Lassa fever prognostic indicators

Feature	Case-Fatality
virus titres>3.5 logs	76%
AST > 150iu/ml	55%
both	85%
neither	<15%

McCormick *et al.* N Engl J Med. 1986 Jan 2;314(1):20-6.

Lassa fever in pregnancy results in abortion with severe haemorrhage

Lassa fever in infancy causes severe sepsis and capillary leak (swollen baby syndrome)

Early diagnosis of Lassa fever

- Early diagnosis must be by specific tests, as clinical features are not helpful
- Exclusion of, or treatment for malaria is very important
- RT-PCR detection of viral RNA, (using whole blood, EDTA-anticoagulated) is rapid and reliable in most cases; rare false-negatives may be due to low annealing temperatures
- Fluorescent antibody tests are less reliable, as antibodies may not develop, and false-positive tests can also occur

Other viral haemorrhagic fevers of concern

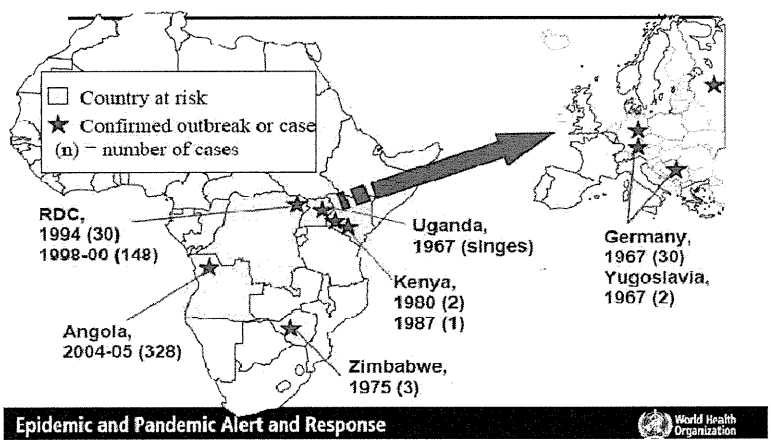
Marburg outbreaks

1967	Germany	Ex Uganda	32 cas (7d)
1975	RSA (Joh.)	Zimbabwe	3 cas (1d)
1980	Kenya	Kenya	2 cas (1d)
1987	Kenya	Kenya	1 cas (d)
1991	Sweden		1 case
1998-2000	DRCongo	Durba DRC	154 (128d)
2004-5	Angola	Uige Angol	335 (283d)

In the first outbreak of Marburg 1967, Frankfurt, Belgrade: virus persistence

- Total of 32 cases, 15 with primary contact
- 7deaths reported (21%): all primary cases
- One secondary case occurred after an afebrile man left hospital to convalesce at home: the man's wife developed Marburg disease, 83 days after her husband's illness began, and recovered; the man had a positive virus test in semen.

Marburg Virus Haemorrhagic Fever in Africa



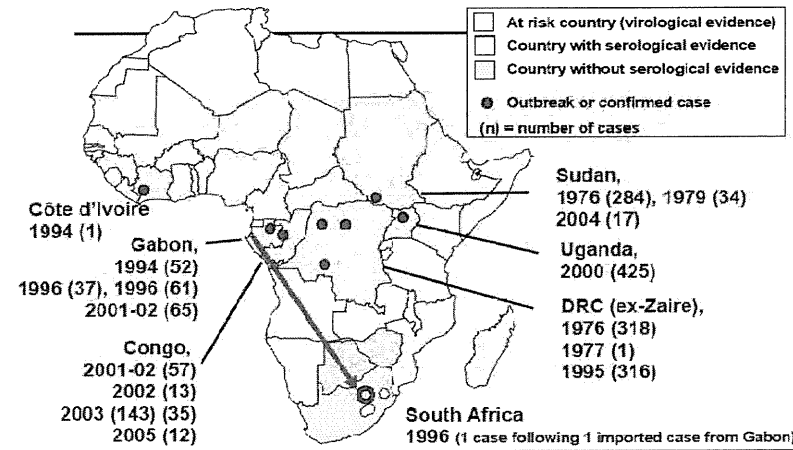
Human Ebola outbreaks: 1

1976	Sudan, Zaire	Local and hospital	Over 300 cases
1976	England	Lab EBOS	1case
1977	Zaire	Tandala	1 case (d)
1979	Sudan	Nzara	34 (65%d)
1994	Gabon EBOZ	Mekouka (gold mines)	49 (59%d)
1994	Switzld	Ivory Coast	1 case

