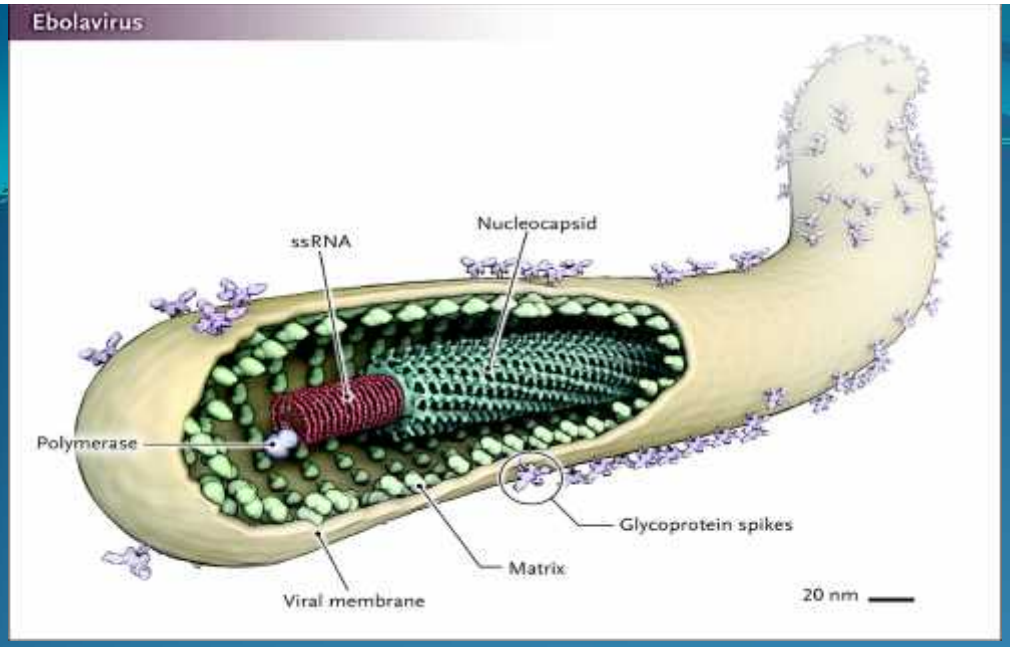
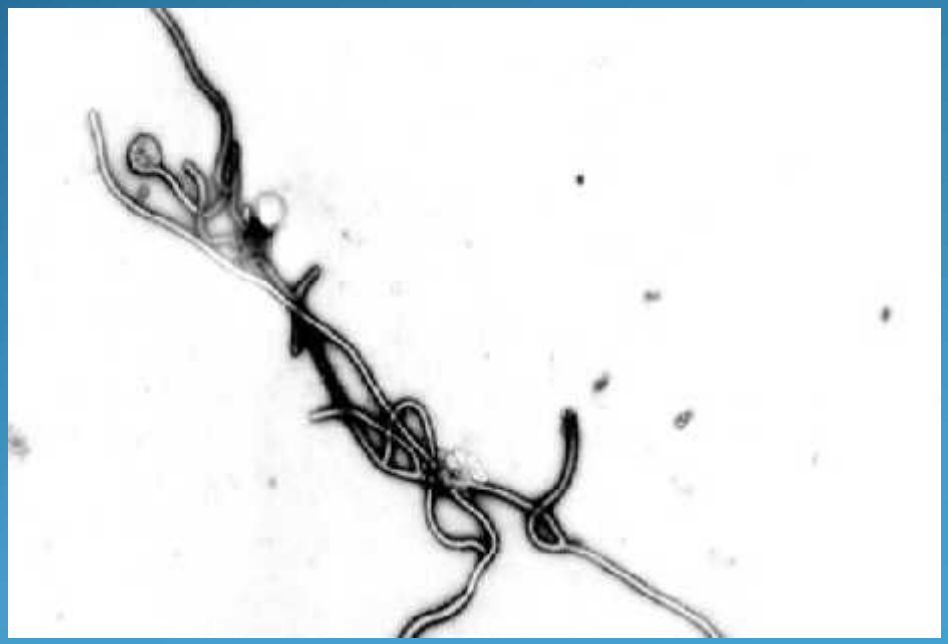




Ebola Virus Disease, Clinical Care.

Overview

- Virology, Pathology & Pathogenesis
- Diagnosis
- Clinical Features
- Transmission
- Treatment, standard & experimental
- Prognosis

family: # Filoviridae

genus

- Marburgvirus

species

- *Marburg marburgvirus* (MARV)

genus

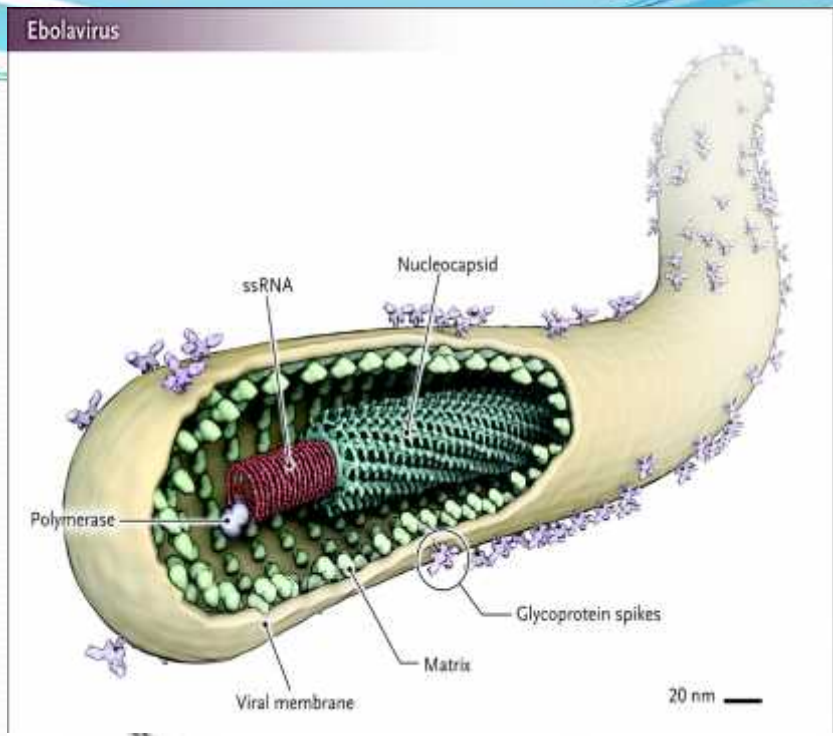
- Ebola*virus*

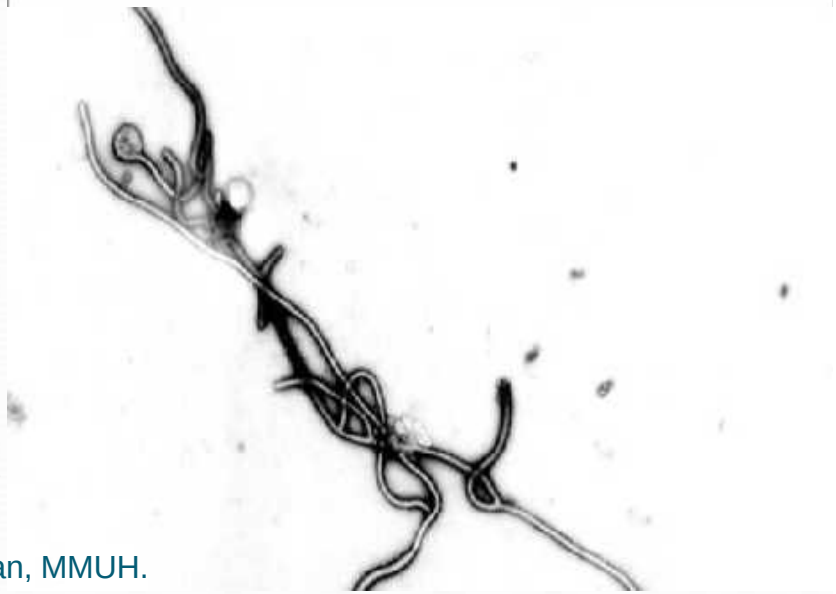
species

1. *Taï Forest ebolavirus* (TAFV)
2. *Reston ebolavirus* (RESTV)
3. *Sudan ebolavirus* (SUDV)
4. ***Zaire ebolavirus* (EBOV)**
5. *Bundibugyo ebolavirus* (BDOV)

