RUHR-UNIVERSITÄT BOCHUM

# Imported virus infections

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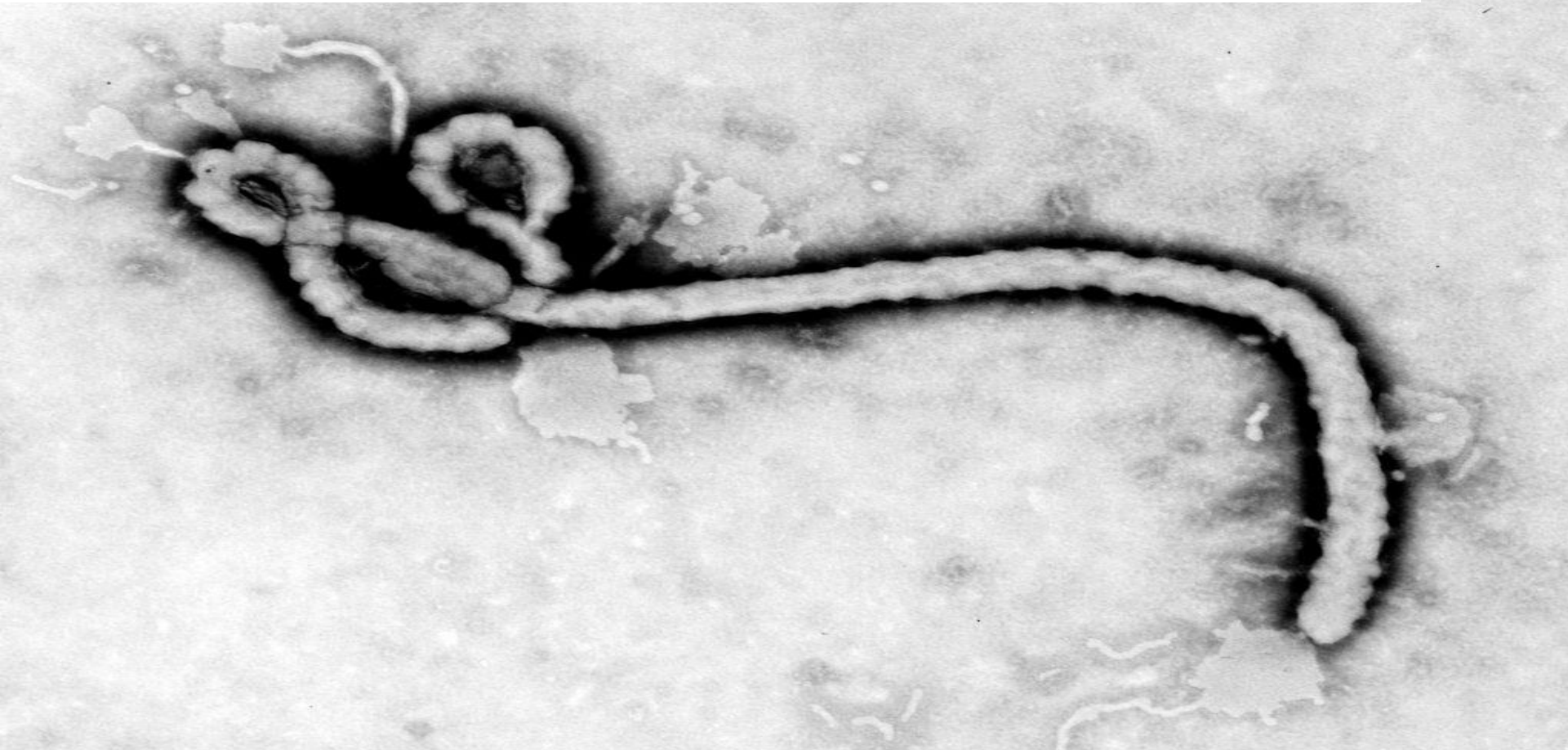