Human Ebola outbreaks: 2

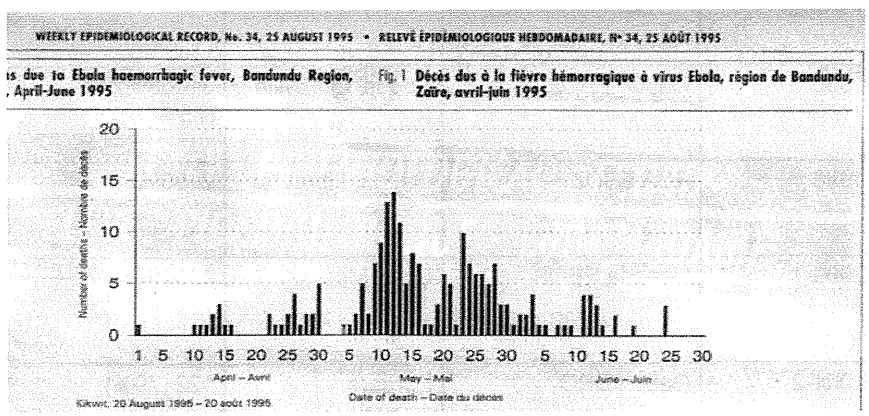
1995	DR Congo	Kikwit	315 (81%d)
1996	Gabon EBOZ	Booue, Libreville	31 (68%); 60 (75%)
1996	RSA EBOZ	Gabon, Libreville	2 (50%)
2000-1	Uganda EBOS	Gulu, Masindi	425 (53%)
2001-2	Gabon/DRC	Borders	122 (79%)

Ebola Virus Haemorrhagic Fever in Africa



Epidemic and Pandemic Alert and Response — World Health Organization

Slow-burning outbreaks: Ebola



Clinical features of Ebola and Marburg

- Phase 1: 3 to 4 days of fever, malaise, muscle aches, headache, conjunctival injection, abdominal pain, diarrhoea
- Phase 2: sudden worsening, severe diarrhoea which may be bloody, low blood pressure, chills, low oxygen saturation
- Phase 3: from 7th or 8th day, shock, renal and other organ failures, increasing oedema, sometimes severe haemorrhage
- Fatalities: 25-40% for Marburg; 50-70% for Ebola Sudan; 80-90% for Ebola Zaire

Marburg and Ebola syndromes

Marburg

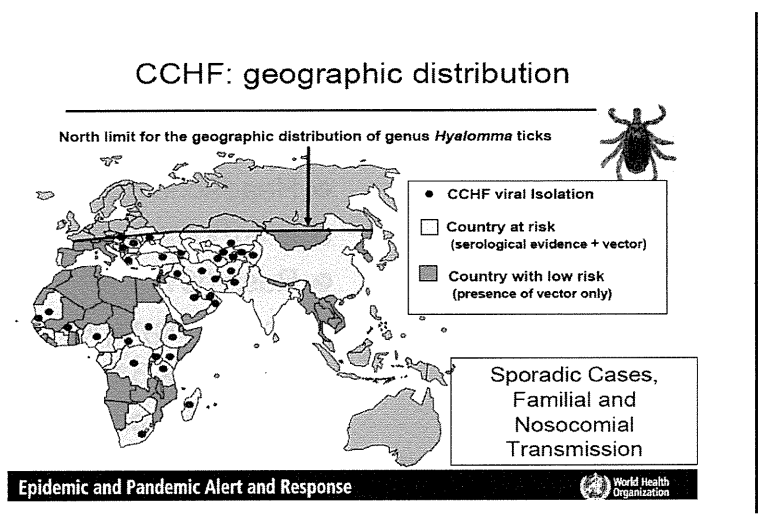
- Myalgia+headache
- Diarrhoea 80%
- Rash 75%
- Conjunctivitis 55%
- Lymphadenopathy 50%
- Haemorrhage 30%
- AST peak day 6/7
- Renal failure predicts death

Ebola

- Abdominal pain
- Headache day 4
- Diarrhoea 70%
- Rash 50%
- Thrombocytopenia
- AST peak 6-8 days
- Declining renal function until +death

Crimean-Congo Haemorrhagic fever

- Bunyavirus (nairovirus) tick-transmitted disease seen in Africa, Asia, E. Europe
- Reservoir in many small and farm animals, and ostriches
- Many variants causing a range of milder and severe disease in different localities
- Severe cases are characterised by fever and severe arthralgia with early, severe haemorrhage which is often difficult to control and is associated with very low platelet counts