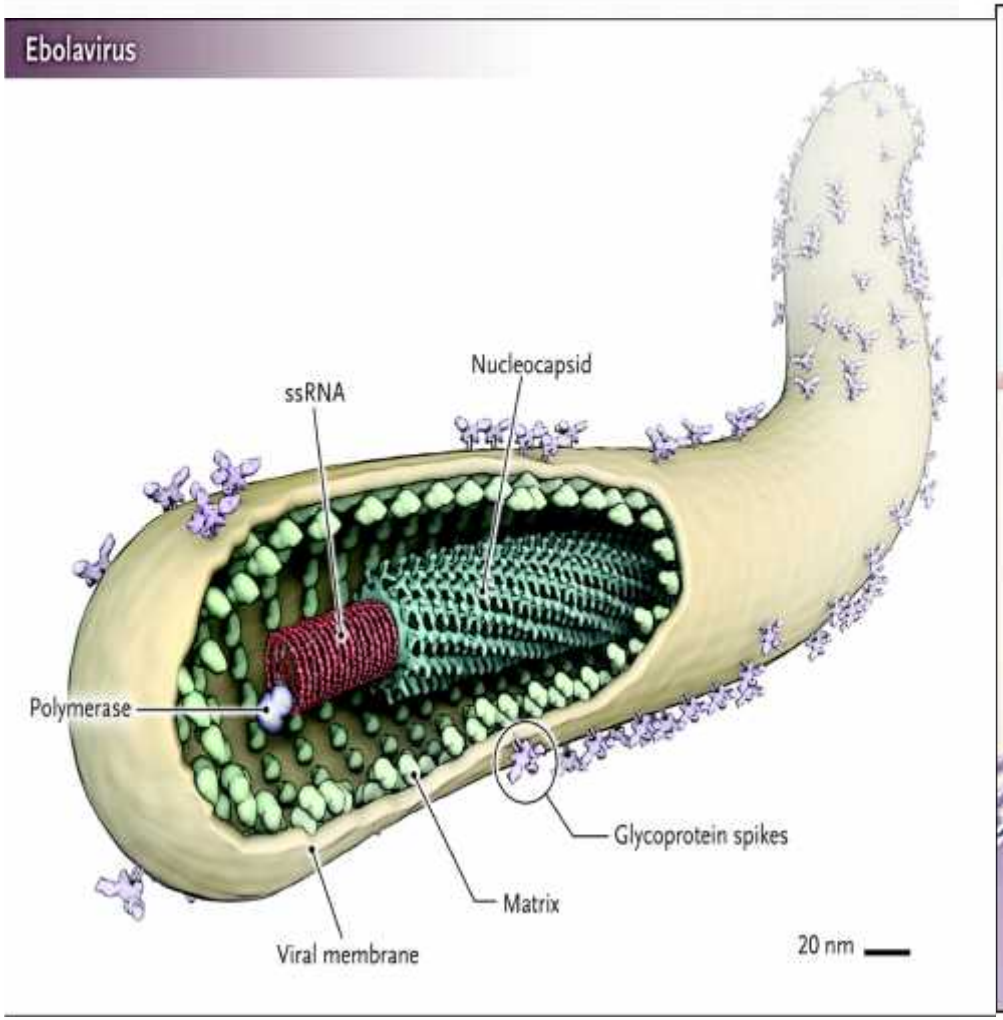
Basic Biology

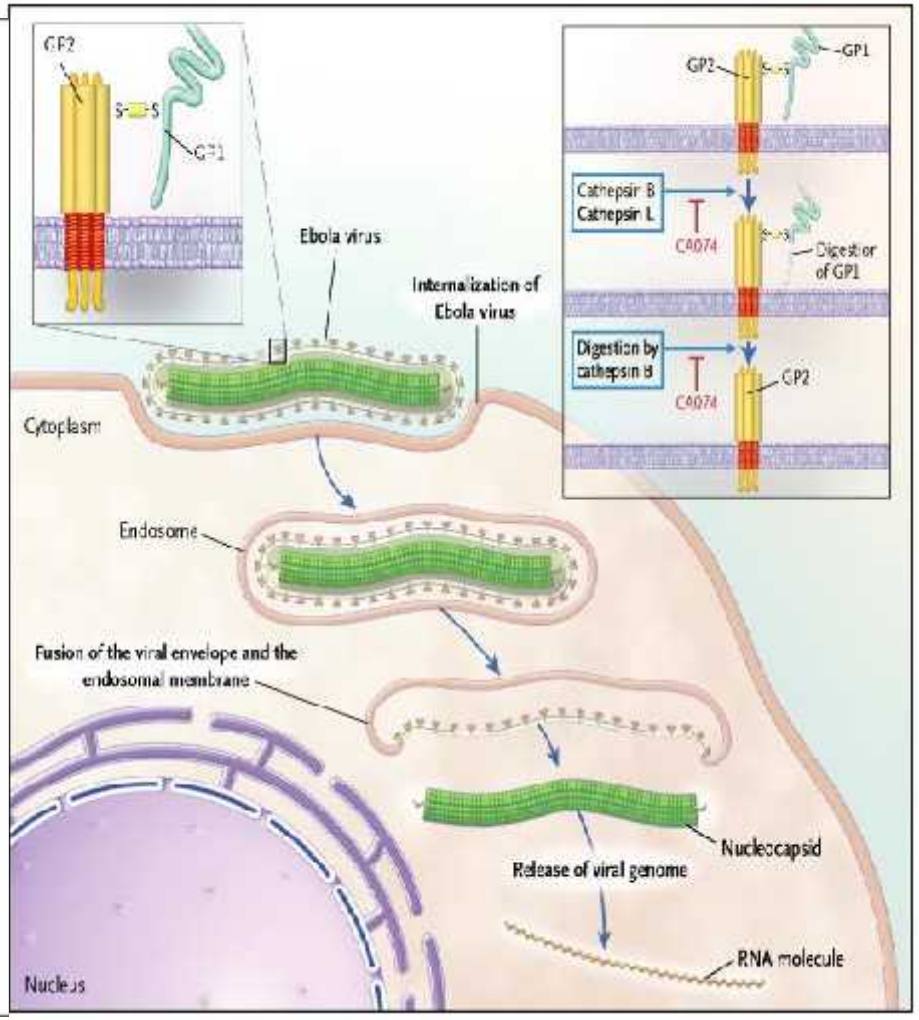
- Filamentous, Enveloped
- Uniform diameter 80 nm, length 600-1400 nm
- Non-segmented, –sense RNA
- 7 structural gene products, 19 kb
  - Nucleoprotein (NP)
  - Virion protein (VP 35)
  - VP 40
  - Glycoprotein (GP)
  - VP 30
  - VP 24
  - Polymerase (L)
- 1 non-structural soluble GP (sGP) encoded by the GP gene





Ebola Virus, entry into a Cell.





Uniform diameter 80 nm, length 600-1400 nm

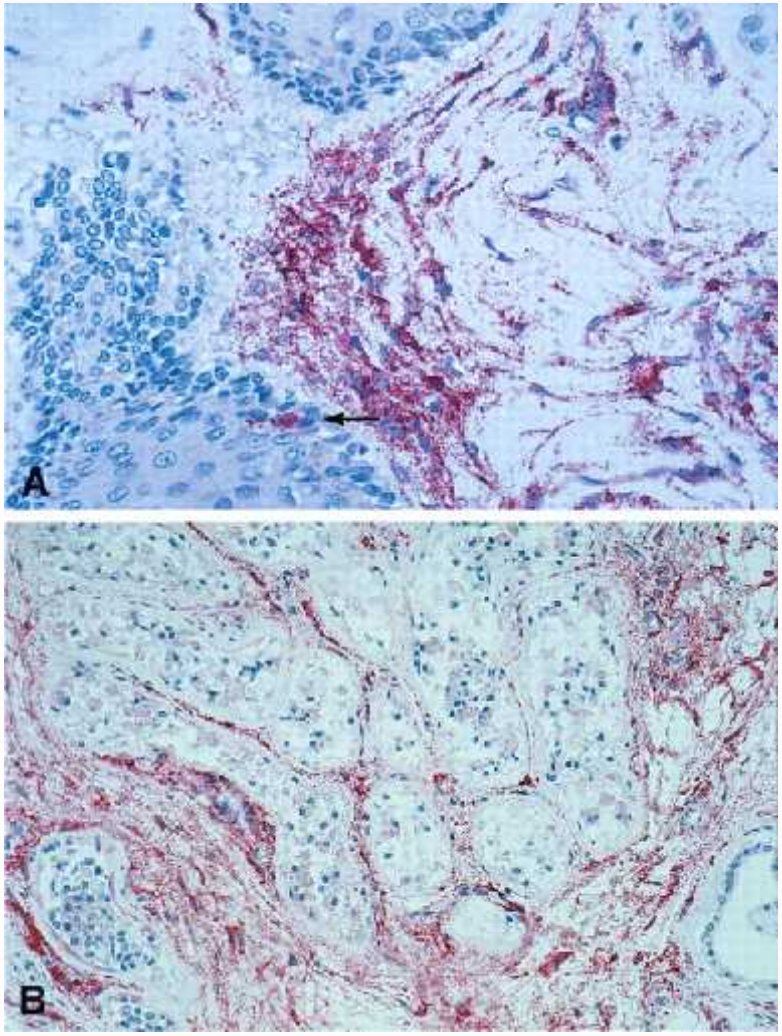
Kawaoka Y. N Engl J Med 2005;352:2645-2646.