# Imported virus infections

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

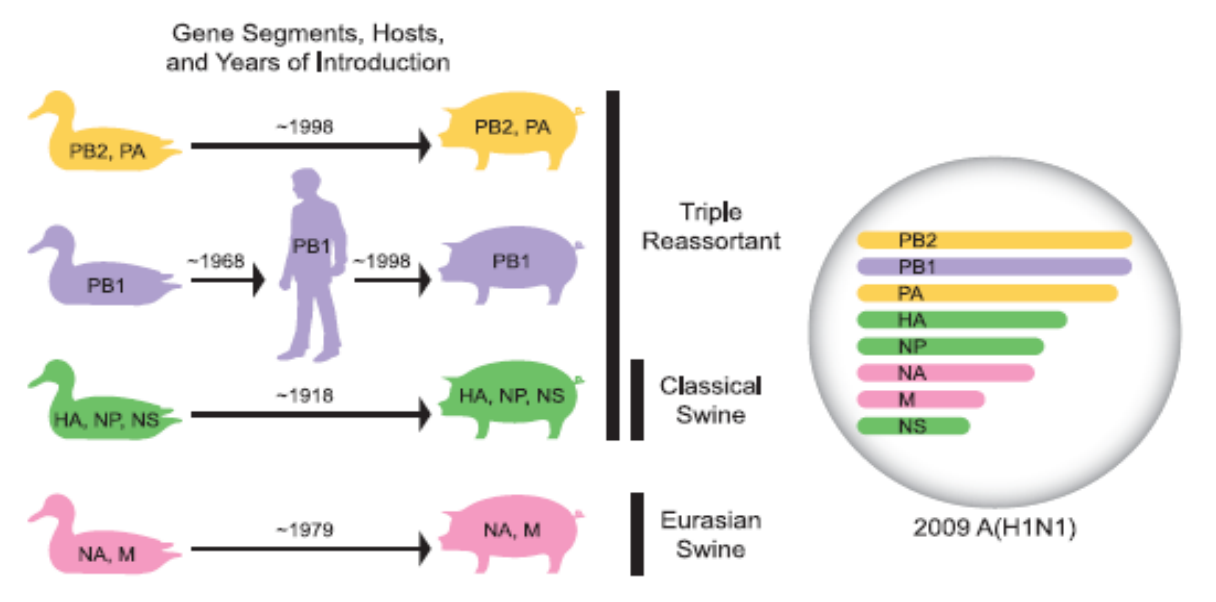
→Increased speed of pandemics

# Imported virus infections

- **Viral haemorrhagic fevers**
- Enzephalitisviuses
- 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 | Deutsch-land | 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

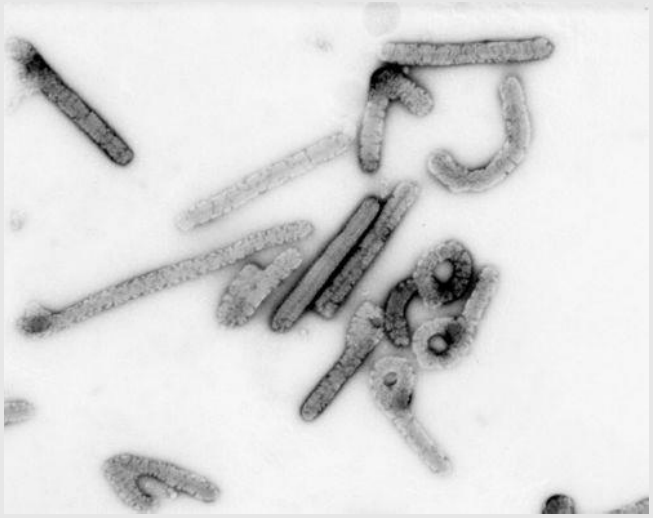
- Not only the final numbers of deaths and severe diseased persons, but also the speed of spreading plays a role in the pandemic‘s outcome
- Risk of collapsing medical care system (Italy, Spain, GB, New York)
- Early lockdown stopped too fast spread in Germany, but collateral damages are huge (economical,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

