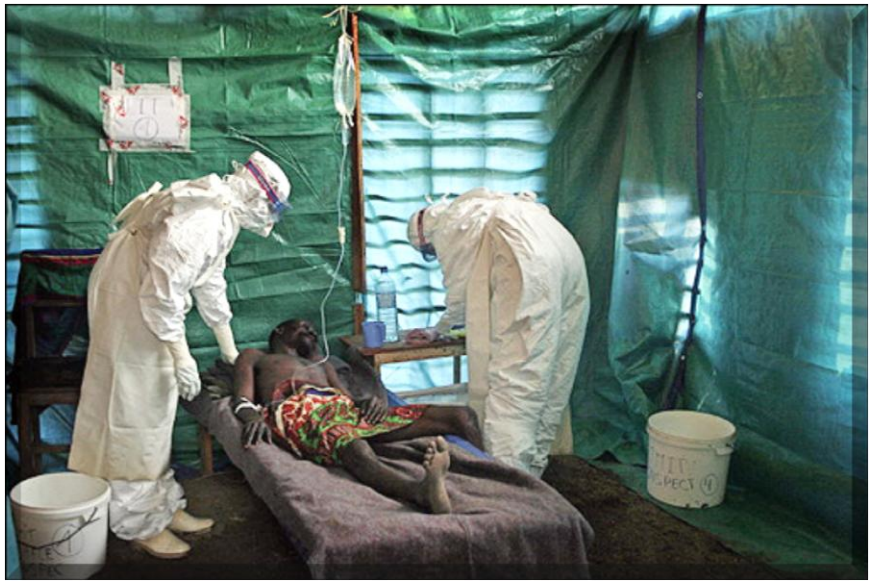
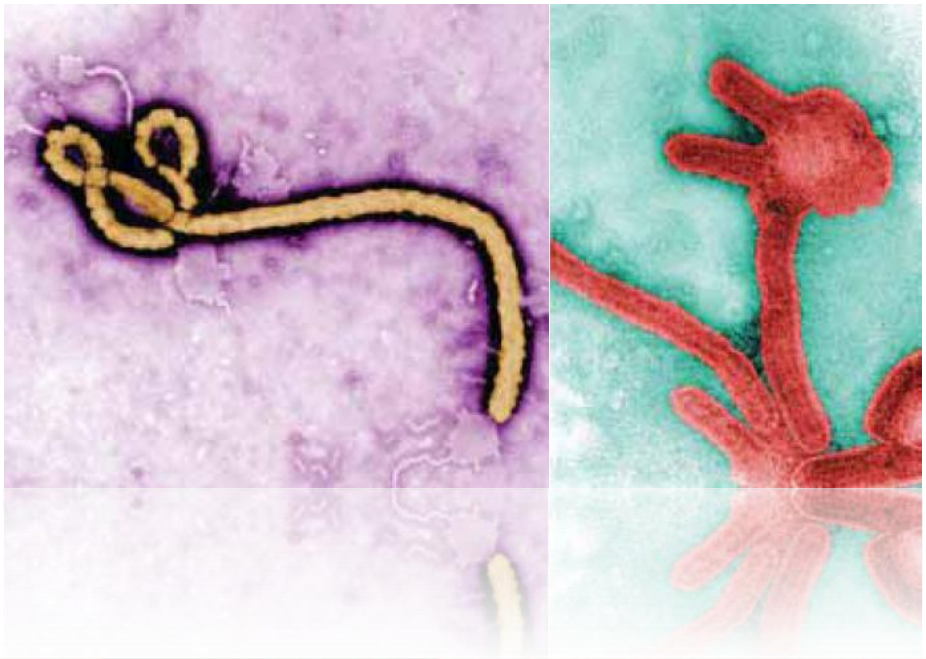
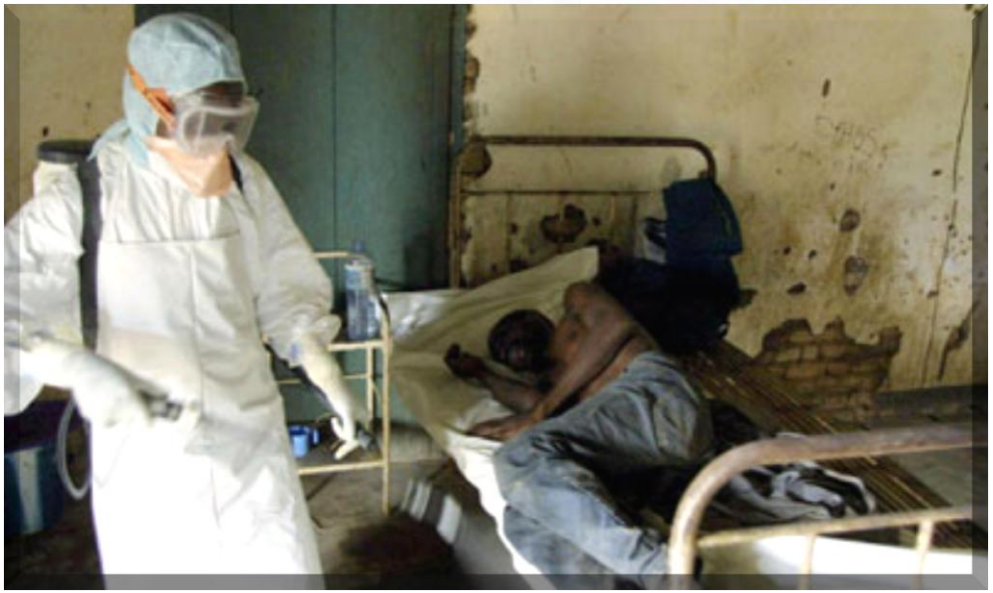
Filovirus: Marburg e Ebola