Pathology

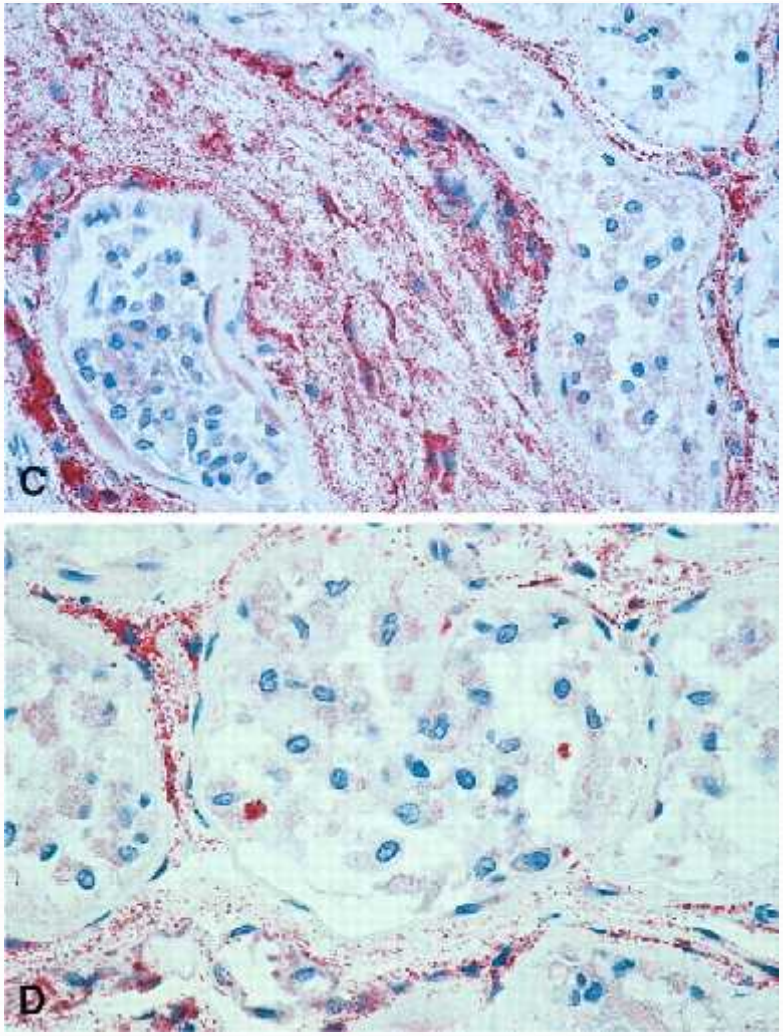
studied in non-human primates

- Primary cells infected
  - Dendritic cells
  - Tissue macrophages & monocytes
  - Endothelial cells
  - Fibroblasts
  - Hepatocytes
    - Small foci of necrosis
  - Splenic red pulp
  - Adrenal cortical cells
- Cytokine release increases recruitment of macrophages & monocytes
  - Increased viral replication
  - Transport of virus to lymph nodes & spleen
- Lymphocytes not infected but rapid loss by apoptosis, causing immunosuppression
- Factor VIIa/tissue factor overexpression
  - DIC
- Protein C decreased

Wyers M, Formenty P, Cherel Y, et al. Histopathological and immunohistochemical studies of lesions associated with Ebola virus in a naturally infected chimpanzee. J Infect Dis **1999**;179(suppl 1):S54–9.

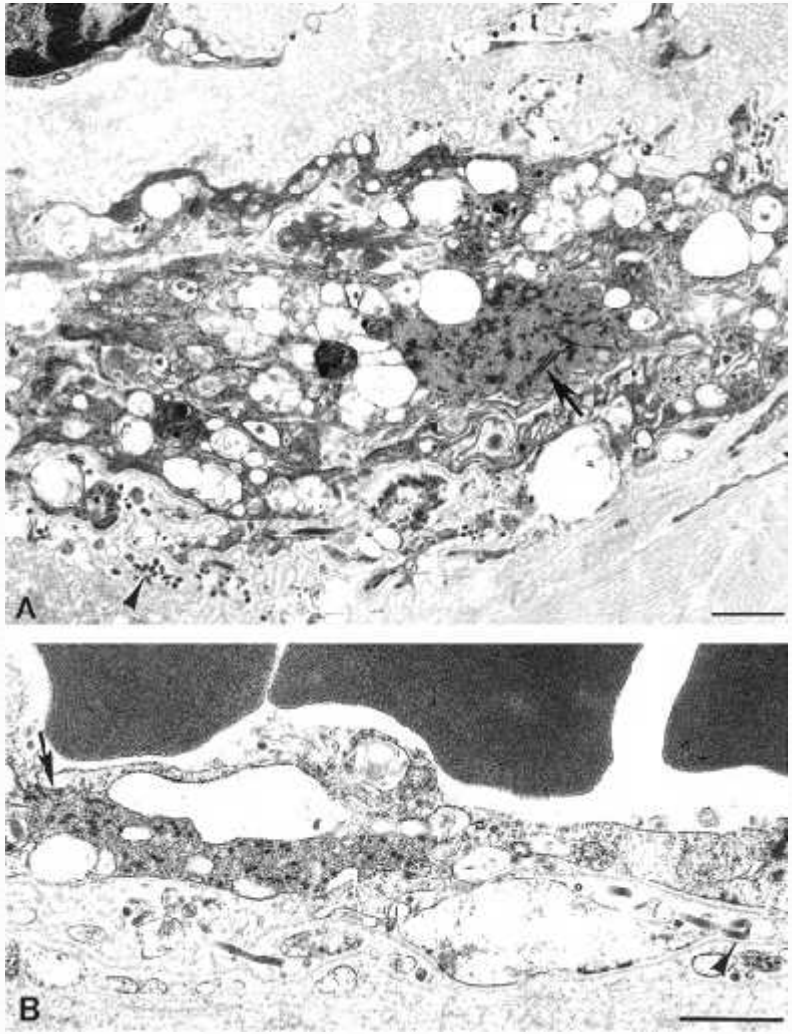


Zaki S R et al. J Infect Dis. 1999;179:S36-S47



Zaki S R et al. J Infect Dis. 1999;179:S36-S47

Ultrastructural features of Ebola (EBO) virus infection in skin of EBO hemorrhagic fever patient.



Zaki S R et al. J Infect Dis. 1999;179:S36-S47

Serum antigen and antibody titres against EBO-CI in a female ethologist who presumably became infected while doing a necropsy on an infected chimpanzee.

Date, day after onset	IFA	IgG ELISA	IgM-capture ELISA	Antigen detection ELISA
27 November 1994, 3	0	0	1250	512
1 December 1994, 7	0	0	15,000	8192
16 December 1994, 22	2048	6000	10,000	0
4 January 1995, 41	4096	10,000	3000	0
13 February 1995, 81	2048	5500	200	0
23 June 1995, 211	1024	5000	0	0
4 March 1996, 466	128	3200	0	0

Formenty P et al. J Infect Dis. 1999;179:S48-S53

The Journal of Infectious Diseases

Pathogenesis

Why does it overwhelm?

Why do some survive?

Why does the virus fail to clear?

- **Failure of Innate Immunity**
  - Interferon induction suppressed by VP35
  - Interferon action blocked by VP24
    - No resistance to viral growth
  - No activation of NK cells, macrophages or dendritic cells
  - A race against time as viral load increases, innate immunity useless, all depends on adaptive immunity
- **No enhancement of Adaptive Immunity**
  - Apoptosis of lymphocytes
    - Immunosuppression, secondary bacterial & yeast infections
  - Race between the virus & adaptive immunity

Why does the patient get Shock?

- Viral infection of endothelial cells
  - Vascular leak, peripheral oedema, “third spacing”
- Correctable hypovolaemia
  - GI losses, 5-10 l/day
  - 3rd spacing
    - No evidence of myocardial dysfunction
    - Possibility of adrenal insufficiency (no direct evidence)
- ? role of excessive cytokines

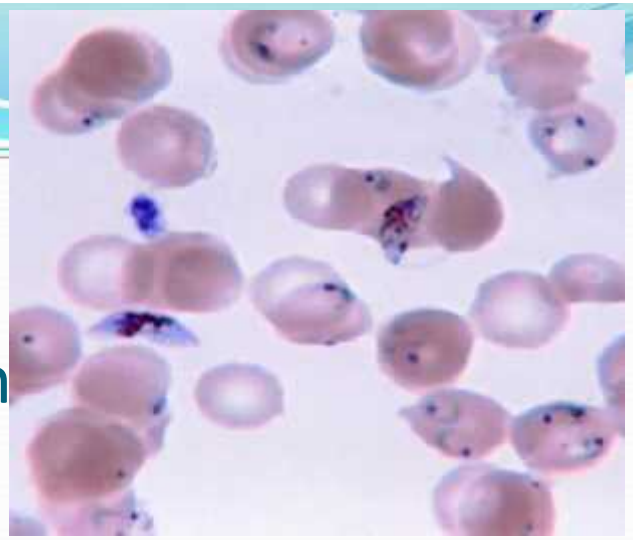
Diagnosis

under bio-safety level 3

- **PCR**
  - NVRL does it 24/7, Senior Consultation, after Risk Assessment
  - Sample transported by contracted company
  - Two assays
  - 6-12 hour turn around
- Others
  - Virus isolation
  - Electron Microscopy
  - Antibodies & Antigen detection