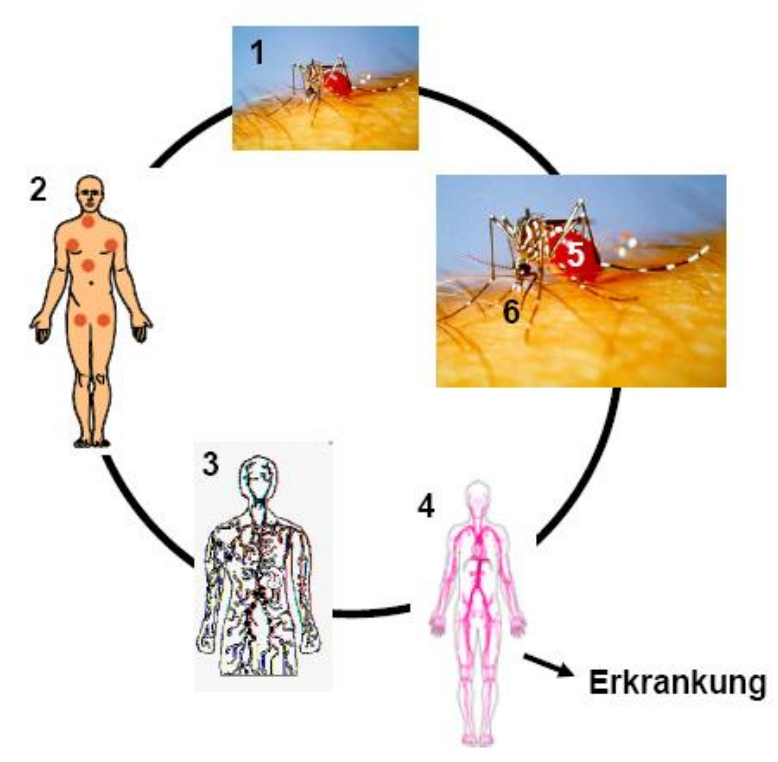
- Similarities:
  - enveloped RNA-Viruses
  - natural reservoir is not humans !

# Transmission

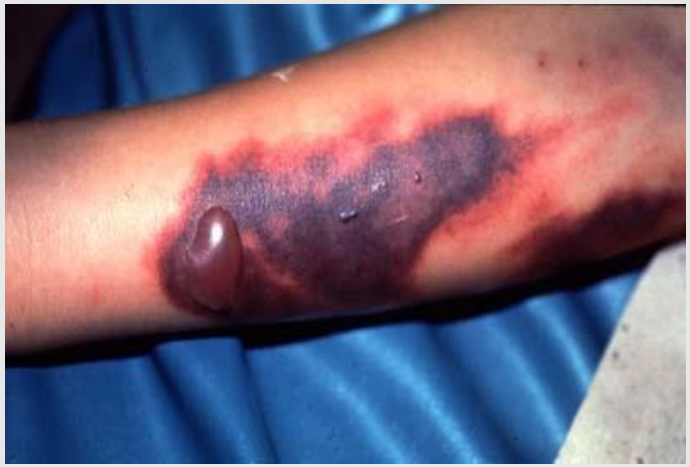
- Natural reservoir rodents (Lassavirus, Hantaviuses):
  - Contact with urine, feces, saliva etc.
- Natural reservoir mosquitoes or ticks (Flaviviruses):
  - Sting or bite, or contact with infected animals (slaughter house)
- Human to human (Filoviruses, Lassavirus):
  - Close contact, body fluids, contaminated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



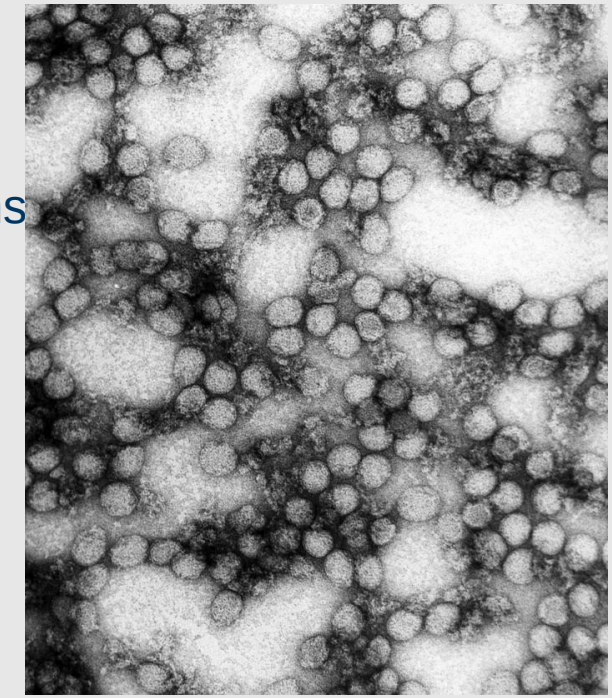
- Incubation period 3-14 days
- Progressions:
  - Classic: Sometimes prodromi with conjunctivitis and coryza (Schnupfen), then sudden fever, strong pain in bones and joints, retroorbital pain, exanthemes, slow recovery
  - Mild-atypical (children first infection): like classic, but < 3 days
  - Dengue 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-Infection

- 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.

