RNA viruses

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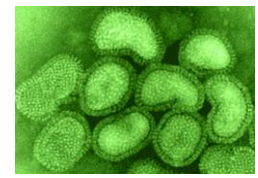
RNA viruses



http://mrstaberswiki.pbworks.com/f/1297256790/influenza.gif

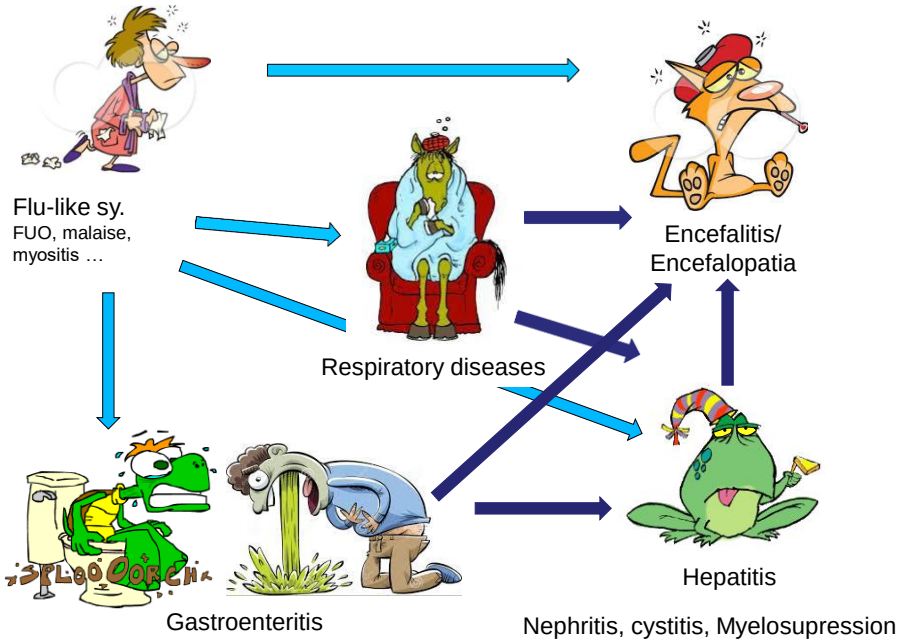
ss RNA

- ***Ortomyxoviridae*** → **Influenza A-C**
- ***Paramyxoviridae*** → **Paramyxovirus** → **PIV 1-4**
  - **Morbillivirus**
  - **Pneumovirus** → **RSV**, **hMPV**
- ***Coronaviridae*** → **HCoV** (229E, NL63, OC43, HKU1, MERS, SARS…)
- ***Picornaviridae*** → **Enteroviruses**
  - **Rhinovirus** → **HRV**
- ***Flaviviridae*** → HCV, Yellow fever Virus, WNV, Denque v…
- ***Caliciviridae*** → Human caliciviruses – Norovirus, Sapovirus
- ***Astroviridae*** → Astrovirus
- ***Rhadboviridae*** → Lyssa virus

ds RNA

- ***Reoviridae*** → **Rotavirus**, **Orbivirus**

Clinical consequences



Group of disease related to RNA viral infections

Respiratory tract infections – influenza, PIV, RSV, hantaviruses…

CNS infections – enteroviruses, parechoviruses, flaviviruses (WNV), TBE,…

Liver infections – picornaviruses (HAV), flaviviruses (HCV, Yellow fever..)…

Kidney infections – hantaviruses,…

Immune related infections – HIV

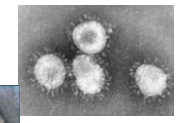
GIT infections – astroviruses, caliciviruses, rotaviruses

Haemorhagic fevers – Lassa virus, Ebola virus, Marburg virus…

Exanthematic diseases – Mumps virus, Rubella, Dengue…


Respiratory
viral infections
Courtesy of CDC

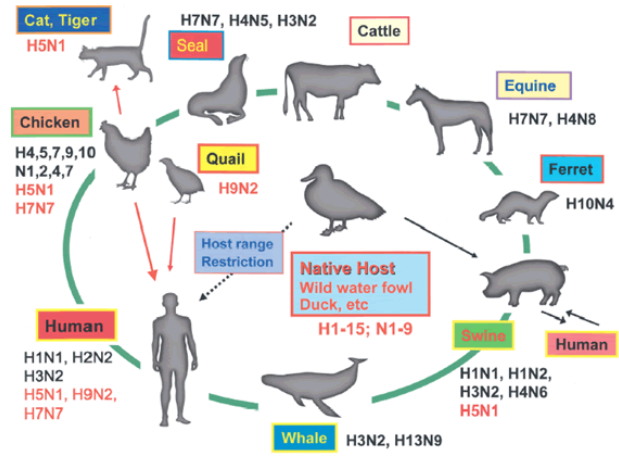
Respiratory viruses



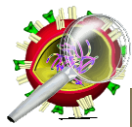
- Often zoonotic:
  - SARS – CoV
  - MERS - CoV
  - …

Bats – Horseshoe bat,…

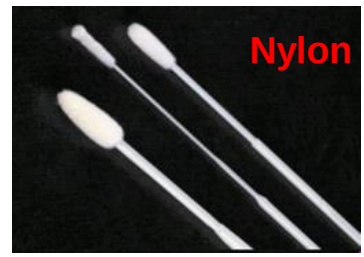
Civet



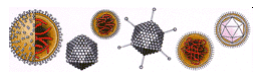
Leads to high Frequence of recombination of new life-threatening infections

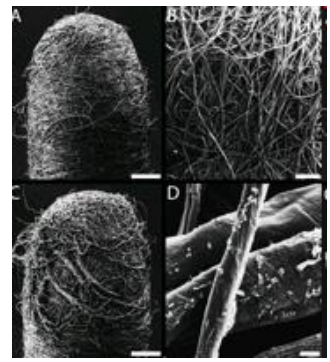


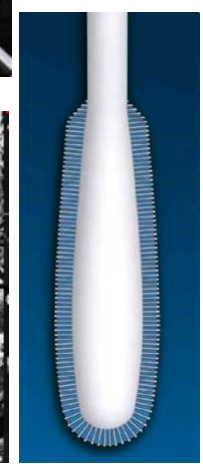
Type of biological material



Nylon swabs







What to aim during the process of dg? **Clinical symptoms**

Adapted ECDC Definitions of Respiratory Tract Infectious Disease (RTID)

Clinical criteria

- *New* onset of symptoms
  AND
  at least one of the following four respiratory symptoms:
  - Cough
  - Sore throat
  - Shortness of breath
  - Coryza

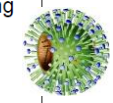
  AND
  - A clinician’s judgement that the illness is due to an infection

Epidemiological Criteria

- An epidemiological link with human to human transmission

Laboratory Criteria

- Detection of CARV in a clinical specimen by at least *one* of the following:
  - Virus isolation by cell culture (VIC)
  - Direct virus antigen testing (DAT)
  - Nucleic acid amplification testing (NAT)



Case Classification

- **Possible case**
  - Any person meeting the clinical criteria of RTID
- **Probable case**
  - Any person meeting the clinical criteria of RTID *and* with an epidemiological link
- **Confirmed case**
  - Any person meeting the clinical of RTID *and* the laboratory criteria

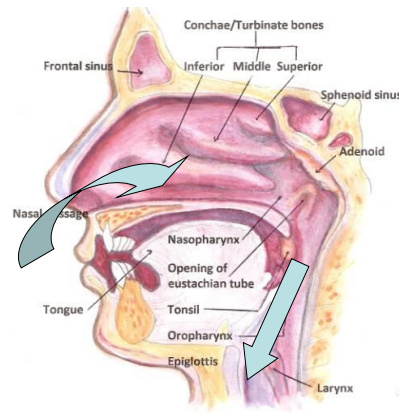
Adapted from ECDC definitions for influenza
http://ecdc.europa.eu/en/activities/surveillance/EISN/surveillance/Pages/influenza_case_definitions.aspx

What to aim during the process of dg?