Differential Diagnosis

Note that such patients also present with other diseases e.g. DKA & Appendicitis



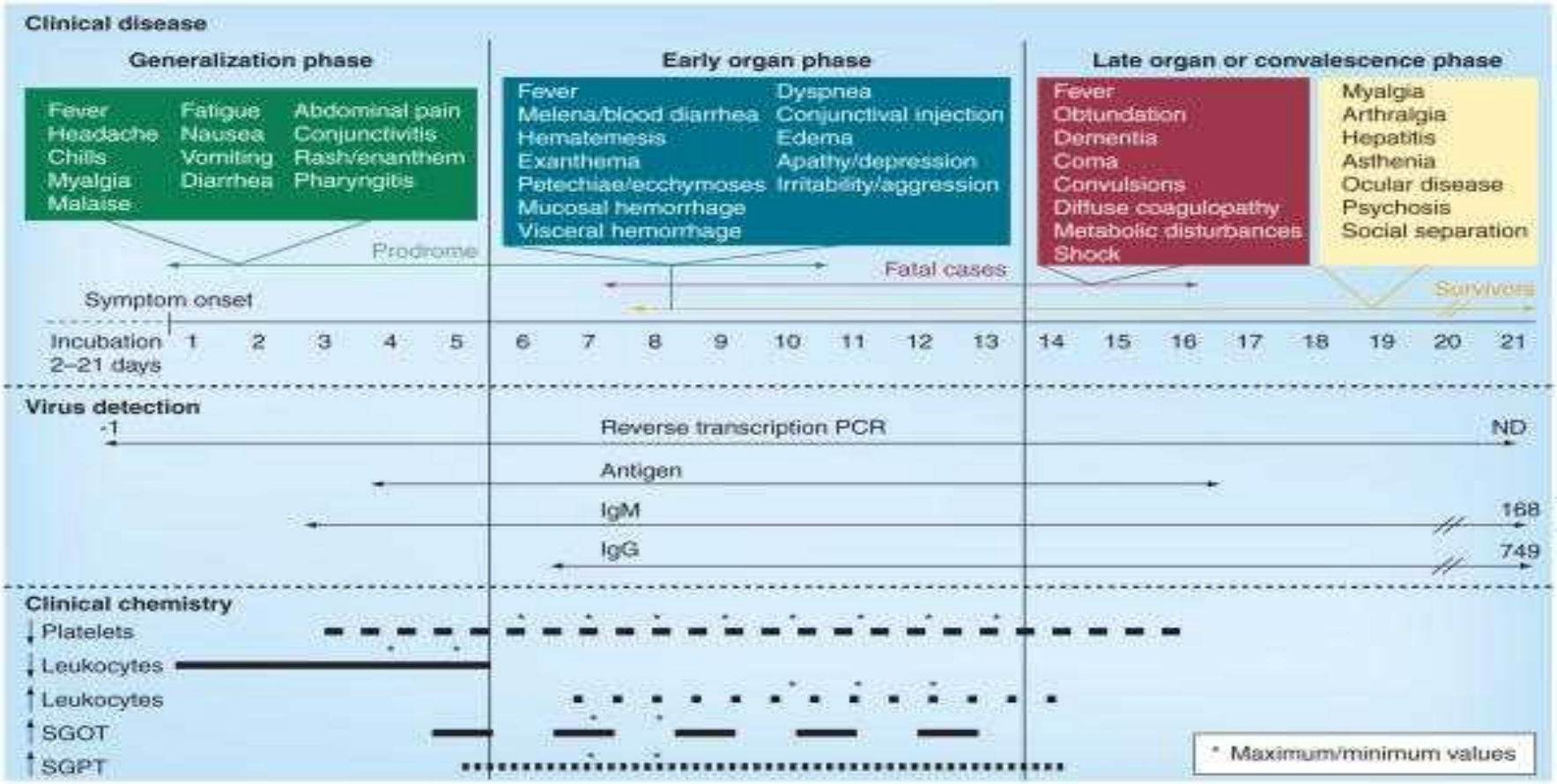
Bacteria	Viruses	Protozoa	Helminths	Rickettsiae
Typhoid Strep pharyngitis Pyelonephritis Pneumonia Gastroenteritis IAS • Appendicitis • Cholecystitis • Diverticulitis etc Meningococcal Sepsis 2nd syphilis Leptospirosis Relapsing fever *B. recurrentis* (lice) *B. duttoni* (tick-borne)	**HIV** **Seroconversion** **AIDS** **Hepatitis A or B** **Dengue Fever** **Influenza** Infectious Mono Rift Valley Fever Yellow Fever **Ebola** Lassa	**Malaria** Amoebiasis Toxoplasmosis	Schistosomiasis (Katayama Fever) Strongyloidiasis Trypanosoniasis (sleeping sickness) *T. rhodesiense* *T. gambiense*	Q-fever Tick-borne Rickettsiosis *R.conorii* *R. africae* *R. prowazekii*

Clinical Features, Monrovia

Chertow D et al. Ebola Virus Disease in West Africa-Clinical Manifestations & Management. Nov 5th 2014 N Engl J Med.

Day	Symptom & Sign	V Load
0-3	Fever: 37.5-40°C. usual >38.5. Malaise, Fatigue, Body aches	PCR+ _
3-5	Epigastric Pain, Nausea, Vomiting, Diarrhoea	PCR+, 10^{2-4}/ml
2-12	Headache, conjunctival injection, Chest Pain, Abd Pain, arthralgia, myalgia, Hiccups, Delirium, Agitation, Seizures, Lethargy, Prostration	PCR+, 10^{5-8}/ ml
10-14	**60%** Thready pulse, hypotension, cold extremities, tachypnoea oligo-anuria, decreased consciousness/coma. All presumeddue to **Hypovolaemic shock & Lactic Acidosis,** leading to **death** in the absence of aggressive critical care.	PCR+: 10^{8-2}/ml
OR		
10-13+	**40% Recovery, some complications**	PCR -, blood, semen+
	Oral/esophageal mucosal candidiasis, Oral ulcers Secondary sepsis, pneumonia	
	Neck rigidity, decreased consciousness, ? bact meningitis or ebola meningo-encephaliltis or post infectious encephalomyelitis	
	Uveitis, Orchitis, Prolonged asthenia, fatigue	

Clinical Course



Hamburg case
crucial role of critical care

- 36 year old WHO epidemiologist in Sierra Leone
- 18/8/14(day 1) myalgia, headache, malaise arthralgia
- Day 2-6 fever, treated as malaria & with ceftazidime
- Day 6 PCR+ EBOV
- Day 7 Nausea, Vomiting, Diarrhoea
- Cipro & Metronidazole
- Iv fluids
- Day 10 transferred to Hamburg

Clinical features

- T 38.4°C, BP 110/80, hr 87/min
- Dehydrated
- PH: chronic HBV,
  - DNA 11,000IU/ml
- Hb: 18
- Cr: 170
- K: 3.4
- AST: 1054
- platelets 103
- D-dimer: 33 (0.1-0.4)
- U/S abd
  - complete collapse IVC
  - Paralytic ileus
  - Severe edema small +large bowel wall

Clinical Variables, Fluid Management, and Laboratory Values during the Course of Illness.

Table 1. Clinical Variables, Fluid Management, and Laboratory Values during the Course of Illness.*

Variable	Day of Illness												Day of Illness					
	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Clinical variables†																		
Temperature (°C)	38.4	39.3	38.8	40.0	40.0	39.8	38.8	38.8	38.5	38.8	39.0	38.6	37.8	37.8	38.0	38.2	37.8	37.6
Respiratory rate (breaths/min)	ND	ND	ND	ND	40	40	39	35	35	40	31	40	32	27	36	30	24	24
Oxygen saturation (%)	97	93	95	88	89	90	92	93	<85	88	<85	<85	<85	97	<85	96	97	96
Heart rate (beats/min)	96	92	80	140	170	160	140	150	144	155	140	150	140	135	120	130	125	120
Oxygen (liters/min)	—	—	—	—	1	5	6	6	8	8	6	5	3	2	3	3	—	—
Noninvasive ventilation (hr)	—	—	—	—	—	—	—	—	4	—	2	10	2	—	4	4	—	—
Fluid measurements (ml)																		
Intravenous fluids‡	7850	13,175	11,675	9200	7510	13,734	7574	4418	3818	3613	4064	6116	4316	2836	5520	3410	1264	1000
Oral fluids§	—	—	—	—	—	—	—	80	180	480	880	780	860	1420	1780	1920	2445	1585
Diarrhea¶	4400	8400	6850	4030	2230	950	500	—	300	100	—	900	800	300	700	—	—	—
Vomiting‖	—	—	1200	1550	—	—	100	200	—	—	—	—	—	—		—	—	—
Urine	1330	1050	400	ND	ND	1760	4940	6870	6770	5870	6800	5690	5480	5500	6600	4480	4450	3550
Balance	2120	3725	3225	3620	5280	11,024	2034	−2572	−3072	−1877	−1856	306	−1104	−1544	0	−850	−741	−965
Laboratory values																		
Hemoglobin (g/dl)	18.0	15.8	15.4	16.0	14.1	13.4	13.2	11.1	12.1	8.8	7.1	8.2	7.7	7.8	8.2	7.7	7.5	8.0
Hematocrit (%)	55.2	48.4	42.9	49.4	43.3	44.1	39.4	33.6	31.5	24.9	24.2	27.1	27.2	24.9	25.1	25.5	25.0	27.2
White cells ($\times 10^3$/mm^3)	6.8	6.4	7.3	14.1	21.8	28.7	19.7	13.0	18.2	14.2	6.3	9.2	11.7	8.3	12.5	9.7	8.1	8.8
Platelets ($\times 10^3$/mm^3)	103	116	152	135	101	81	83	46	50	77	63	119	123	153	230	267	243	261
D-dimer (mg/liter)	33	38	38	37	35	28	24	11	9	4	5	9	27	13	9	8	5	2
AST (U/liter)	1054	942	924	950	834	592	321	205	183	157	152	224	143	219	270	154	268	181
CRP (mg/liter)	11	13	23	43	59	123	127	65	79	60	39	37	34	33	34	30	35	37
Lactate (mmol/liter)	1.8	2.7	1.5	2.8	6.5	9.3	1.7	1.1	1.0	0.9	0.6	0.4	0.4	0.6	0.5	0.4	0.8	0.6
Creatinine (mg/dl)**	1.9	1.3	1.0	1.0	1.1	1.2	1.0	1.3	1.5	1.5	1.2	1.0	0.9	0.7	0.7	0.7	0.7	0.7
Sodium (mmol/liter)	135	135	138	141	144	147	144	148	154	159	155	148	148	144	143	141	136	133
Potassium (mmol/liter)	3.4	3.5	3.5	3.6	3.3	3.9	4.4	3.9	4.6	3.8	3.9	5.0	4.3	3.8	4.1	4.4	3.9	3.7
Chloride (mmol/liter)	102	103	109	110	116	119	117	118	120	122	125	116	115	112	111	108	105	100
pH	7.45	7.38	7.45	7.44	7.45	7.37	7.47	7.43	7.40	7.50	7.51	7.22	7.23	7.48	7.42	7.26	7.51	7.46
Bicarbonate (mmol/liter)	20.5	24.1	22.9	21.9	15.5	14.2	24.7	27.6	29.4	32.4	28.8	29.1	29.8	28.5	27.2	29.8	28.0	28.9

* Data are for the period starting with the patient's arrival in Hamburg, Germany, and ending on the day before transfer of the patient to the infectious disease ward. AST denotes aspartate aminotransferase, CRP C-reactive protein, and ND not determined.