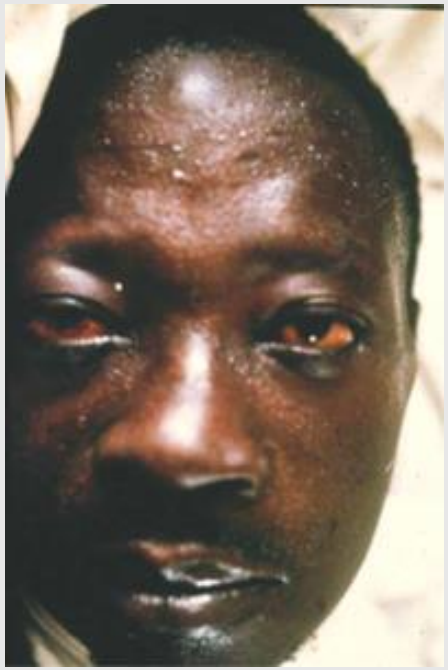
  After 3-4 days remission for 1-2 days, again increased fever

  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 life attenuated yellow fever virus

# Lassa fever

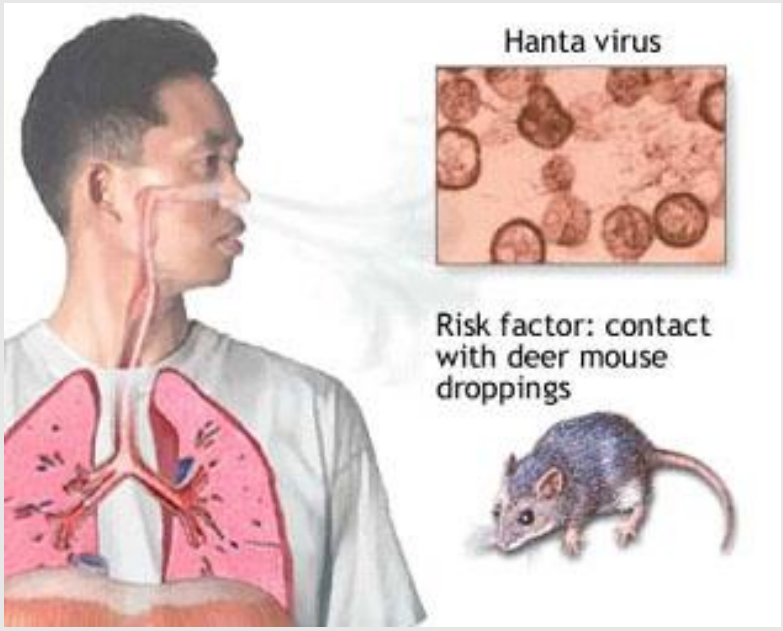
- Arenavirus, Western Africa, Southamerica
- Reservoir: Rodents
- Infections can also occur by close contact and nosokomial
- progression: slow with fever, headaches and soar throte, cough, gastro intestinal pain, up to hypotension, haemorrhages and encephalitis
- Lethality: 5-20% of hospitalized cases
- 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, human to human?

