

Imported virus infections

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Imported virus infections

- increasing globalization
- Not only better exchange of trade goods, but also pathogens
- Changing flight and holiday habits
- Refugees
- Climate change → Extension of habitats of hosts and vectors
- Bioterrorism (possible, but unlikely)

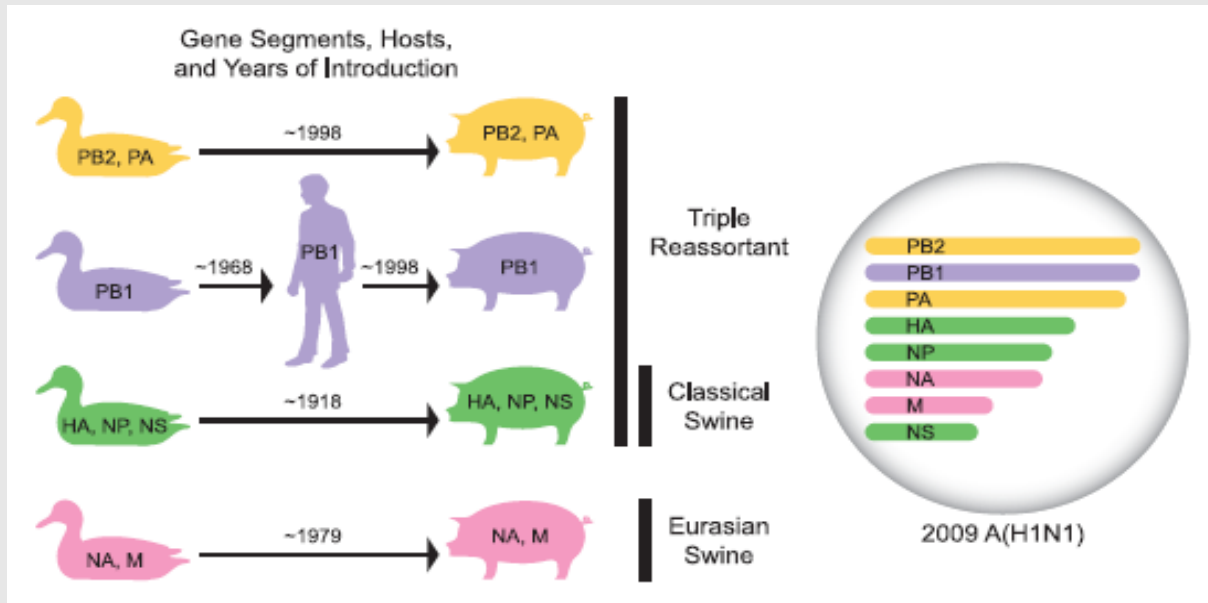
→ Increased speed of pandemics

Imported virus infections

- **Viral haemorrhagic fevers**
- Enzephalitisvires
- Poliovirus
- Corona viruses
- **Rabies (Tollwut)**

- **Influenzaviruses**

Schweinegrippe Evolution (Pandemie 2009)



From: Garten et al.; Science 325, 197 (2009)

- 1998 Dreifach Reassortante eines H3N2-Virus, spätere Vermischung mit Schweine-Influenzaviruses generierte H1N1 und H1N2 Virusvarianten, die sporadisch auch Menschen infizierten
- 2005 erste Vermischung zwischen klassischen Schweineviruses (Nordamerika) und den eurasischen viruses

Schweinegrippe Ausbreitung (2009)

Datum (P-Stufe)	Welt	Mexiko	US	Deutschland	Anzahl Länder
24.4.	25	18	7		2
26.4.	38	18	20		2
27.4. (IV)	73(7†)	26(7†)	40		4
28.4.	105(7†)	26(7†)	64		7
29.4. (V)	148(8†)	26(7†)	91(1†)	3	9
30.4.	257(8†)	97(7†)	109(1†)	3	11
1.5.	367(10†)	156(9†)	141(1†)	4	13
2.5.	658(17†)	397(16†)	160(1†)	6	16
3.5.	898 (20†)	506(19†)	226(1†)	8	17

Influenza pandemics: Possible scenario (based on data from the pandemic of 1918)

- Novel unknown **Influenza** subtype, no or low immunity in population, fast spread, highly pathogenic
- Incidence 25% => 20 Millions inhabitants
- Pneumonia rate 6% => 1.2 Millions
- Hospitalization rate 1% => 200.000 additional patients, for 8.2 days stay
=> 1,6 Millions of additional hospital days
- Lethality 0,6% => 120,000 deaths
- **Novel Coronavirus**, zero immunity in population
- Incidence 50% => 40 Millions inhabitants
- Pneumonia rate 6% => 2,4 Millions
- Hospitalization rate 1% => 400.000 additional patients, for 8.2 days stay
=> 3,2 Millions of additional hospital days
- Lethality 1% => 400.000 deaths

01/01/2020

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RTÉ News

New experiences

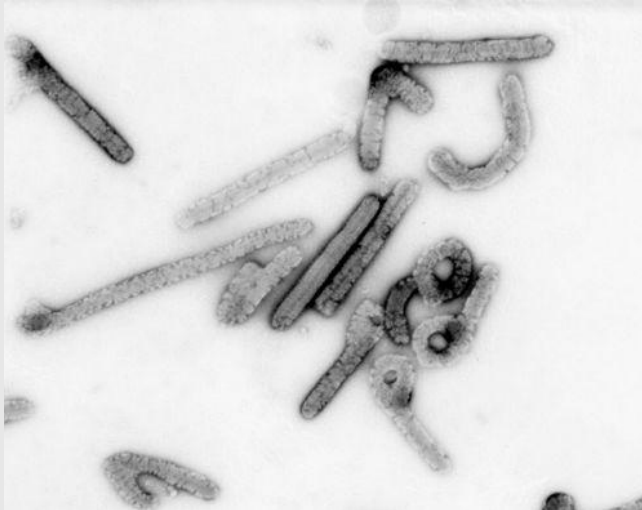
- Not only the final numbers of deaths and severe diseased persons, but also the speed of spreading plays a role in the pandemic's outcome
- Risk of collapsing medical care system (Italy, Spain, GB, New York)
- Early lockdown stopped too fast spread in Germany, but collateral damages are huge (economical, social, education...)