† Temperature was measured tympanically until the insertion of a urinary catheter on day 15. The maximum respiratory rate, minimum oxygen saturation (as measured with the use of pulse oximetry), and maximum heart rate were assessed by means of continuous measurement on a medical monitor. The inspired oxygen concentration was not measured, but the patient was receiving oxygen with the use of a nasal cannula. Data on noninvasive ventilation are the number of hours of noninvasive ventilation delivered by means of the Exita 2 dura (Dräger) in 24 hours.

‡ Intravenous fluids included 5% glucose solution, Sterofundin ISO (B. Braun Medical Supplies), and intravenous nutrition.

§ Oral fluids included water, tea, and oral nutrition (low-fiber standard formula providing 1 kcal per milliliter).

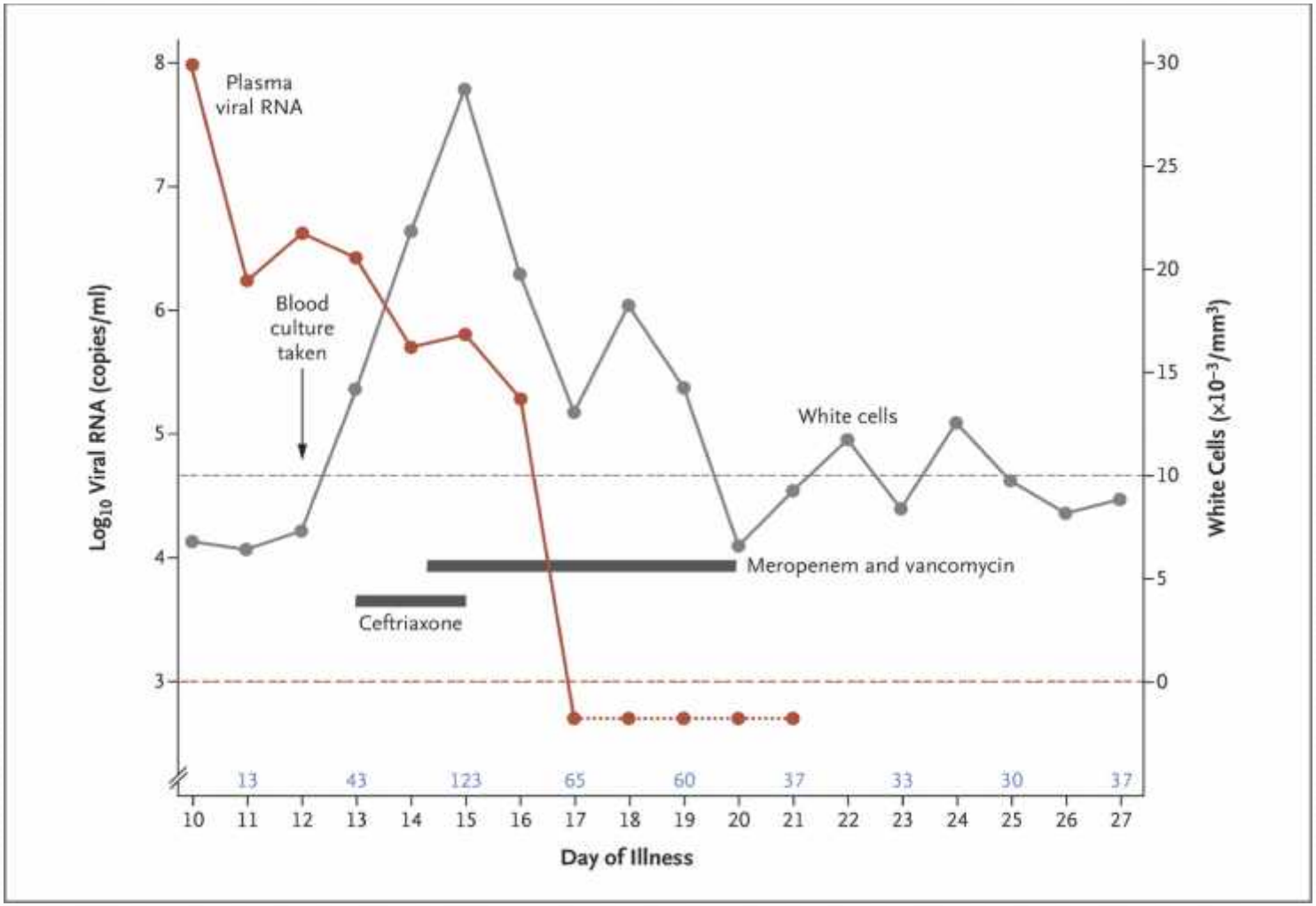
¶ A fecal collector was inserted on day 16.

‖ A nasogastric tube was inserted on day 16.

** To convert values for creatinine to micromoles per liter, multiply by 88.4.

Kreuels B et al. N Engl J Med 2014. DOI: 10.1056/NEJMoa1411677

Timeline of Plasma Viral RNA Load, Septicemia, and Antimicrobial Therapy in a Patient with Severe Ebola Virus Disease.



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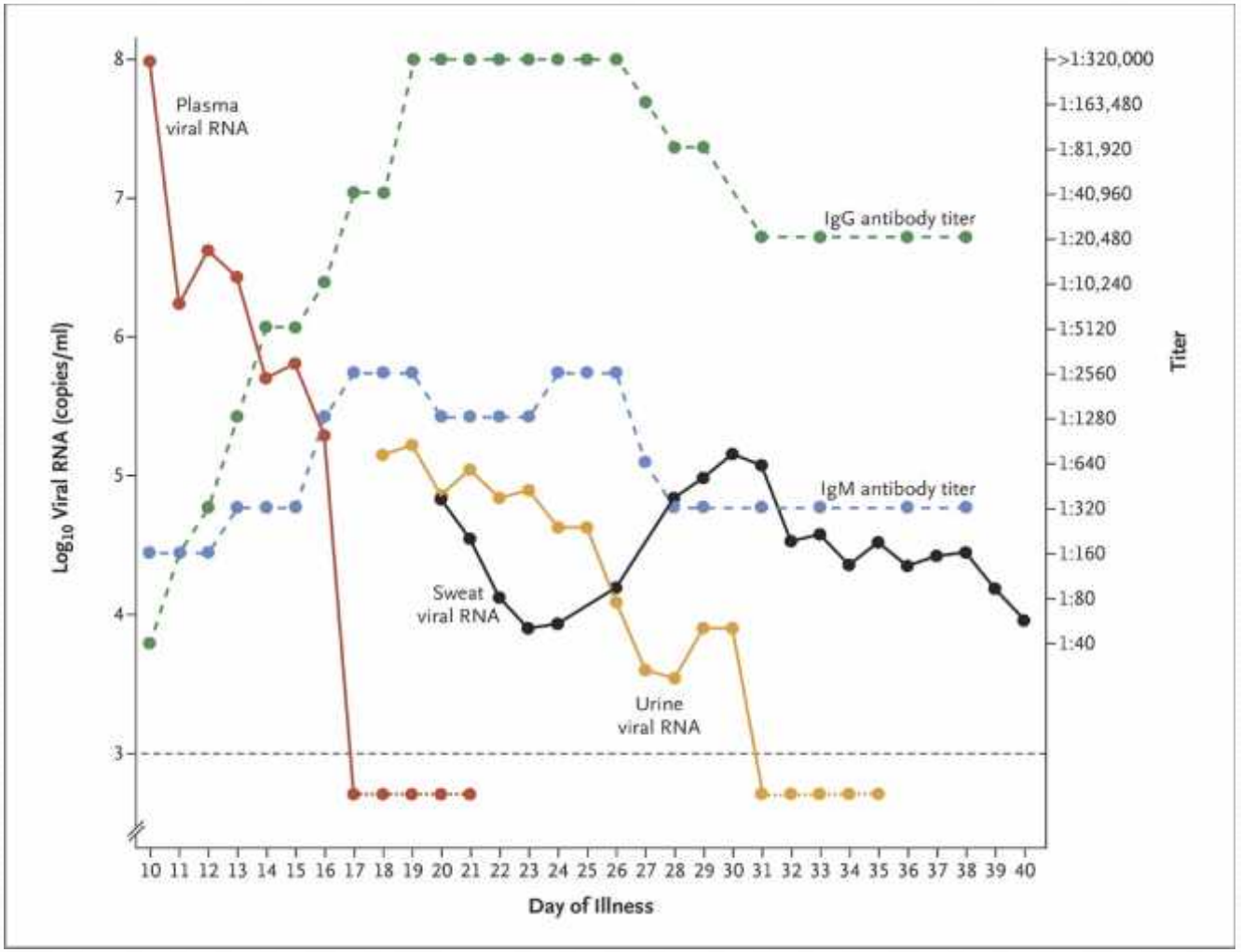
Timeline of Viral RNA Load in Plasma, Sweat, and Urine and Antibody Titers in Plasma.



