scars indicated that 13% of the patients had been immunised against smallpox, most of these >10 years previously. Primary or co-primary infections resulting from animal-to-human contact accounted for 72% of the cases, with inter-human transmission responsible for 28%. Clustering of cases in households was rare, as were chains of inter-human transmission beyond 2 generations; only 11, 3 and 1 cases proceeded to the third, fourth, and fifth generations, respectively. The overall case-fatality ratio was 10%.

4. Diagnosis of haemorrhagic fever

In the absence of hospital or laboratory exposure VHFs are acquired almost exclusively in rural areas. The incubation period ranges from a minimum 3 days to a maximum 21 days. Initial signs and symptoms are usually systemic and consistent with an "influenza-like" illness with symptoms of marked fever, fatigue, dizziness, myalgias, arthralgias, fatigue and exhaustion. Fever may last as long as 16 days with temperatures reaching 41º C. Such symptoms in a returning traveller who has a history of rural travel exposure, who has a history of contact with an ill individual or who has travelled to an endemic area, or one affected by an outbreak, could suggest a risk of VHF (Appendix A).

A careful analysis for an existing risk of an imported disease could be evaluated following the questionnaire and contacting an expert laboratory. However, a more likely diagnosis would be one of the following more common infectious diseases: malaria, followed by typhoid fever, other bacterial infections, such as pyelonephritis, pneumonia, septicaemia, meningococcemia, leptospirosis and rickettsial infections as the most likely.

Severe cases of VHF often show signs of bleeding under the skin, in internal organs or from body orifices such as the mouth, eyes or ears. Obvious bleeding is a later or terminal event. Those severely ill may also develop shock, nervous system malfunction, coma, delirium and seizures. Four agents of VHF are of particular concern in Europe because of possible person-to-person spread. These are Lassa, Ebola, Marburg and Crimean-Congo haemorrhagic fever viruses.

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4.1. Communication lines in case of suspected VHF

The most likely site of presentation of a suspected or definite VHF case is in the Accident and Emergency Department of a hospital, either as a self referral or a referral from a general practitioner or a clinic for tropical diseases
If the patient’s illness is compatible with VHF the attending consultant must get in contact with the appropriate authorities and experts.

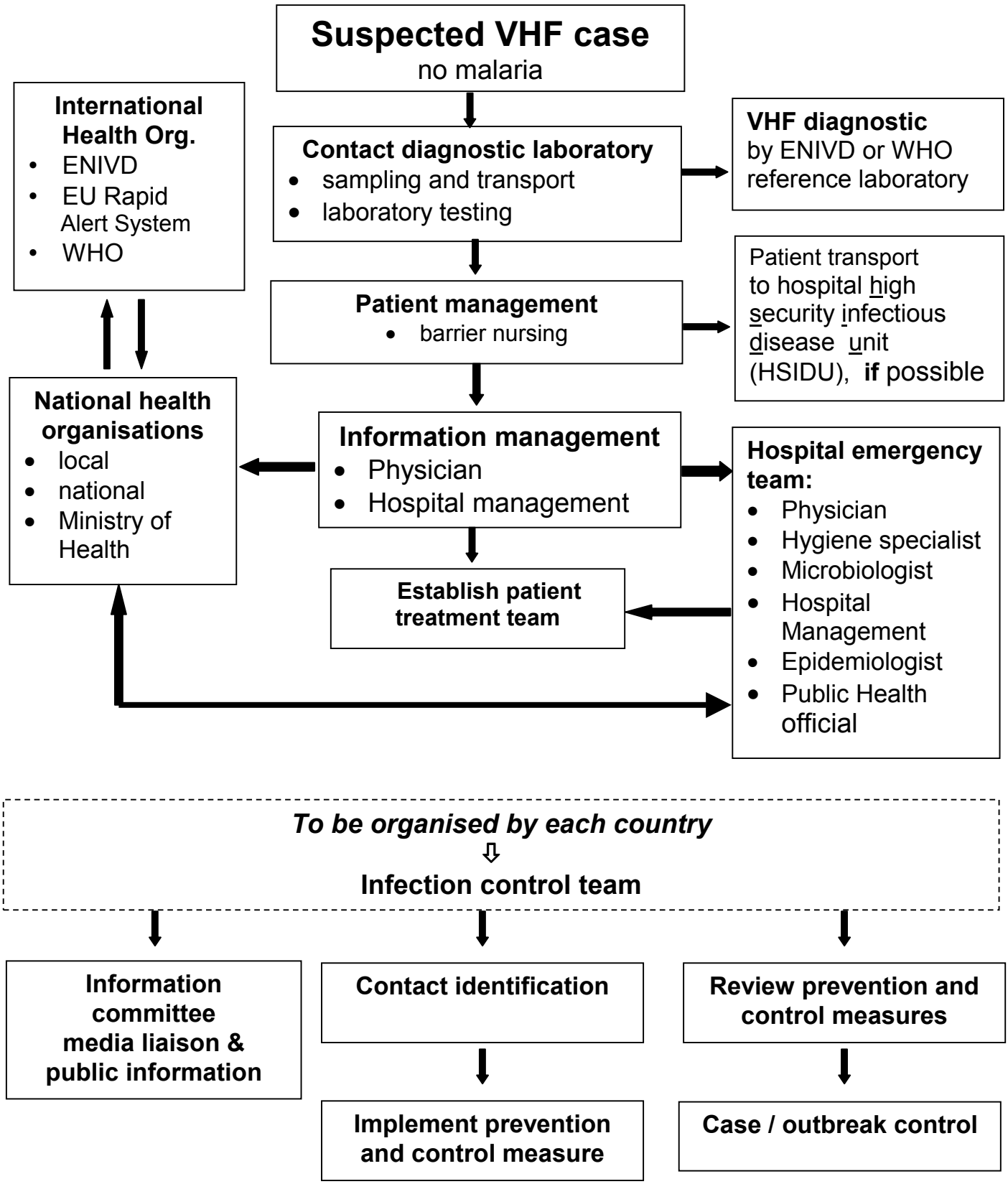
It is highly recommended to obtain all information as soon as possible from a suspected VHF case. (see Appendix A for example)

Imported unusual or emerging communicable diseases may also be identified or suspected at European ports of entry, i.e. airports or harbour ports.

In hospitalised patients where the diagnosis is suspected or in cases where a suspect case is being moved to a hospital, it is essential that the appropriate authorities be notified immediately.