How could the pandemic be stopped

- Herd immunity: if around 75% of people are seropositive (and protected), case numbers fall by nature and the pandemic comes to a halt
- Effective drug worldwide available
- Effective vaccine

Viral hemorrhagic fevers (VHF)

- Group of diseases caused by various viruses
- Mostly life threatening
- Mostly S4, some S3 viruses



Marburg-Virus

Laboratories of biological safety level 4

- 4 Labs in Germany:
 - Hamburg; Institut für Tropenmedizin (BNI)
 - Insel Riems; Friedrich-Loeffler- Institut
 - Marburg; Philipps-Universität Marburg
 - Berlin; Robert Koch-Institut (2011, 2015)
- Highest security level:
 - Distinct building
 - Inlet- and Outlet-air must be filtered
 - Able to close hermetically (decontamination)
 - Ventilated overpressure protective suits



Symptoms of hemorrhagic fever

- Dependent of pathogen
- Frequent similarities:
 - High fever
 - Exhaustion
 - Muscle pain
 - Bleedings (subcutaneous, inner organs, mucosa)
- Severe proceedings with shock, coma, epileptic seizure (sometimes kidney failure)

VHF-Pathogenesis

- Viral pathogenesis is complex, not completely understood and different for different virus types:
 - Direct destruction of vascular system of target organs through Virus replication (very strong viremia)
 - Activation of complement system and high levels of cytokines
 - Activation of the immune system at pathogenesis of Hantaviruses or Dengue-viruses
- Some VHF are connected with injury of certain organs
 - Kidneys at HF with renal syndrome (Kidney dysfunction; Hantavirus)
 - Lungs at Hantavirus with cardio-pulmonary syndrome
 - Liver at Yellow Fever (Hepatic failure)

Pathogens of hemorrhagic fever

- Bunyaviruses (**Hantan**, Rift-Valley, Krim-Kongo)
- Arenaviruses (**Lassa**, Junin, Machupo...)
- Filoviruses (Marburg, **Ebola**)
- Flaviviruses (**Dengue**, **yellow fever**...)

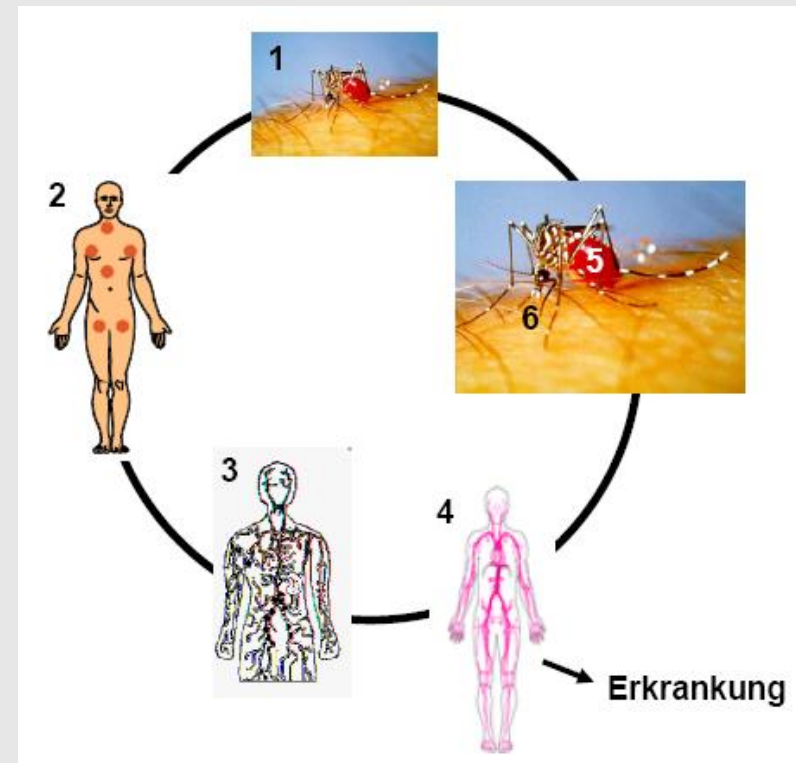
- Similarities:
 - enveloped RNA-Viruses
 - natural reservoir is not humans !

Transmission

- Natural reservoir rodents (Lassavirus, Hantaviuses):
 - Contact with urine, feces, saliva etc.
- Natural reservoir mosquitoes or ticks (Flaviviruses):
 - Sting or bite, or contact with infected animals (slaughter house)
- Human to human (Filoviruses, Lassavirus):
 - Close contact, body fluids, contaminated instruments, rarely aerosols?

Denguevirus (Flavivirus)

- 4 serotypes (DEN 1-4)
- Transmission by Aedes species all tropical regions (Southeastern-asia, Southpacific, Africa, Middle- and Southamerica, Caribbean)
- WHO:
 - 50 Million infections/year;
 - In Germany: around 50-100/year.