Kreuels B et al. N Engl J Med 2014. DOI: 10.1056/NEJMoa1411677

Monitoring & Treatment

Standard

Experimental

Standard Monitoring

- Foley catheter
- N/G tube
- Rectal tube
- Non-invasive BP monitoring
- HR
- RR
- Temperature
- O2 Sat monitor

- Bloods (POCT)
  - U/E,
  - lactate, pH, pO2, pCO2
  - FBC, PT, PTT, LFTs
  - EBOV PCR
- ? Portable CXR
  - iatrogenic fluid overload
  - Secondary pneumonia
  - U/S
    - IVC collapse

Standard Therapy

- IV Fluids 5-15 L/day
- IV/po electrolyte replacement
- Nutrition
- Antimicrobials
- Transfusion
  - O-neg, packed cells
  - Plasma
  - Platelets
  - Coagulation products

Untested Treatment

Convalescent serum or blood

Monoclonal IgG

New anti-viral agents

Old drugs

Vaccines

Whole Blood/Convalescent Serum

- English NSI-induced EVD, 1976 survived with both interferon and convalescent serum at early phase. Viral titres 10^{4-5} gpi units/ml to 3-10 gpi units/ml.
- Eight severe EVD patients, Kikwit, 1995 transfused blood from 5 convalescents, +for IgG anti-ebola virus. One (12.5%) died, compared to 80% overall mortality. Transfused patients' standard of care was higher.
- Polyclonal serum from monkeys who survived filovirus infection, consistently protected other monkeys when given at day 2, 4 & 8 post-infection
  - Dye JM, Herbert A, Kuehne AI, et al. (2012). "Postexposure antibody prophylaxis protects nonhuman primates from filovirus disease." Proc Natl Acad Sci USA **109**(13): 5034-5039.

2 monoclonal anti-GPs developed

MB-003

- Chimeric mAbs (c13C6, h-13F6, and c6D8) against 3 non-overlapping anti-GP epitopes in Chinese hamster ovary cells and in whole plant (Nicotiana benthamiana) cells
- monkey survival at 24 & 48 hr post infection

Zmab

- mice vaccinated with VSV∂G/EBOV-GP
- 3 of 8 EBOV GP-specific mAbs (1H3, 2G4, and 4G7) selected
- Individually effective in mice at 1-2 days. Less effective in guinea pigs individually, but fully effective in combination
- 100% effective 24 hr, 50% 48 hr. cynomolgus monkeys
  - Xiangguo Qiu *et al.* **Successful Treatment of Ebola Virus–Infected Cynomolgus Macaques with Monoclonal Antibodies** *Sci Transl Med* **4**, 138ra81 (2012);

ZMapp, from components of both MB-003 & Zmab

- Longer ½ life in humans
  - individual murine antibodies in ZMab were chimerized with human constant regions (cZmab)
  - Then produced in *Nicotiana benthamiana*
- Individual components of both MB-003 and Zmab tested in guinea pigs & monkeys
  - In MB-003 only C13C6 yielded any survivors
  - Added to multiple combinations of components of Zmab

Z-Mapp effective at 5 days

- Z-Mapp-1 & 2 carried forward for NHP trials
- Z-Mapp1 > Z Mapp2 in trials in monkeys treated from day 3
- Z-Mapp 100% effective rhesus monkeys at 5 days advanced disease

Qiu X, W. G., Audet J et al. (2014). "**Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp**." Nature **514**(7520): 47-53.

Brincidofovir

- Broad-spectrum active against dsDNA viruses
  - CMV, HSV, HHV-6, adenovirus, polyoma viruses, papilloma virus, monkeypox, variola and vaccinia
- Active in vitro against EBOV, but not published
- Lipid (hexadecyloxypropyl) pro-drug of cidofovir
- Cleaved, phosphorylated to intra-cellular CDV-PP
- CDV-PP >100 more potent than cidofovir
- Not a substrate for organic ion transporter 1 (hOAT1)
- Main adverse effect diarrhoea & vomiting
  - N Engl J Med (2013) 369:1227-36
- Likely available but only for confirmed case
- Phase II, Ebola, USA & EU by Chimerix

Favipivavir (Avigan®) Toyama Chemical/Fuji Film

- Potent in vitro: segmented, negative-strand RNA viruses
  - RNA polymerase inhibitor
  - influenza, yellow fever, other flaviviruses, enteroviruses, arenaviruses, bunyaviruses, alphaviruses
- Approved for human use in Japan for influenza
  - EBOV effective in vitro and in interferon receptor-1 def mice
  - At 6 days, induced rapid EBOV clearance, reduced biochemical parameters of disease, and 100% survival.
  - French nurse survived, received favipivavir
- Tested >1000 people, no major ae,
  - but dose proposed EVD 2-5 times higher.
    - Confirmed case: call the Embassy of Japan.

Others

- TKM-Ebola, Burnaby, BC
  - Phase I stopped, in healthy volunteers, July 2014, concern about cytokine release syndrome
- Chloroquine

Prognosis

- Mortality: 50-70%
- Fowler reported 43% mortality with good hydration in Guinea

Age < 40 yrs: 20%

Age >40 yrs: 80%

? Effect of pregnancy

Other immunosuppressive conditions

Vaccines

- Vesicular Stomatitis Virus
  - a cause of self-limited oral ulceration in horses and other animals in Central & S America
  - Occasional cause of influenza-like illness in humans with close animal contact
- Recombinant VSV with one gene removed, a vaccine platform onto which GP of EBOV is inserted
- Works well in monkeys
- It and an adenovirus vector are to undergo trials
- ? Role in Needlestick Injury

Mode of Transmission

Needle Stick Injury

Direct Person to Person

? Indirect

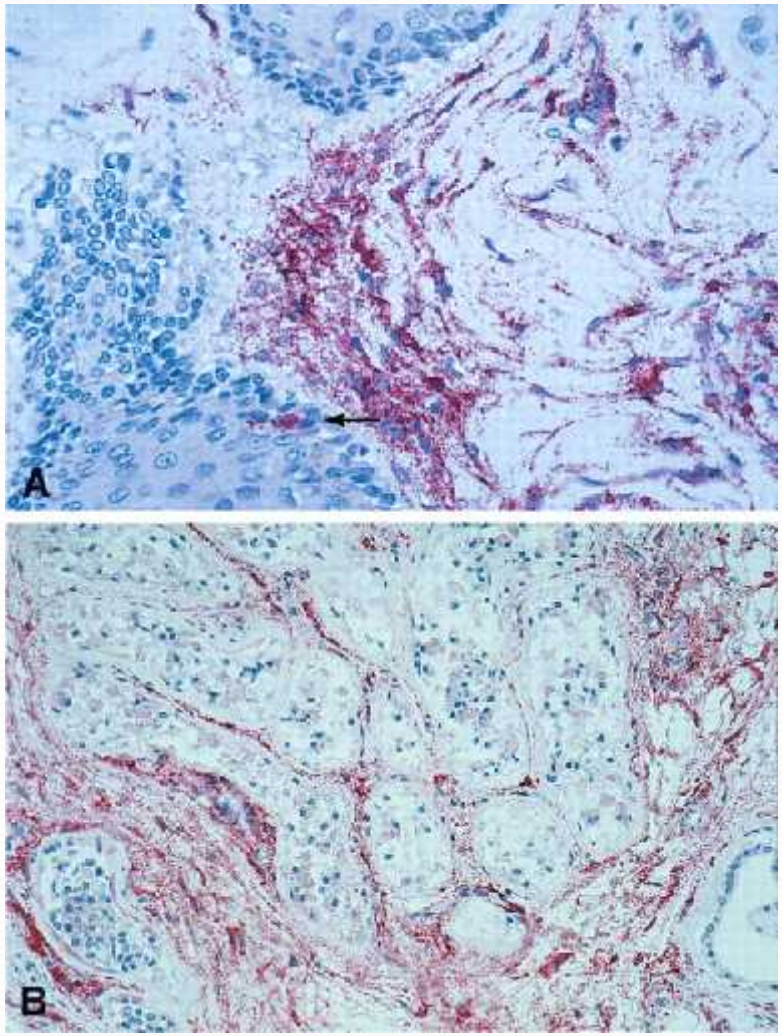
?? Fomites

???? Airborne

Transmission

- Not a hardy virus
  - Enveloped, degrades quickly in environment
  - Inactivated by soap, alcohol, dilute bleach & other agents
- All* transmission arises from direct contact with patient or body fluids
  - Blood, saliva, vomitus, diarrhoea, urine, sweat, semen, breast milk

- Intact skin ? a source



Direct Contact Kikwit

Dowell SF1, et al. (1999). "Transmission of Ebola hemorrhagic fever: a study of risk factors in family members, Kikwit, Democratic Republic of the Congo, 1995. Commission de Lutte contre les Epidémies à Kikwit." J Infect Dis **179**(Suppl): S87-91.