After informing the national health authorities and in accordance to the national regulations the European communicable disease Early Warning System should be notified of any case by the National Response Co-ordinator. The virology reference laboratory should liase with the relevant parties in the World Health Organization (WHO) in Geneva and the European Network for Diagnostics of Imported Viral Diseases (ENIVD) regarding the VHF diagnosis.

Figure 1: Follow-up for suspected VHF case, communication lines



4.2. Patient assessment

A VHF infection is possible in any patient presenting with a febrile illness of unknown origin shortly after having returned from countries where VHF is endemic. However in most cases this can be dismissed on epidemiological grounds alone. The suggested checklist of enquiries shown in **Appendix A** is designed to help identify patients at risk. It is difficult to make a firm diagnosis solely on clinical grounds, so epidemiological evidence is essential in assessing a feverish patient with a history suggestive of VHF.

Experience has shown that most ill patients suspected of VHF will be suffering from **malaria**. Laboratory tests to exclude or confirm malaria should be undertaken as soon as possible. **Malaria** is a serious infection which can be life threatening: prompt treatment can significantly affect the course of disease. Therefore we strongly recommend patient examination by somebody experienced in tropical diseases.
(For general information on Malaria see Appendix B)

Other relatively common causes of febrile illness in travellers returning from Africa include typhoid fever, dengue, rickettsial infections and tropical parasites (Table 2). Multiple infections are not uncommon in the tropics and the finding of malarial parasites does not absolutely exclude one of the haemorrhagic fevers or other serious infections. In unconscious patients, other conditions such as diabetes, meningitis or stroke should be considered. It is also **very** important to rule out common “non-tropical” infections such as herpes, EBV, CMV etc.

Table 2: Pathogens to be considered for differential diagnosis of VHF

Pathogen	Overview to diseases
Viruses	Yellow Fever, Rift Valley Fever, Infectious mononucleosis, Dengue, Dengue Shock Syndrome, Dengue Haemorrhagic Fever, Hepatitis, HIV, Herpes
Bacteria	Typhoid, Pyelonephritis, Pneumonia, Sepsis, Meningococcal disease, Leptospirosis *Rickettsia:* Typhus, Q Fever, Tick-borne rickettsiosis
Parasites	*Helminths*: Schistosomiasis, Katayama syndrome *Protozoa*: Malaria, Amoebic liver abscess

4.3. Patient risk assessment and categorisation

The purpose of risk assessment and patient categorisation in relation to VHF is to provide efficient and timely management for patients, while affording maximum protection for the laboratory and clinical staff involved. For this purpose, patients are assigned to one of two risk groups: **at-risk** or **high-risk**.

At-risk group

This category applies to febrile patients who have within 3 weeks before the onset of fever:

- travelled or lived in the specific local area of a country where VHF occurred but who have none of the additional risk factors which would place him/her in the **high-risk** category.

High-risk group

This category applies to febrile patients who have within 3 weeks before the onset of fever:

- travelled or lived in the specific local area of a country where VHF occurred

and with at least one of the following criteria

- have lived in a house or stayed in a house where there were ill, feverish persons known or strongly suspected to have a VHF
- having unexplained hemorrhagic manifestations
- took part in nursing or caring for ill, feverish patients known or strongly suspected to have a VHF, or had contact with the body fluids, tissue or the dead body of such a patient
- are a laboratory, health or other worker who has or has been likely to have come into contact with the body fluids, tissues or the body of a human or animal known or strongly suspected to have a VHF
- were previously diagnosed "**at-risk**" but who have developed organ failure and/or evidence of haemorrhage in the absence of any other diagnosis
- The category **high-risk** group also applies to febrile patients who have not been in an endemic area but who during the 3 weeks before the onset of fever:

- have cared for a patient or animal known or strongly suspected to have a VHF

or

- came into contact with the body fluids, tissues or dead body of such a patient or animal

or

- handled clinical specimens, tissues or laboratory cultures known or strongly suspected to contain the agent of a VHF

4.4. Laboratory diagnosis of VHF

The diagnosis of VHF is performed by viral genome detection by polymerase chain reaction (PCR), virus isolation (VI), by antigen detection employing enzyme-linked immunosorbent assay (ELISA), and by the demonstration of IgM antibody or by a four-fold rise in IgG antibody titer in serum. Antibodies may not appear in the blood until the second week of illness. In fatal cases it is unlikely to detect specific antibodies (IgG, IgM) before death. Moreover it is becoming apparent that in some instances infection may involve virus variants, which may not react in currently employed assays. Virus is usually recovered from blood, although the virus may also be isolated from throat secretions or urine. Skin, liver or spleen tissue may also be a rich source of virus.

Viral isolation of Level 3 and 4 agents is not advised in a normal diagnostic laboratory and should only be performed in a Biosafety 3 or 4 laboratory .

4.5. Laboratory specimen collection

Because of the potential risks associated with handling infectious materials, laboratory testing should be the minimum necessary for diagnostic evaluation and patient care (12). Upon presentation of a possible case of VHF tests that the clinician in charge judges as necessary for the immediate treatment and for differential diagnosis should be performed immediately e.g.:

- A thin blood smear to look for **malaria** parasites on at least two occasions. Blood smears are not infectious after fixation in solvents.
- Two sets of blood cultures using routine blood culture bottles taken from separate vein punctures at least 30 minutes apart with a total volume per set of 20 to 30 ml.
- White blood cell and differential count and either haemoglobin or haematocrit.