Denguevirus-Infektion

- Incubation period 3-14 days
- Progressions:
 - Classic: Sometimes prodromi with conjunctivitis and coryza (Schnupfen), then sudden fever, strong pain in bones and joints, retroorbital pain, exanthemes, slow recovery
 - Mild-atypical (children first infection): like classic, but < 3 days
 - Dengue haemorrhagic fever (DHF) and Dengue shock syndrome (DSS): After reinfection with a different subtype in children (enhancing antibodies); additional shock or increased bleeding risk (thrombocytopenia, Verbrauchskoagulopathie)

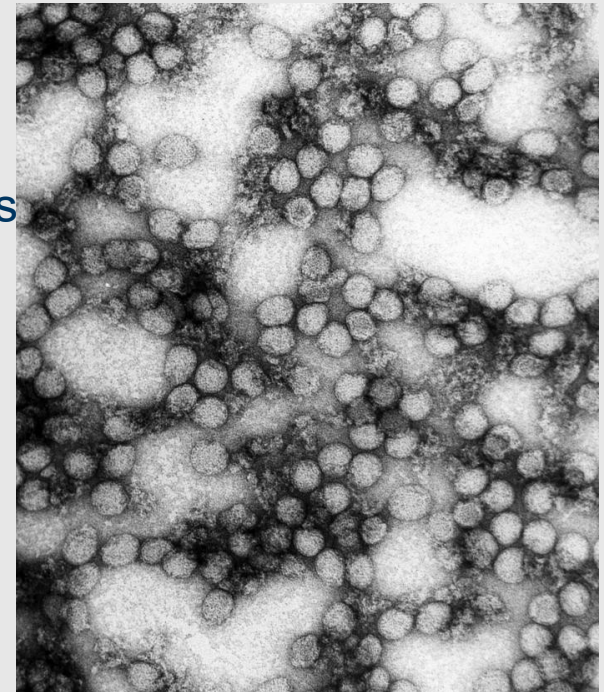


Denguevirus-Infektion

- Diagnosis: IgM-detection (cross reactions!), RT-PCR, virus isolation
- Therapy: symptomatic (antifebrile, pain-relieving, no ASS)
- Prognosis of DHF: lethal: 10-15% without care, <1% with care

Yellow fever

- Flavivirus, in tropical Africa and Middle- and Southamerica
- WHO: 200.000 yellow fever cases/year; 30.000 deaths
- Way of infection:
 - Bush- or Jungle yellow fever:
Enzootia in primates, rarely humans,
(sylvatic cycle, *Aedes africanos*)
Monkey -> Mosquito -> Monkey (Humans)
 - Urban yellow fever: *Aedes aegypti*
Human -> Mosquito -> Human



Yellow fever infection

- Symptoms:
 - 3-6 days incubation period, rather short time, from light flu like to HF.
 - Sudden increase of fever, headache, low pulse, stomach pain.
 - After 3-4 days remission for 1-2 days, again increased fever
 - with organ symptoms: liver coma, kidney failure, haemorrhages,
 - CNS-symptoms
- Lethality: 10-50% of diagnosed cases
- Diagnosis: IgM, RT-PCR, virus isolation
- Prophylaxis: Vaccination with live attenuated yellow fever virus

Lassa fever

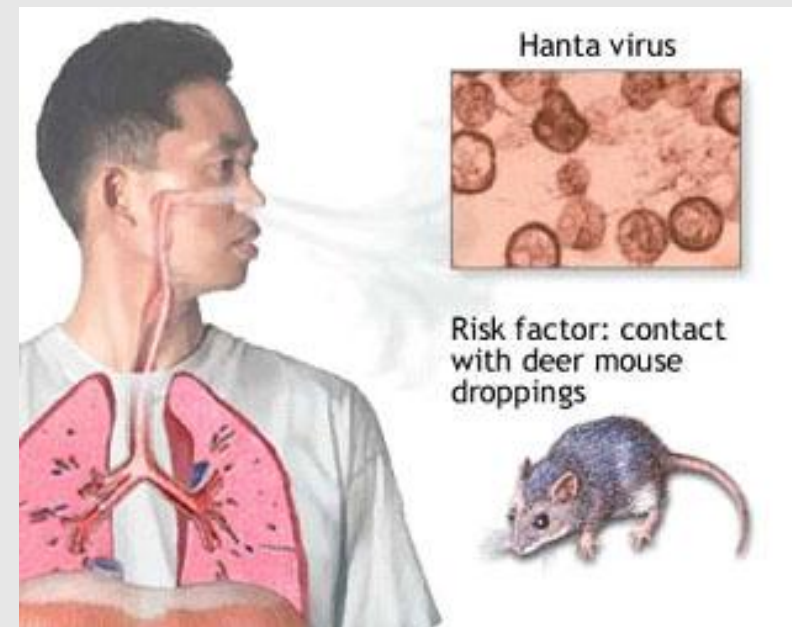
- Arenavirus, Western Africa, Southamerica
- Reservoir: Rodents
- Infections can also occur by close contact and nosokomial
- progression: slow with fever, headaches and soar throte, cough, gastro intestinal pain, up to hypotension, haemorrhages and encephalitis
- Lethality: 5-20% of hospitalized cases
- Diagnosis: IgM, IgG, RT-PCR, virus isolation
- Therapy: Ribavirin (i.v.; oral), symptomatic
- Prophylaxis: Control of rodents, patient isolation