Good sampling of biological material

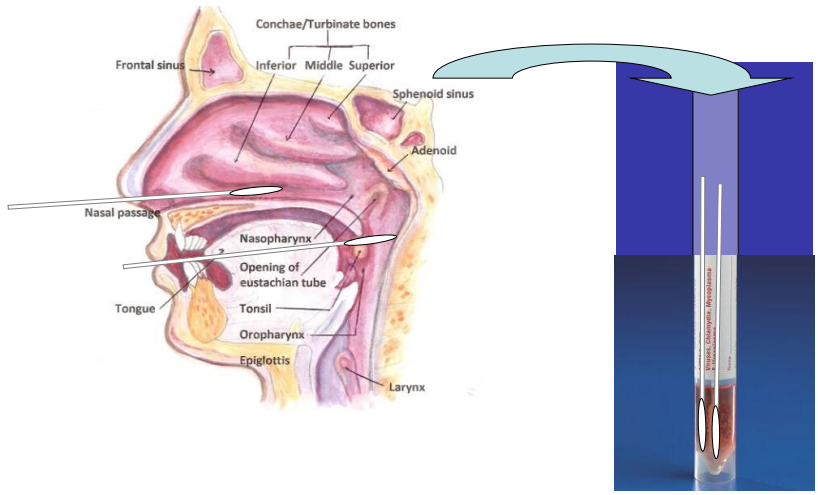
First proliferation at the mucos of upper respiratory tract.

Virus	*Transmission from upper to lower RT*	*Mortality*
RSV	20-68%	17-70%
PIV	13-37%	10-30%
HRhV	<10%	<10%

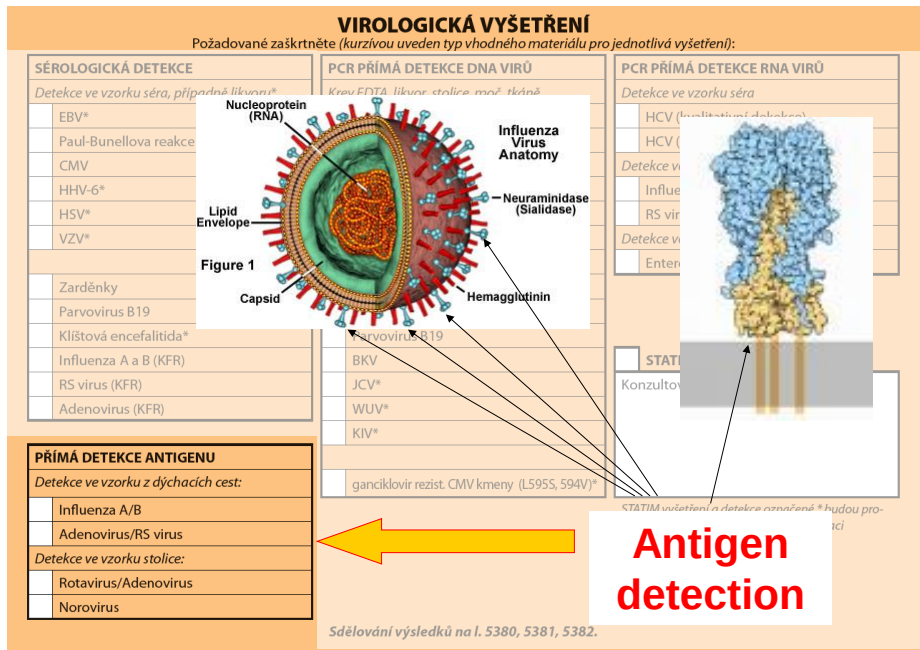


What to aim during the process of dg?

Good sampling of biological material



Direct detection



Direct detection - antigen

Požadované zaškrtněte (kurzívou uveden typ virologického materiálu pro jednotlivá vyšetření):

SÉROLOGICKÁ DETEKCE	
Detekce ve vzorku séra, případně likvoru [L]	
	EBV [L]
	Paul-Bunellova reakce
	CMV
	HHV-6 [L]
	HSV [L]
	VZV [L]
	Zarděnky
	Parvovirus B19
	Klíšťová encefalitida [L]
	Influenza A a B (KFR)
	RS virus (KFR)
	Adenovirus (KFR)

PŘÍMÁ DETEKCE ANTIGENU	
Detekce ve vzorku z dýchacích cest:	
☒	Influenza A/B
☒	Adenovirus/RS virus
Detekce ve vzorku stolice:	
	Rotavirus/Adenovirus
	Norovirus

PCR PŘÍMÁ DETEKCE DNA VIRŮ — *Krev EDTA, likvor, moč, stěr*

HSV 1, VZV, CMV, HHV-6, HHV-7, EBV, HHV-8, Adenovirus, Parvovirus B19, BKV, JCV*, WUV*, KIV*, ganciklovir rezist. CMV

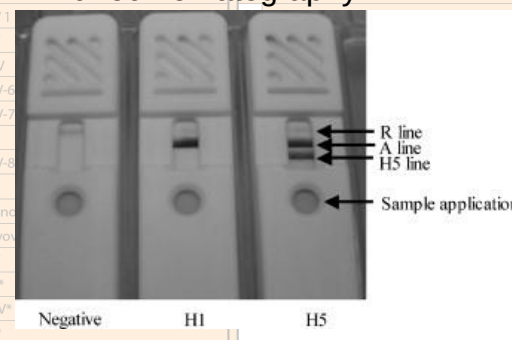
PCR PŘÍMÁ DETEKCE RNA VIRŮ — *Krev EDTA, likvor, moč, stěr*

*STATIM vyšetření a detekce označené * budou provedena v PCR laboratoři. Výše zmíněná konzultace*

Sdělování výsledků na l. 5380, 5381, 5382.

Example of the result

Imunochromatography

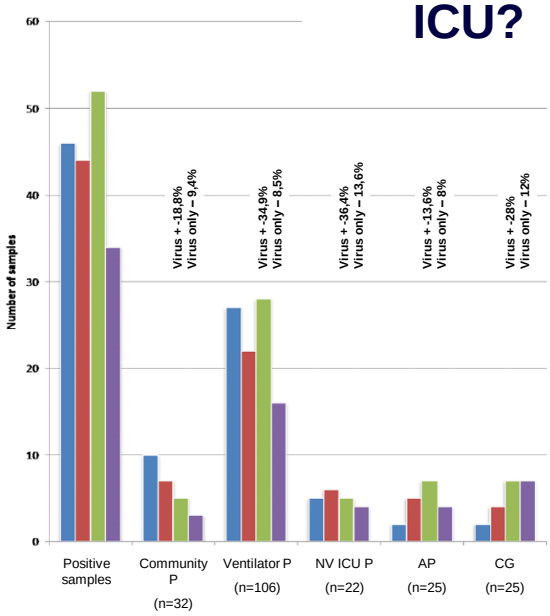


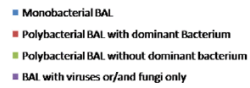
Result in ± 15 minutes.

Sensitivity approx. 30-40% comparing to PCR.

Price of the test approx. 4-6 Euro

How often do we detect viruses at ICU?





Detected	*Pneumonia (n=185)*	*Control group (n=25)*
HSV	51 (27,5%)	7(28%)
CMV	31 (16,8%)	3 (12%)
PIV-1	3 (1,6%)	1 (4%)

Bousbia et al. PloS 2012

BMC Pulmonary Medicine 2009, **9**:22 http://www.biomedcentral.com/1471-2466/9/22