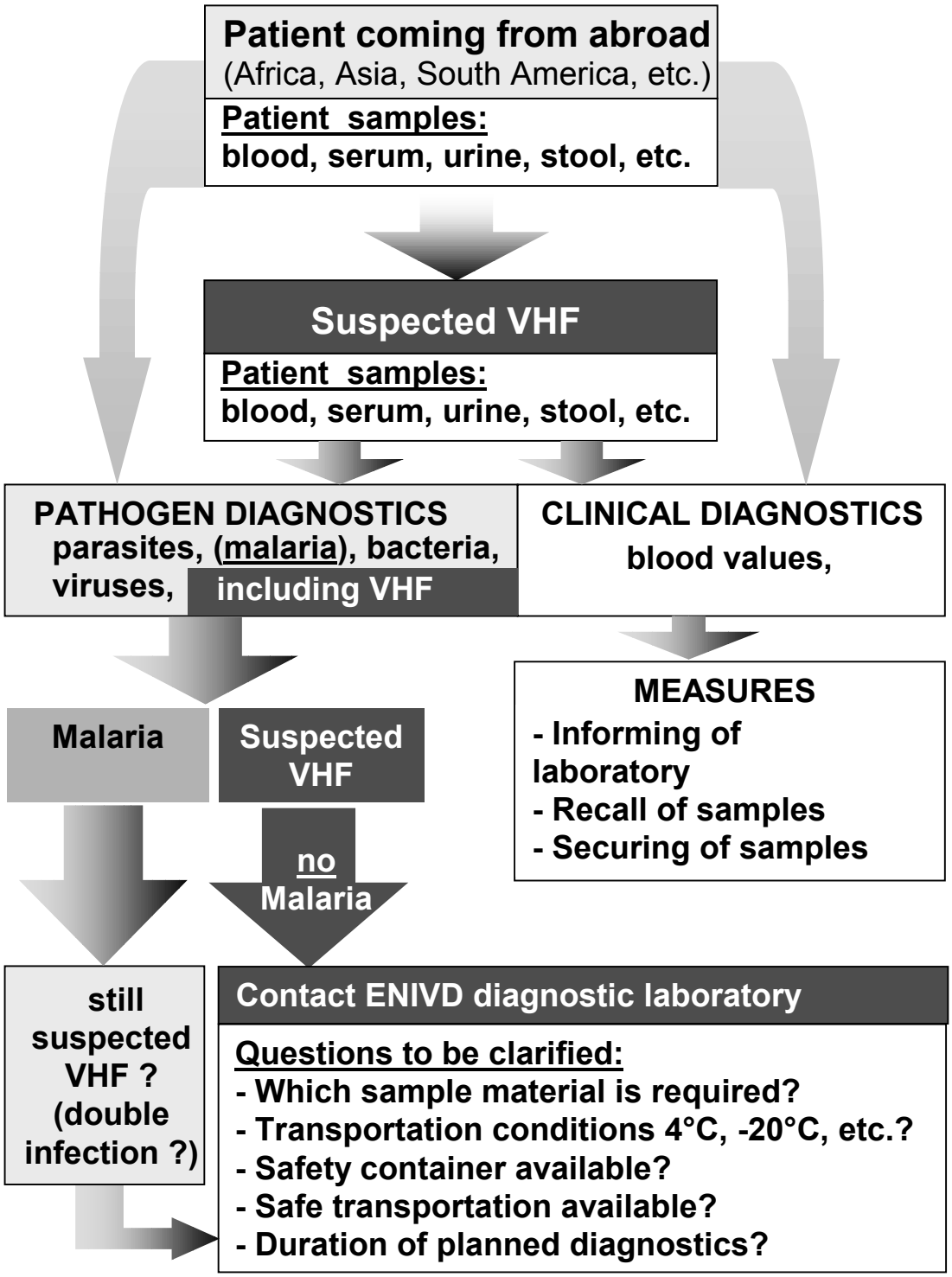
- Urea and electrolytes
- Urine culture, if urinalysis results suggest an infection
- The clinical diagnostic laboratory must be informed on the suspicion of VHF

The following 5 principles should be observed in the collection of all patient specimens:

1. Only specimens essential for diagnosis or monitoring should be obtained **after** consulting the specialised laboratory (see Appendix A).
2. Staff experienced in phlebotomy should obtain the specimens, using a vacuum sampling system.
3. Glass containers should be avoided whenever possible. Disposable sharp objects such as scalpel blades should be placed in a sharps box immediately after use and later autoclaved before disposal.
4. Blood samples must be collected with extreme care to avoid self-inoculation. Standard precautions should be strictly adhered to. Needles must not be bent, broken, removed from disposable syringes, recapped or otherwise handled. Dry cotton balls or gauze (not disposable alcohol swabs) should be used to apply pressure to the vein puncture wound.
5. A label, bearing the patient details, should be attached on the specimen container before collection of the specimen.

When a patient suspected of having a VHF has died it may be necessary on public health grounds to undertake some diagnostic tests including malaria tests. Advice should be obtained from appropriate specialists.

Figure 2: Handling of samples



4.5 Clinical diagnosis

The laboratory receiving the specimen should be alerted to the potentially hazardous nature of the material being sent. Each laboratory should have a contingency plan for these situations.

Laboratory staff dealing with specimens from patients with a suspected VHF must take, as a minimum, the same personal protective precautions as the patient care staff; i.e. disposable gloves, a particulate filter respirator mask with fluid shield protection , impermeable gowns and protective eye wear should be worn.

Specimens in clinical laboratories should be handled in a class II biological safety cabinet following biosafety level 3 practices (12,13).

Centrifugation with open containers should be strictly avoided.

Blood smears for malaria should be fixed in the appropriate solvent (methanol) which renders them non-infectious. Serum used in laboratory tests may be pre-treated with polyethylene glycol p-tert-octylphenyl ether (Triton XR-100). Treatment with 10 µL of 10% Triton XR-100 per 1 ml of serum for 1 hour reduces the titre level of some of the VHF viruses in serum. 100% efficacy in inactivating these viruses should not be assumed. The inactivation procedures should be performed after consultation of the clinical laboratory. (14).

Routine automated equipment (dry chemistry) should be used in the usual manner in order to prevent infections. Following use these should be disinfected as recommended by the manufacturer or with 500 parts per million solution of sodium hypochlorite.

Specimens which cannot be processed in closed automated systems such as urine, blood cultures (when manually processed), swabs etc. should be handled **by experienced personnel**, in at a minimum, laboratory containment level 3 facilities such as those laboratories which are normally used to process specimens for mycobacteria. These laboratory facilities should be separate from other laboratory facilities with

restricted access, maintained at an air pressure negative to the rest of the facility, capable of being sealed to permit disinfection and contain a Class II or III safety cabinet or equivalent that exhausts through a high efficiency particulate absorption (HEPA) filter or equivalent to the outside air or the laboratory air extract system.

Personnel **accidentally exposed** to potentially infected material through spills, splashes, injections, cuts or abrasions should take immediate action. Eyes, if affected should be irrigated with water. For other areas, immediately wash the affected part with soap or detergent, apply an antiseptic solution and notify the hospital emergency VHF team. Such individuals as well as those with mucous membrane exposure to biologic fluids or unprotected inhalation of aerosolised material should then be considered as **high-risk** contacts and placed under surveillance.

Accidental spills of potentially contaminated material should be covered with absorbent paper towels, liberally covered with disinfectant and left to soak for 30 minutes before being wiped up. The area should be evacuated and secured. Following the removal of the initial material, the process should be repeated once again. Individuals must wear protective clothing, in carrying out this task. Disposable gloves, impermeable gowns and protective eyes ear should be placed in an autoclave bag and sterilized prior to disposal.