Quelle: BNI Hamburg

Hanta virus

- Bunyaviruses
- Subtypes:
 - Puumala: Skandinavia, Germany, Southeastern Europe
 - Dobrava: Southeastern Europa
 - Hantaan: Korea, China, Southeastern Europe
 - Seoul: worldwide
 - Sin Nombre: USA
- Transmission: Aerosoles of rodent excrements, rarely human to human (Andes Virus)
 - e.g. sweep the shed



Hantavirus infection

- Incubation period 5-42 days;
- NE: Nephropathia epidemica: Oliguria, then Polyuria with proteineuria
- HFRS: Haemorrhagic fever with renal symptoms,
toxic phase: Fever, head- and backache, swindle,
petechia, hypotension through „capillary leak“ syndrome
Renal phase: oliguria, polyuria, hypertension, bleedings, lung edema
- Lethality: 6%, Puumala: 1%, Sin Nombre: 40%
- HCPS: Hantavirus cardial-pulmonary syndrom; Lethality 50%
- Diagnostics: IgM and IgG-ELISA (not always +),
Virus detection in urine (RT-PCR)
- Therapy: Ribavirin?, symptomatic (Dialysis)

Ebola fever (EVD): Symptoms

Ebola virus

- Severe often deadly haemorrhagic fever in humans and other mammals
- First signs: high fever ($>38^{\circ}\text{C}$), massive head- and muscle pain, nausea, conjunctivitis
- then: vomiting, diarrhoea, rash
- later: mucosal bleedings (gastrointestinal and genital), bleedings into skin
- decreased blood coagulation, liver damage
- Olig- and anuria up to kidney failure
- Death: cardio-pulmonary shock

