2. Clinical Assessment, Risk Categorisation and Management in Acute and Primary Care settings

Contents

Key Points

- Use the VHF Clinical Risk Assessment Form to determine the risk of VHF infection in anyone meeting both the clinical and travel history criteria for VHF at patient triage.
- Summary algorithms for risk assessment and transfer processes are as follows:
  - Acute hospital setting
  - Ambulance service
  - Primary Care
- The patient's risk category and symptoms determine the infection control precautions and the management of the patient.
- The patient's risk category can change depending on the patient's symptoms and/or the results of diagnostic tests. A patient with VHF infection can deteriorate rapidly.
- The risk of a VHF case in Ireland is **very low**.
- Those infected with VHF can only spread the virus to others once they have developed symptoms. In the early stages these include **fever, headache, joint and muscle pain, sore throat, and intense muscle weakness**.
- VHF is **NOT transmitted through normal social contact** (such as shaking hands or sitting next to someone), especially in the early stages of the disease
- VHF is **NOT transmitted when Personal Protective Distance (>1 metre)** is maintained (apart from handshaking etc.)
- **Immediate HAND HYGIENE** is an extremely important infection control measure; VHF tend not to be robust viruses, and can be readily **inactivated, by soap and water or by alcohol.**
- Those patients that are at highest risk of onward transmission are those who are bleeding, vomiting and coughing.
- It is important to remember that transmission of VHF from person to person is only through **DIRECT CONTACT** with the blood or body fluids of a symptomatic infected person. The infectivity of VHF increases with duration of illness; it tends to be less infectious in the early phases of illness.
- National waste management guidance should be followed

2.1 Introduction

Patients occasionally present with fever and travel history to a country where VHF is endemic. During the early stages of illness (first three to seven days), patients present with influenza-like symptoms.

The possibility of VHF should be considered in any sick traveller from an endemic country, who has no clear features of an alternative diagnosis.

The questions in the VHF Clinical Risk Assessment Form are designed to thoroughly assess the risk of VHF infection.

2.2 Clinical presentation of VHF by specific VHF type

Initial signs and symptoms are usually systemic, non-specific, and consistent with an "influenza-like" illness that lasts up to seven days. The incubation period ranges from 1-21 days. Clinical features of individual VHFs are summarised in Tables 2-5.

Table 1. General clinical presentation of VHFs

Symptoms	Early Signs	LATE SIGNS
• marked fever • dizziness • myalgia • arthralgia • fatigue • anorexia • diarrhoea • exhaustion	• fever • hypotension • relative bradycardia • tachypnoea • conjunctivitis • pharyngitis • cutaneous flushing or a skin rash.	• progressive haemorrhagic diathesis, such as petechia, • mucous membrane and conjunctival haemorrhage • haematuria • haematemesis • melaena • disseminated intravascular coagulation and circulatory shock • central nervous system dysfunction may be present and manifested by delirium, convulsions, cerebellar signs, or coma

Table 2. Clinical presentation of Crimean-Congo haemorrhagic fever

Disease (virus)	**Crimean-Congo haemorrhagic fever** (Crimean-Congo haemorrhagic fever virus)
Vector/Host	*Ixodid* ticks of *Hyalomma* genus
Mode of transmission	Direct contact with blood or other infected tissues from livestock, or via tick bite, or nosocomial - direct contact with infected patients blood or body fluids, or through contaminated medical equipment or supplies
Incubation period	Following tick bite: 1-3 days (max 9). Following contact with livestock, blood, or tissues: 5-6 days (max 13)
Risk groups	Farmers, vets, abattoir workers. (CCHF doesn't survive cooking); healthcare workers without PPE, outdoor activities
Clinical features	Sudden onset. Fever, myalgia, dizziness, neck pain and stiffness, backache, headache, sore eyes and photophobia. Nausea, vomiting, sore throat early on, +/- diarrhoea and abdominal pain. Over next few days, may develop sharp mood swings, confusion and aggression. After 2-4 days changes to sleepiness, depression and lassitude, abdominal pain may localise to Right Upper Quadrant, with hepatomegaly. May have tachycardia, lymphadenopathy, petechial rash on mucosa, palate and on skin. Echymoses may develop, beginning on day 4 or 5 and melaena, haematuria, epistaxis etc. Hepatitis. If severely ill, may develop hepatorenal failure
Duration of infectivity	Infectious when symptomatic – duration of infectivity not well established
Mortality rate	10-50%
Treatment	Supportive and ribavirin (both oral and IV) - no Randomised Control Trials, so evidence for use not strong