Marco Martini
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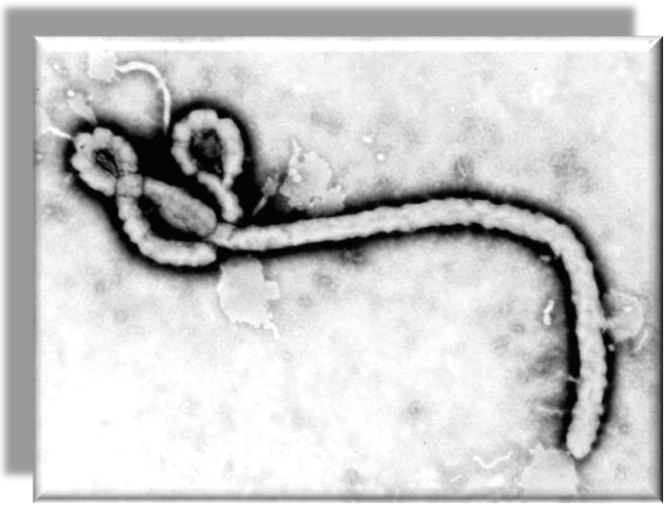
FILOVIRIDAE

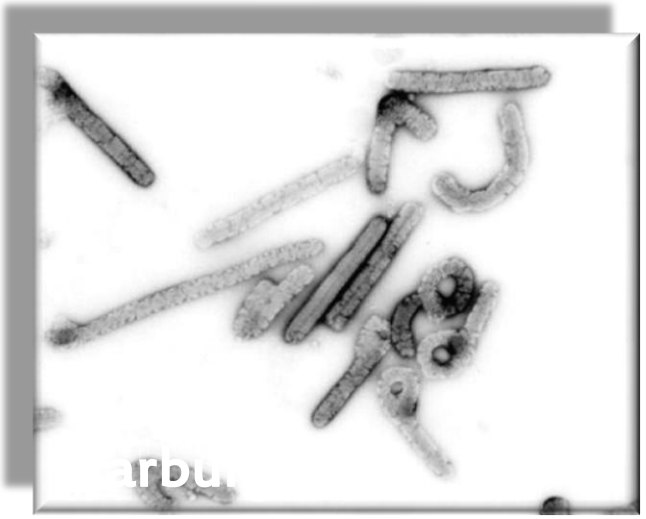
Morfologia bacilliforme con particelle filamentose lunghe 800-1000 nm con diametro di 80 nm.

Capside elicoidale

Genoma ss RNA lineare che richiede una polimerasi per la trascrizione prima della duplicazione

Tra i virus a patogenicità più spiccata per l'uomo





Virus geneticamente distinti appartenenti alla famiglia delle Filoviridae capaci di provocare elevata mortalità nei primati e nell'uomo.

Marburg virus isolato per la prima volta nel 1967 in Europa

Ebola virus isolato per la prima volta nel 1976 in Sudan e Repubblica Democratica del Congo

Sottotipo Reston dell'Ebola virus è stato identificato nel 1989 negli USA da scimmie importate dalle Filippine

Nel 2010 è stato identificato in pipistrelli insettivori (*Miniopterus schreibersii*) un nuovo Filovirus, non patogeno per l'uomo, in pipistrelli nella Spagna settentrionale

Marburg Virus

Focolai sinora descritti:

- **1967, Germania e Yugoslavia. 25 casi umani (7 decessi, 6 casi secondari). Casi primari: lavoratori di laboratori in cui erano impiegate scimmie importate dall'Uganda (*Cercopithecus aethiops*)**
- **1975, South Africa. 3 casi umani con 1 decesso.**
- **1980, Kenya, 2 casi, 1 decesso (visitatore Kitum cave nel Mount Elgon National Park)**
- **1987, Kenya, 1 caso fatale (visitatore Kitum cave)**
- **1998 – 2000, RD Congo, 154 casi, 128 (83%) decessi . In gran parte minatori, scarsi i casi secondari, diversi stipiti virali coinvolti**
- **2004- 2005, Angola, 252 di cui 227 (90%) fatali**
- **2007, Uganda, 3 casi (1 fatale) in minatori**
- **2008, Olanda, turista di ritorno dall'Uganda dove ha visitato caverne**
- **2009, USA, turista di ritorno dall'Uganda dove ha visitato caverne**

