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Viral Haemorrhagic Fevers: Frequently Asked Questions

1. What is viral haemorrhagic fever?

Viral hemorrhagic fevers, or VHFs, are a group of diseases with symptoms that vary but frequently include 1) Fever 2) Fatigue, weakness, or malaise 3) Dizziness 4) Aches in the muscles, bones, or joints and headache 5) Vomiting and nausea and diarrhea and 6) Bleeding or hemorrhaging as a result of damage to the walls of tiny blood vessels, which causes them to leak and impairs the blood's capacity to clot. It can progress to a life-threatening condition that affects numerous organ systems, destroys the cardiovascular system as a whole, and diminishes the body's ability to function on its own.

Viral hemorrhagic fevers are caused by viruses from one of six RNA virus families: belonging to the Bunyavirales order (*Nairoviridae*, *Penuiviridae*, *Arenaviridae*, *Hantaviridae*), the *Filoviridae*, and the *Flaviviridae*. Crimean-Congo haemorrhagic fever (CCHF) and Rift Valley fever (RVF) viruses of the Nairovirus and Phenuivirus families respectively are endemic to South Africa, while some viruses, like the Ebola virus disease, Marburg fever (Filovirus family), and Lassa fever (Arenavirus family), are not found in South Africa, they can be brought in by travelers leaving other sub-Saharan African countries, primarily from West and Central Africa. Annual reports of hantavirus cases resulting in hantavirus pulmonary syndrome (HPS) are made in the US and Canada; the cumulative total for the US between 1993 and 2020 was 821. Outside of North America, reports of HPS have been made from Argentina, Bolivia, Brazil, Chile, Ecuador, Paraguay, Panama, Uruguay, and Venezuela, as well as from isolated individuals and small clusters. The majority of human cases of hanta virus-induced renal syndrome (HFRS) are found in China, while there are also cases in Kazakhstan, Russia, India, Iran, Turkey, and a few other European and South-East Asian countries. There haven't been any endemic human cases of the hantavirus, despite serological evidence from Africa and cases that have been brought into South Africa by travelers. Tropical and subtropical regions of South America and Africa are home to the yellow fever virus (Flavivirus family). Outbreaks of yellow fever are emerging and reemerging due to low immunization in these regions. Due to the availability of an effective vaccination against yellow fever and the requirement for re-entry into countries that are not endemic like South Africa, yellow fever is an extremely infrequent cause of illness among travelers. Almost 4 billion people, or nearly half of the world's population, live in countries where dengue outbreaks are common. Up to 400 million people can contract the dengue viruses (Flavivirus family) annually. About 100 million people have infections, and 40,000 of those cases result in severe dengue deaths. 40000 suspected cases were reported during a significant outbreak in Durban, South Africa, in 1927. Although the disease is not thought to be endemic, it is commonly seen in visitors going into South Africa. When people come into contact with infected animals or insects (mosquitoes or ticks mainly), they can contract VHF viruses. Person-to-person transmission of many VHFs can then persist, frequently through direct contact or in healthcare settings without appropriate infection control protocols. VHF outbreaks happen occasionally and infrequently, and it can be challenging to forecast when they will happen. When the animal host is unknown or

difficult to control (like rodents or ticks), prevention is more challenging. Certain VHFs result in high case-fatality rates in underdeveloped areas since there are few effective vaccinations or medication treatments available. As a result, some VHFs are treated with just minimal medical care, which is frequently insufficient to stop the virus's transmission and save lives.

2. Who can get viral haemorrhagic fever?

People who live in or travel to an area where a particular VHF is endemic and are exposed to vectors, either direct animal sources or via the arthropod-borne route, of VHF or persons infected with VHF have an increased risk of acquiring VHF. Human cases or outbreaks of VHF occur sporadically and irregularly, and are hard to predict.

3. Where does viral haemorrhagic fever occur in South Africa?

VHFs are rare disease; CCHF is endemic South Africa but fewer than ten cases of CCHF per year are reported in South Africa. CCHF cases occur in drier areas of South Africa such as the Northern Cape and Free State Provinces, in the areas where the ticks are found. Outbreaks of mosquito-borne and zoonotic RVF occur in South Africa on an irregular basis; the most recent epidemic was extensive and occurred from 2008 to 2011, and a solitary outbreak occurred on an isolated farm in central South Africa, where outbreaks have historically been concentrated. Importation of Marburg and Ebola haemorrhagic fever into South Africa occurred in 1986 and 1996 from Zimbabwe and Democratic Republic of Congo, respectively. Lujo virus, a new VHF virus was identified during a nosocomial outbreak, imported into Johannesburg, South Africa from Lusaka, Zambia in 2008. Five people were infected of which four died (80%). Travelers from West Africa are routinely tested for Lassa virus, and two infections have been confirmed, both from Nigeria, in 2007 and 2022, with no secondary cases. Serological evidence (presence of specific antibodies in the blood) of Hantavirus infection in patients has been reported in single studies across Africa and a first case of hantavirus was detected in 2022 in traveler that had visited South Africa from Croatia, Europe.