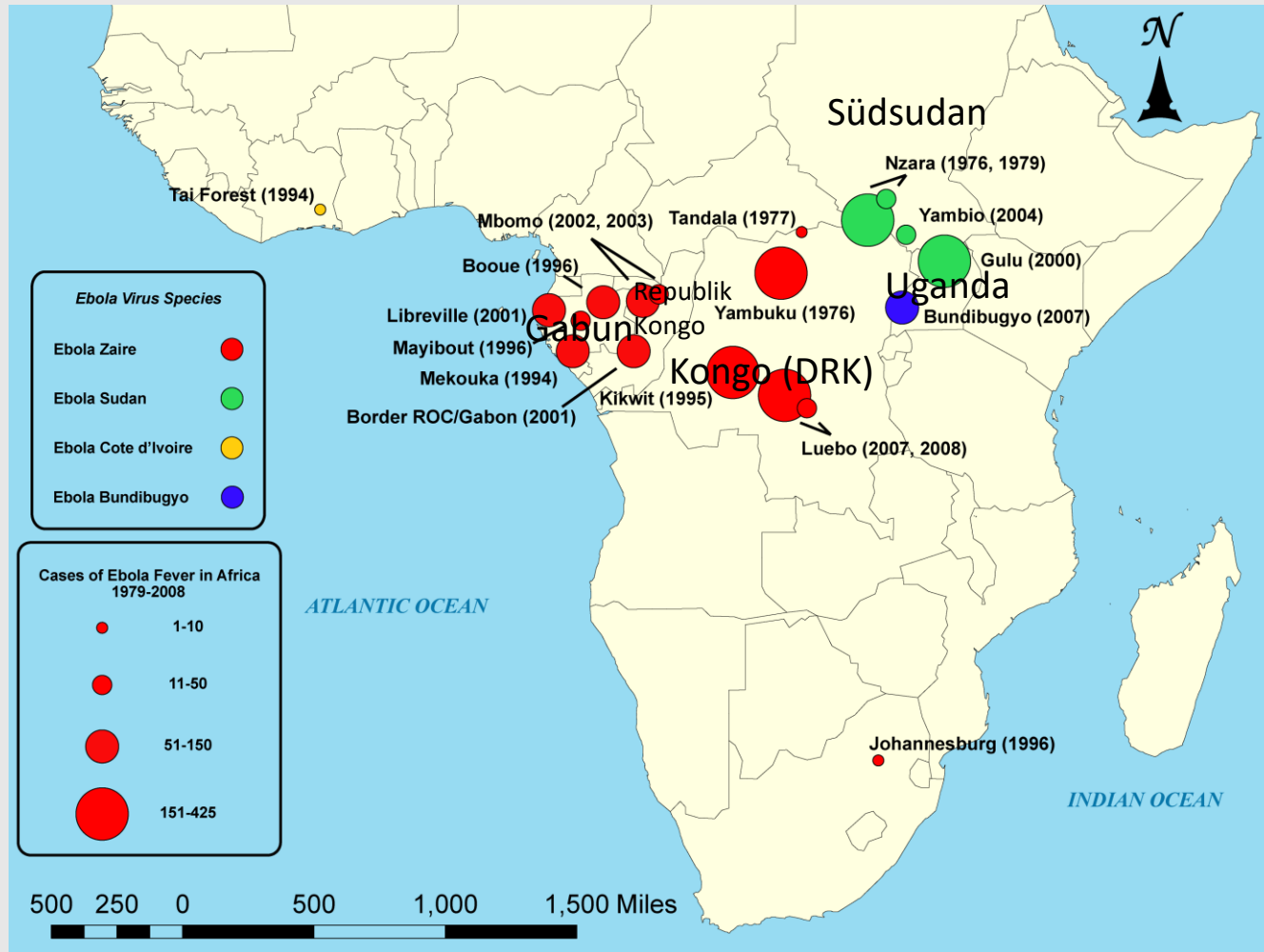
- **Mortality: 30-90%**



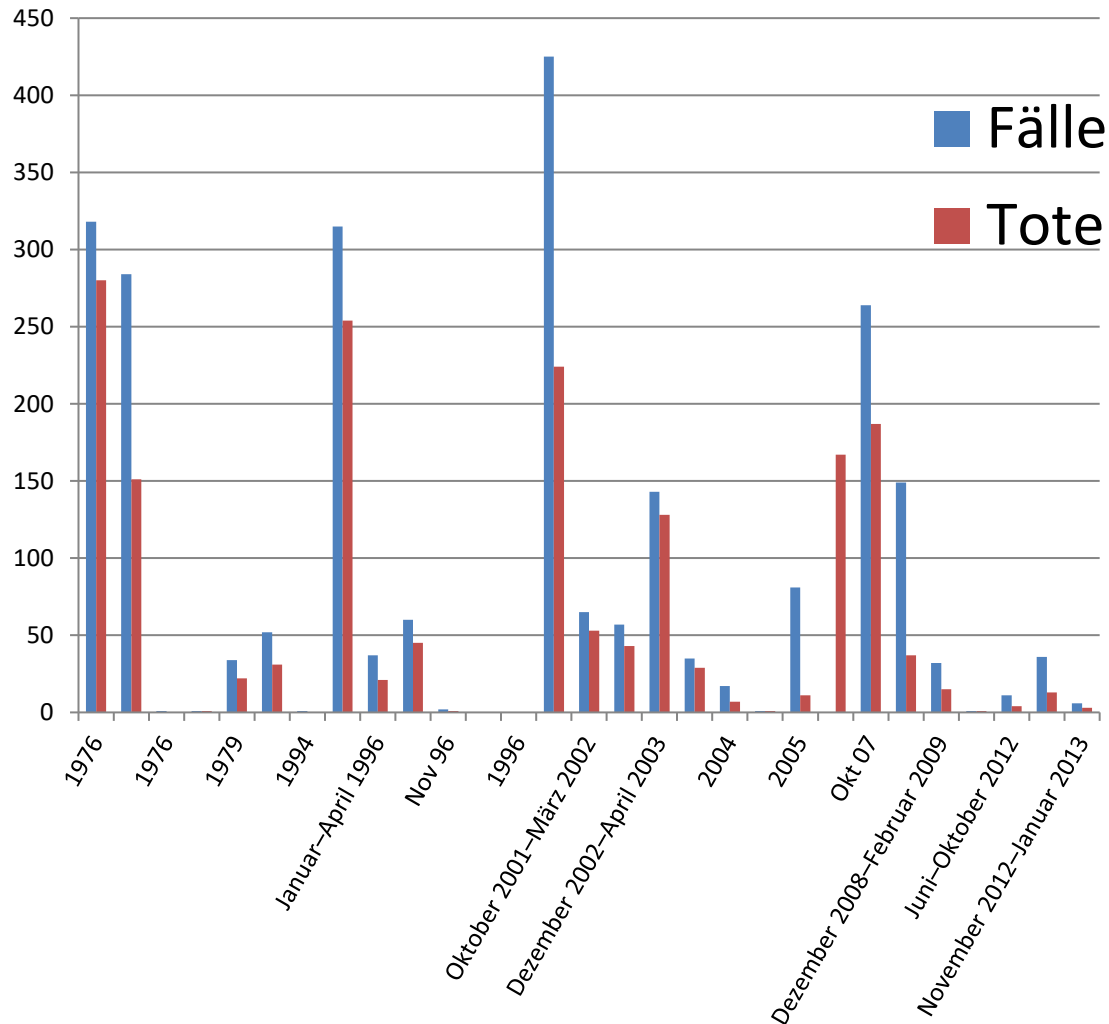
Ebola outbreaks

Year	Country	Cases	Ways of infection
1976	Zaire	318 (88%)	Close contact and contaminated needles and syringes
1976	Sudan	284 (53%)	Close contact in hospitals, al lot of med. personnel
1979	Sudan	34 (65%)	identic area like in 1976
1994	Gabon	44 (63%)	In rainforest, first assumed to be yellow fever, 1995 as Ebola HF identified
1995	Zaire, Kikwit	315 (78%)	Indexpatient was forest worker, families and Hospital personnel and patients
2000	Uganda	425 (53%)	
2003	Kongo	143 (89%)	
2007	Kongo	264 (71%)	
2007/8	Uganda	149 (25%)	
2007/8	Uganda	149 (25%)	