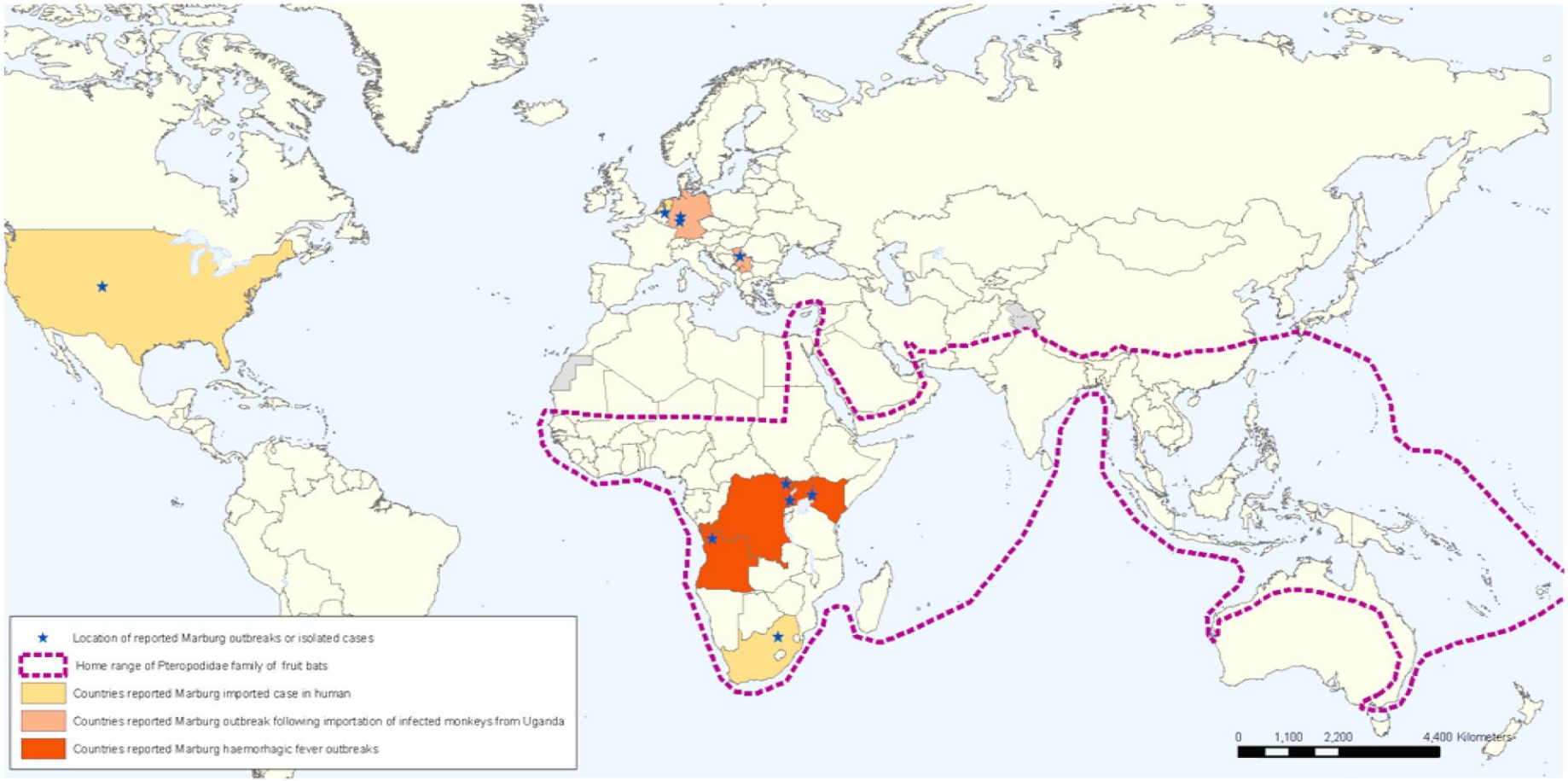
Marburg Virus

Focolai sinora descritti:

2012, (19.10 – 23.11) Uganda: 20 casi, 9 fatali, 4 distretti coinvolti.

Origine: ipotizzata introduzione del virus da parte di profughi provenienti da RDC o la raccolta in foresta di frutta contaminata da fruit bats (*Rousettus aegyptiacus*)

Geographic distribution of Marburg haemorrhagic fever outbreaks and fruit bats of Pteropodidae Family