5. Treatment of suspected VHF patients

The treatment of the VHF patient is primarily supportive, the same as that provided to any other critically ill patient. Careful fluid management of patients is important to minimize the risks of pulmonary congestion and oedema.

The antiviral drug ribavirin should be used intravenously to treat all confirmed cases of Lassa fever. It is most effective when given **early** in the course of the disease. Ribavirin also has some effect in the treatment of Crimean-Congo VHF and its use in patients with confirmed Crimean-Congo VHF should be considered. Ribavirin does not appear to be indicated for filovirus infections i.e. Marburg and Ebola VHF. If a non-filovirus VHF is strongly suspected, treatment with ribavirin may begin while confirmation of the diagnosis is pending. (15, 16)

The dose and route of administration are recommended as follows: ribavirin 30 mg/kg loading dose intravenously, then 16 mg/kg intravenously every 6 hours for 4 days and then 8 mg/kg intravenously every 8 hours for 6 days. Total treatment duration is 10 days. (17)

6. Management of haemorrhagic fever patients

6.1. Hospitalisation of suspected VHF patients

At-risk patients:

At-risk patients may, if necessary, be admitted to a general hospital, to an infectious diseases or tropical diseases department. Patients in hospital should be managed with standard isolation in a single private room with barrier nursing (5, 18, 19) (i.e. good clinical practice, universal precautions and safe disposal procedures). Over 95% of seriously ill patients in the at-risk category will have malaria, and symptoms will resolve with appropriate anti-malarial treatment.

The **hospital emergency team** should be informed **before** the patient is admitted, or immediately after admission (Fig. 1). The local public health institution may also wish to be informed in certain circumstances, and the locally agreed procedures should be included in routine infection control policies. For patients in the at-risk category it is not anticipated that any public health action will be needed; statutory notification of suspected VHF is not recommended at this level. Standard procedures for transport of specimens should be used. Patients may be transported by ambulance without special precautions. Patient care should only be carried out by well trained individuals.

High-risk patients:

Any patient known or strongly suspected to be suffering from a VHF should be admitted to the designated high security infectious disease unit (HSIDU), an appropriate care facility. The minimum criteria for such facilities include:

- Negative air pressure room is recommended
- Intensive care unit (ICU) availability
- Patient treatment team: Experienced clinician, anaesthetist, microbiologist, haematologist and good contact to infectious disease specialist
- Appropriate laboratory facilities / experience (safety cabinet for handling the samples)
- Appropriate transport / ambulance for patient (drivers cabinet separated)

Clinical waste of patients in the **high-risk** category, or confirmed cases, should be adequately decontaminated (autoclaved).

6.2 Transport of suspected VHF patients

Transport of suspected VHF patients should only be performed **after** consultation of the HSIDU.

For inter- or intra-hospital transport, transportation should be done as early as possible in the course of the disease. The use of ambulance services for transportation should be based on the clinical condition of the patient in consultation with the medical experts in charge.

Transport personnel must be informed of the patient's condition prior to moving. Because of the possible risk of the contact to body fluids of the patient and the risk of transmission of the virus the staff should be properly protected (gloves, gowns, goggles, respirator masks etc.)

When a suspected VHF patient is being transferred by ambulance, appropriate preparation must take place. Having established the extent of the person's illness in terms of dependency, remove all unnecessary structural and medical equipment from the ambulance. (Appendix C, Figure 4) Competent, responsible personnel should be designated for the transfer. Ensure the ample supply of protective clothing for transfer personnel, stored if possible in the front cabin to avoid possible contamination. The driver should be physically separated from the patient to ensure safe driving conditions.

After transport in the ambulance all disposable items should be placed into autoclave bags and left with the appropriate personnel in the designated hospital for autoclaving. If there are items needing specialist decontamination (e.g. ventilators, i.v. infusion pumps) outer surfaces of such equipment should be first wiped with 1% hypochlorite solution and then washed with detergent and water. The exact type of decontamination will be determined by the piece of equipment in question and its intended use and the manufacturer's recommendations.

The disinfection of the ambulance should be performed either by fumigation with formaldehyde* or dispersion of 1% hypochlorite solution followed by thorough cleaning

* We strongly recommend a certified person for this procedure to avoid damage of the ambulance

with water and detergent. Protective clothing should be removed, disposed of in an autoclave bag and left with the appropriate personnel in the designated hospital. Wash hands and shower if possible.

Due to the difficulties to disinfect helicopters and aeroplanes transportation by air is **not** recommended. Also the proper protection of the pilot might not be possible (20). The transport of the patient in isolation-tents cannot be recommended since no correct intensive care treatment is virtually achievable (Appendix C, Figure 5).

6.3. Protective clothing for suspected VHF patients management

Standard Precautions (Good Clinical Practice) apply to all patients regardless of their infectious status. They apply to:

- blood
- all body fluid secretions and excretions
- non-intact skin
- mucous membranes

They include hand hygiene, use of gloves and protective clothing, environmental hygiene, safe disposal of waste and precautions for the prevention of sharps injuries. Standard Precautions are designed to reduce the risk of transmission of pathogens in hospitals (Appendix C, Figures 6 and 7)

Gloves:

Double gloves (a long-sleeved pair over a short-sleeved pair, the sleeve of the outer pair of gloves should go over the sleeves of the disposable suit) should be worn when handling any body substance, mucous membranes and non-intact skin of all patients and when handling any equipment or surfaces that have been contaminated with body secretions.

Hands should be washed and dried well, prior to donning gloves **and** after their removal with a suitable disinfectant. Gloves should be disposed of into designated autoclave bags before leaving the patients room.

Masks:

- With air supply and HEPA filter (Fig. 6 & 7)
- A particulate filter respirator mask with fluid shield protection should be worn on entering the room of a suspected VHF patient.
- **Surgical masks are insufficient !!!**

Masks are for single use only and should be disposed of in a designated autoclave bag **after** leaving the patients room.

Masks should not be worn around the neck and should be removed carefully to avoid contamination (21).

Hands must be washed and gloves replaced after touching masks.

Gowns: Long-sleeved disposable liquid-proof gowns should be worn, and be disposed of in a designated autoclave bag after leaving the patients room in the ante room.

Goggles: Disposable single-use goggles should be available and always be worn.