Table 3. Clinical presentation of Lassa fever

Disease (virus)	**Lassa fever** (Lassa fever virus**)**
Vector/Host	Rodents of genus Mastomys ("multimammate rat") shed virus in urine and faeces
Mode of transmission	Direct exposure to excreta of infected mastomys - or direct contact with blood, urine, faeces or other bodily secretions of person with Lassa fever. Sexual transmission has been reported. No epidemiological evidence for airborne spread.
Incubation period	6-21 days - majority present within 7-14 days after exposure
Risk groups	Those who live or visit areas with large populations of infected mastomys rodents
Clinical features	Gradual onset. 80% are asymptomatic, the remaining have severe multi-system disease. Fever, general weakness, malaise. After few days, headache, sore throat, muscle pain, chest pain, nausea, vomiting, diarrhoea, cough and abdominal pain. Severe cases may have facial oedema, pleural effusions, bleeding from mouth, nose, vagina or GI tract, and low blood pressure. Shock, seizures, tremor, disorientation and coma may be seen in late stages. Deafness in 25-30% - of whom 50% recover in 1-3 months. Transient hair loss and gait disturbance during recovery.
Duration of infectivity	Urine up to 32 days; Semen up to 3 months
Mortality rate	1% of cases overall, 15-20% of hospitalised cases, usually within 14 days of onset symptoms. Very severe in late pregnancy, with 80-95%% foetal loss in 3rd trimester

Treatment	Ribavirin, if given early on

Table 4. Clinical presentation of Ebola haemorrhagic fever

Disease (virus)	**Ebola haemorrhagic fever** (Ebola virus, 4 distinct species: Zaire, Sudan, Cote d'Ivoire and Bundibugyo)
Vector/Host	African fruit bat
Mode of transmission	Close contact with blood or other body fluids, including semen of ill patient (infectiousness increases with severity of illness), burial ceremonies with direct contact with body, contaminated injection equipment, or needle stick injuries. Contact with infected animals e.g. African fruit bat and primates.
Incubation period	2-21 days (mean 4-10)
Risk groups	Mostly in adults. Lab workers working with primates
Clinical features	Sudden onset. Fever, intense weakness, muscle pain, headache and sore throat. Followed by vomiting, diarrhoea, rash, impaired renal and liver function, and in some cases, hiccups, internal and external bleeding.
Duration of infectivity	Liver & fluid of anterior eye chamber up to 2 months; Semen up to 12 weeks
Mortality rate	50-90%
Treatment	Supportive only

Table 5. Clinical presentation of Marburg haemorrhagic fever

Disease (virus)	**Marburg haemorrhagic fever** (Marburg virus)
Vector/Host	African fruit bat
Mode of transmission	Close contact with blood or other body fluids, including semen of ill patient (infectiousness increases with severity of illness), burial ceremonies with direct contact with body, contaminated injection equipment, or needle stick injuries. Contact with infected animals e.g. African fruit bat and primates.
Incubation period	3-10 days
Risk groups	Mostly in adults. Lab workers working with primates
Clinical features	Sudden onset. Severe headache and severe malaise, muscle aches and pains. Fever on day 1, followed by progressive and rapid debilitation. Severe watery diarrhoea, abdominal pain and cramping, nausea and vomiting on day 3. A rash may occur. Diarrhoea persists for a week; patients look “ghost-like” with drawn features, deep-set eyes, and extreme lethargy. Haemorrhagic manifestations on day 5 – 7. CNS involvement can lead to confusion, irritability and aggression. Death occurs on day 8-9.
Duration of infectivity	Liver & fluid of anterior eye chamber up to 2 months; Semen up to 12 weeks
Mortality rate	83 – 88% in 2 outbreaks. CDC report a Case Fatality Rate of 23-25%
Treatment	Supportive only

2.3 Differential diagnosis

The differential diagnosis includes a wide array of both infectious and non-infectious aetiologies. In most circumstances the diagnosis will be one of the more common infectious diseases summarised in Table 6 below. Of these, malaria, followed by typhoid are the most likely.