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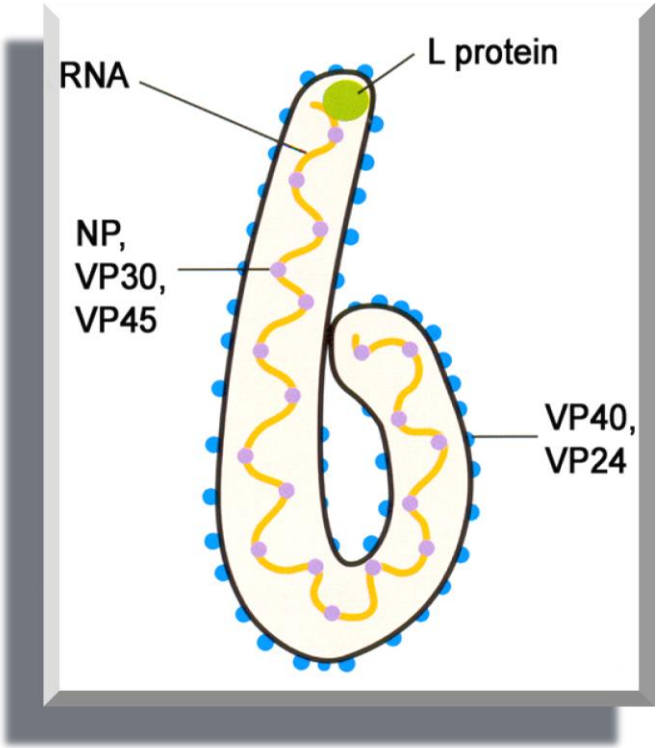
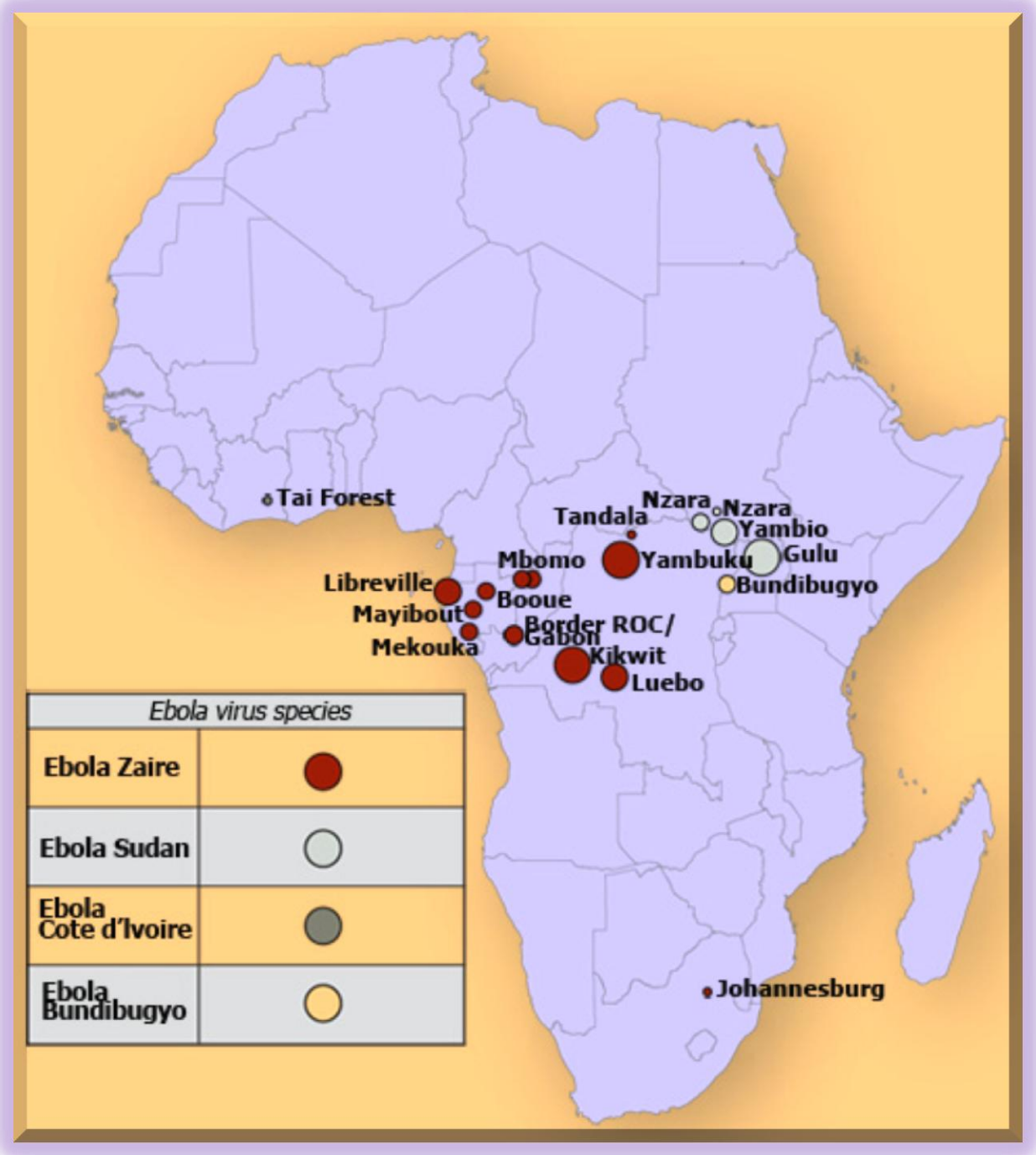
EBOLA VIRUS



1976: descritto per la prima volta in Africa centrale (RD Congo, ex Zaire); successivamente diverse segnalazioni in Africa.


Tai Forest
Nzara
Nzara
Tandala
Yambio
Mbomo
Yambuku
Gulu
Libreville
Booue
Bundibugyo
Mayibout
Border ROC/
Gabon
Mekouka
Kikwit
Luebo
Johannesburg
Ebola virus species
Ebola Zaire
Ebola Sudan
Ebola Cote d'Ivoire
Ebola Bundibugyo

Year(s)	Country	Ebola Subtype	Reported no. of human cases	Reported no. (%) of deaths among cases	Situation
1967	Zaire[Democratic Republic of Congo(DRC)]	Ebola-Zaire	318	280 (88%)	Occurred in Yambuku and surrounding area. Disease was spread by close personal contact and by use of contaminated needles and syringes in hospitals/clinics. This outbreak was the first recognition of the disease. [1]
1976	Sudan	Ebola-Sudan	284	151 (53%)	Occurred in Nzara, Maridi and the surrounding area. Disease was spread mainly through close personal contact within hospitals. Many medical care personnel were infected. [2]
1976	England	Ebola-Sudan	1	0 (0%)	Laboratory infection by accidental stick of contaminated needle. [3]
1977	Zaire	Ebola-Zaire	1	1 (100%)	Noted retrospectively in the village of Tandala. [4]
1979	Sudan	Ebola-Sudan	34	22 (65%)	Occurred in Nzara, Maridi. Recurrent outbreak at the same site as the 1976 Sudan epidemic. [5]
1989	USA	Ebola-Reston	0	0 (0%)	Ebola-Reston virus was introduced into quarantine facilities in Virginia, Texas, and Pennsylvania by monkeys imported from the Philippines. [6]