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

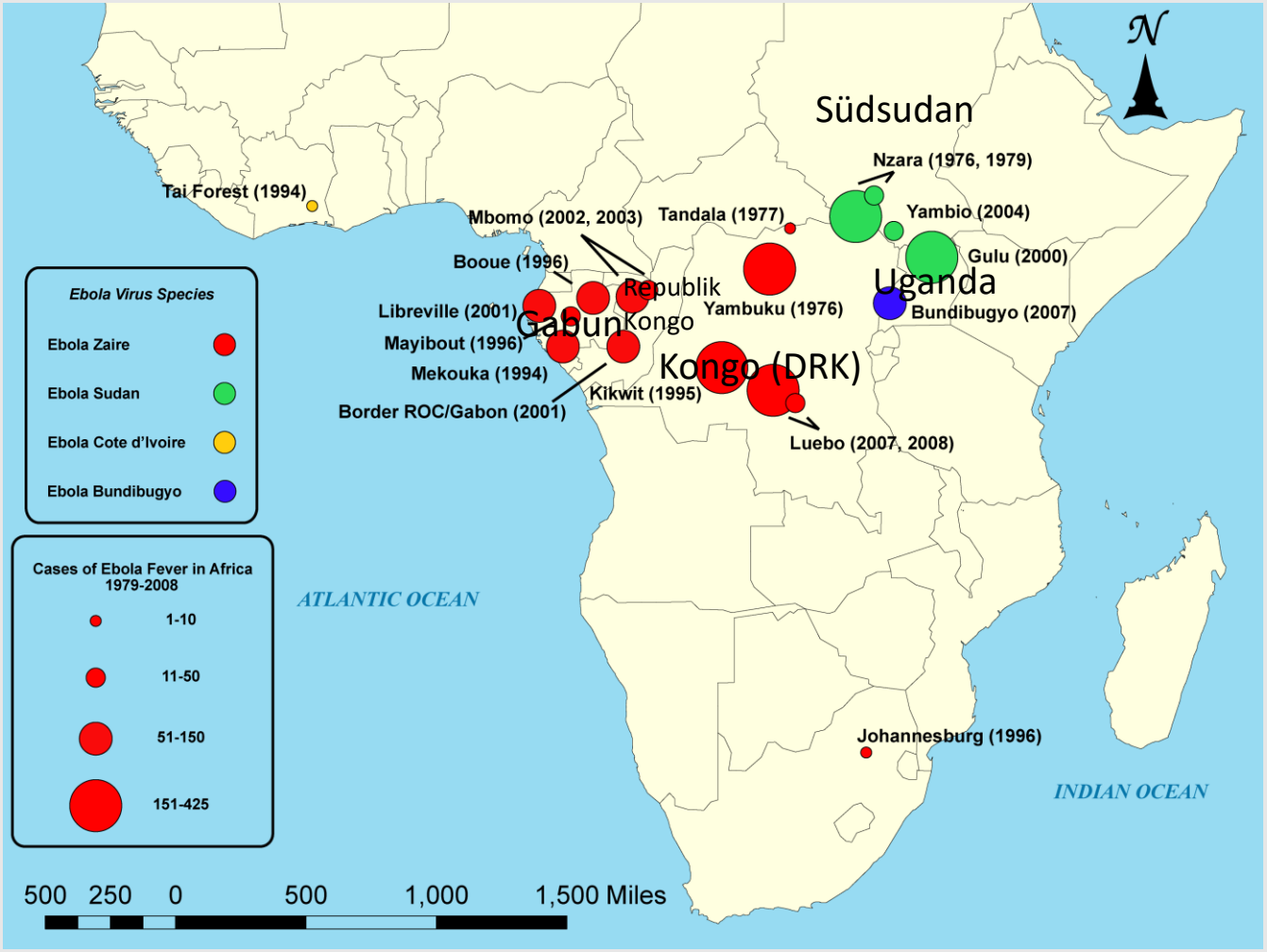
- Severe often deadly haemorrhagic fever in humans and other mammals
- First signs: high fever (>38°C), massive head- and muscel pain, nausea, conjunctivitis
- then: vomitting, diarrhoe, rash
- later: mucosal bleedings (gastrointestinal and genital), bleedings into skin
- decreased blood coagulation, liver damage
- Olig- and anuria up to kidney failure
- Death: cardio-pulmonary shock