Table 6. Differential diagnosis of viral haemorrhagic fever

Bacterial	**Typhoid**; Pyelonephritis; Pneumonia; Sepsis; Meningococcal disease; Leptospirosis; Shigellosis; Systemic plague; Systemic tularaemia; Rheumatic fever; Non typhoidal salmonellosis; Toxic shock syndrome, Haemorrhagic E. Coli
Helminthic	Schistosomiasis; Katayama syndrome; (Disseminated) Strongyloidiasis?
Viral	Yellow fever; Rift Valley Fever; Infectious mononucleosis; Dengue; Hepatitis A; HIV infection; Fulminant Hepatitis; Systemic herpes infection; Systemic CMV, EBV; Varicella zoster infection; Hantavirus pulmonary syndrome; Haemorrhagic smallpox
Rickettsial	Typhus; Q fever; Tick borne rickettsiosis
Protozoal	**Malaria**; Amoebic liver abscess; Trypanosomiasis

*Diagnosis in **bold** are the most likely alternate diagnosis.

Non-infectious disease causes should also be considered, as disseminated intravascular coagulation could be mistaken for acute leukaemia, lupus erythematosis, idiopathic or thrombotic thrombocytopaenic purpura, and Haemolytic Uraemic Syndrome.

2.4 Risk assessment of sick travellers for potential VHF

Based on the completed VHF Clinical Risk Assessment Form (signs, symptoms and exposure), either the diagnosis will be definitively excluded, or the patient will be categorised into one of two categories as follows:

a) **High risk exposure category :** If the answer is YES to any of the exposure assessment questions below, in conjunction with fever or a history of fever, and travel, there is a high possibility of VHF, and the person is categorised as *High Risk*.

b) **Low risk exposure category:** If the answer is NO to ALL of the exposure assessment questions, and the patient meets the clinical and travel history criteria, then VHF is still a possibility, but the patient is labelled '**at risk'** and initially a malaria screen is done, as this is more likely.

The categorisation of the patient into ***low*** or **high risk** is a key step which determines the infection control precautions required, further investigations to be carried out, whether the patient will be considered for immediate transfer to the National Isolation Unit at the Mater Misericordiae

University Hospital, and whether the relevant Area Director of Public Health/Medical Officer of Health (DPH/MOH) needs to be informed.

For definitions for contact exposure categories see Public Health Management of cases and contacts of VHF.

Note: The patient's risk category can change depending on the patient's symptoms and/or the results of diagnostic tests. A patient with VHF infection can deteriorate rapidly.

Exposure assessment – key questions

Has the patient:

1. Lived or worked in basic rural conditions where Lassa fever or CCHF is endemic?
2. Travelled to any area where a VHF outbreak has recently occurred (in the last 6 months?
3. Received a tick bite and or/crushed a tick with their bare hands and/or travelled to rural environments where contact with livestock or ticks is possible, in a CCHF endemic area?
4. Travelled to a rural environment where contact with livestock or ticks is possible in a CCHF endemic area?
5. Visited mines or caves in a VHF endemic area?
6. Been in an area contaminated by bats?
7. Eaten food which could have been contaminated by rats in a Lassa fever endemic area?
8. Swept/cleaned dust which could have been contaminated by rats in a Lassa fever endemic area?
9. Handled or butchered dead primates or been involved in drying, smoking their meat or consuming their meat in a VHF endemic area?
10. Come into contact with the body fluids of an individual or animal (live or dead) known or strongly suspected of having VHF e.g. during routine patient care, transport of patient, resuscitation, autopsy?
11. Handled clinical/laboratory specimens (blood, urine, faeces, tissues, laboratory cultures) from a live or dead individual or animal known or strongly suspected of having VHF?
12. Received IM or IV injections while in an endemic country?
13. Had close contact with a live or dead individual known or strongly suspected of having VHF e.g. kissed, been breastfed by?
14. Had sex in the last 3 months with an individual known or strongly suspected to have VHF?
15. Been involved in the funeral preparations of an individual known or strongly suspected to have VHF?
16. Come into contact with body fluids of a live or dead individual known or strongly suspected of having VHF either directly, e.g. handled blood, urine, faeces, or indirectly, e.g. soiled clothes or bedding?