1990	USA	Ebola-Reston	4 (asymptomatic)	0 (0%)	Ebola-Reston virus was introduced once again into quarantine facilities in Virginia, and Texas by monkeys imported from the Philippines. Four humans developed antibodies but did not get sick. [7]
1989-1990	Philippines	Ebola-Reston	3 (asymptomatic)	0 (0%)	High mortality among cynomolgus macaques in a primate facility responsible for exporting animals in the USA. [8] Three workers in the animal facility developed antibodies but did not get sick. [9]
1992	Italy	Ebola-Reston	0	0 (0%)	Ebola-Reston virus was introduced into quarantine facilities in Sienna by monkeys imported from the same export facility in the Philippines that was involved in the episodes in the United States. No humans were infected. [10]
1994	Gabon	Ebola-Zaire	52	31 (60%)	Occurred in Mékouka and other gold-mining camps deep in the rain forest. Initially thought to be yellow fever; identified as Ebola hemorrhagic fever in 1995. [11]
1994	Ivory Coast	Ebola-Ivory Coast	1	0 (0%)	Scientists became ill after conducting an autopsy on a wild chimpanzee in the Tai Forest. The patient was treated in Switzerland. [12]
1995	Democratic Republic of the Congo (formerly Zaire)	Ebola-Zaire	315	250 (81%)	Occurred in Kikwit and surrounding area. Traced to index case-patient who worked in the forest adjoining the city. Epidemic spread through families and hospitals. [13]

1996 (Jan-April)	Gabon	Ebola-Zaire	37	21 (57%)	Occurred in Mayibout area. A chimpanzee found dead in the forest was eaten by people hunting for food. Nineteen people who were involved in the butchery of the animal became ill; other cases occurred in family members. [11]
1996-1997 (July-Jan)	Gabon	Ebola-Zaire	60	45 (74%)	Occurred in Booué area with transport of patients to Libreville. Index case-patient was a hunter who lived in a forest camp. Disease was spread close contact with infected persons. A dead chimpanzee found in the forest at the time was determined to be infected. [11]
1996	South Africa	Ebola-Zaire	2	1 (50%)	A medical professional traveled from Gabon to Johannesburg, South Africa, after having treated Ebola virus-infected patients and thus having been exposed to the virus. He was hospitalized, and a nurse who took care of him became infected and died. [14]
1996	USA	Ebola-Reston	0	0 (0%)	Ebola-Reston virus was introduced into a quarantine facility in Texas by monkeys imported from the Philippines. No human infections were identified. [15]
1996	Philippines	Ebola-Reston	0	0 (0%)	Ebola-Reston virus was identified in a monkey export facility in the Philippines. No human infections were identified; one animal handler has Ebola antibody. [16]

2000-2001	Uganda	Ebola-Sudan	425	224 (53%)	Occurred in Gulu, Masindi, and Mbarara districts of Uganda. The three most important risks associated with Ebola virus infection were attending funerals of Ebola hemorrhagic fever case-patients, having contact with case-patients in one's family, and providing medical care to Ebola case-patients without using adequate personal protective measures. [17]
2001-2002 (Oct 01-March 02)	Gabon	Ebola-Zaire	65	53 (82%)	Outbreak occurred over the border of Gabon and the Republic of the Congo. [18]
2001-2002 (Oct 01-March 02)	Republic of Congo	Ebola-Zaire	57	43 (75%)	Outbreak occurred over the border of Gabon and the Republic of the Congo. This was the first time that Ebola hemorrhagic fever was reported in the Republic of the Congo. [18]
2002-2003 (Dec 02-April 03)	Republic of Congo	Ebola-Zaire	143	129 (89%)	Outbreak occurred in the districts of Mbomo and Kéllé in Cuvette Ouest Département. [19]
2003 (Nov-Dec)	Republic of Congo	Ebola-Zaire	35	29 (83%)	Outbreak occurred in Mbomo and Mbandza villages located in Mbomo district, Cuvette Ouest Département. [20]
2004	Sudan	Ebola-Sudan	17	7 (41%)	Outbreak Occurred in Yambio county of southern Sudan. This outbreak was concurrent with an outbreak of measles in the same area, and several suspected EHF cases were later reclassified as measles cases. [21]

2007	Democratic Republic of Congo	Ebola-Zaire	264	187 (71%)	Outbreak occurred in Kasai Occidental Province. The outbreak was declared over November 20. Last confirmed case on October 4 and last death October 10. [22] [23]
Dec 2007-Jan 2008	Uganda	Ebola-Bundibugyo	149	37 (25%)	Outbreak occurred in the Budibugyo District in western Uganda. First reported occurrence of a new strain. [24]
Nov 2008	Philippines	Ebola-Reston	6 (asymptomatic)	0 (0%)	First known occurrence of Ebola-Reston in pigs. Strain closely similar to earlier strains. Six workers from the pig farm and slaughterhouse developed antibodies but did not become sick. [25] [26]
Dec 2008-Feb 2009	Ebola-Zaire	Democratic Republic of the Congo	32	15(47%)	Outbreak occurred in the Mweka and Luebo health zones of the Province of Kasai Occidental.

