Viral haemorrhagic fevers

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Viral haemorrhagic fevers are severe viral infections with a variable tendency to progress to multi-organ dysfunction and severe endothelial injury, leading to shock and haemorrhage. Not all are tropical in distribution, though their incidence may increase in summer or rainy seasons, when vectors are most active.

Aetiology and epidemiology

Worldwide, the most common causes of viral haemorrhagic fever are as follows.

Dengue – any of the four serotypes of the mosquito-borne dengue virus can cause viral haemorrhagic fever. Those who are immune to infection with one serotype have partial immunity to infection with a second serotype, which increases the severity of the second attack, leading to dengue haemorrhagic fever or dengue shock syndrome, with haemorrhage, serous effusions and shock. This particularly affects children resident in the highly endemic Far East, Caribbean and northern regions of South America.

Hantavirus – infection with rodent-borne Hantaviruses causes haemorrhagic fever with renal syndrome. Severe infections, with Hantaan, Seoul or Dobrava virus, occur in the Far East, South East Asia and parts of Eastern Europe; milder illness, caused by Puumala virus, is seen in Scandinavia.

Crimean–Congo haemorrhagic fever virus is a tick-borne nairovirus causing asymptomatic viraemia in warm-blooded animals, farm animals and farmed ostriches. The endemic range is large and the many virus strains vary in virulence. Severe infections occur in western and Central Asia, Eastern Europe and the Middle East; less severe infections occur in Central and southern Africa.

Lassa fever – Lassa virus[1,2] is an arenavirus that is endemic in multi-mammate rats in West Africa. Its range extends from Guinea to Cameroun (Figure 1), with epidemic activity in Sierra Leone and Nigeria. Other arenaviruses associated with harvest or field mice in South America that are rarely imported into Westernized countries include Junin (Argentine haemorrhagic fever), Machupo (Bolivian haemorrhagic fever), Guanarito (Venezuelan haemorrhagic fever) and Sabia (Brazilian haemorrhagic fever).

Marburg and Ebola viruses are filoviruses.[3] Their reservoir is unknown, but cases may follow exposure to sick or dead monkeys or apes. Ebola occurs in forested areas in north Central Africa (Figure 1) and has caused epidemics in DR Congo, Sudan and Gabon. Marburg epidemics have occurred in rural Uganda and

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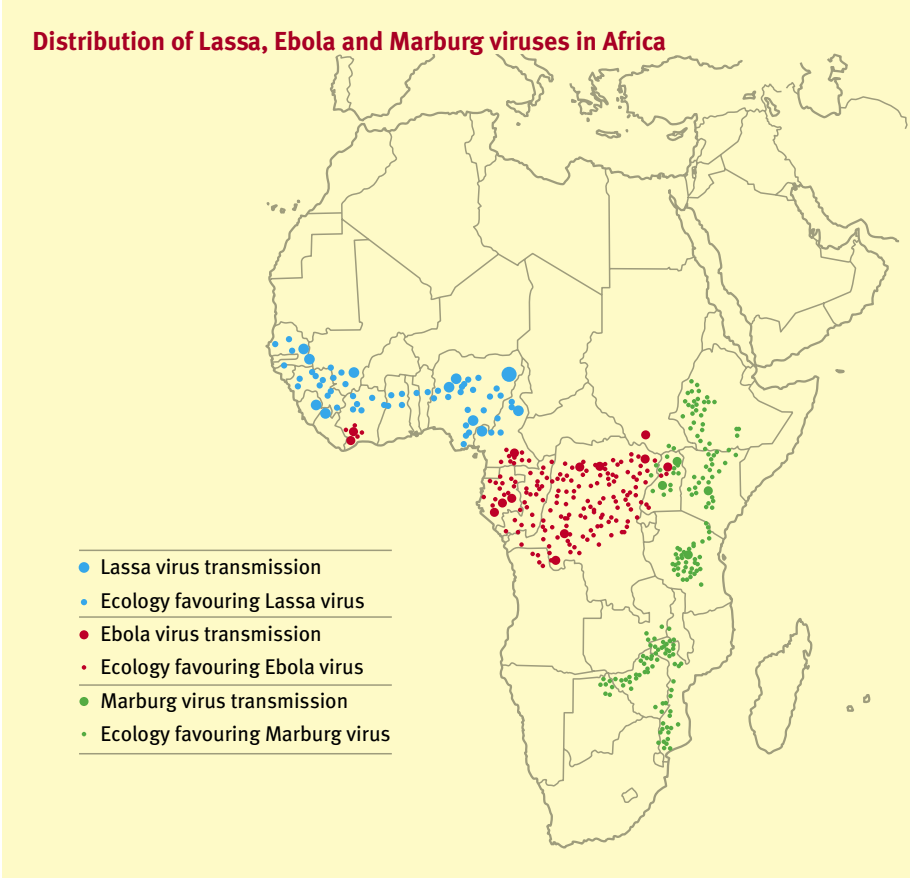
Distribution of Lassa, Ebola and Marburg viruses in Africa



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Clinical features, diagnosis and management of viral haemorrhagic fevers