Risk assessment of suspected viral haemorrhagic fever patients

Epidemiological indicators-important as clinical features not distinct

- Exposure to endemic environment (NOT simply to named country)
- Exposure to vector (animal, bird, arthropod)
- Exposure to contaminated dust or food
- Exposure to **infectious** animal or human (may not be in a recognised endemic area)
- Exposure to laboratory specimens including aerosols (in, or not in, an endemic area)
- *NB needlestick and centrifuge accidents*

Risks for contracting VHFs

Lassa	**Healthcare work; aid work; surveying camping; backpacking, handling rats**
Ebola/Marburg	**Living in endemic area; healthcare; aid, handling dead primates**
CCHF	**Tick exposure; farm working; healthcare; caring for sick family member**

Incubation periods are helpful in risk assessment

- Lassa: average 7-12 days; wide range of 5 to 17 days
- Ebola and Marburg: average 4-8 days; wide range up to 18 days

Lassa, Ebola and Marburg can be discounted if period between last exposure and onset of fever exceeds 21 days

- CCHF: shorter incubation of 1-3 days via tick bite; 5 or 6 days via contact with blood or tissues-maximum 14 days

Patient assessment

Might they have Viral haemorrhagic fever?

- Have they been in exposure environment?
- Was it within the incubation period?
- Did they do any exposure-prone activities?
- Are they actually unwell?
- Ask advice from infectious disease expert or consult WHO/National guidance for information

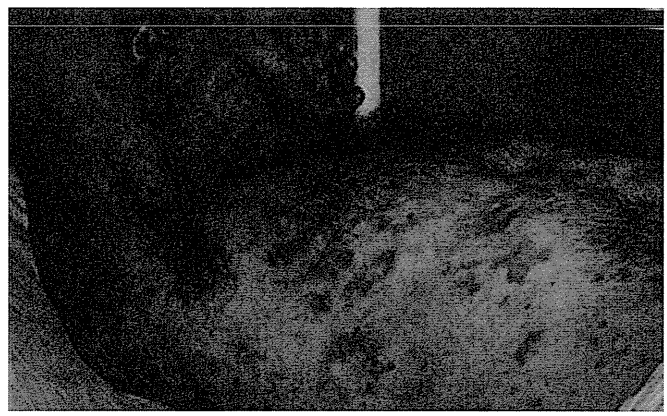
Do they present an infection hazard?

- Is the patient ambulant and self-caring?
- Is the patient causing splash or potential aerosol (by coughing or vomiting)
- Is the patient highly dependent, incontinent or bleeding?
- Does the patient need intubation?

Diagnostic tests

- Rapid RT-PCR-tests for Lassa, Ebola and Marburg RNA are reliable
- FATs are widely used, but may be persistently negative in severe cases, as no antibodies develop
- ELISA tests are not yet widely validated
- An antigen test for CCHF is reliable early in the illness (but not in later cases)
- Arenaviruses and Filoviruses grow readily in standard cell-cultures and allow strain identification-but high containment is needed

A rapid differential diagnosis, eg malaria, may help to exclude-VHF



This patient with fever headache and haemorrhagic features had *Neisseria meningitidis* in the cerebrospinal fluid

Patient-based hazard assessment

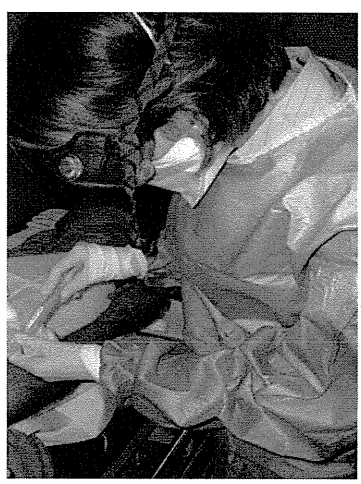
Patient status	Risk level	Isolation level
Ambulant; no rash, continent	No extra risk	Local rules; and face/eye PPE
Nose/puncture, bleeding	Low, HCW environment	Single room, glove gown, face/eye
Gut bleeding, cough, rash +/- bedbound	significant,: HCW, others; environment	Airflow control, glove, gown, face/eye (?HID)
HDU or ITU/CCU	High	HID Unit and staff

☐ **Transfer while safe** ☐ **Special transfer arrangements needed**

Potentially infectious patients should be isolated or cohorted

This is a negative-pressure room with ensuite WC and shower

Basic PPE is valuable in allowing safer patient assessment



Standard precautions, as used every day, offer significant protection for almost every purpose-provided that they are properly used at each contact