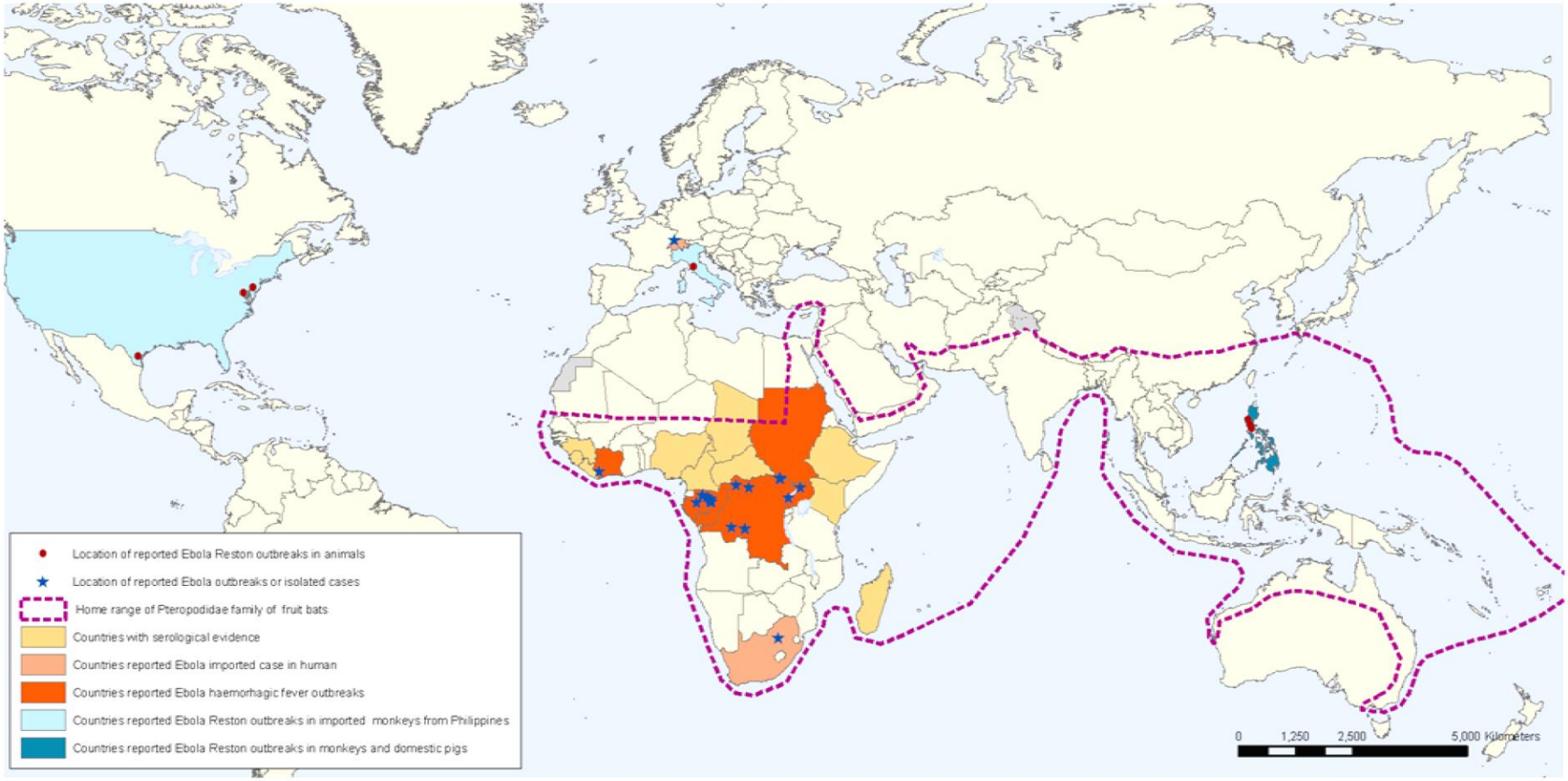
Maggio 2011: 1 caso, fatale, in Uganda (da Ebola-Sudan virus)

EBOLA VIRUS

2012:

- **RDC: focolaio agosto-novembre, ufficialmente estinto il 27.11.2012. 62 casi, 32 fatali, sostenuto da virus Ebola Bundibugyo**
- **Uganda: virus Ebola Sudan: luglio-agosto, 24 casi, 17 fatali**
- **Uganda: virus Ebola Sudan: novembre, 10 casi, 5 fatali**

Geographic distribution of Ebola haemorrhagic fever outbreaks and fruit bats of Pteropodidae Family



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EBOLA VIRUS

5 distinte specie di Ebola virus:

- **Bundibugyo**
- **Costa d'Avorio**
- **Reston**
- **Sudan**
- **Zaire**

Trasmissione all'uomo tramite sangue, liquidi corporei e tessuti di persone infette, tramite contatti con scimpanzè, gorilla, cercopitechi, macachi, antilopi e fruit bats.