- Mortality: 30-90%

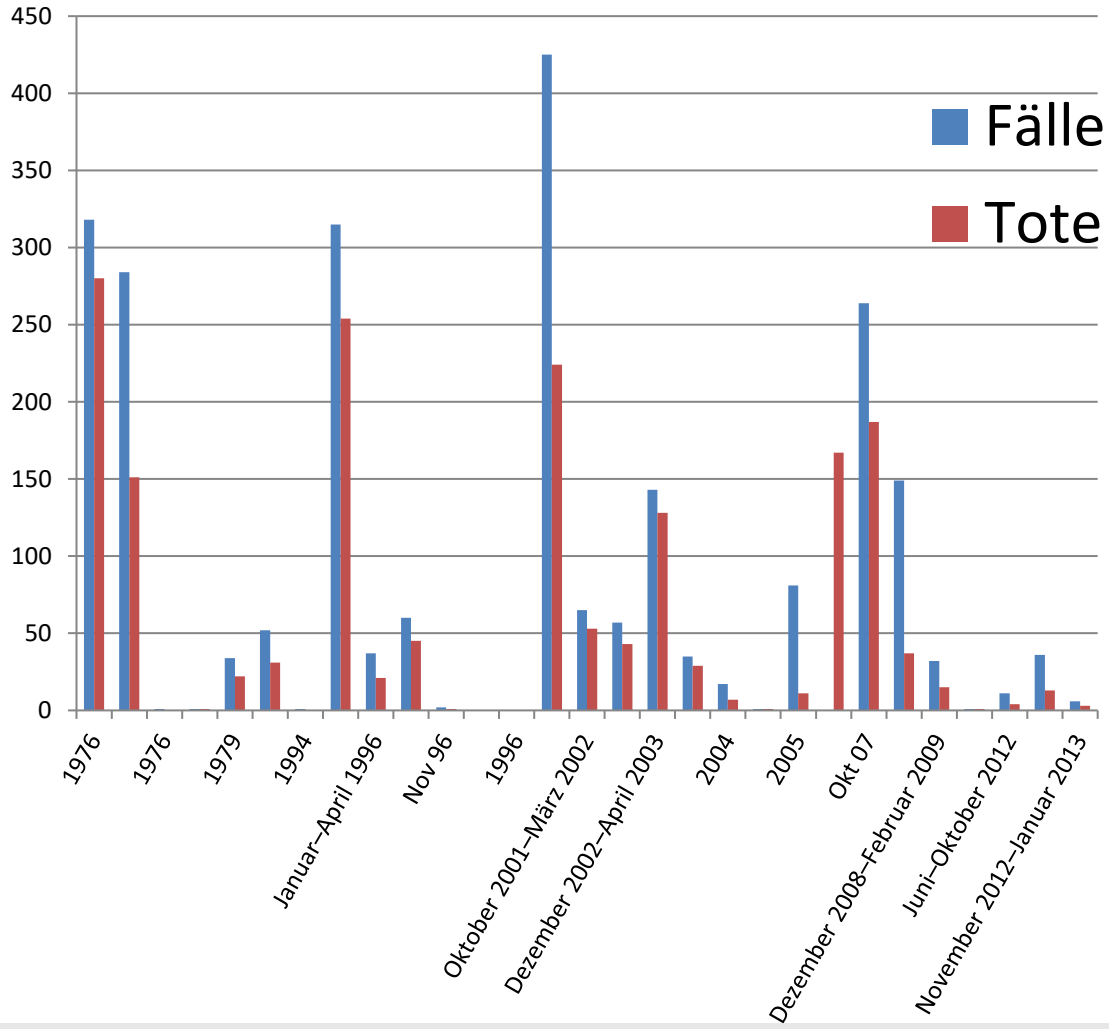
# Ebola outbreaks

| Year | Countryt | 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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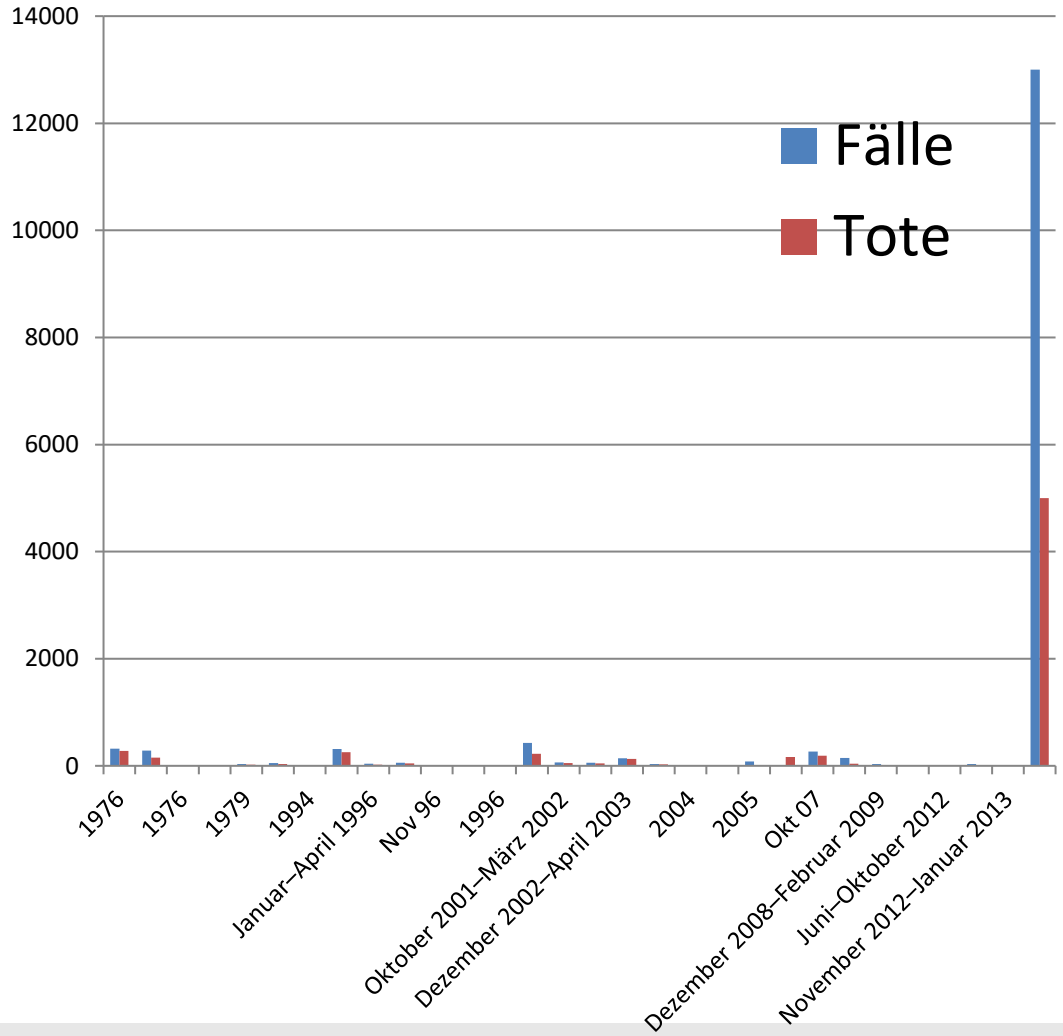
# Ende 2014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November 2012–Januar 2013