Definition of healthcare workers with occupational exposure

- **Low risk exposure**:
    - Occupational exposure of anyone working in a healthcare setting involved in caring for a case of VHF, *or* dealing with inanimate objects contaminated or possibly contaminated with blood and/or body fluids, *or* laboratory workers processing specimens of a VHF case while using **appropriate personal protective equipment (PPE)**
- **High risk exposure:**
    - Occupational exposure of anyone working in a healthcare setting involved in caring for a case of VHF, *or* dealing with inanimate objects contaminated or possibly contaminated with blood and/or body fluids, *or* laboratory workers processing specimens of a VHF case is considered to be a high risk exposure where:
        - there is a breach in PPE (e.g. needle-stick injury, or incorrect donning and doffing technique)

          OR
        - when not wearing appropriate PPE

NOTE: Given the **continuous nature** of the occupational exposure for some healthcare staff when caring for VHF patients, healthcare workers will be **actively monitored**.

2.5 Care pathway for suspected VHF adult patient in an acute hospital setting

This section is intended to provide guidance for **RISK ASSESSMENT** and **CLINICAL CARE** delivered by appropriately trained acute hospital health care professional staff. Its application to individual patients must take account of the clinical circumstances. The document should not be applied or interpreted in a way that impedes delivery of safe and effective clinical care.

How a patient is referred:

Via:

Self-referral to VHF receiving hospital Emergency Department without prior notification, with history of fever and travel to an affected country within the **past 21 days**, or contact with a confirmed or probable case of VHF.

OR

Referral from GP, Public Health, ambulance service or airport to designated location within acute hospital for assessment of cases, when notified in advance

Immediate actions

Please note phlebotomy should not be performed at triage in any patients meeting the criteria for suspected VHF.

Step 1: Preliminary safety steps

- Place patient in a single room immediately.
- Give the patient a brief explanation of the process and why it is needed.
- If direct observation of the patient in the single room is not possible ensure that the patient has access to a means of communication (e.g. a mobile phone) and a number that will be answered. Remember, the patient is likely to be frightened and should not feel that they have been abandoned in the single room.
- In addition to Standard Precautions, implement Contact and Droplet infection prevention prevention.
- Healthcare worker to put on appropriate Level 2 PPE
- Inform local infection control team/microbiologist.

Step 2: Risk Assessment

- A senior member of the medical team responsible for acute care of patients (e.g. Emergency Medicine Consultant, ID consultant or admitting team Consultant) should commence clinical risk assessment, using the VHF Clinical Risk Assessment Form , using appropriate Level 2 PPE

The on-call Consultant in Infectious Diseases at the Mater Hospital National Isolation Unit (NIU) is available for consultation at this stage, if required (**Tel. 01 8032000** and ask for ID consultant on call).

- **If local risk assessment determines low risk :** Patient remains in a single room, with standard, contact and droplet infection control precautions, and investigations are undertaken to determine the cause of the illness, including a malaria test.
- **If local risk assessment determines high risk** :
    - Initial evaluation and management for immediate care of the patient should be undertaken.
    - Contact NIU to discuss detailed risk assessment, case management and investigation (including urgent VHF test, malaria test, blood cultures and other investigations).
    - If VHF test required: in consultation with NIU, sample can be taken and sent to NVRL with appropriate precautions. Contact NVRL prior to sending sample and ensure courier is available to transfer sample.[1] The NVRL must be notified before dispatch from hospital of any suspect VHF specimens (see footnote[2] below for NVRL contact details. Samples should be packaged, labelled, and shipped as a Category A infectious substance affecting humans (UN 2814) as per the Guidelines for the Preparation for Transport of Patient Specimens and other Biological Materials 2019.
    - Patient to remain in single room, with staff continuing to apply standard, contact and droplet precautions. Patient may be transferred directly to the NIU if it is not possible to take sample at referral site, or if patient has clinical features strongly suggestive of VHF and no alternative diagnosis.

[1] Biomnis, the courier service, can be contacted at 1800252967 from 09:00-17:00, Monday – Friday.
[2] The NVRL can be contacted 09:00-17:00, Monday to Friday at 01-7164401. For out-of-hours, contact 01-7164050.