4. How is viral haemorrhagic fever transmitted?

VHFs are zoonotic diseases (spread from animal hosts to humans). Bats are suspected as the natural reservoirs of Marburg and possibly Ebola viruses and rodents are reservoirs for Lassa and hanta fever. The hosts of the CCHF or RVF viruses include a wide range of wild and domestic animals such as cattle, sheep and goats with arthropod-borne spead, primarily *Aedes* and *Culex* species mosquitoes. The reservoir animal host are unknown for RVF virus but ticks are the reservoirs and vectors for CCHF. Birds are resistant to infection, but ostriches are susceptible and may show a high prevalence of infection in endemic areas. Humans may acquire infection when they come into close contact with live animal host, animal carcasses during slaughtering or rodent droppings in the case of Arenavirus family. Ticks of the genus *Hyalomma* are the principal vector of CCHF. Lassa, Ebola, Marburg and CCHF viruses can spread from person-to-person through close contact with symptomatic patients or contaminated body fluids and are not arthropod-borne. Yellow fever and dengue viruses can only be transmitted through mosquito bites like for example *Aedes aegypti*.

5. How does viral haemorrhagic fever affect animals?

Ebola and Marburg infection in non-human primates cause severe, often fatal haemorrhagic fever. Bats are asymptomatic. Clinical signs of infection in animals may include fever, anorexia, vomiting, diarrhoea, splenomegaly, weight loss, hair loss, emaciation, dyspnoea, a skin rash and bleeding from the nostrils. Haemorrhages can occur from any organ which may include petechiae, bleeding into the gastrointestinal tract and mucous membranes. Non-human primates can experience symptoms of yellow fever and dengue fever. CCHF only cause disease in humans, and does not affect livestock or ostriches except for short-lived viraemia, and ground feeding birds, despite high exposure in cattle based on seroprevalence studies. RVF causes abortion storms in livestock and high mortality primarily in sheep. Rodents and arthropod vectors, such as mosquitoes and ticks, are unaffected by the viruses that cause Lassa fever, hantavirus, CCHF, dengue, and yellow fever.

6. What are the signs and symptoms of viral haemorrhagic fever in humans?

VHF symptoms differ according on the disease. They frequently include: early in the illness:
1) Fever 2) Fatigue (extreme tiredness), weakness, or malaise 3) Dizziness, 4) Muscle, bone, or joint pain, as well as headache. A petechial rash (blood spots beneath the skin) may appear.
VHFs can also cause: in severe circumstances 5) Severe nausea, vomiting, and diarrhea, 6) Bleeding or hemorrhaging: Patients may experience bleeding from the nose, eyes, gums, or vagina. Internal organ bleeding may occur, leading in vomiting blood and bloody diarrhea. Patients may bleed from the sites of venipuncture (during blood collection, drip insertion, and so on). Grave illness patients may exhibit shock symptoms such as hypotension, kidney failure, dyspepsia, and nervous system dysfunction,

Disease	Signs and symptoms	Additional information
Ebola Virus Disease	Fever, headache, muscle pain, fatigue, weakness, diarrhea, vomiting, abdominal pain, conjunctival injection, chest pain, hemorrhage	Ebola: Signs and Symptoms
Marburg Virus Disease	Fever, chills headache, muscle pain, maculopapular, rash, nausea, vomiting, chest pain, sore throat, abdominal pain, diarrhea, jaundice, hemorrhage	Marburg hemorrhagic fever (Marburg HF): Signs and Symptoms
Lassa Fever	Fever, nausea, vomiting, diarrhea, retrosternal chest pain, sore throat, muscle pain, enlarged cervical lymph nodes, abdominal pain, bleeding, maculopapular rash, conjunctivitis, headache	Lassa Fever: Signs and Symptoms
Crimean-Congo Hemorrhagic Fever	Fever, headache, back pain, join pain, abdominal pain, vomiting, conjunctival injection, facial flushing, petechial rash, jaundice, bleeding, photophobia, sore throat	Crimean-Congo Hemorrhagic Fever: Signs and Symptoms

including chest pain, neck pain, dyspnea, delirium, seizures, and coma.