If disposable goggles are not available the goggles should be washed with detergent and water and wiped down with 1% hypochlorite solution or 70% alcohol, left for 2-3 minutes, rinsed off and left to dry.

Booties should be worn to prevent contamination of footwear. Better : rubberboots

After use, all protective clothing e.g. gloves, gowns, booties, protective eye wear etc. should be placed in an autoclave bag and sterilised prior to disposal.

6.4. Suspected VHF patient's room

A patient categorised as **at-risk** should be admitted to a single private room. An anteroom stocked with supplies, with facilities for hand washing and an area for donning protective equipment is useful.

A patient categorised as **high-risk** should be admitted to a private room preferably with negative air-pressure in a tertiary care facility. An anteroom stocked with supplies, with facilities for hand washing and an area for donning protective equipment is essential.

Gowns and gloves are recommended (and should be obligatory) for all persons who enter the room of a **at-risk** or **high-risk** patient. Fluid resistant masks and goggle or other eye protection are highly recommended. Blood splashes and aerosolisation of blood can occur when starting an Intra venous, taking blood for laboratory analysis or dropping a container containing blood. Extreme vigilance is required to prevent needle sticks or other sharp injuries. Parenteral exposure has been associated with a **high-risk** of transmission, a short incubation period and severe disease. Eliminate sharp instruments wherever possible and if feasible use a needle less intravenous system. The likelihood of staff exposure to blood or other body fluids and the opportunities for virus aerosolisation increase with the deterioration of the patient's condition.

Patient care equipment e.g. thermometers, blood pressure cuffs, stethoscopes, commodes etc. should be dedicated to the patient. Use disposable supplies whenever possible .

6.5. Clinical waste management for the suspected VHF patient

All waste generated in the course of caring for a suspected VHF patient including soiled linens and clothing, should be placed in autoclave bags for autoclaving prior to disposal, separately from the routine management of clinical waste in the hospital setting. All personnel involved in this process should be competent, specifically trained and wear full protective clothing.

Disposable bedpans should be used, the contents being solidified with high-absorbency gel and then autoclaved or incinerated.

If waste is generated in a hospital without suitable autoclaving facilities, the waste should be stored carefully in impermeable plastic bags and transferred to a designated institution with such facilities. Autoclave bags / impermeable plastic bags should be wiped with a 1% hypochlorite solution prior to leaving the patients room.

Personal protective equipment including gloves, booties, fluid-resistant masks with face shields/goggles and fluid-resistant gowns should be worn for cleaning up a spill of blood or other body fluid. Such spills should be covered with absorbent paper towels, liberally covered with 1% hypochlorite solution and left to soak for 30 minutes before being wiped up. Discard the towels into a plastic lined receptacle and place this in an autoclave bag for sterilisation prior to disposal. Following the removal of the initial material the area of contamination should again be liberally covered with 1% hypochlorite solution and left for 30 minutes before rinsing.

6.6. Infected bodies management

Staff wearing protective clothing (non-permeable apron, gown, rubber boots, gloves, face and eye protection) should place the body in a body bag, seal the bag, and spray or wipe it thoroughly with hypochlorite or other appropriate disinfectant before placing it in a robust coffin which should have sealed joints. It should then be kept, by special **prior** arrangement with mortuary staff, in a separate, identified, cold store unit to await prompt cremation or burial. The body bag should not be opened except by a designated person after consultation with the hospital emergency team and the public health institution.

7. Laboratory specimens transport

The following 3 principles should be observed for the transport of all patient specimens:
Should also refer to the relevant EU rules on the subject!!!!!

1. Place the specimen into the appropriate container **UN 6.2 category** (22, 23, 24) (Figure 3) and ensure that the lid is tightly screwed on. Disinfect the entire outside surface of each specimen container. Ensure that the patient details (patient label); patient name, hospital number, age, sex, specimen type, test required, ward, doctors name and contact number, are still legible. Sufficient absorbent material to absorb the entire contents in case of leakage must be inside of the container.

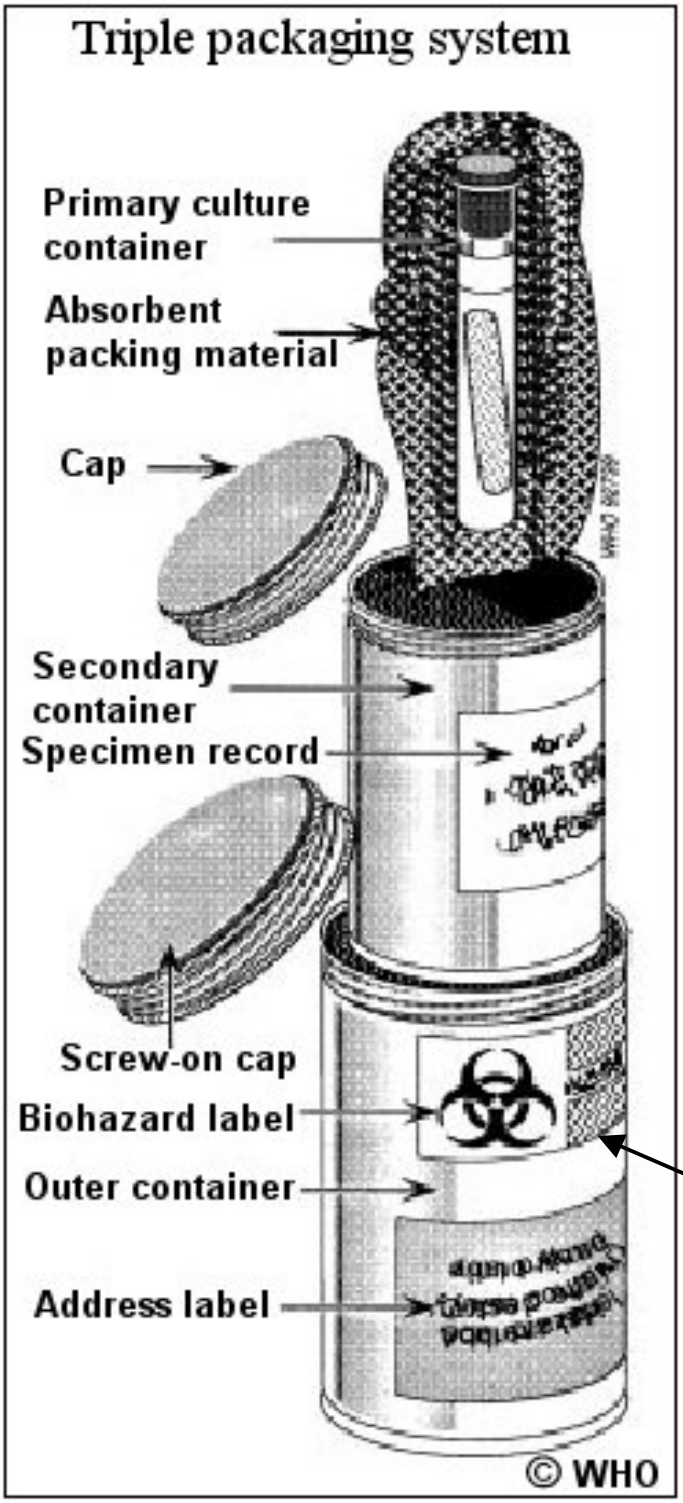
2. Each specimen should be packed separately so that each can be individually attended to.