- Contact the local ID clinician/microbiologist and infection control team urgently if not already informed at time of assessment.
- Of note, it is essential that no samples are sent to the local laboratory before discussion with ID clinician/microbiologist.
- Notify the Area Director of Public Health

Step 3: Actions to be taken when VHF test available

- If **high risk** and VHF is not detected on the initial test:
  - Manage patient with support from National Isolation Unit
  - Maintain possibility of VHF until an alternative diagnosis such as malaria is found
  - Consider repeat VHF test particularly if sample taken less than 3 days since symptom onset and no alternative diagnosis.
  - Continue to apply standard, contact and droplet precautions.

- If VHF test is **POSITIVE**:
  - Inform the ID consultant on call in the National Isolation Unit immediately, who will activate the NIU protocol and arrange transfer of the patient
  - Ensure appropriate infection control and PPE for management of a confirmed case
  - Notify the Area Director of Public Health so that contact tracing investigations can commence.
  - Patients can be transferred prior to laboratory confirmation of VHF if there is no alternative diagnosis and they have a **high risk exposure**

Step 4: Transfer to the National Isolation Unit, Mater Hospital.

- Transfer is arranged by NIU, who contact the National Ambulance Service and activate the VHF transfer protocol.
- Stable patients can be transferred to NIU by the National Ambulance Service VHF-trained paramedic team.
- The National Ambulance Service to be advised of patient's condition and requirements, to ensure appropriate vehicle and equipment.
- All patients transferred to the Mater Hospital will be admitted directly to the NIU.

Note: It is intended that cases of VHF will be managed in the NIU. The NIU in Ireland is undergoing reconfiguration, during which time patients may be transferred to a High Level Isolation Unit within the EU (Germany).

2.6 Care pathway for the management of a suspected VHF patient in a Primary Care setting

- Assessment of a patient's risk of VHF should be undertaken by appropriate medical team in the designated VHF receiving hospital. However, despite being extremely unlikely, the possibility exists that such patients may present initially to primary care and General Practitioners (GPs) should be aware of how to safely triage, and refer such patients, to the designated VHF receiving hospital for review and care.

- In the event that a patient, who might pose a risk of VHF, either telephones the surgery or presents in person, follow the VHF Risk Assessment for Primary Care Setting Algorithm to ensure safe and effective management of the patient.

SCENARIO 1: Patient Phoning the Surgery

- **If a patient with possible VHF telephones seeking an appointment, go through their travel history in detail and clinical status over the phone**:
    1. Has the patient **returned from or was resident in an affected country in the 21 days** before onset of symptoms? AND
    2. Does the patient **have a fever or has a history of feve**r in the last 24 hours?

  (If the patient does not have the above two features, they can be assessed as normal)
- If the patient answers **yes to both questions:**
    - Instruct patient **NOT to visit surgery/OOH centre** and to
    - **Self-isolate** pending arrangements for assessment in an acute setting
    - **Complete a clinical risk assessment, using the VHF Clinical Risk Assessment Form**
- Contact the on call Infectious Diseases Consultant at the Mater Hospital NIU to discuss detailed risk assessment and case management (**Tel. 01 8032000** and ask for ID consultant on call).
- Based on the clinical risk assessment categorisation and clinical status of patient, the on-call ID Consultant will determine:

1) If patient should be referred to the NIU or another hospital for onward assessment and management

AND

2) appropriate transport requirements

- If the patient is to be transferred to the NIU, the on-call ID Consultant will contact the National Emergency Operations Centre to arrange transfer
- If the patient is to be transferred to a hospital other than the NIU, the GP will contact the National Ambulance Service to arrange transfer; advise of VHF risk status to ensure ambulance staff have appropriate precautions in place. The National Ambulance Service will then contact the receiving hospital to inform and discuss transfer of the patient. The GP should also consider contacting the receiving hospital to advise them of the patient's clinical history and clinical status.

- Notify local Public Health Area immediately

SCENARIO 2: Patient Presenting in Person to the Surgery

- Should a patient present unannounced to the Surgery with suspected VHF, staff should immediately ask the following:
    1. Has the patient **returned from or was resident in an VHF affected country in the 21 days** before onset of symptoms? AND
    2. Does the patient **have a fever (≥38^{0}C) or has had a history of feve**r in the last 24 hours?