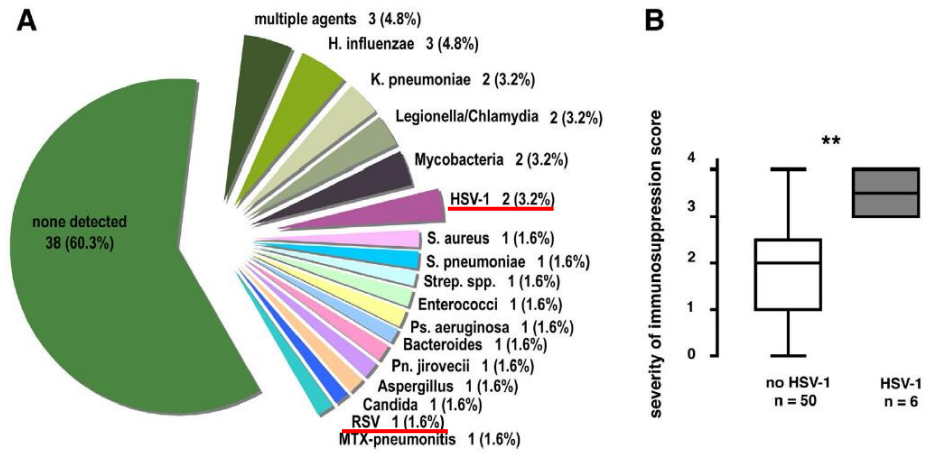


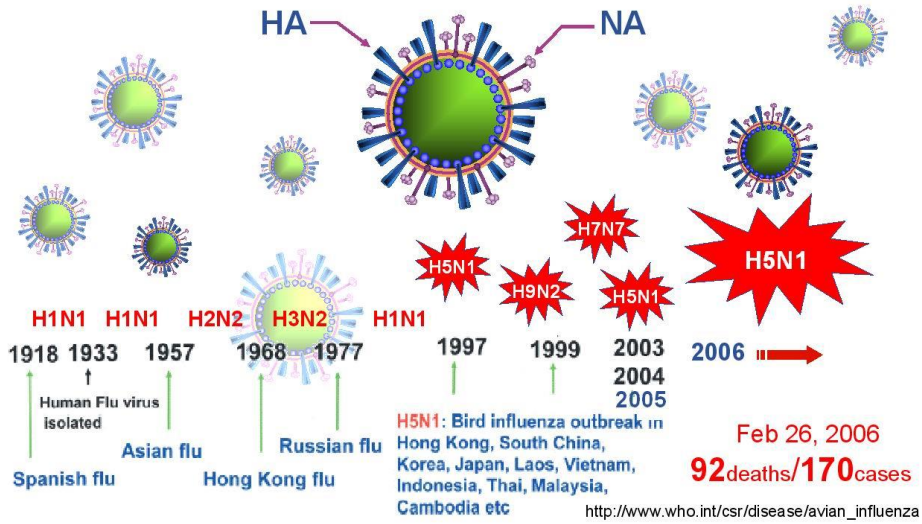
Figure 3
A: Detected primary responsible (leading) infectious agents in 63 patients with ambulatory-acquired pneumonia/pneumonitis and autoimmune disease. RSV = respiratoy syncytial virus. B: Immunosuppression scores were significantly more severe in the 6 patients with HSV-1 detection in BAL than in those subjects without clinical or laboratory evidence for HSV-1 (as assessed for 56/63 patients with reliable information on immunosuppressive regimens available; ** $p < 0.01$, Mann-Whitney two-sided test).

How often do we detect viruses at ICU?

Hematooncological patients

- **RSV**
  - **in 0.3% - 2.2% of paediatric pts with AML and 1%-12% adult HSCT pts**
  - UTRI to LRTI progression in 20-68% pts.
  - RSV related mortality 17-70%
- **PIV**
  - PIV causes URTI during year from laryngotracheitis, bronchiolitis to pneumonii in **15% of children from autumn to spring**
  - In patients after **HSCT in 2% - 7% symptomatically**, when asymptomatic patients are included up to 18%
  - Long lasting expression can lead to nosocomial epidemy.
  - PIV-3 is after HSCT most frequently (up to 90% of cases) later PIV-1 a -2
  - URTI decrease of ventilation up to 40%, infection progress to LRTI in 13-37% with fatal end 10-30%.
- **hMPV**
  - Related to RSV causing **5%-20% of URTI** and tracheobronchitis in children and adults during winter
  - At HSCT patients described in **5%-9% during first 2 years after HSCT**.
- **Coronaviry**
  - In pts. after **HSCT detected in 6.7% - 15.4%**, asymptomatic shedding in 41%..
  - In symptomatic pts. often coinfections
- **HRhV**
  - HRhVs most frequent viral cause of CARI with cumulative incidence up to **22.3% at D+100**.
  - Asymptomatic in 13% of HSCT patientů, detection with other CARI viruses in 19%
  - LRTI in allogeneic HSCT rare (<10%), might be associated with bad outcome in less then 10%

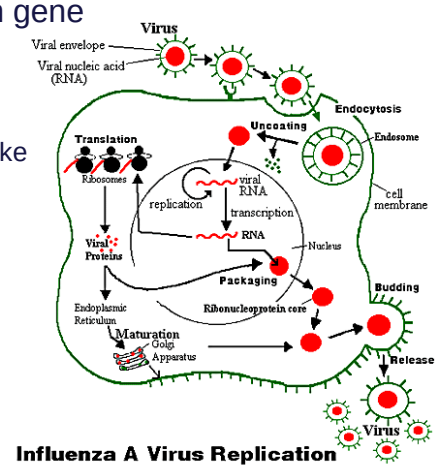
Influenza A viruses



Influenza Antigenic Changes

- **Antigenic Drift** - seasonal
  - Minor change, same subtype
  - Caused by point mutations in gene
  - May result in epidemic

Example of antigenic drift
- In 2003-2004, A/Fujian/411/2002-like (H3N2) virus was dominant
- A/California/7/2004 (H3N2) began to circulate and became the dominant virus in 2005

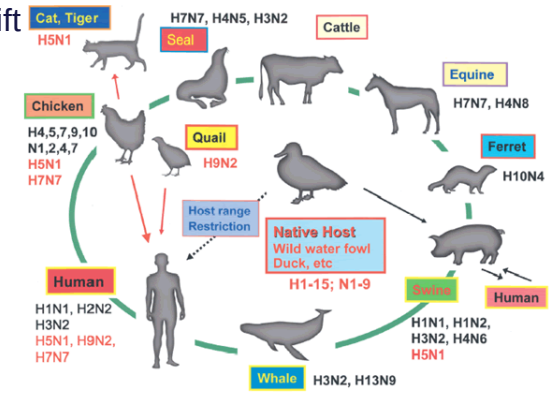


Influenza A Virus Replication

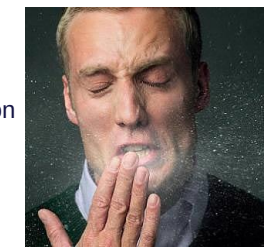
Influenza Antigenic Changes

- **Antigenic Shift**
  - Major change, new subtype
  - Caused by exchange of gene segments
  - May result in pandemic

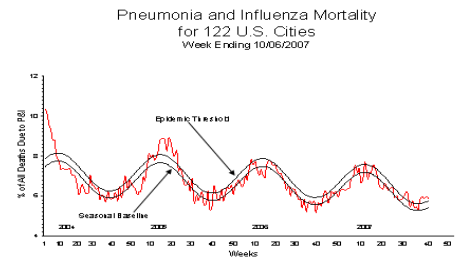
- Example of antigenic shift
  - H2N2 virus circulated in 1957-1967
  - H3N2 virus appeared in 1968 and completely replaced H2N2 virus



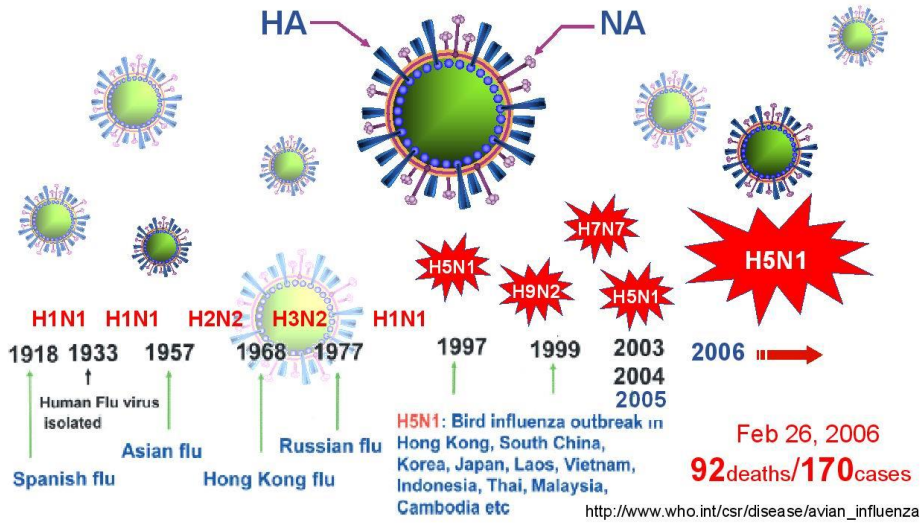
Influenza Epidemiology



- Reservoir: Human, animals (type A only)
- Transmission: - inhaling respiratory aerosols containing the virus, produced when infected person talks, coughs, or sneezes
  100,000 - 1,000,000 virions/droplet
  » touching an infected person or an item contaminated with the virus and then touching your eyes, nose, or mouth
- Incubation: 18-72 hours
- Communicability: Maximum 1-2 days before to 4-5 days after onset