3. If the journey to the laboratory is expected to be more than 1 hour, the specimens must be placed in a cold box with cold packs. The cold box must have a biohazard label and a warning that the box should not be opened except in the specified laboratory by a specified person.

The laboratory must be notified that samples are on route so that the designated personnel can receive the samples.

To preserve the life of the patient (suspected VHF in critical condition), general hospitals without immediate access to an HSID Laboratory may be obliged to conduct emergency tests to manage critically ill **high-risk** patients. In such circumstances, the advice of HSID specialists should be sought at an early stage, to agree on what emergency tests are required (none of which involves or allows replication of the virus), while minimising the risk to hospital and laboratory staff.
Emergency tests should be reduced to a minimum while expert advice is sought immediately and care should be taken to minimise risk for laboratory personnel.

Figure 3: Packaging system for infectious material



Packaging Specification Marking

Example: un **4H''/Class 6.2/94 GB/2470**

The packaging marking consists of:

- The United Nations packaging symbol
- Type of packaging
- The text "Class 6.2"
- The last two digits of the year of manufacture of the packaging
- State authority
- Manufacturer's code

8. Identification, management and surveillance of VHF contacts

A contact is defined as a person who has been exposed to an infected person or to infected persons secretions, excretions or tissues within 3 weeks of the patients onset of illness. Contacts may be subdivided into:

(a) **At-risk contacts** and

(b) **High-risk contacts**

All contact persons should be identified by responsible authorities e.g. Public Health institution or infection control team or hospital emergency team etc. (Figure 1)

At-risk contacts:

These are persons who have **not** had close personal contact with the ill patient. These may include persons on the same airplane, visitors to the patient's home etc. VHF's are not usually spread during this type of contact and no special surveillance of these contacts is indicated unless the index VHF patient had acute respiratory symptoms with intense sneezing and coughing. In such a situation a low risk contact should be place under surveillance as for **high-risk** contacts.

Occupational contact with patients in situations where the diagnosis has been considered and appropriate isolation precautions implemented are classified as at-risk contacts.

At-risk contacts should be told that the risk of infection is minimal. There is no need to restrict work or movement. They should be advised to contact their responsible Public Health institution in case they become unwell or develop a temperature > 38ºC within 21 days after their last possible exposure to infection.

High-risk contacts:

These are persons who have had more than casual contact with the VHF patient. They include persons living with the patient, nursing or serving the patient. High-risk contacts also include those who have kissed or had sexual intercourse with the patient, had direct contact with the patient's blood, urine or secretions or with clothing, bedding etc. soiled by the patients blood, urine or secretions.

Once the diagnosis is confirmed, high-risk contacts should be placed under surveillance. These individuals should record their temperature twice daily and report any temperature above 38°C or any symptom of illness to the public health officer responsible for surveillance. Those incubating the infection are in general not infectious before the onset of symptoms. Surveillance should be continued for 21 days after the person's last contact with the index patient. During surveillance there need be no restriction on work or movement within the country unless they suffer a rise in temperature above 38°C at which time they should be immediately isolated and treated as a potential VHF patient.

Occupational contact such as handling the patient's laboratory specimens before the recognition of the nature of the diagnosis or having had a needle stick or other penetrating injury involving contact with the patient's secretions, excretions, blood, tissues or other body fluids are classified as high-risk contacts.

The use of ribavirin for **post-exposure prophylaxis** for high-risk contacts of patients (Lassa fever, CCHF) has not been studied. Although experience is limited, post-exposure prophylaxis with ribavirin should be considered for high-risk contacts of those patients. The prophylactic regimen is ribavirin 500 mg by mouth every 6 hours for 7 days (17, 25).

9. Media relations in case of suspected VHF

It is anticipated that the diagnosis of a VHF in Europe will create significant publicity and considerable efforts will have to be made to ensure that the media and public obtain accurate, consistent and timely information.

It is suggested that an Information Committee composed of public health officials, microbiologists, the responsible clinician, the head of the virology reference laboratory, and the head of the hospital involved or representatives thereof will be responsible for all interactions with the media and public. There should be no release of information to, or discussions with, the media without the agreement of **all** parties.

It is suggested that an appointed spokesman relates to the media after discussion and agreement of all involved parties in order to avoid contradictory information.

We suggest regular press releases to keep the public and media as fully informed as possible without compromising any statutory responsibilities, legal requirements or patient confidentiality (Figure 1).

Appendix A: Assessment of a suspected VHF patient

Patient data		
Surname:	Forenames:	Date of Admission: Time:
Address:		Phone:
Nationality:	Passport-number:	
Date of birth:	Date of onset of Illness:	

Physician: Address:	Phone: Fax: Email

Please tick the relevant answers to the following questions (and give additional information)

1. Did the patient have contact (body fluids/tissue) with a confirmed or suspected VHF case less than 21 days before onset?