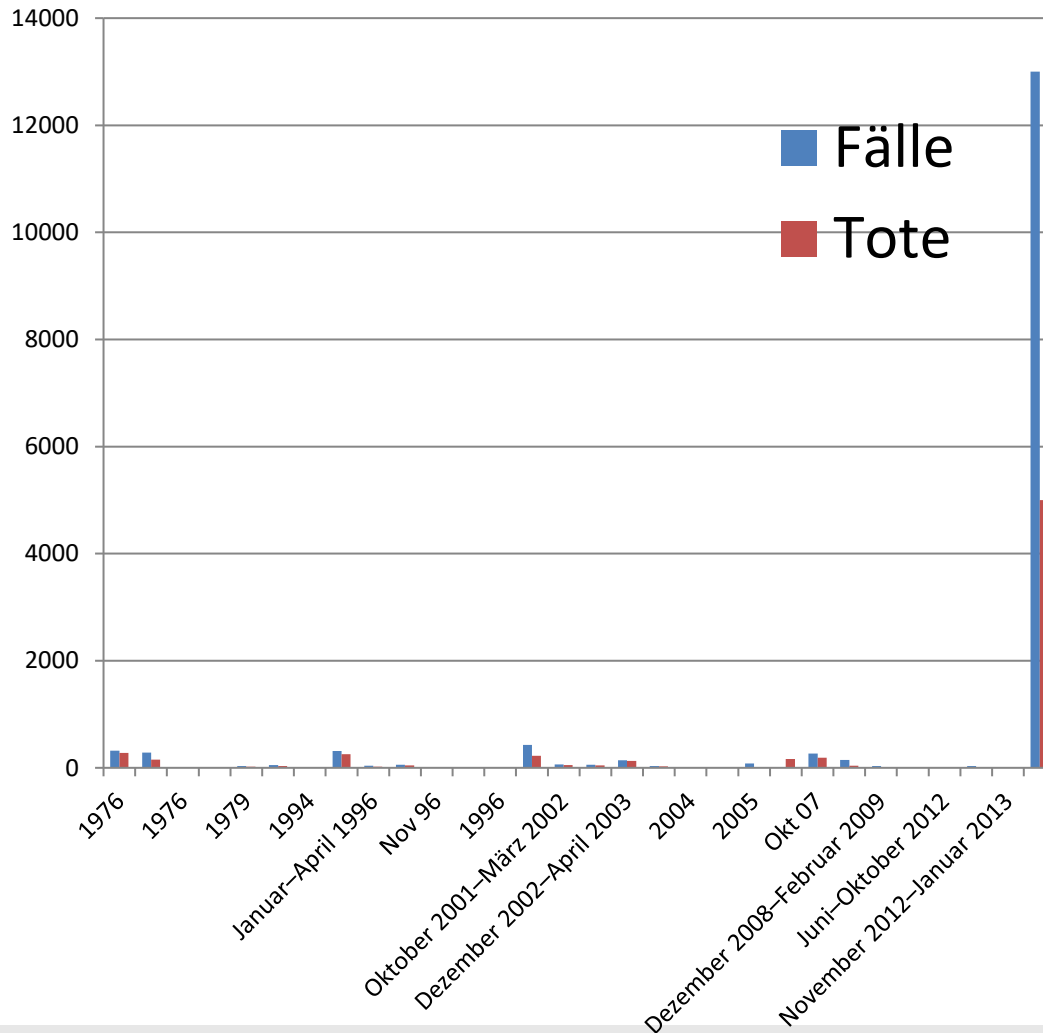
3. Outbreaks and the epidemia 2014



bis 2013

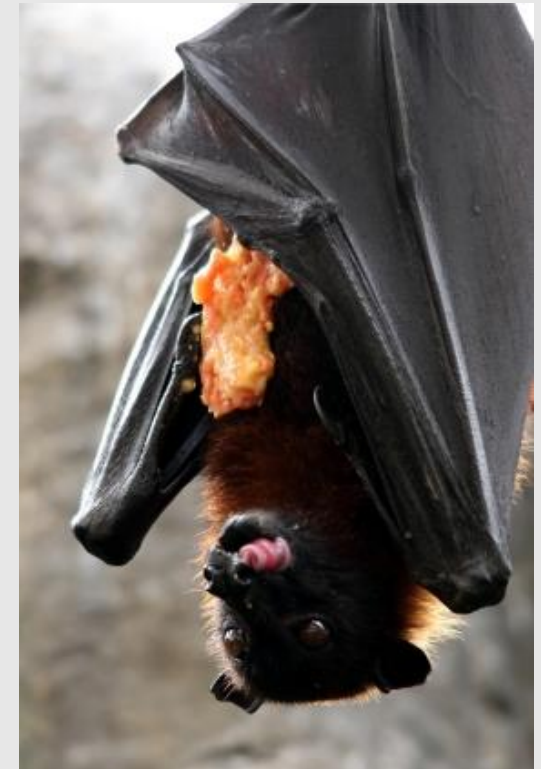


Ende 2014



2. Ebola fever (EVD): transmission

- Transmission from animals to humans
- Probably by consumption of „bushmeat“ (some delicacy) or by contact to body fluids of wild animals
- Animal reservoir: Flying foxes/bats and maybe non-human primates