- Retrospective interview survivors in 27 households
- Primary case died 1/1/95-7/5/95 Interviews 17/5-7/6/95
- 173 contacts, 95 direct contact. 28(16%) got EVD
  1. All had direct physical contact
  2. Exposure to bodily fluids conferred additional risk
     1. After adjusting for 1 & 2, additional risk
        - Touching a cadaver
        - Adults
        - Physical contact in late illness
          - However, 4 contacts were early
- None of 78 with no physical contact were infected

Fomites, Gulu Uganda, 2000

Bausch DG, et al. (2007). "Assessment of the risk of Ebola virus transmission from bodily fluids and fomites." J Infect Dis **196**(Suppl 2): S142-147.

- 54 convenience patient samples, from plastic receptacles of patients with proven EVD
  - urine, sputum, vomitus, stool.
  - Dacron swabs of nasal blood, tears, skin surface
  - Sterile containers: semen, breast milk, saliva
  - 33 environmental samples
- Cold chain to Atlanta for culture & RT-PCR
  - 33 environmental samples all negative, except Doctors bloody glove & Iv set (+controls)
- Saliva 8/12 +, Skin 1/8+, Stool 2/4+, Tears 1/1, Bloody nasal 1/1, convalescent semen ½+.Total 16/54+ 4 culture+

Airborne

Evidence Against

- Not like airborne pathogen epidemiologically
- Strict contact precautions, PPE, contact tracing & quarantine abruptly terminated all previous epidemics
- Pathology is against it
- Many cases of persons sharing air but not acquiring EVD
- Viral pneumonia not described

Concerns

- REBOV transmitted in caged monkeys well separated
- Experiment 4 monkeys, 2 controls
  - Dose 2.6 & 4.7 log, 10 min
  - Monkey head encased exposed to 0.8-1.2 µm aerosol
  - Transmission & death in all 4
  - Pneumonia prominent but otherwise pathology same
- Aerosol induction a concern
  - Nebulizers
  - Non-Invasive ventilation
  - Intubation & ETT suctioning

Transmission Prevention

Diagnosis

Public Health

- Contact tracing
- Appropriate Quarantine

Hospital Infection Control

- Personal Protective Equipment (PPE)
- Environmental Controls

Reserve slides

yr.		spec	No	Death	
1976	Zaire	EBOV	318	280 (88%)	Index case: monkey/antelope meat. First cases acquired from chloroquine IM. Most meds IM, 5 syringes per day. Yambuku & 20 nearby villages. Spread by antenatal clinic or close personal contact in hospital. 82 pregnant women had EVD, due to IM vitamins. Mortality 89% and 10 live infants born to mothers who died, all babies died within 19 days. Hospital closed, 11 of 17 HCWs died. Blood of nun sent to Antwerp, in simple flask with melting ice, broken vial in luggage! 2nd Belgian nun & Zairian nurse infected, despite convalescent Marburg serum.
1976	Sudan	SUDV	284	151 (53%)	Nzara, Maridi & surrounds. Spread by close personal contact in hospitals. Many HCWs.
1976	UK	SUDV	1	0	Lab NSI
1977	Zaire	EBOV	1	1	Retrospectively in Tandala village
1979	Sudan	SUDV	34	22 (65%)	Nzara, Maridi, 5 families. Transmission only by intimate contact, but not in confined spaces.

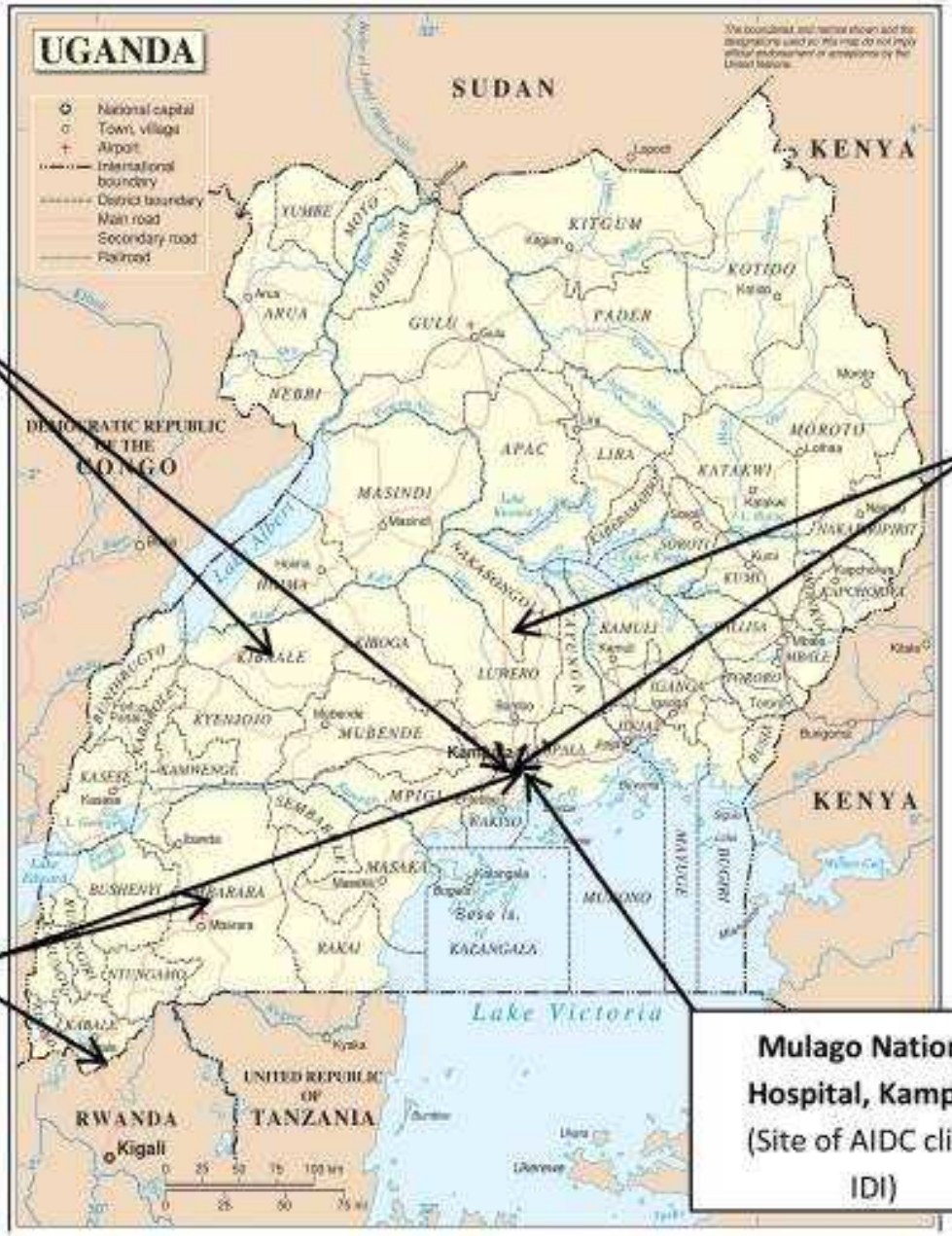
year	country	species	No	Deaths	
1989	VA, USA	RESTV	0	0	Cynomolgus (crab eating) monkeys Philippines in quarantine. Animals in non-adjoining cages & uninvolved rooms, infected, ? Airborne.
1990	VA & Texas	RESTV	4	0	Cynomolgus monkeys from Philippines in quarantine 4 asymptomatic antibody+ workers
1990	Philippines	RESTV	3	0	High mortality in monkeys in primate fac, 3 asymptomatic antibody + workers
1992	Italy	RESTV	0	0	Quarantine, monkeys from Philippines
1994	Gabon	EBOV	52	31 (60%)	Gold mining camps deep in rain forest.? Yellow fever, confirmed Ebola 1995.
1994	Cote d'Ivoire	TAFV	1	0	Zoologist does autopsy on wild chimp, Tai Forest, evacuated to Switzerland
1995	DRC/Zaire	EBOV	315	250 (81%)	Jan-May, Kikwit & surrounds. Index case worked in forest. Spread families & hospitals. Family members provided basic hospital care. Spouses often slept in the bed with the patient. Ro: 1.83
1996	Gabon	EBOV	37	21 (57%)	Mayibout. Dead chimpanzee found in forest & eaten. 19 infected + family cases

year	country	specie	No	Deaths	
1996-7	Gabon	EBOV	60	45 (74%)	Booue patients moved to Libreville. Index case forest hunter, dead infected chimp
1996	S. Africa	EBOV	2	1 (50%)	Doctor travelled Gabon to Jburg, ill. Cared for Ebola, but not diagnosed initially. He recovered, nurse exposed to his blood died
1996	USA	RESTV	0	0	Monkeys in Texan quarantine only
1996	Phil	RESTV	0	0	Monkeys in quarantine
1996	Russia	EBOV	1	1 (100%)	Laboratory
2000-1	Uganda	SUDV	425	224 (53%)	Risks: funeral attendance, family contact, providing care without adequate PPE. Ro: 1.34
2001-2	Gabon	EBOV	65	53 (82%)	Border outbreak
2001-2	Rep Congo	EBOV	57	43 (75%)	Traced to multiple animals dying in rain forest, chimpanzees, antelopes, porcupines

year	country	specie	No	Deaths	
2002-3	Rep Congo	EBOV	143	128 (89%)	2 villages in Mbomo district
2003	Rep Congo	EBOV	35	29 (83%)	Same 2 villages in Mbomo district
2004	Sudan	EBOV	17	7 (41%)	Yambio. Measles, index: baboon hunting. sleeping with dead body.
2004	Russia	EBOV	1	1 (100%)	Laboratory
2007	DRC/Zaire	EBOV	264	187 (71%)	Kasai Province
2007-8	Uganda	BDBV	149	37 (25%)	Western Uganda, new strain.
2008	Philippines	RESTV	6	0	First RESTV outbreak pigs. 6 farm & abattoir workers asympto antibody+
2008-9	DRC/Zaire	EBOV	32	15 (47%)	Kasai Province
2011	Uganda	SUDV	1	1 (100%)	Luwero. Quick diagnosis, new CDC lab, 1 Case, 12 yr. old girl. Bats in school, IC immediate announcement
2012	Uganda	SUDV	11	4 (36.%)	Kibaale
2012	DRC/Zaire	BDBV	36	13 (36%)	Field lab PHAC, no link to Kibaale
2012-3	Uganda	SUDV	6	3 (50%)	Luwero, CDC, rapid diagnosis