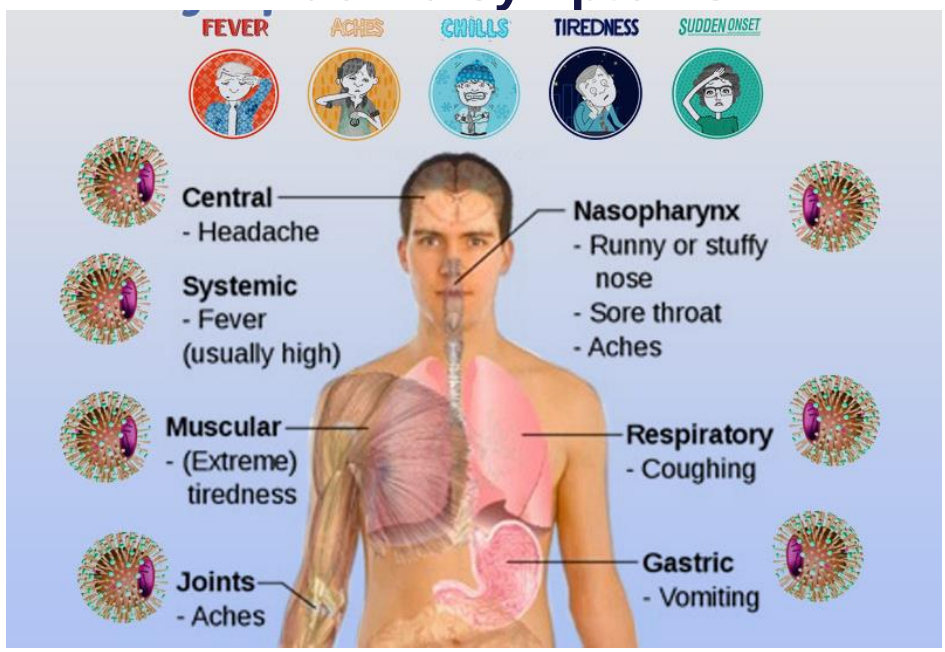


Influenza A viruses



http://www.who.int/csr/disease/avian_influenza

Influenza symptoms



Diagnosis

- Virus isolation
  - Tissue culture or eggs
- Serology
- Rapid tests (ussually antigen detection)
- Provisional - clinical picture + outbreak
- PCR

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Treatment (prevention) - drugs

- RIMANTADINE (M2)
  - type A only, needs to be given early
- AMANTADINE (M2)
  - type A only, needs to be given early
- OSELTAMIVIR (NA) – p.o.
  - types A and B, needs to be given early
- ZANAMIVIR (NA) – i.v.
  - types A and B, needs to be given early
- PERAMIVIR (NA) – i.v.
  - types A and B, needs to be given early

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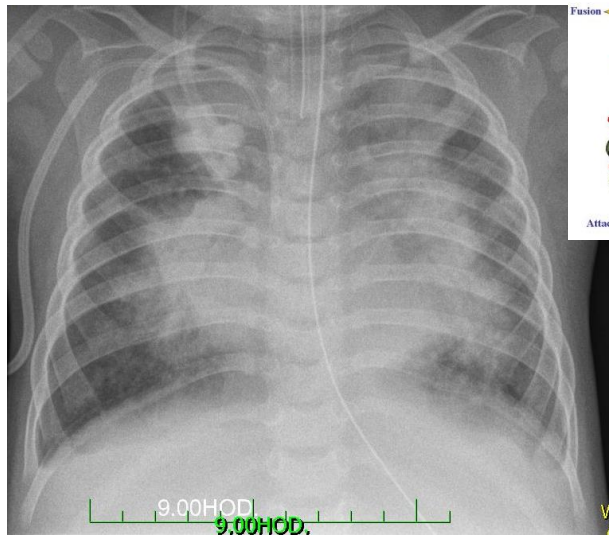
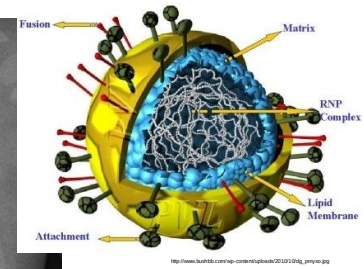
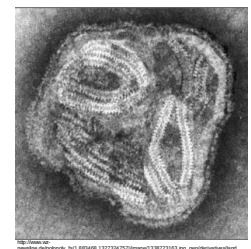
Paramyxoviridae

Respiratory-syntitial virus

RSV (boy treated for AML)



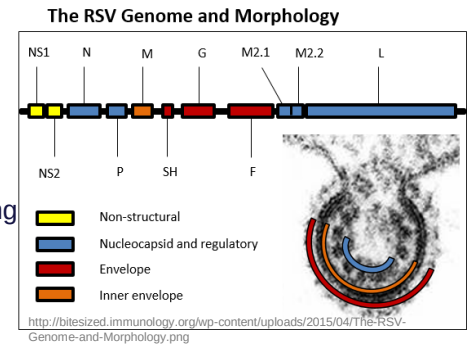




Paramyxoviridae

Pathophysiology

- ss (-) RNA virus
- Genome length approx. 15 kb
- Family *Paramyxoviridae*
  (similar other related viruses)
- RSV season late fall to early spring
- Peak in January/February
- Incubation 4-5 days
- LRI between days 5-7
- Most common cause of **bronchiolitis** & pneumonia in children under 1
- 25-40% of children develop bronchiolitis or pneumonia during first RSV infection
- 31/1,000 under 1 yr. are hospitalized with RSV
- 2% will die
- Often long term effects of the bronchiolitis – pulmonary fibrosis



http://bitesized.immunology.org/wp-content/uploads/2015/04/The-RSV-Genome-and-Morphology.png

Paramyxoviridae

Prophylaxis

- **RSV-IGIV (RespiGam)**
- Children under 24 mo. w/ CHD or less than 35 wks. gestation
- Given IV monthly during RSV season
- Volume overload possible
- Not for infants w/ hemodynamically significant heart disease.

- **Palivizumab (Synagis)** – anti protein F antibody
- Given IM monthly
- Can reduce hospitalization of high risk infants by 45%
- Expensive
- Many providers reluctant to give
- Many parents unaware

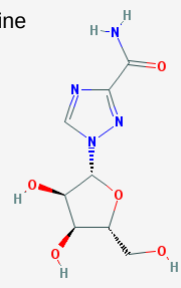
Paramyxoviridae

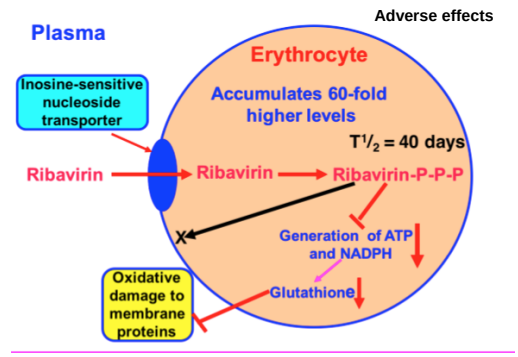
Treatment

- Mostly symptomatic
- Salbutamol MDI drug of choice
- Also use epinephrine, ipratropium bromide, & oral steroids only if hospitalized

- Virostatics – **ribavirine**
- In hospitalised patients with immune system impairment
- Inhalatory or per oral (preffered)

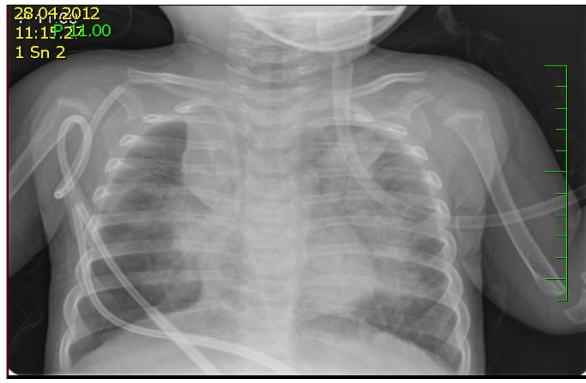
ribavirine

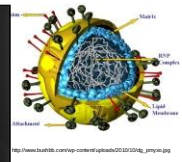




Paramyxoviridae

Respiratory syncitial virus - RSV





AML M7, M. Down,
age 16 month

Symptoms: long lasting febrilie, tachydyspnoe, neccesity of O_2 support, alteration of the clinical status
Detection: RSV in NFS by antigen test, PCR negative, RSV confirmed from ET tube
Lung X-ray: both sided atelectatical interstitial changes
Terapy: Maxipime, Amikin, Zyvoxid,Noxafil, Gammagard Synagis 120mg i.m.
parenteral nutrition, oxygenoterapy, bronchodilatancia
Transfer to ICU for artificial ventilation, AH – total 14 days

Paramyxoviridae

Parainfluenzavirus 4

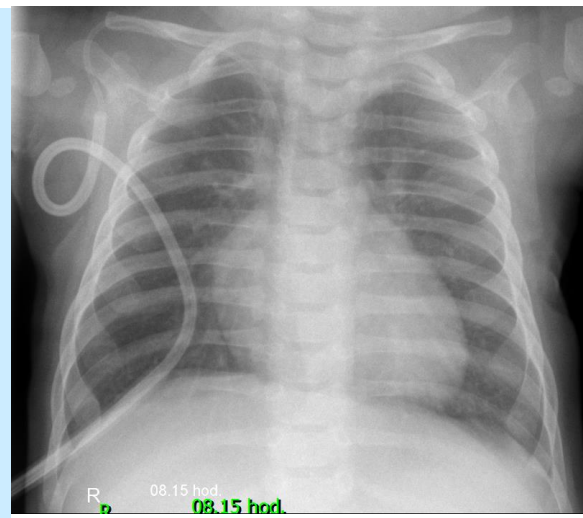
Boy with dg. of Ommen sy., at 4 month of age (RAG2 mut.)