☐ No ☐ Unknown ☐ Yes, w. suspected case ☐ Yes, w. confirmed case

if yes, specify:_____
☐ Patient ☐ Dead body ☐ Body fluids/tissue Date of exposure:_____
Other relevant contact information:_____
_____

2. Was the patient in a VHF endemic area less than 21 days before onset?

☐ No ☐ Unknown ☐ Yes if yes, specify:_____

Country:_____ Place(s) of residence:_____
Date of staying: from_____ to_____
Staying in rural areas: ☐ No ☐ Yes
Travelling means: ☐ Holiday ☐ Business ☐ other:_____
Accommodation: ☐ Hotel ☐ Camping ☐ other:_____
Outdoor activity: ☐ No ☐ Yes type of outdoor activities:_____
Contact with animals: ☐ No ☐ Yes nature of contacts with animals:_____
specify_____date of exposure:_____

Vaccination: ☐ Polio ☐ Jap. Encephalitis ☐ TBE ☐ Rabies ☐ HAV
☐ HBV ☐ Yellow Fever ☐ other:_____

Malaria prophylaxis: ☐ No ☐ Unknown ☐ Yes:_____(specify)
Other pharmaceutical treatment/drugs:_____

Medical care during the stay: ☐ No ☐ Unknown ☐ Yes if yes:
Name, address, phone of medical care facility:_____

_____ date of medical care:_____

Other relevant epidemiological information:

3. Signs/Symptoms:

Symptoms	**date of onset:**	**Symptoms**	**date of onset:**
☐ Fever ____°C	_____	☐ Myalgia	_____
☐ Headache	_____	☐ Pharyngitis	_____
☐ Diarrhoea	_____	☐ Cutaneous bleeding	_____
☐ Red conjunctivitis	_____	☐ Jaundice	_____
☐ Gastrointestinal bleeding	_____	☐ Hypovolemic shock	_____
☐ Vomiting	_____	☐ Oedema	_____
☐ Morbilliform rash	_____	☐ Retrosternal/abdominal pain	_____
☐ Proteinuria	_____	☐ Thrombocytopenia	_____
☐ Dark urine	_____	☐ Elevated serum transaminases	_____
☐ Lymphopenia	_____		
☐ Multiple organ failure	_____	☐ Death	_____

Other relevant clinical information: _____

4. Contacts since onset of illness:

Had the patient symptoms/ was ill during stay in endemic area? ☐ No ☐ Unknown ☐ Yes
if unknown or yes: list of contact persons (name, address, phone):_____(as appendix)
Date of travel from endemic area:_____ Flight No.:_____ Airline:_____
Intermediate Stopping Point:_____
Had the patient symptoms/ was ill during journey? ☐ No ☐ Unknown ☐ Yes
Had the patient symptoms/ was ill during stopover? ☐ No ☐ Unknown ☐ Yes
if unknown or yes: list of contact persons (name, address, phone):_____(as appendix)
Contact persons since onset of illness before hospitalisation: ☐ None ☐ Relatives, Friends
☐ Physician, Nurse ☐ Ambulance staff ☐ Laboratory staff ☐ Other:_____
_____
list of contact persons (name, address, phone):_____(as appendix)
Contacts during hospitalisation: ☐ Hospital staff ☐ Laboratory staff ☐ Physician, Nurse
list of contact persons (name, address, phone):_____(as appendix)
Other relevant contact information:_____

5. Which laboratory specimens have been taken since onset of illness?

☐ Samples for hospital laboratory dates of sampling:_____
☐ Samples for virology diagnostic laboratory dates of sampling:_____
☐ First malaria test date of sampling:_____ result:_____
☐ Second malaria test date of sampling:_____ result:_____

Diagnostic laboratory:
Address: Phone:
Fax:
Email:
Results: ☐ Malaria ☐ VHF:_____ ☐ Other pathogen:_____

Public health institution:
Address: Phone:
Fax:
Email:
Talking to:_____ Date:_____ Time:_____
Agreement about further actions:_____

Other information:

Appendix B: Malaria

Infection with any of four different species of *Plasmodia* (*P. falciparum, P. vivax, P. ovale*, and *P. malariae*), causing periodic paroxysms of chills, fever and sweating, anemia, and splenomegaly.

Malaria is endemic in Africa and most tropic areas in the word: South and Southeast Asia, Central America, and the northern part of South America.

The incubation period varies from 10 to 20 days for *P. vivax*, 12 to 14 days *for P. falciparum*, and about 1 month for *P. malariae*. However, some strains of *P. vivax* in temperate climates may not cause clinical illness until a year after infection. Malaria is often atypical in a person who has been taking chemoprophylaxis. The incubation period may extend weeks after the drug is stopped. Instead of periodic chills and fever, the person may have headache, backache, and irregular fever; parasites may be difficult to find in blood samples. Manifestations common to all forms of malaria include anemia, jaundice, splenomegaly, hepatomegaly, and the malarial paroxysm (rigor) that coincides with the release of merozoites from ruptured red blood cells. A paroxysm starts with malaise, abrupt chills and fever rising to 39 to 41° C, rapid and thready pulse, polyuria, and increasing headache and nausea. Next, fever falls and profuse sweating occurs over a period of 2 to 3 hours. Malarial paroxysms typically occur about every 48 hours *with P. vivax, P. falciparum*, and *P. ovale* and about every 72 hours with *P. malariae*. These intervals are not rigid: paroxysms may occur daily in mixed infections or early in the course of infection (especially with *P. falciparum*).

Cases in Europe occur in persons infected abroad (imported malaria); a small number result from blood transfusions. This also leads to several imported cases in European countries, for example 20 death cause by malaria each year from 931 / 1008 imported cases for the year 1998 and 1999 in Germany. Among these are also cases of malaria communicated by mosquitoes which were imported to Europe by planes. This is known as “airport malaria” and usually infects people working at the airport or living close to it.