# 2. Ebola fever (EVD): transmission

- Transmission from animals to humans

- Probably by consumtion of „bushmeat“ (some delicacy) or by contact to body fluids of wild animals

- Animal reservoire: Flying foxes/bats and maybe non-human primates

# 2. Ebola fever (EVD): transmission

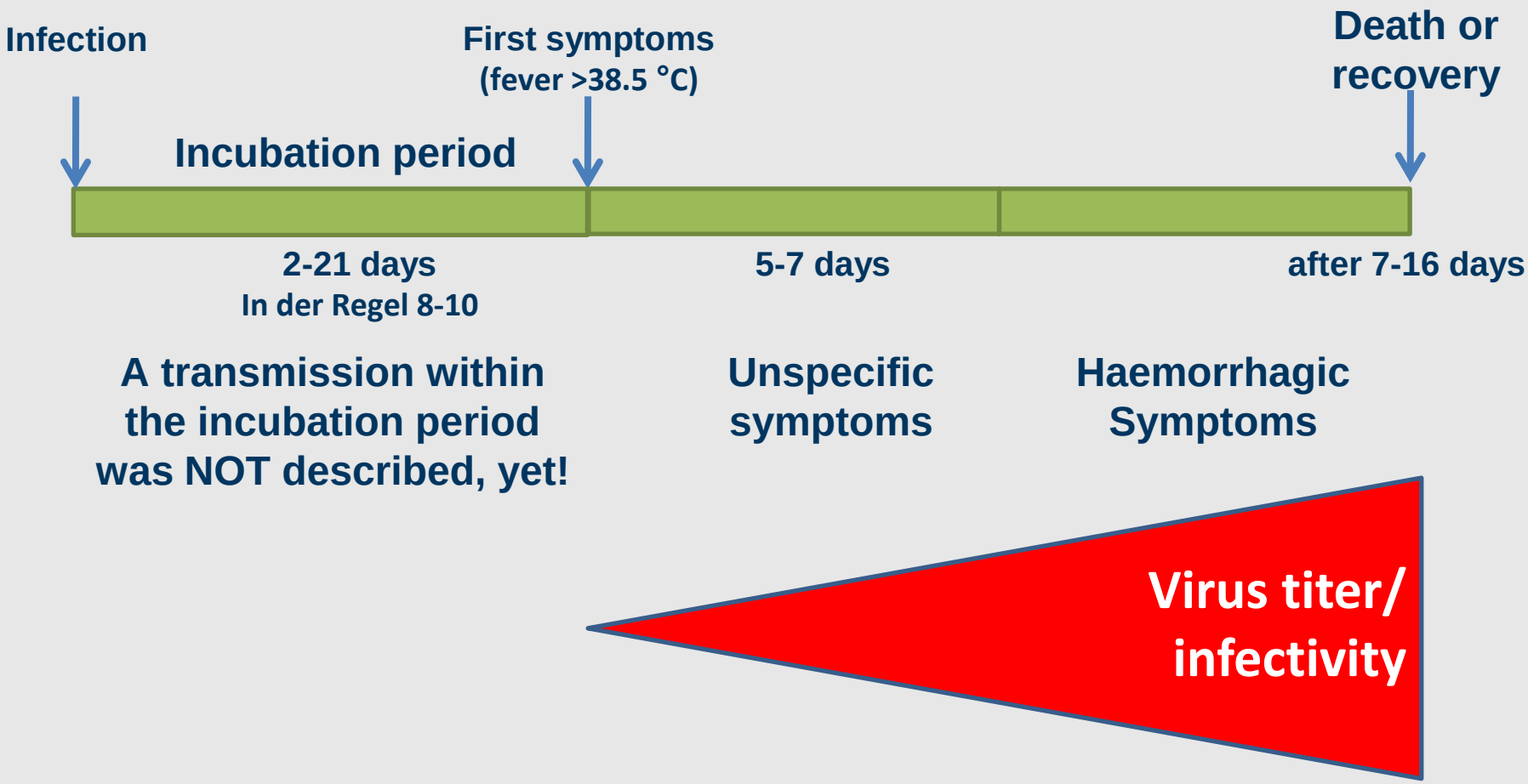
## From human to human:

- 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 last 3 weeks
  - or contact to body fluids of a VHF patient
  - or lab personnel with contact to VHF pathogens
- Kontaktaddresse: 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 desinfection 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<br>Puumala: 5 | 5-15<br><1 | Nierenversagen<br>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, repellentia

- Human to human:

  Barrier nursing, desinfection and secure disposal of

  instruments and materials, secure burial

# Informationsquellen

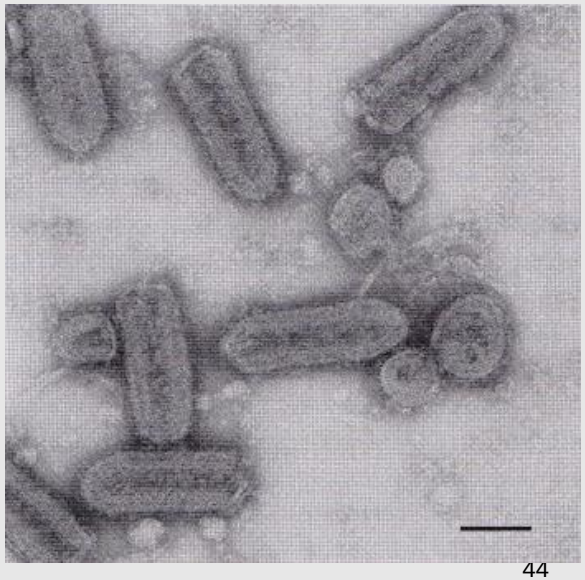
- Bernhard-Nocht-Institut für Tropenmedizin:
  http://www.bni-hamburg.de

- Robert-Koch-Institut: Infektionskrankheiten von A-Z :
  http://www.rki.de

- CDC:
  http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/filoviruses.htm

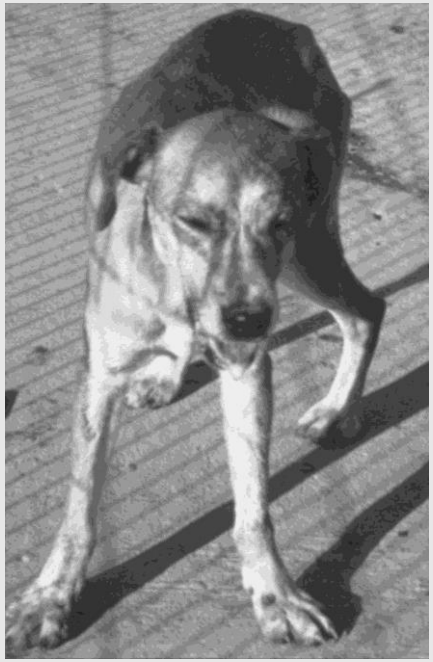
# Rabies (Tollwut)

- 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

# Diagnostics 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

- Prexpositional: Veterinarians, hunters, lab personnel with risk

  Vaccine: Inactiviated rabiesvirus; yearly testing for neutralizing antibodies: if < 0,5 IU/ml => re-vaccination
- Travelers to high risk countries (Trekking)
- Postexpositional: Simultanous-vaccination after wound was cleaned (water + soap) and desinfection (70% Ethanol)

Simultanous-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 veterinerian! Obligation to report!

# Vielen Dank für ihre Aufmerksamkeit