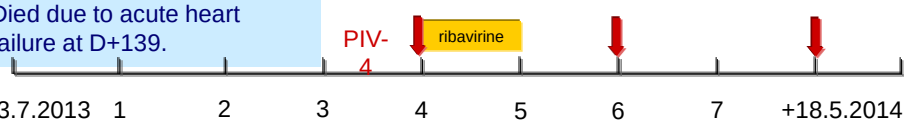
Before HSCT neccesity of O_2 therapy with PIV-4 detection.
Started p.o. ribavirine
15 mg/kg/d in 3 doses combined with IVIG.

After 12 days started conditioning.
Conditioning in 5 months of age: fludarabine, busulfan, alemtuzumab
Ribavirine stopped during busulfan therapy.
Graft: CB

PIV-4 positivity lasted 4 months.

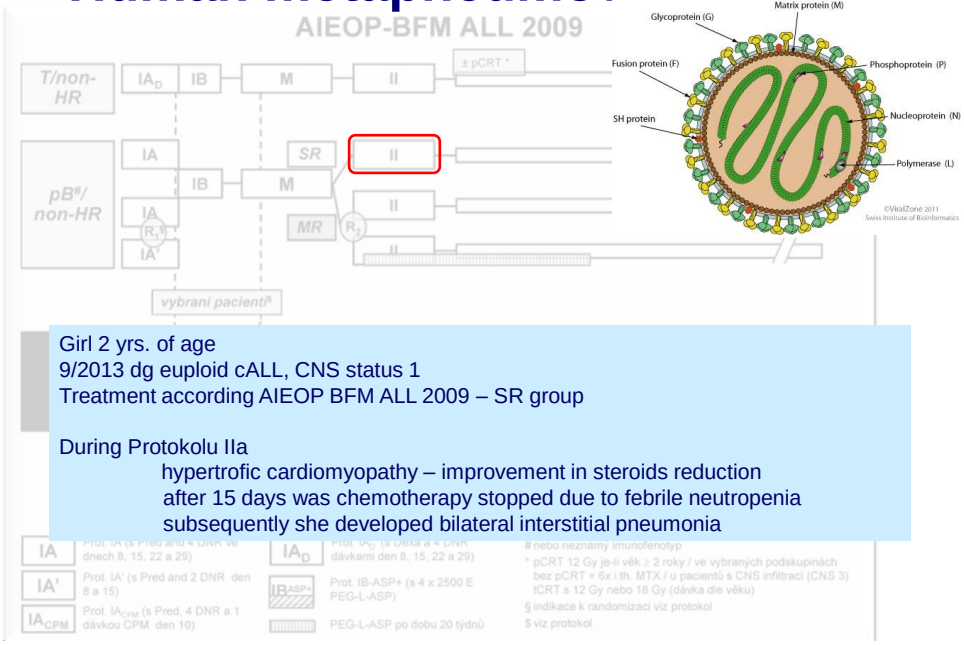
Died due to acute heart failure at D+139.





Paramyxoviridae

Human metapneumovirus (hMPV)

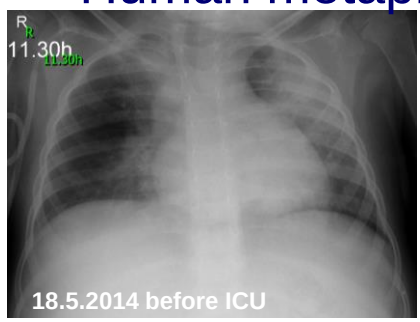


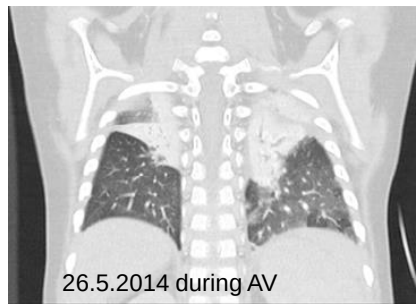
Girl 2 yrs. of age
9/2013 dg euploid cALL, CNS status 1
Treatment according AIEOP BFM ALL 2009 – SR group

During Protokolu IIa
hypertrofic cardiomyopathy – improvement in steroids reduction
after 15 days was chemotherapy stopped due to febrile neutropenia
subsequently she developed bilateral interstitial pneumonia

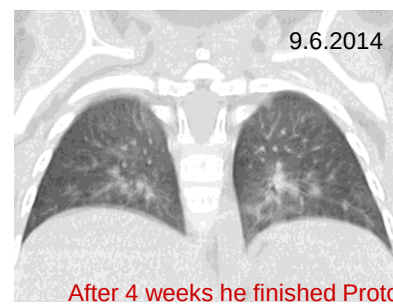
Paramyxoviridae

Human metapneumovirus (hMPV)



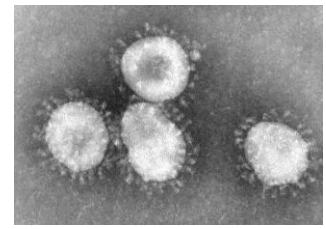


- 9.5.2014 positive NF swab for hMPV
- Treatment:
  - IVIG (substitution 0.3 g/kg - 4 doses)
  - ribavirine 6 mg/kg á 8 hod p.o. 5 weeks
- Respiratory failure with 8 days of AV (FiO_2 1,0)
- hMPV confirmed for ET tube
- hMPV positivity 4 weeks
- Control CT after 10 days of AV - regression



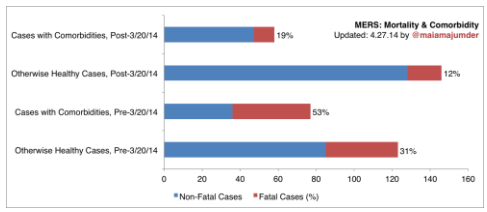
After 4 weeks he finished Protokol IIa.

Coronaviruses

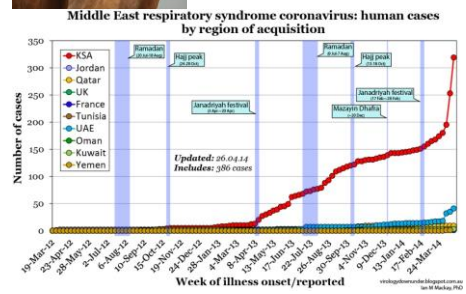


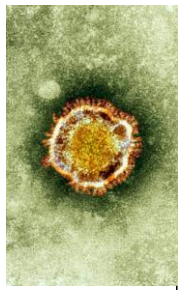
- Coronaviridae
- ss (+) RNA, 26-32 kb genone length (largest RNA)
- first identified in the mid-1960s
  - alpha – HCoV 229E and NL63
  - beta - HCoV OC43, HKU1, SARS-CoV (severe acute respiratory syndrome), and MERS-CoV (Middle East Respiratory Syndrome)
- **SARS**
  - Cellular receptor – ACE2
  - mortality rate – approx. 9.5%
- Incubation period – 2-4 days
- **Treatment symptomatic**

MERS - transmission through camels, their milk and cheese



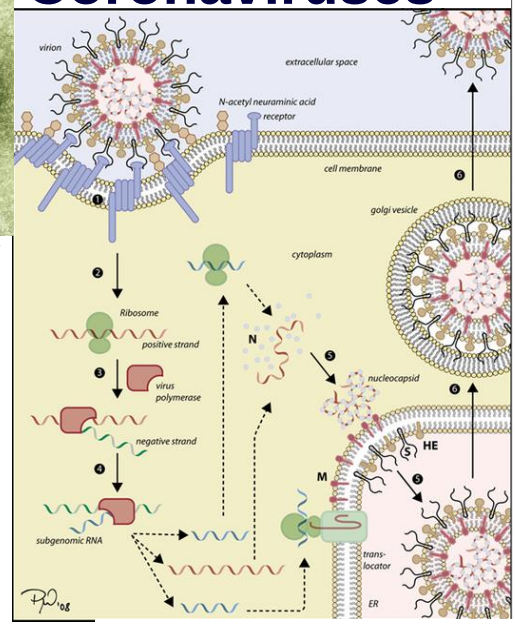
https://maimunamajumder.files.wordpress.com/2014/04/mers_comorbidity_mortality_4-271.png





http://www.nature.com/polopoly_fs/7.6657.1349187529!/image/1.11513_coronavirus_HPA.jpg_gen/derivatives/landscape_630/1.11513_coronavirus_HPA.jpg

Coronaviruses



Replication of Coronavirus

1 With their S-protein, coronaviruses bind on cell surface molecules such as the metalloprotease »amino-peptidase N«. Viruses, which accessorily have the HE-protein, can also bind on N-acetyl neuraminic acid that serves as a co-receptor.