Table 1: Signs and Symptoms of More Common VHFs: Ebola Virus Disease, Marburg Virus Disease, Lassa Fever and Crimean-Congo Hemorrhagic Fever

(Source: Assessing Viral Hemorrhagic Fever Risk in a Returning Traveler | Viral Hemorrhagic Fevers (VHFs) | CDC)

7. How is viral haemorrhagic fever diagnosed?

Typical findings of full blood count tests in VHF patients include thrombocytopenia (low platelets count), leucopenia (a low white cell counts) or normal white cell counts and raised liver enzymes (AST and ALT). Specific laboratory tests include serological screening for IgG and IgM antibodies. PCR detection of viral genomic material (RNA) or virus isolation can be done on blood (molecular diagnostic tests). Using particular primers, a reverse transcription polymerase chain reaction (PCR) assay amplifies DNA or RNA sequences to detect viruses. Fluorescent probes are then used to find the amplified product. Antigen detection is particularly useful in the early acute stage of illness. During the first seven days of illness, patients exhibiting symptoms typical of dengue might undergo testing using molecular and serologic diagnostic assays. A diagnosis of is confirmed if a PCR or antigen test yields positive results. These tests are performed under biosafety level 4 conditions (i.e. maximum bio-containment). Only use serologic diagnostic testing after the first seven days of illness. If a serology test produces positive IgM antibody reactions, the diagnosis of CCHF, LSF, EVD, or MHF, hantavirus, is confirmed. One of the limitations of dengue serologic tests is cross reactivity. Dengue viruses can cross-react with other flaviviruses, such as West Nile, Japanese encephalitis, Zika, and yellow fever, as demonstrated by serologic testing conducted to identify antibodies against them. Patients who reside in or have been to places where other flaviviruses co-circulate need to take this limitation into account. Presumptive dengue virus infection (probable case) is the laboratory diagnosis made in the event that the PCR test yields a negative result and the IgM antibody test is positive. On the other hand, laboratory diagnosis is confirmed as well if a fourfold increase in antibody titre is detected between acute and convalescent samples. Serum, plasma, whole blood are the samples used for testing but when a suspect patient exhibits clinical signs of the central nervous system, such as encephalopathy or aseptic meningitis, testing of the cerebrospinal fluid is recommended. NICD can only accept blood samples for VHF testing with prior consultation with NICD medical officer and receiving laboratory using NICD hotline for Clinical Advice: 0800 212 552.

8. How is viral haemorrhagic fever treated?

Treatment of VHF is supportive only as specific treatment is not available. For hemorrhagic fever caused by arenaviruses or bunyaviruses, such as Lassa fever, Rift Valley fever, and Crimean-Congo hemorrhagic fever, the Merck Manual recommends ribavirin, an antiviral drug. In vitro susceptibility findings for this and other Bunyaviruses support the appropriate use of ribavirin to treat the disease and prevent infection in high-risk contacts. It's crucial to remember that ribavirin treatment for Bunyavirus infections is currently still being studied and debated. Treatment with convalescent-phase plasma has been used to treat Ebola virus patients. VHF patients might require fluids to help keep the electrolyte balance in balance to prevent dehydration. Dialysis of the kidneys may be beneficial for some patients with severe

illness. VHF patients are managed under strict infection prevention and control protocols that include isolation.

9. How is viral haemorrhagic fever prevented?

Vaccinations exist for only a few types. On December 19, 2019, the U.S. Food and Drug Administration (FDA) authorized the rVSV-ZEBOV (also known as Ervebo®) Ebola vaccine. Given as a single dose, this vaccine has been shown to be safe and effective only against the Zaire ebolavirus, which is the source of the worst and most widespread Ebola epidemics to date. 2019 saw the use, as part of a research protocol, of a two-dose vaccination regimen of a separate vaccine that was also intended to protect against the Zaire ebolavirus species of Ebola during an outbreak in the Democratic Republic of the Congo. Ad26.ZEBOV and MVA-BN-Filo are the two vaccine components used in the two doses of this regimen; an initial dose and a "booster" dose are administered 56 days apart. This vaccination has not yet been approved by the FDA. For those who are 9 months of age or older and who are visiting or residing in regions of Africa and South America where the yellow fever virus is present, vaccination against the virus is recommended and is a visa requirement for entry. Children between the ages of 9 and 16 who have had a prior dengue virus infection verified by a laboratory and who reside in dengue-endemic (often or continuously occurring) areas are eligible to receive a new dengue vaccination. Certain U.S. territories and states with free associations are examples of endemic areas. Travelers who are traveling but do not reside in an area where dengue fever is prevalent are not eligible to receive the vaccine. Outbreaks of VHF are associated with transmission via contact with blood, bodily fluids and tissues of infected persons and are often associated with hospital setting, were healthcare workers are particular at risk. Strict infection control procedures in health care settings are paramount for containment of VHF outbreaks. Prevention measure includes avoiding contact with animal reservoirs, vectors for the diseases, infected animal and human blood or tissues, tick bites, mosquito bites, contact with rodent urine and faeces.

10. Where can I find more information?

Medical/clinical related queries: NICD Hotline +27 0800212552 (for use by healthcare professionals only)

Surveillance and Response:

Suspected VHF is a notifiable disease (ICD-10 A96). All laboratory confirmation in South Africa is performed by the Centre for Emerging and Zoonotic Diseases, NICD-NHLS under appropriate biosafety conditions. Guidelines are available on the NICD website at www.nicd.ac.za on the 'Diseases A-Z' tab.

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