Disease (incubation period)	Clinical course	Diagnosis	Management and prevention
Haemorrhagic fever with renal syndrome (14 days, range 5–42 days)	*Febrile stage* 4–7 days, with prostration, myalgia, flushing of skin, scattered petechiae, declining platelet count; often, blurred vision *Hypotensive stage* Shock and capillary leak *Oliguric stage* 3–10 days, with renal failure, pulmonary oedema, haemorrhage, haemodynamic instability *Polyuric phase* Slow recovery	IgG and IgM ELISA, viral culture from whole blood; urine; 'dipstick' antigen detection test in trials	Intravenous ribavirin (not licensed in UK – named-patient only); loading dose 30 mg/kg, then 15 mg/kg 6-hourly for 4 days, then 7.5–8 mg/kg 8-hourly for 6 days (validated by randomized controlled trial) Close attention to hydration and haemodynamic support is needed Case fatality averages 5%
Crimean–Congo haemorrhagic fever (5–12 days)[1]	Abrupt onset with very severe myalgia, and back and abdominal pain; declining platelet count, increasing transaminases; often, very severe haemorrhage	Rapid antigen test or PCR analysis of whole blood; IgG and IgM ELISA	Anecdotal reports of improvement with ribavirin; frequent, severe haemorrhage increases risk of nosocomial transmission to health-care workers Case fatality 10–30%
Lassa fever (7–12 days, range 3–16 days)[1]	*Onset* 5–10 days, with fever, myalgia, sore throat, oedema and hypotension, doughy swelling of face and neck; often, mild mucosal bleeding; nerve deafness (aspartate aminotransferase › 150 u/litre and/or viraemia › 3 log TCID50 predicts 55–85% mortality) *Late features in fatal cases* Haemorrhage and multi-organ failure	PCR analysis of whole blood; IgG and IgM ELISA (antibodies may be absent in severe cases)	Intravenous ribavirin commenced in first 7 days reduces mortality in poor-prognosis cases (data from open-label trial with retrospective controls)[2] Case fatality averages 12–15%
Marburg and Ebola (5–10 days, range 3–6 days)[1]	Abrupt onset with severe myalgia, back and abdominal pain, prostration, hypotension, drowsiness or coma; most patients have morbilliform rash by 5th day; one-half have haemorrhage	PCR analysis of whole blood; IgG and IgM ELISA	No effective antiviral treatment Case fatality – Marburg, 25–30%; Ebola, 50–60% in Sudan, 80–90% in DR Congo

ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction analysis; TCID50, tissue culture infective dose 50 (the dose that infects 50% of exposed tissue cultures in a defined system)

[1]Disease has been transmitted to household or health-care contacts, or by laboratory exposure. Carers are usually infected by droplet or blood-borne route. Aerosols are highly infectious, but are seldom generated outside laboratory settings.
[2]Following mucosal or transdermal exposure, or laboratory accidents, prophylaxis with oral ribavirin may be effective for Lassa fever and other sensitive infections (no evidence from trials).

Sources: Mandell G L, Bennett J E, Dolin R, eds. *Mandell's principles and practice of infectious diseases*. Philadelphia: Elsevier, 2004 and McCormick J B *et al. N Engl J Med* 1986; **314:** 20–6.

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Congo (Figure 1), and cases are seen in Kenya. A human Ebola case was reported in Côte d'Ivoire, and a strain affecting monkeys, but not humans, occurs in the Philippines.

Assessment and management

The early clinical features of viral haemorrhagic fever are non-specific, so a detailed history must be taken, including:

- travel destinations and dates (viral haemorrhagic fevers are excluded if incubation periods are exceeded, Figure 2)
- type of terrain and living accommodation (to assess vector exposure)
- other cases in the area.

Individuals most at risk in endemic areas are independent travellers, workers, aid workers, peacekeepers and medical teams. Patients with suspected viral haemorrhagic fever should be isolated

Advice on suspected cases or occurrence of viral haemorrhagic fever

In the UK

- Consultant on-call, Royal Free Hospital Infectious Diseases Service – tel: 0207 794 0500
- Consultant on-call, Newcastle General Hospital Infectious Diseases Service – tel: 0191 256 3131
- On-call Specialist, Enteric, Respiratory and Neurological Virus Reference Laboratory, Health Protection Agency Centre for Infections – tel: 0208 882 4400
- On-call Specialist, Special Pathogens Reference Unit, Health Protection Agency Centre for Emergency Preparedness and Response – tel: 01980 612 100
- Other infectious diseases and tropical medicine units may be able to offer general advice and information

Web sites

- www.hpa.org.uk/infections/topics_az/list/htm
- www.cdc.gov (search for 'viral haemorrhagic fevers')
- www.who.int/en/

and infection control precautions implemented (risk of transmission is insignificant from casual contact and low from ambulant and continent patients). Support the patient as indicated with hydration, analgesia and empirical antibiotics when necessary (take blood cultures, and keep them with the patient, pending decision on referral).

More than 90% of fevers in travellers to tropical areas are caused by malaria, and delay in treating *Plasmodium falciparum* infection can be fatal. Malaria should be excluded, using usual local laboratory procedures; blood should be disposed of after the test. Do not send (or recall) specimens not needed for urgent tests. Aspartate aminotransferase and platelet count may aid risk assessment.

Advice should be sought from referral centres on detailed risk assessment and possible referral (they will assist with ambulance transfers). Collaborate with local laboratory and infection control teams to pack and transport laboratory specimens. ◆

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FURTHER READING

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