Recentemente dimostrata la suscettibilità dei suini e la loro capacità di trasmettere in condizioni sperimentali il virus per contatto diretto e iniretto a primati

Negli animali infetti i Filovirus causano necrosi a carico dei diversi organi.

Nell'uomo si presenta con febbre, diarrea, rash, emorragie.

SYMPTOMS / SIGNS	NUMBER = (N) N = 17	PERCENTAGE (%)
Acute Fever (>38°)	16	94.1
Generalized weakness	15	88.2
Joint pains	15	88.2
Vomiting	13	76.5
Severe headache	13	76.5
Muscle pain /myalgia	6	35.3
Difficult breathing	9	52.9
Loss of appetite	11	64.7
Difficult swallowing	3	17.6
Fatique	10	58.8
Diarrhoea	10	58.8
Haematemesis	7	41.2
Diarhoea with blood	9	52.9
Reduced urine output	9	52.9
Chest pains and coughs	12	70.6
Bleeding tendencies (eyes, mouth, ear, vagina)	7	41.2
Terminal shock	9	52.9
Maculopapular skin rash	1	5.9

Reservoir naturali dei Filovirus sono considerati essere chirotteri frugivori. Recenti studi evidenziano che il fruit bat *Rousettus aegyptiacus,* diffuso in molti Paesi africani, lungo il Nilo, in Medio Oriente, presenta sieropositività (5%) per Marburg e Ebola virus

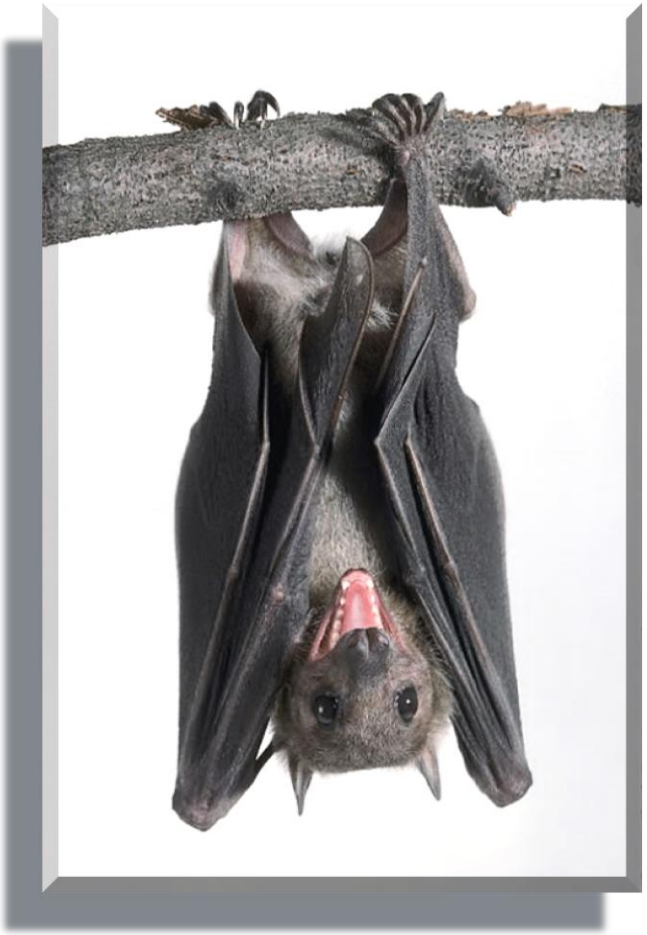

FIGURE 2.5

Flying foxes for sale in a community market in Manado, Indonesia

HUME FIELD; © THE STATE OF QUEENSLAND (DEEDI)

Bags of bat guano harvested from a cave in the Philippines

DIAGNOSI E CONTROLLO

La diagnosi deve essere eseguita in laboratori di livello 4. La paura collettiva evocata ha portato alla drastica riduzione nell'utilizzazione di primati nella sperimentazione scientifica e rigorose misure di quarantena e di controlli sierologici e virologici all'atto dell'esportazione.

È allo studio un vaccino per uso umano.

Geographical and epidemiological characteristics of VHFs			
Disease	**Geography**	**Vector/Reservoir**	**Human Infection**
Crimean Congo HF	• Africa • Balkans • China (Western) • Former Soviet Union (Southern) • Middle East	Ticks. Tick-mammal-tick maintenance.	• Tick bites. • Squashing ticks. • Exposure to aerosols or fomites from slaughtered cattle and sheep (domestic animals do not show evidence of illness but may become infected when transported to market or when held in pens for slaughter). • Nosocomial epidemics have occurred.
Dengue HF, Dengue Shock Syndrome (DHF/DSS)	All Tropic and subtropical Regions	***Aedes aegypti*** mosquitoes. Mosquito-human-mosquito maintenance. Transmission occurs with the frequent geographic transport of viruses by travellers.	Increased world-wide distribution of the mosquito and the movement of dengue viruses in travellers is increasing the areas that are becoming infected.
Ebola HF and Marburg HF	Africa	Unknown.	• Virus is spread by close contact with an infected person. • Route of infection of the first case is unknown. • Infected non-human primates sometimes provide transmission link to humans. • Aerosol transmission is suspected in some monkey infections.
Lassa Fever	West Africa	Mice. The *Mastomys* genus of the mouse.	• Transmitted by aerosols from rodent to man. • Direct contact with infected rodents or their droppings, urine, or saliva. • Person-to-person contact. Note: The reservoir rodent is very common in Africa and the disease is a major cause of severe febrile illness in West Africa.
Rift Valley Fever	Sub-Saharan Africa	Floodwater mosquitoes. Maintained between mosquitoes and domestic animals, particularly sheep and cattle.	• Mosquito bite. • Contact with blood of infected sheep, cattle, or goats. • Aerosols generated from infected domestic animal blood. • No person-to-person transmission observed.
Yellow Fever	• Africa • South America	***Aedes aegypti*** mosquitoes. Mosquito-monkey-mosquito maintenance. Occasional human infection occurs when unvaccinated humans enter forest. In an urban outbreak, virus maintained in infected *Aedes aegypti* mosquitoes and humans.	• Mosquito bite. • In epidemics, mosquitoes amplify transmission between humans. • Fully developed cases cease to be viremic. Direct person-to-person transmission is not believed to be a problem although the virus is highly infectious (including aerosols) in the laboratory.