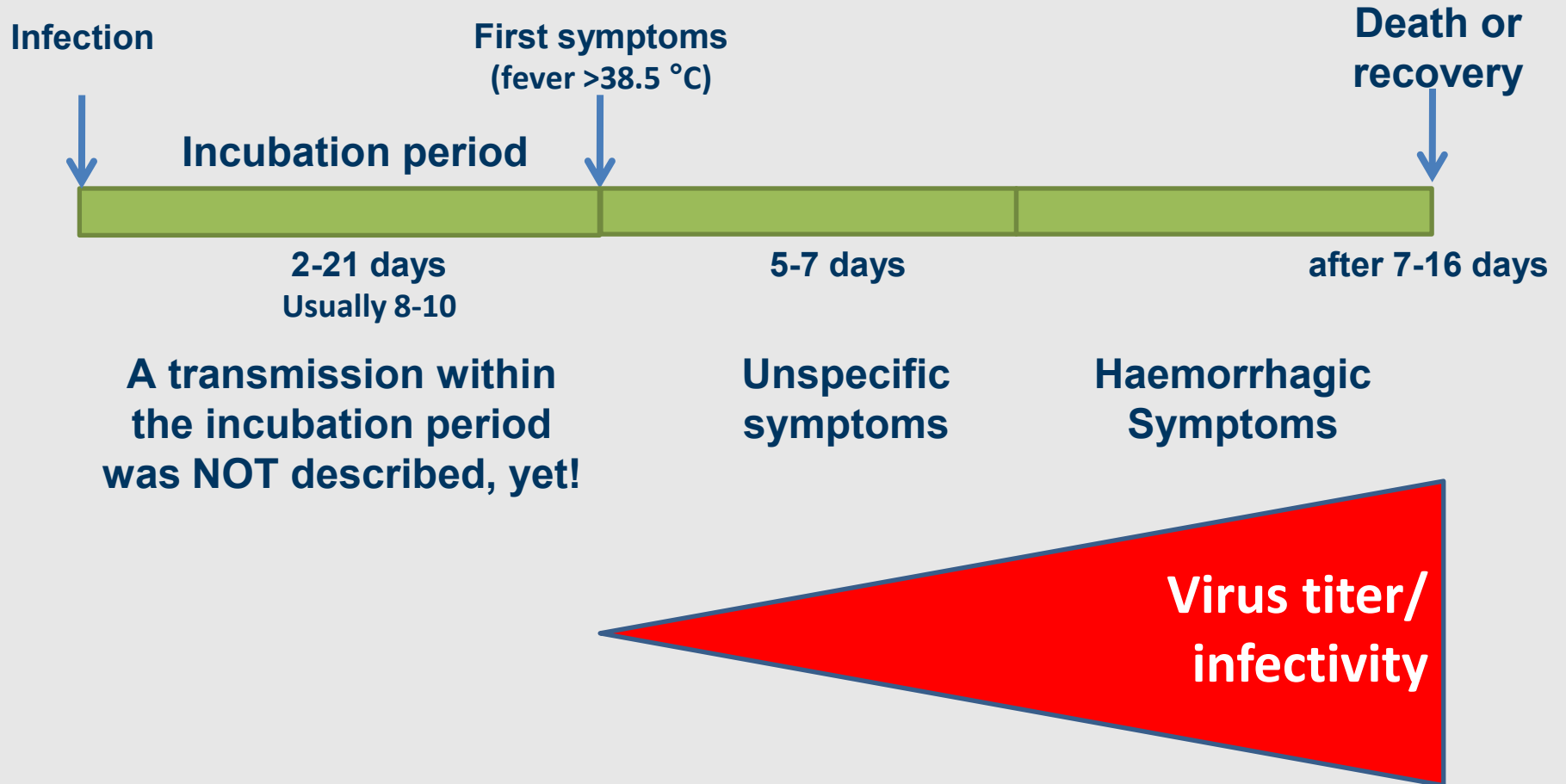


2. Ebola fever (EVD): transmission

From human to human:

- Direct contact with body fluids (blood, semen, saliva, vomit, urine, feces)
- sweat?
- **NO transmission via the air!! (aerosoles)**
- Ebola viruses can keep infectious outside the body for a few days

2. Ebola fever (EVD): time course



2. Ebolafieber (EVD): Diagnose

Differential diagnosis:

- Malaria
- Other haemorrhagic fevers (yellow fever, Lassavirus, Denguevirus, Hantaviruses)
- Typhus abdominalis or Leptospirose

2. Ebolafieber (EVD): 2018 Epidemia (Stand Ende 2019)

- Since Juli 2018 in NE of the Democratic Republic of the Congo
- Strain Ebola Zaire
- 3300 proved and probable cases
- more than 2100 deaths (63 %)
- Vaccination with rVSV ZEBOV (Ervebo)
- 250.000 people vaccinated (mostly medical personnel, helpers and contact persons of diseased)
- estimated vaccination efficiency 97 %
- Works also as post exposition prophylaxis (early after contact)
- first time antibody therapies: REGN-EB3, mAb114
- application at early time point 90 % probability for recovery

Recommendations for suspected VHF

- Patients with high fever and
 - travelling anamnesis within the last 3 weeks
 - or contact to body fluids of a VHF patient
 - or lab personnel with contact to VHF pathogens
- Kontaktadresse: Bernhard-Nocht-Institut für Tropenmedizin, Bernhard-Nocht-Str. 74, 20359 Hamburg, Notfall-Nr.: 040 428 18-0.
Außerdem: Meldepflicht an das Gesundheitsamt bereits bei Verdacht.
- Med. personnel:
 - hospital: single room with restricted entry, gloves, protective suit, surgical mask, protective glasses
 - If vomit, bleedings, feces: protective shoes, protective trousers up to low pressure rooms, HEPA-filter-masks
 - Secure disinfection of contaminated material
 - = „**barrier nursing**“
- Diagnostic: reduce to minimum, secure transport
- Differential diagnosis: e.g.: Malaria, Typhus

Summary of VHF

- Pathogens: Bunya-, Arena-, Filo- und Flaviviruses
- Symptoms: high fever, muscle pain, bleedings
- At suspected cases: travel anamnesis (Hantaviruses!), report to authority,
 - Safety precautions (up to isolation), only necessary diagnostics
- Human-to-human transmission: Ebola, Lassa
- Therapy: symptomatic, Ribavirin (Lassa, Hanta)

Klinische Charakteristika der VHF

Erkrankung	Inkubation (Tage)	Manifest. (%)	Todesrate (%)	Charakteristika
Südam. HF	7-14	>50	15-30	Neurologische Symptomatik
Lassa-Fieber	5-16	milde Verläufe	2-15	Prostration, Schock, Taubheit
Rift-Valley-F	2-5	1	50	Ikterus
Krim-Kongo-F	3-12	20-100	15-30	Schwerste Blutungen
HF mit renalem S.	9-35	Hanta: >75 Puumala: 5	5-15 <1	Nierenversagen milder Verlauf
HCPS	7-28	sehr hoch	40-50	Lungenödem, Schock
Marburg/Ebola HF	3-16	hoch	25-90	Schwerste HF, Prostration, Makulo-Papulöser Ausschlag
yellow fever	3-6	50%	20-50	Ikterisch und Nierenversagen
Dengue HF	3-15	0,007 (1 bei Immunen)	10-15 (<1 behandelt)	Hohes Fieber, auch Dengue- Schock-Syndrom