Ebola Outbreak – Kibale District
July –October 2012
24 cases
11 lab confirmed
17 deaths (1 health care worker)

Marburg Outbreak – 5 Districts in South-West
October-November 2012
18 cases
9 lab confirmed
9 deaths (1 health care worker)



Ebola Outbreak – Luweero District
November 2012
7 cases
6 lab confirmed
4 deaths

Mulago National Hospital, Kampala
(Site of AIDC clinic, IDI)

Marburg cases & outbreaks

Year	Country	Origin	Deaths/cases
1967	Germany/Yug	Uganda	7/32 (22%)
1975	RSA (Joh.)	Zimbabwe	1/3
1980	Kenya	Kenya, Kitum Cave	1/2
1987	Kenya	Kenya Kitum Cave	1/1
1988	USSR	Koltsovo NSI Lab	1/1
1990	USSR	Koltsovo Lab	0/1
1991	Sweden	Filovirus,sero+	1 /1

Marburg outbreaks

Yr.	Country	Comments	Origin	d/case
1998-2000	DRC Congo	Overlapping outbreaks, Goldmine. Haem synd of Durba 1987. Short family transmission chains	Durba Watsa	128/154 (83%)
2004-5	Angola	Single introduction, per-per spread. children/women. ?breast milk. R0: 1.6	Uige Hosp	283/ 335 (84%)
2007	Uganda	Visits to mine (Kitaka cave)		1/4
2008	Holland	Visit to python cave Uganda		1/1
2008	USA	Visit to python cave Uganda		0/1

Marburg outbreaks

Yr.	Country	Comments	Origin	d/case
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2004-5	Angola	Per-per spread. children/women. ?breast milk.	Uige Hosp	283/ 335 (84%)
2007	Uganda	Visits to mine (Kitaka cave)		1/4
2008	Holland	Visit to python cave Uganda		1/1
2008	USA	Visit to python cave Uganda		0/1
2012	Uganda		Kabale	4/15 (27%)
2014	Uganda		Kampala	1/1

Standard v enhanced precautions

Against

- Early Russian proof-of- concept with equine and ovid hyper-immune serum protected baboons, but a low challenge (<30 LD50 and <1 LD50) when initiated at < 1 hr.
- Investigated by USAMRIID
  - Worked in guinea pigs, day 0 but not day 4
  - Demonstrated high titres of neutralizing antibodies
  - Clinical illness delayed, viral titres reduced
  - but 11 of 12 monkeys died

Efficacy of equine IgG as treatment for Ebola virus infection in cynomolgus monkeys.

Day of treatment	Passive antibody titer	No. of monkeys (dead/total)	Viremia on day 7	Day of death
0	160	6/6	7.0	7, 7, 8, 8, 8, 8
0 + 5	640	2/3	ND	8, 9
−2	1280	3/3	ND	10, 12, 12
none	—	5/5	7.5	6, 6, 7, 7, 7

NOTE. Animals were intramuscularly (im) infected with 1000 pfu of EBO-Z on day 0 and treated with 6/mL IgG im (1.0–2.2 mL/kg) at various times before, on, or after day of infection. ND = not detectable.

Jahrling P B et al. J Infect Dis. 1999;179:S224-S234

Frequency of Symptoms Reported in 103 Cases in Kikwit, in 1995 & in 1,415 patients in the first nine months, 2014 in West Africa.

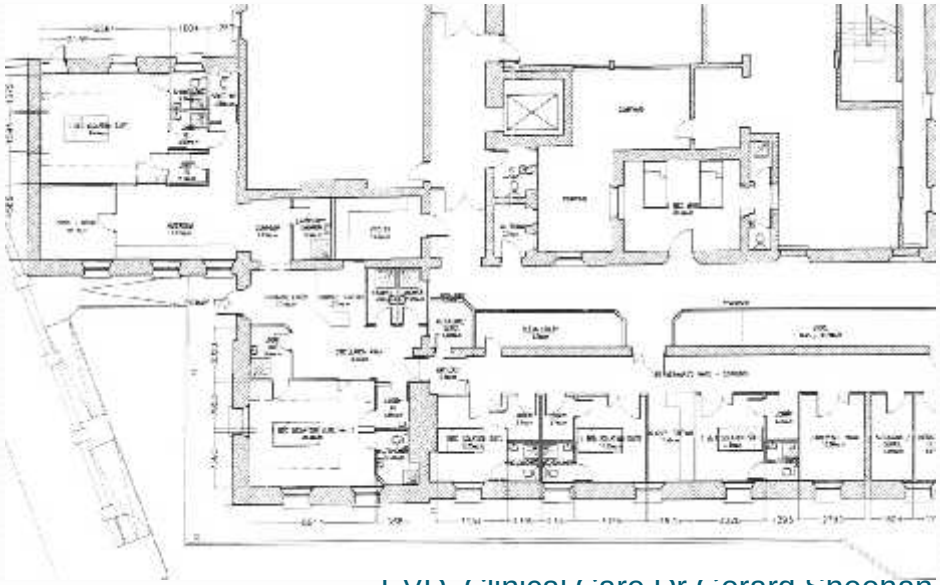
Symptom or Sign	%	Symptom or Sign	%
Fever (subjective in many centres)	87.1%	Hiccups	11.4%
Fatigue	76.4%	Jaundice	10.4%
Anorexia	64.5%	Eye Pain	7.7%
Vomiting	67.6%	Rash	5.8%
Diarrhoea	65.6%	Coma/unconsciousness	5.9%
Headache	53.4%	Unexplained bleeding	18%
Abdominal Pain	44.3%	Hematemesis	3.9%
Myalgia	38.9%	Blood PR	5.7%
Arthralgia	39.4%	Bleeding Gums	2.3%
Chest Pain	37%	Bloody Nose	1.9%
Cough	29.6%	Bloody Cough	2.4%
Dyspnoea	23.3%	Other bleeding	1.2%
Dysphagia	32.9%	Bleeding at Injection Site	2.4%
Conjunctivitis	20.8%	PV bleeding	3.2%
Sore Throat	21.8%	Hematuria	1.2%
Confusion	13.3%	Bleeding under Skin	0.6%

Frequency of Symptoms Reported in 103 Cases of Ebola Virus Disease in Kikwit, Democratic Republic of Congo, in 1995.*

Symptom	Percent of Patients with Symptom
Fever	≥90
Weakness	80–90
Diarrhea	80–90
Nausea and vomiting	70–80
Abdominal pain	60–70
Headache	50–60
Sore throat, odynophagia, dysphagia	50–60
Arthralgia or myalgia	50–60
Anorexia	40–50
Rash	10–20
Bleeding	
Any type	40–50
Gingival	10–20
Hematemesis	10–20
Melena	0–10
From puncture sites	0–10
Hemoptysis	0–5

* The sample included 84 patients who died and 19 who survived, representing approximately one third of the total cases in the outbreak. Adapted from Bwaka et al.[1]

National Isolation (NIU)



NIU

NIU Standard PPE

- Scrubs
- Water repellant gown
- Double gloving
- Apron
- Head/neck cover
- Goggles+-face shield
- Rubber boots/boot covers
- All skin covered, with water repellant material
- Mask N95/FFP3 (high specification)
- Repeated use of disinfectant in removal process
- Slow methodical, by protocol
- Buddy supervises
- Shower

NIU Enhanced PPE

- Powered Air-Purifying Respirators (PAPR)
- cough/aerosol generating procedures
  - Intubation/ventilation
  - N/G tube passage
- For presence > 1 hour in room
- For heavy viral shedding, based on clinical judgment. (e.g. copious vomiting /diarrhoea)

PPE importance of training

- Vulnerable point is at removal
- The more complicated the PPE, the more hazardous the removal, in the absence of training
- Vital importance of repeated training and simulation

High Spec Isolation rooms NIU

- External Entrance Ramp
- Both rooms separated from rest of ward
- Anteroom & exit room
  - Shower in exit room
- Negative pressure 12 air-exchanges
- 2 large rooms, big windows in direct line of sight of nursing station
- PPE removal within room
- All routine bloods done in room by POCT
  - U/E, glucose, LFTs, FBC
  - ABG, PT, PTT
- Keep virus in the room
- Minimize personnel
- ICU support possible within room
  - Renal support
  - Ventilation

Chloroquine

CQ is lysosomatropic and accumulates in endosomes, where it interferes with acidification, and inhibits the events that trigger fusion and release of viral components into the cytosol.

It has inhibitory effects on the pH-dependent cathepsins B and L, in EBOV GP processing events prior to fusion