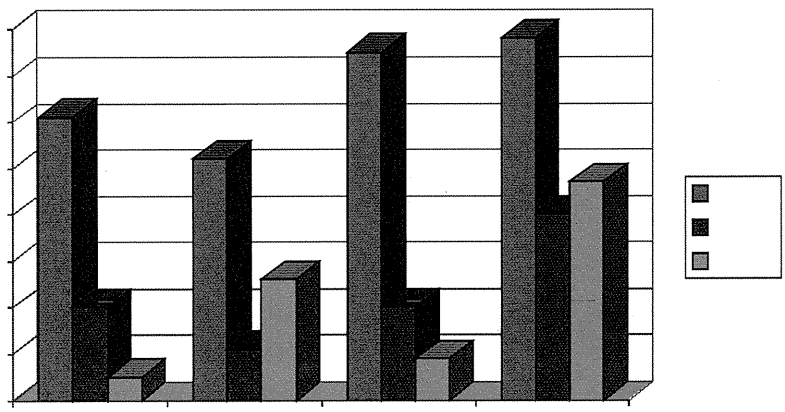
Management of Lassa fever

- Good clinical care: resuscitation, hydration, nutrition, hygiene, encouragement
- RIBAVIRIN, give as soon as strongly suspected or proven Lassa fever:

Treatment of Lassa fever with intravenous Ribavirin
Loading dose: 30 mg/kg IV (up to 2 g)
THEN 16 mg/kg IV (up to 1 g) q6hr for 4 days
THEN 8 mg/kg IV (up to 500 mg) q8hr for 6 days

Lassa: ribavirin treatment

(McCormick *et al* NEJM 1986; 304: 20-26)



Adverse effects of ribavirin

- Dose-dependent haemolysis
- Restlessness, agitation
- Nausea, malaise, fatigue
- Abnormal hepatic enzymes
- Pancreatitis (rare)

Potential new antiviral treatments

PloS Negl Trop Dis. 2011 Oct;5(10):e1342. Epub 2011 Oct 11.

Effective oral favipiravir (T-705) therapy initiated after the onset of clinical disease in a model of arenavirus hemorrhagic Fever**.**

Mendenhall M, Russell A, Smee DF, Hall JO, Skirpstunas R, Furuta Y, Gowen BB.

(effective but toxic in guinea pigs)

Antiviral Res. 2011 Apr;90(1):70-9. Epub 2011 Mar 1.

Evaluation of Lassa **antiviral compound ST-193 in a guinea pig model.**

Cashman KA et al

(Anti cell-entry: only 67% survival in guinea pigs)

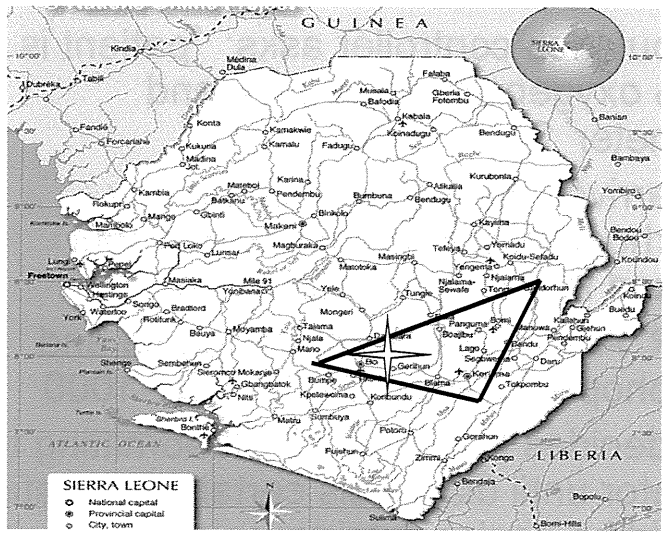
How much Intensive Care?

- One report of survival (but patient had stable BP and renal function) (Fisher-Hoch *et al*, Lancet 1985 (ii): 1227-1229)
- five attempts at multi-organ support for VHFs all failed (3 are unpublished, others: Holmes *et al* NEJM 1990 [Lassa] and Haselton *et al* Crit Care Med 2000 [Ebola])
- decision-protocol needed

Case 1

- Aid worker from rural Sierra Leone, working in an abandoned school building near to Bo, disarming rebels when civil war ended
- Referred from a tropical diseases unit, with a 12-day history of fever malaise and increasing fatigue with no response to malaria treatment or antibiotics and negative tests for Dengue fever
- On this day, had nosebleed and elevated aspartate transaminase (140 u/l)

Sierra Leone 'Lassa triangle'



Lassa fever in Europe

- 2000: Germany (fatal after intensive care)
- 2000 Netherlands (fatal)
- 2000 UK (fatal after intensive care)
- 2000 UK (recovered)
- 2003 Germany (recovered from ventilator-associated pneumonia)
- 2009 UK (Fatal due to myocardial infarction during convalescence)
- 2009 (died on admission to hospital)