2 So far, it is not clear whether the virus get into the host cell by fusion of viral and cell membrane or by receptor mediated endocytosis in that the virus is in-corporated via an endosome, which is subsequently acidified by proton pumps. In that case, the virus have to escape destruction and transport to the lysosome.

3 Since coronaviruses have a single positive stranded RNA genome, they can directly produce their proteins and new genomes in the cytoplasm. At first, the virus synthesize its RNA polymerase that only recognizes and produces viral RNAs. This enzyme synthesize the minus strand using the positive strand as template.

4 Subsequently, this negative strand serves as template to transcribe smaller subgenomic positive RNAs which are used to synthesize all other proteins. Furthermore, this negative strand serves for replication of new positive stranded RNA genomes.

5 The protein N binds genomic RNA and the protein M is integrated into the membrane of the endoplasmatic reticulum (ER) like the envelope proteins S and HE. After binding, assembled nucleocapsids with helical twisted RNA budd into the ER lumen and are encased with its membrane.

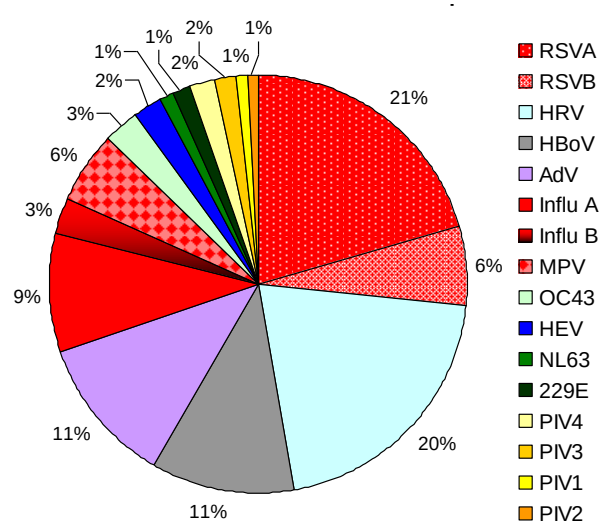
6 These viral progeny are finally transported by golgi vesicles to the cell membrane and are exocytosed into the extracellular space.

Not drawn to scale! Not all cellular compartments and enzymes are shown. Colors: positive strand RNA (red), negative strand RNA (green), subgenomic RNAs (blue).
Based on: Lai MM, Cavanagh D (1997). The molecular biology of coronavirus. Adv. Virus Res (48) 1-100.

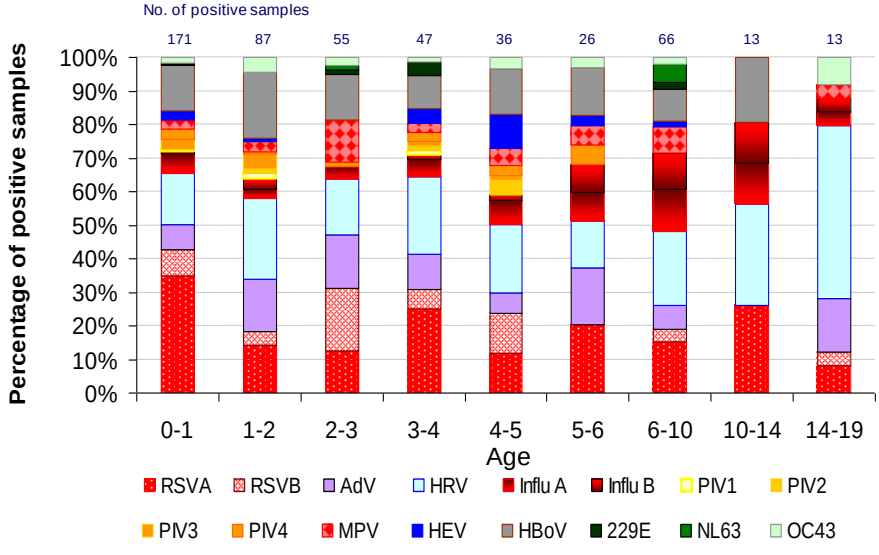
https://upload.wikimedia.org/wikipedia/commons/thumb/f/f4/Coronavirus_replication.png/800px-Coronavirus_replication.png

Detection of respiratory viruses in patients in Motol University Hospital (PCR)

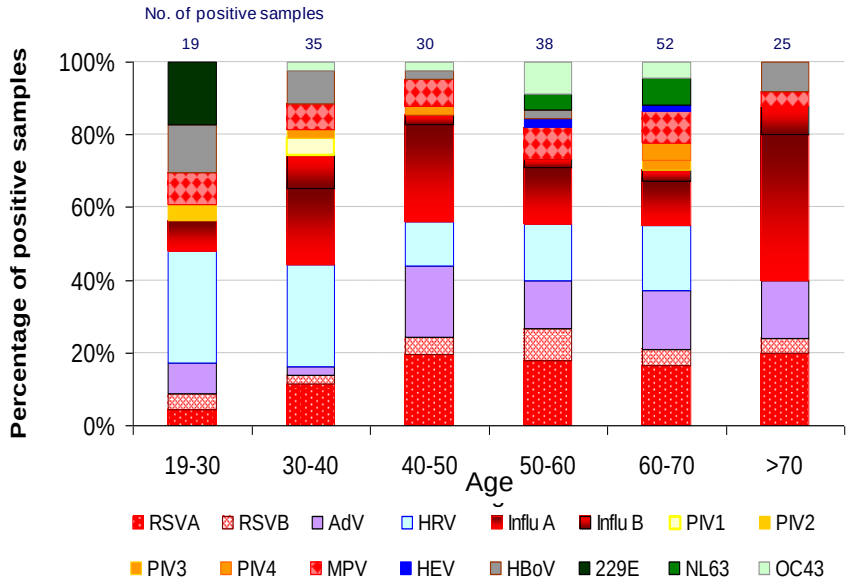
RSV-A and RSV-B, HRV, HBoV, AdV, Influenza A and B and hMPV represent 87% of positive results.



Detection of respiratory viruses in chilren patients in Motol University Hospital (PCR)

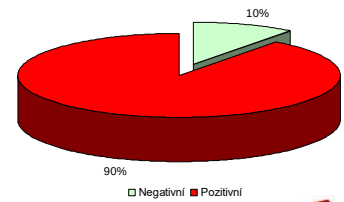


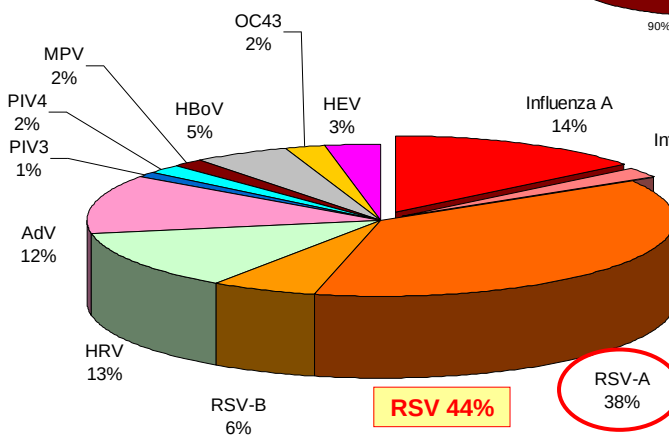
Detection of respiratory viruses in adult patients of Motol University Hospital (PCR)



Detection of respiratory viruses in patients of Dept. of Paediatrics of Motol UH (PCR)

Tested 197 samples.