Common clinical features of VHFs			
Disease	Incubation Period	Case Fatality	Characteristic Features
Crimean Congo HF	3-12 days	15% - 30%	Most severe bleeding and ecchymoses (a purplish patch caused by blood coming from a vessel into the skin) of all the HF.
Ebola HF and Marburg HF	2-21 days	25% - 90%	• Most fatal of all HF. • Weight loss. • Exhaustion and loss of strength. • A maculopapular (a lesion with a broad base) rash is common • Post infection events have included hepatitis, uveitis and orchitis.
Lassa Fever	5-16 days	Approximately 15%	• Exhaustion and loss of strength. • Shock. • Deafness develops during recovery in 20% of cases.
Rift Valley Fever	2-5 days (uncomplicated disease; incubation for HF may differ)	50% of severe cases (about 1.5% of all infections)	• Shock. • Bleeding. • Reduced or no urine production. • Jaundice. • Inflammation of the brain. • Inflammation of the blood vessels in the retina of the eye.
Yellow Fever	3-6 days	20%	• Acute febrile period followed by a brief period of remission. • Toxic phase follows remission with jaundice and renal failure in severe cases.

Specific clinical findings in different VHFs

Disease	haemorrhage	Thrombo-cytopenia[1]	leukocyte count [2]	rash	icterus [3]	renal disease	pulmonary disease	tremor[4], dysarthria[5]	encephalo-pathy[6]	deafness	eye lesions
Crimean Congo HF	+ + +	+ + +	↓↓ ranging to ↑		+ +		+		+		
Ebola HF and Marburg HF	+ +	+ + +	data not available	+ + +	+ +		+		+ +	+	Retinitis
Lassa Fever	+ ranging to S	+	no change	+ +			+	+	+ ranging to S	+ +	
Rift Valley Fever	+ + +	+ + +	data not available		+ +	+	data not available		E		Retinitis
Yellow Fever	+ + +	+ +	no change ranging to ↓↓		+ + +	+ +	+		+ +		

[1] abnormally low number of platelets in the circulating blood

[2] white blood cell count

[3] jaundice

[4] shaking

[5] difficulty speaking and pronouncing words due to problems with the muscles used for speaking

[6] disease of the brain

+	occasional or mild
+ +	commonly seen and may be severe
+ + +	characteristic
S	characteristic and seen in severe cases
↑	occasionally or mildly increased
↓↓	commonly decreased
E	May develop true encephalitis

A summary of prevention and treatment of VHFs		
Disease	Prevention	Treatment
Crimean Congo HF	• Tick avoidance. • Avoid contact with acutely infected animals, especially slaughtering. • Use VHF Isolation Precautions when a case is suspected.	• Ribavirin is effective in reducing mortality. • Ribavirin should be used based on in vitro sensitivity and of limited South African experience.
Dengue HF, Dengue Shock Syndrome (DHF/DSS)	• Mosquito control of *Aedes aegypti*. • Vaccines currently under investigation for probable use in travellers but unlikely to be a solution to hyperendemic dengue transmission that leads to dengue HF.	• Supportive care. It is effective and greatly reduces mortality.
Ebola HF and Marburg HF	• Standard Precautions including needle sterilization in African hospitals are particularly important. • Use VHF Isolation Precautions when a case is suspected. • Avoid unprotected contact with suspected patients or infectious body fluids. • Avoid contact with monkeys and apes.	• None other than supportive care, which may be of limited utility. • Antiviral therapies urgently needed.
Lassa Fever	• Rodent control. • Use VHF Isolation Precautions when a case is suspected.	• Ribavirin is effective in reducing mortality. • Use Ribavirin in higher risk patients, e.g. if aspartate aminotransferase (AST) is greater than 150.
Rift Valley Fever	• Vaccination of domestic livestock prevents epidemics in livestock but not sporadic, endemic infections of humans. • Human vaccine safe and effective, but in limited supply. • Veterinarians and virology workers in sub-Saharan Africa are candidates for vaccine.	• Supportive care. • Use Ribavirin in haemorrhage fever patients (based on studies in experimental animals).
Yellow Fever	• Mosquito control of *Aedes aegypti* would eliminate urban transmission but forest transmission remains. • Vaccine is probably the safest and most effective in the world.	• Supportive care.