Appendix C : Figures

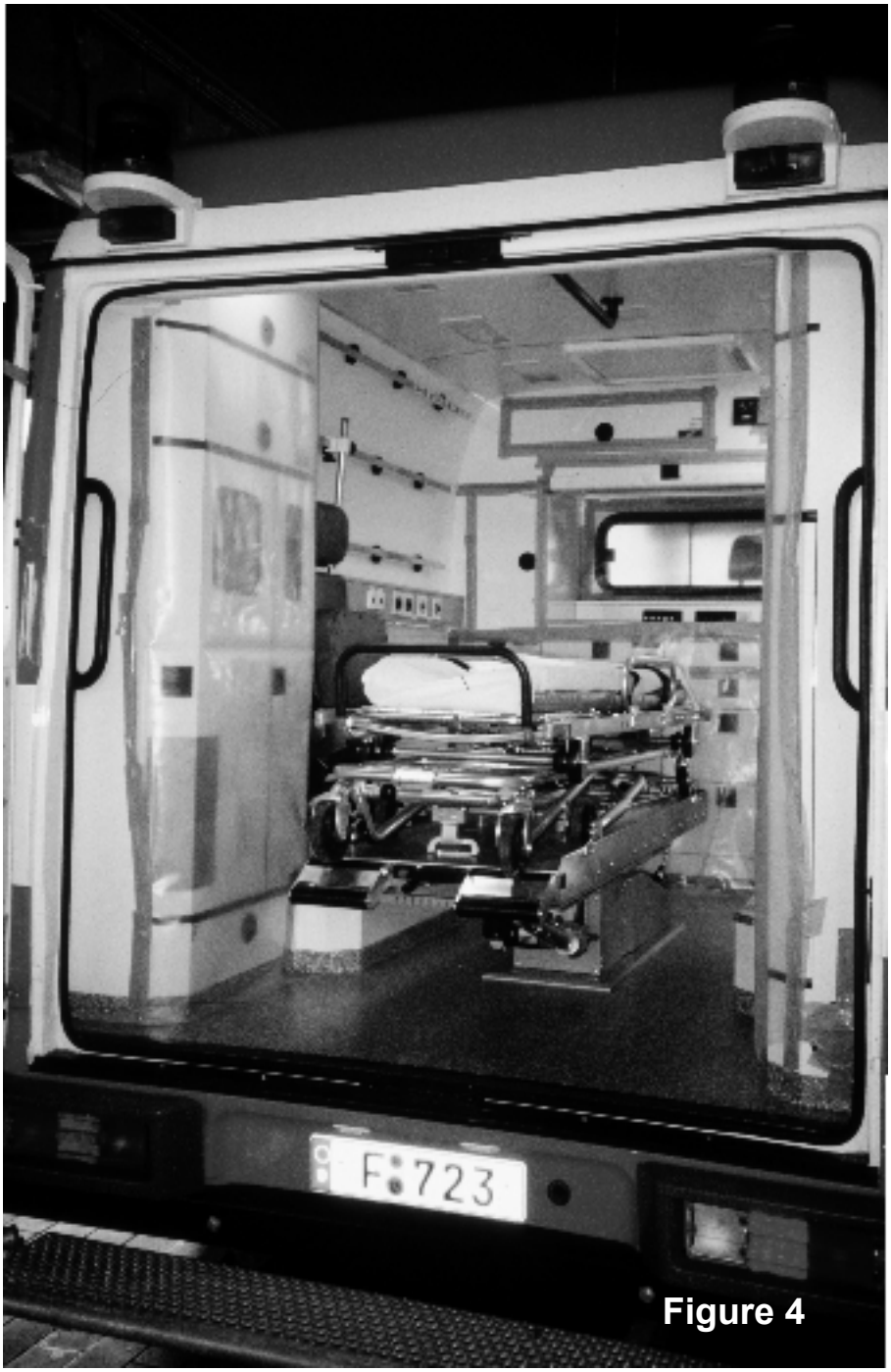


Figure 4: Ambulance medical equipment sealed or removed.
Figure 5: Transport incubator not recommended for transport for an acute VHF patient
Figure 6: Protective cloth for a VHF care person, mask with air supply with HEPA filter
Figure 7: Protective cloth for VHF care person, suit with mask and air supply with HEPA filter

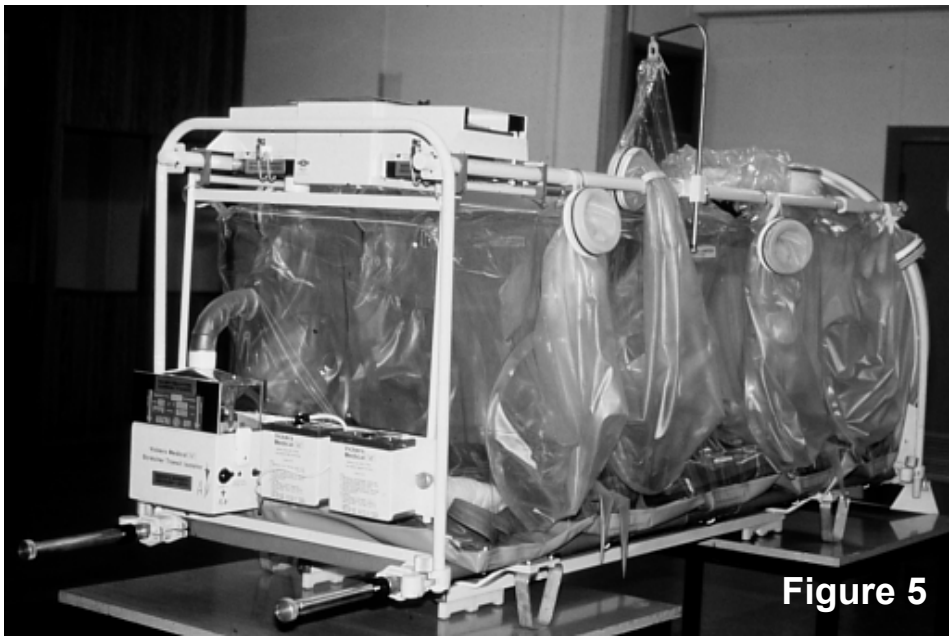


Figure 5

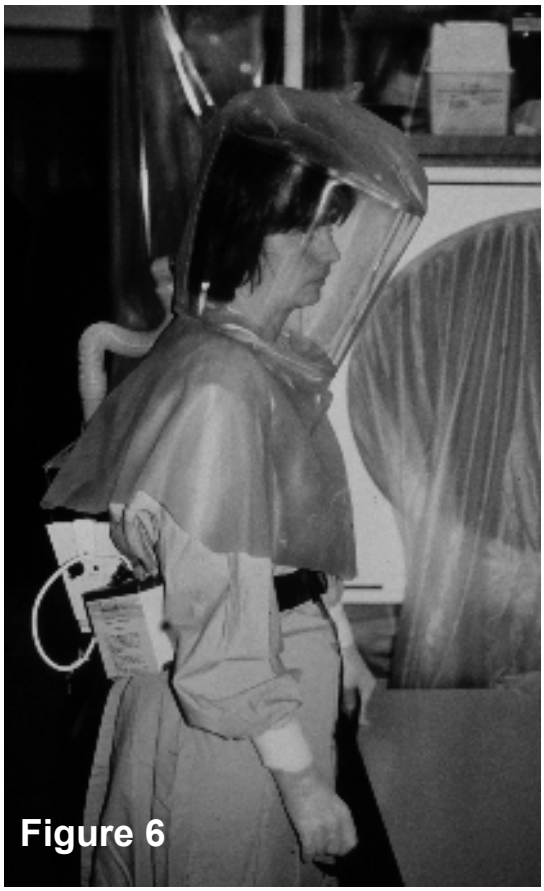


Figure 6


Figure 7

(all pictures taken by R. Fock / M. Niedrig, Berlin, Germany)

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