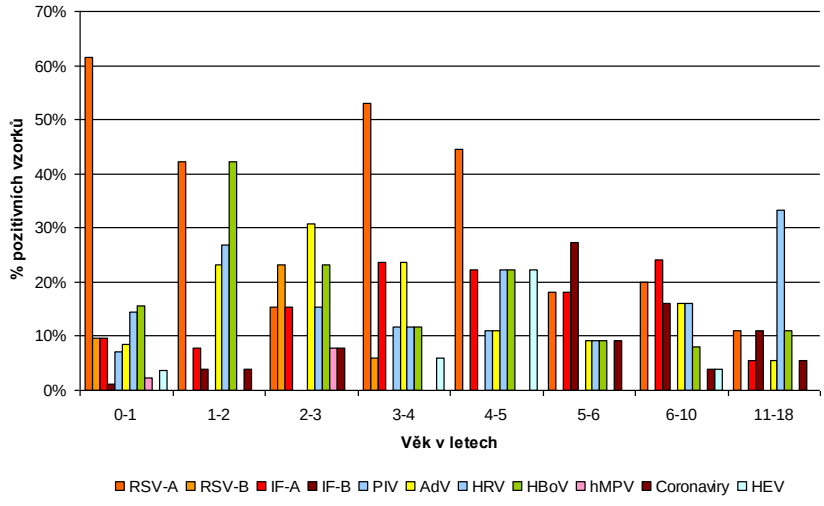




Influenza in 16% only

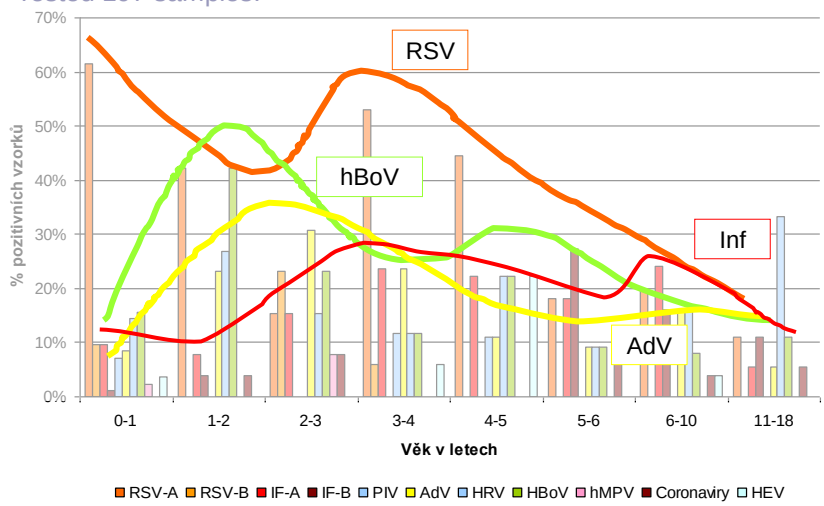
Detection of respiratory viruses in patients of Dept. of Paediatrics of Motol UH (PCR)

Tested 197 samples.



Detection of respiratory viruses in patients of Dept. of Paediatrics of Motol UH (PCR)

Tested 197 samples.



CAVE

Every detection has its limits!

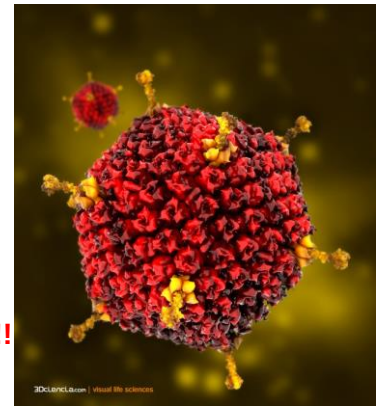
Even molecular-biological detection = PCR!

Even commertially available kits – e.g. in one CE IVD kit, there is certain detection of only

10 adenovirus serotypes from approx. 60 described.

There are most frequently detected AdV serotypes but not the only!!!

Even PCR negativity in therefore can not omit the possibility of false negative result and infection!!!!



What is the sensitivity of antigen vs. PCR?

	Ag detection			PCR detection		
	No. of tests	+	Diskrep.	No. of tests	+	Diskrep.
IF-A	256	19	35	248	50	3
IF-B	256	1	3	248	4	0
RSV	207	19	47+14	248	85	1
AdV	207	3	29	248	34	2

% of Ag positive vs. PCR

Influenza A = 38%

Influenza B = 25%

RSV = 22%

AdV = 8,8%

REVIEW ARTICLE

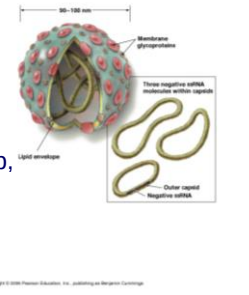
258 • CID 2013:56 (15 January) • Hirsch et al

Fourth European Conference on Infections in Leukaemia (ECIL-4): Guidelines for Diagnosis and Treatment of Human Respiratory Syncytial Virus, Parainfluenza Virus, Metapneumovirus, Rhinovirus, and Coronavirus

Hans H. Hirsch,[1,2] Rodrigo Martino,[3] Katherine N. Ward,[4] Michael Boeckh,[5] Hermann Einsele,[6] and Per Ljungman[7,8]

http://www.ebmt.org/Contents/Resources/Library/ECIL/Pages/ECIL.aspx

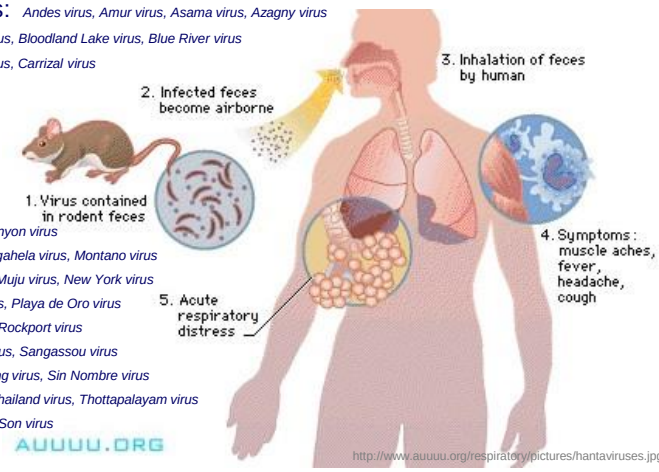
Hantaviruses



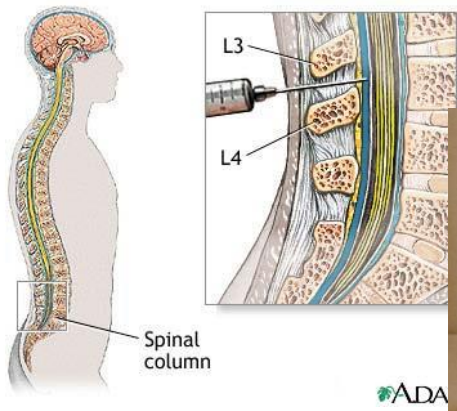
- Bunyaviridae
- ss(-) RNA - 3 segments (small ~ 1.7-2 kb, medium ± 3.7 kb, large ± 6.5 kb)
- enveloped 120-160 nm in diameter
- Incubation period – 2-4 weeks
- The described in 1951, where a hantavirus caused hemorrhagic fever with renal syndrome (HFRS) in North and South Korea.
- Transmitted from rodens, even pet rodens.
- The viruses that caused HFRS in Asia were later grouped as Old World Hantaviruses.
- In 1993 (southwestern USA) was described hantavirus pulmonary syndrome (HPS) - Sin Nombre.
- Hantavirus strains that occur globally – affecting kidneys and lungs mainly.
- Airborne transmission
- Underdiagnosed diseases.

Hantaviruses

- HFRS – viruses - Dobrava, Hantaan, Puumala a Seoul. Mortality is highest in Hantaan virus – 5–15 %; Puumala and Seoul virus about 1%.
- HPS (Sin Nombre) rare 534 case (1993-2009) – mortality rate 36%.
- List of Hantaviruses: *Andes virus, Amur virus, Asama virus, Azagny virus Bayou virus, Black Creek Canal virus, Bloodland Lake virus, Blue River virus Cano Delgadito virus, Calabazo virus, Carrizal virus Catacamas virus, Choclo virus Dobrava-Belgrade virus El Moro Canyon virus Gou virus, Hantaan River virus Huitzilac virus, Imjin virus Isla Vista virus, Khabarovsk virus, Laguna Negra virus, Limestone Canyon virus Magboi virus, Maripa virus, Monongahela virus, Montano virus Mouyassue virus, Muleshoe virus, Muju virus, New York virus Nova virus, Oran virus, Oxbow virus, Playa de Oro virus Prospect Hill virus, Puumala virus, Rockport virus Rio Mamore virus, Rio Segundo virus, Sangassou virus Saaremaa virus, Seoul virus, Serang virus, Sin Nombre virus Soochong virus, Tanganya virus, Thailand virus, Thottapalayam virus Topografov virus, Tula virus, Xuan Son virus*



CSF



Neurotropic viruses

- Neurotropismus (encefalitis)
  - Coronaviridae -
  - Flaviviridae – e.g. West Nile virus (WNV), Japanese encephalitis virus (JEV), Murray Valley encephalitis virus (MVEV), St. Louis encephalitis virus (SLEV), tick-borne encephalitis virus (TBEV)
  - Lentiviridae - HIV
  - Herpesviridae – HSV-1, 2, CMV, HHV-6, HHV-7, EBV (?)
  - Paramyxoviridae – Morbilivirus, Hedra a Nipah virus
  - Picornaviridae - enteroviry
  - Rhabdoviridae – Lyssa
  - Polyomaviridae – JCV (PML)

Symptoms associated with CNS disease

Observed -- Rare ++ Often

Clinical symptoms	***Encefalopathy***	***Encefalitis***
Fever	--	++
Head ache	--	++
Decrease of the mental status	Stabil worsening	Status fluctuation
Focal neurological symptoms	--	++
Seisures	Generalized	Generalized and focal
Lab.-Blood	Leukocytosis --	Leukocytosis ++
Lab.-CSF	Pleocytosis --	Pleocytosis ++
Lab.-EEG	Diffuse decrease of waves	Diffuse decrease of waves and focal abnor.
Lab.-MRI	Often normal	Focal abnormalities

Kennedy J Neurol Neurosurg Psychiatry 2004;75 (Suppl I).