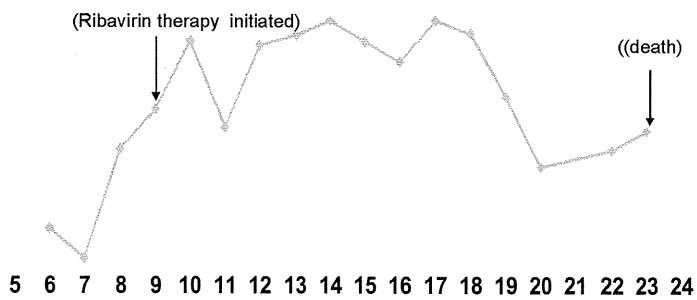
UK: Case 1

- Ambulance controller asks: 'patient is on 60% oxygen-OK to use O2 and oximeter' ?
- On arrival; the patient had bloody diarrhoea and more nosebleed (but walked to toilet with self-care)
- CXR: ARDS; Blood: neutropenia and lymphopenia, Plts 60,000; AST 1000
- BB decides to hold back on admitting to isolator until diagnosis certain (intubation would be easier outside isolator)

Case 1

- Lassa PCR is positive, ribavirin given intravenously; patient ventilated, then treated for multi-organ failure for 12 days
- Intensive care doctors and nurses supervised his critical care
- Specialist laboratory in the Royal Free performed patient management tests
- UK reference laboratory monitored PCR and virus culture on blood, urine and respiratory secretions

Serum Lassa Fever Viral Load (patient IJ)



Lassa Fever Virus PCR

Date	*Sample*		
	Serum	*Urine*	*Throat Swab/ Sputum*
6-3-00	▮		
7-3-00	▮		
8-3-00	▮		
9-3-00	▮		
10-3-00	▮		
11-3-00	▮		
12-3-00	▮		
13-3-00	▮	▮	▮
14-3-00	▮		
15-3-00	▮	▮	
16-3-00			
17-3-00			
18-3-00	▮		▮
19-3-00	▮		▮
20-3-00	▮	▮	▮
21-3-00	▮	▮	▮
22-3-00	▮	▮	▮
23-3-00	▮	▮	

UK: Case 2

- 30 years old, soldier; feverish after 18 months peacekeeping in Kenema
- Billeted in windowless brick building
- Admitted to local military hospital with fever, sore throat, myalgia: treated for malaria: developed chest pain and cough
- Day 3: Ambulant, so returned to a UK hospital on a commercial flight.
- Initial tests: White cell count 3.2; aspartate transaminase 30 u/l; given quinine

Support for staff

- Effective team training to ensure confidence in infection control procedures and trust in colleagues' safety behaviour
- Adequate off-duty and resting time
- Time to review and discuss issues during and after the admission of the patient
- Psychological support and stress management for challenging events
- Post-event audit and update of protocols

Post-Exposure Prophylaxis?

- No good-quality evidence
- Ribavirin for Lassa: 800-2.4g daily for 10 days for adults-this is a high dose

adverse effects such as nausea, sleep disturbance, haemolysis, pancreatitis, and hepatitis, limit tolerability

Prophylaxis is therefore only justified for high-risk exposure: assess the risk!

Suggested risk assessment for follow-up and management of Lassa fever contacts

TABLE 1

Level of risk related to exposure to a patient with Lassa fever, and action, by category

Risk Category	Description	Action
No risk (Category 1)	No contact with the case Casual contact (e.g. sharing a room with the case, without direct contact with a potentially infectious material	Inform of absence of risk Give Category 1 (general) factsheet
Low risk (Category 2)	Close direct contact with the case (e.g. routine medical/nursing care, handling of clinical/ laboratory specimens), but did not handle body fluids or wore personal protective equipment (PPE) appropriately	Self-monitor* for fever and other symptoms compatible with Lassa fever Report to the senior nurse if temperature ≥38°C, with further evaluation as necessary Give Category 2 factsheet
High risk** (Category 3)	Unprotected exposure of skin or mucous membranes (e.g. mucosal exposure to splashes, needlestick injury) to potentially infectious blood or body fluids, or unprotected handling of clinical/laboratory specimens	Record own temperature daily* and report this temperature to the senior nurse by 12 noon each day, with further evaluation as necessary Give Category 3 factsheet

* Contacts to be monitored for 21 days from last possible exposure to case
** Within this group, consideration for ribavirin prophylaxis, if any extreme exposure e.g. percutaneous injury

A. Kitching *et al.* Eurosurveillance, Volume 14, Issue 6, 12 February 2009