Prevention of haemorrhagic fevers

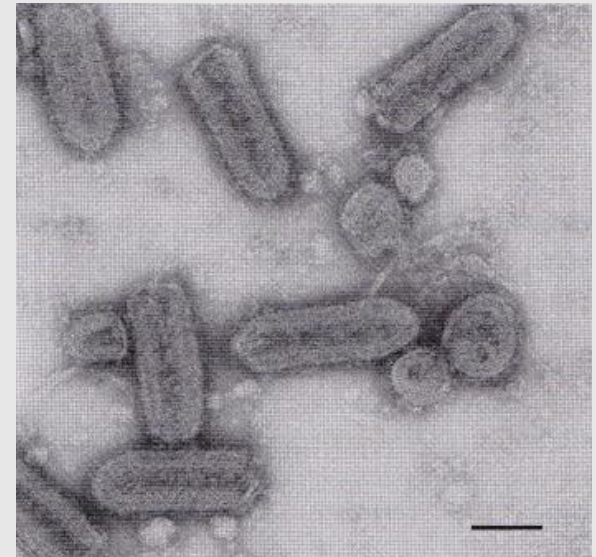
- Vaccination:
 - yellow fever, Argentine HF (Junin), Ebola
- Rodents reservoir:
 - Population control, prevent access to houses,
secure removal of rodent excreta
- Insect reservoir:
 - Insecticides, clothes, nets, repellents
- Human to human:
 - Barrier nursing, disinfection and secure disposal of
instruments and materials, secure burial

Informationsquellen

- Bernhard-Nocht-Institut für Tropenmedizin:
<http://www.bni-hamburg.de>
- Robert-Koch-Institut: Infektionskrankheiten von A-Z :
<http://www.rki.de>
- CDC:
<http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/filoviruses.htm>

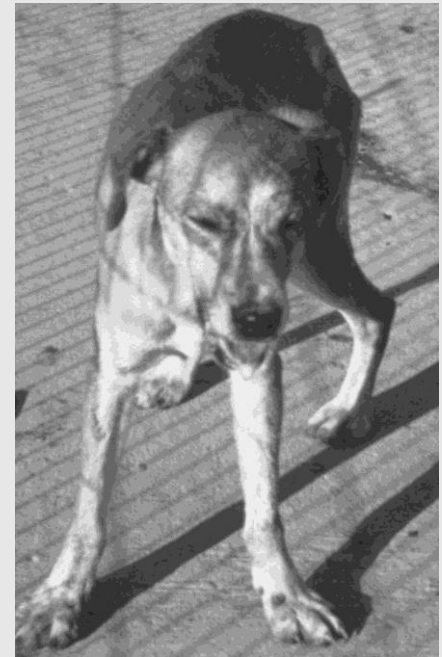
Rabies (Tollwut)

- Pathogen: Rabies virus, Family Rhabdoviruses, non-enveloped (-)-Strand-RNA-Virus
- transmission: Bite or contact with saliva of diseased animal
 - Europe: Foxes (80%), Deers (10%), others: Martens, badgers (Dachs), polecat (Iltis), Weasles AND bats;
 - USA: Bats, racoons (Waschbären), skunks
 - Developing countries: dogs
 - Most frequent transmission to humans by dogs (99 %)
- Incidence:
 - Europe and USA: few cases/year
 - India z.B.: 10.000 cases/year
 - D: 2005: 3 cases after transplantation



Pathogenesis of Rabies

- Replication in muscle and connective tissue at entry area
- Receptor mediated endocytosis in peripheral motoneurons and axonal transport
- cell-to-cell transmission; replication in CNS
- Centrifugal dissemination along neurons with replication also in epithelia of salivary glands
- replication in the limbic system: behavioural changes
- Incubation period dependent of heavyness of bite and bite position distance to the CNS (5 cm/day) :
Mostly between 3 weeks and 3 months



Clinical signs of rabies

- Prodromal state:
 - unspecific, febrile infection
- Sensoric phase:
 - local paresthesia at recovered bite
- Excitation phase:
 - Impaired consciousness, agitation, pharyngeal spasm, hydrophobia, photophobia, spasmic seizures
- Paralytic phase:
 - paralysis, coma, death

- Quasi all cases are lethal

Diagnosics of rabies

- Anamnesis: animal contact with bite
- Virus antigens in cornea, skin and brain biopsies
- Virus isolation from saliva (RT-PCR)
- Antibody detection mostly only in late phase positive
- Secure proof on infection only post mortem possible
Samples from hippocampus, cerebellum or brainstem

Vaccination against rabies

- Preexpositional: Veterinarians, hunters, lab personnel with risk
Vaccine: Inactivated rabiesvirus; yearly testing for neutralizing antibodies: if $< 0,5$ IU/ml \Rightarrow re-vaccination
- Travelers to high risk countries (Trekking)
- Postexpositional: Simultaneous-vaccination after wound was cleaned (water + soap) and disinfection (70% Ethanol)

Simultaneous-vaccination: 50% of hyperimmunglobulins around the wound, Remaining i.m.; Active-immunization: 0, 3, 7, 14, 28 days after exposition
Each suspected case of rabies also consult official veterinarian! Obligation to report!



Vielen Dank für ihre Aufmerksamkeit