- Staff should adopt a "**Talk, don't Touch"** approach, **maintaining a distance of >1 metre** at all times (**NB if the patient is coughing or vomiting then a distance of 2-3 metres should be maintained**).
  (If the patient does not have the above two features, they can be assessed as normal)
- If the patient answers "**Yes" to both questions:**
  - **immediately isolate the patient in a side room** away from all other patients/staff
  - the patient should be instructed to **remain in the side room** until arrangements for transfer have been organised
  - If the patient needs to use the **WC, this must be sealed off** and not used by other patients/staff.
- **Standard Precautions must be maintained for ALL PATIENTS at ALL TIMES. Point of Care Risk Assessment (PCRA) Poster available here**
- The patient should **NOT** be examined, unless **ABSOLUTELY NECESSARY**
- In the event of any clinical interaction with the patient , use Level 1 PPE (see page 10)
- Complete a clinical risk assessment, using the VHF Clinical Risk Assessment Form
- Contact the on call ID Consultant at the Mater Hospital NIU to discuss detailed risk assessment and case management (**Tel. 01 8032000** and ask for ID consultant on call).
- Based on the clinical risk assessment categorisation and clinical status of patient, the on-call ID Consultant will determine:

1) If patient should be referred to the NIU or another hospital for onward assessment and management

AND

2) appropriate transport requirements

If the patient is to be transferred to the NIU, the on-call ID Consultant will contact the National Emergency Operations Centre to arrange transfer.

If the patient is to be transferred to a hospital other than the NIU, the GP will contact the National Ambulance Service to arrange transfer; advise of VHF risk status to ensure ambulance staff have appropriate precautions in place. The National Ambulance Service will then contact the receiving hospital to inform and discuss transfer of the patient. The GP should also consider contacting the receiving hospital to advise them of the patient's clinical history and clinical status.

- Notify local Public Health Area immediately

Post-transfer of patient presenting from Primary Care to Acute Hospital

Once the patient has left the practice:

- Practice staff must ensure the room the patient was assessed in and any other areas the patient accessed such as the toilet are taken out of use and risk-assessed to determine the likelihood/degree of environmental contamination.
- These work areas must not be put back into use until after they have been appropriately cleaned and disinfected. Professional cleaning by a trained contract cleaning agency may be required depending on the outcome of the VHF test result.

- In instances where a suspected VHF patient presents to a GP surgery and has uncontrollable diarrhoea, vomiting or bleeding while on the premises, the practice should close the premises until the results of the VHF PCR test are available. Local Public Health Area teams will advise on next steps.
- Segregate and quarantine all waste generated in the management of the patient pending the outcome of the VHF PCR test.
- VHFs are primarily spread through direct and indirect contact; hand hygiene is therefore very important in addition to environmental hygiene.
- Practice staff should compile a contact list of all the patients and staff who may have been in direct contact with the patient and give to the local Public Health team.

Results of VHF Assessment/Test

Public Health will inform you of the outcome of the VHF test/risk assessment.

If the patient is **positive for VHF**:

- Public Health will initiate contact identification and assessment.
- Where VHF specific cleaning and waste management have been deemed necessary, it is recommended that this is performed by a quality-assured, trained contract cleaning agency trained and competent in the use of appropriate level PPE.

If the patient is **negative for VHF:**

- Dispose of waste as per national guidance
- Clean and disinfect sealed off areas in usual manner.

Surgery Pre-Incident Preparation

- **Any patients identifying themselves to reception staff should not sit in the general waiting room once VHF is considered a possibility.** These **patients should be isolated in a single side room immediately** to limit contact. It may be appropriate to ask them to return to their car pending assessment by telephone.

Notification of Infectious Disease and Tracing/Monitoring of Contacts

Once a thorough assessment has been made and VHF is either considered likely or has been confirmed by laboratory testing, the hospital clinicians will inform the local Public Health Area who will immediately undertake the necessary public health response and appropriate follow up of contacts. The Public Health Area will identify and organise follow up for any primary care contacts, which will include health care staff who dealt with the patient while symptomatic. A confirmation of VHF and subsequent initiation of public health action usually occurs within 24 hours of admission to hospital. Contacts are required to self-monitor and report relevant symptoms to Public Health. Where contacts develop relevant symptoms or signs they will be assessed in an appropriate acute hospital setting, and not referred to primary care.

If there are specific concerns in the primary care setting, your local Public Health Area can be contacted to discuss any specific public health issues at the point of referral to hospital or if the patient has additional high-risk factors.