Differential diagnosis of encephalitis

ADEM – acute disseminated encefalomyelitis

CNS vasculitis (including VZV)

Non-virus associated infectious encefalitis

Encephalopathy

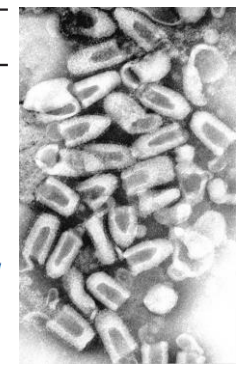
- Anoxic/ischaemic
- Metabolic
- Nutritional deficiency
- Toxic
- Systemic infections
- Critical illness
- Malignant hypertension
- Mitochondrial cytopathy (Reye's and MELAS syndromes)
- Hashimoto's encephalopathy
- Paraneoplastic
- Neuroleptic malignant syndrome
- Traumatic brain injury
- Epileptic (non-convulsive status)

Bacterial
Mycobacterium tuberculosis
Mycoplasma pneumoniae
Listeria monocytogenes
Borrelia burgdorferi
Leptospirosis
Brucellosis
Leptospirosis
Legionella
Tropheryma whippeli (Whipple's disease)
Nocardia actinomyces
Treponema pallidum
Salmonella typhi
All causes of pyogenic meningitis
Rickettsial
Rickettsia rickettsia (Rocky Mountain spotted fever)
Rickettsia typhi (endemic typhus)
Rickettsia prowazekii (epidemic typhus)
Coxiella burnetti (Q fever)
Ehrlichiosis (*Ehrlichia chaffeensis*—human monocytic ehrlichiosis)
Fungal
Cryptococcus
Aspergillosis
Candidiasis
Coccidiomycosis
Histoplasmosis
North American blastomycosis
Parasitic
Human African trypanosomiasis (sleeping sickness)
Cerebral malaria
Toxoplasma gondii
Echinococcus granulosus
Schistosomiasis

Kennedy J Neurol Neurosurg Psychiatry 2004;75 (Suppl I).

Most frequently detected viruses according the risk factors

Risk factor	Possible aetiological agent
Unvaccinated status	Polio, measles, mumps, rubella viruses
Animal contact	Rabies virus, cat scratch disease, Hendra virus, Q fever
Bird contact	WNV, Japanese encephalitis, *Cryptococcus neoformans*
Insect contact	Malaria, WNV, tick-borne encephalitis virus, typhus, Lyme disease, trypanosomiasis
Ingested meat/unpasteurised milk	Toxoplasmosis, listeria, Q fever
Sexual contact	HIV, syphilis
Swimming	Enteroviruses, *Naegleria fowleri*
Camping/hunting	Malaria, tick-borne encephalitis virus, typhus



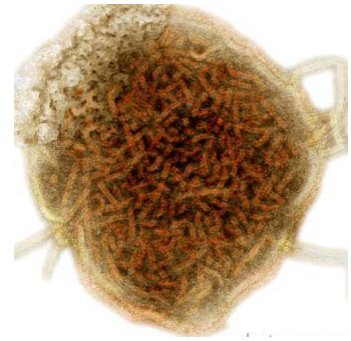
Virus vztekliny

http://www.stanford.edu/group/virus/rhabdo/2004bischoffchang/rabies.gif

Thompson et al. Arch Dis Child 2012;97:150-161.

Most frequently detected viruses according to the clinical symptoms

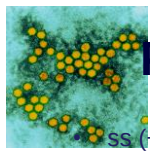
Clinical presentation	Possible aetiological agent
Cranial nerve abnormalities	HSV, EBV, listeria, tuberculous meningitis, syphilis, Lyme disease, *Cryptococcus neoformans*
Cerebellar ataxia	VZV, EBV, mumps virus, trypanosomiasis
Dementia	HIV, measles virus, syphilis, human transmissible spongiform encephalopathies
Poliomyelitis-like flaccid paralysis	JEV, poliovirus, enteroviruses, WNV, tick-borne encephalitis virus
Parkinsonism	JEV, WNV, Nipah virus
Retinitis	CMV, WNV, cat scratch disease, syphilis
Rash	VZV, HHV-6, rubella virus, typhus, syphilis, Lyme disease, WNV, HIV, enteroviruses, *Mycoplasma pneumoniae*
Respiratory tract findings	Flu virus, adenovirus, *M pneumoniae, Mycobacterium tuberculosis*, Q fever
Parotitis	Mumps virus
Lymphadenopathy	HIV, EBV, CMV, measles virus, rubella virus, WNV, syphilis, cat scratch disease, tuberculous meningitis, toxoplasmosis, trypanosomiasis
Hepatitis	Q fever



Parotitis virus

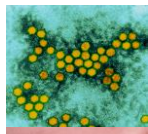
http://www.sciencephoto.com/image/87300/350wm/C0023030-Mumps_virus,_TEM-SPL.jpg

Thompson et al. Arch Dis Child 2012;97:150-161.

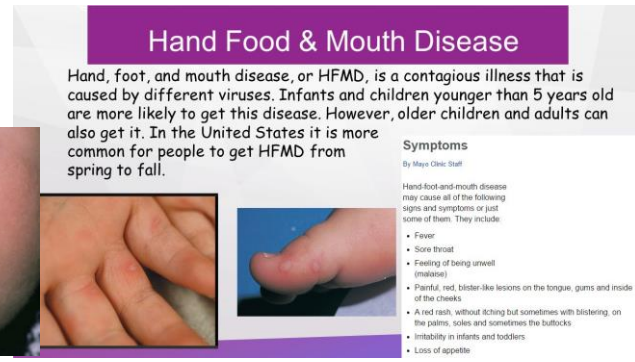


Picornaviridae - Enteroviruses

- ss (+) RNA, genome 7.2-8.5 kb
- Most frequent cause of encephalitis/meningoencephalitis (90%)
- Different serotypes (dividing to) – Polioviruses
  - Coxackieviruses (e.g. Myocarditis, Hand Foot Mouth disease…)
  - Echoviruses
  - Other… (e.g. Enterovirus 71, human rhinoviruses, HAV)
- Symptoms – very different – conjunctivitis, hepangine, start of T1DM, exanthema, neonatal sepsis, pleurodynia…
- Encephalitis/myeloencephalitis
  - Prodromal symptoms - fever, chills, headache, photophobia and nuchal rigidity; rash and upper respiratory symptoms
  - fever and meningeal signs subside within 2-7 days
  - Most frequent - Coxsackievirus B, echoviruses
    - EV-71 particularly aggressive CNS infection



http://www.nhs.uk/tools/documents/visual_guides_v2/data/baby_rashes/images/slideshow_6.jpg



http://images.slideplayer.com/19/5871386/slides/slide_27.jpg

http://healthosphere.com/wp-content/uploads/2012/02/Hand-Foot-and-Mouth-Disease-images.jpg

http://www.blogcdn.com/www.parentdish.co.uk/media/2012/12/hand-foot-and-mouth.jpg

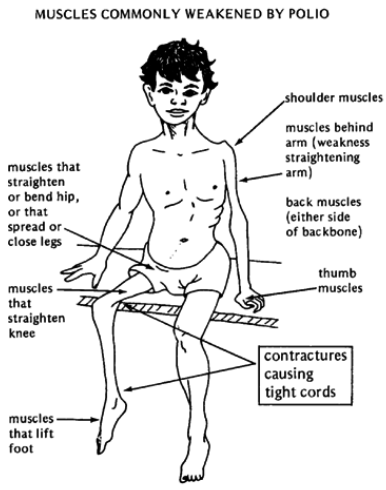
http://healthosphere.com/wp-content/uploads/2012/02/Hand-Foot-and-Mouth-Disease1.jpg

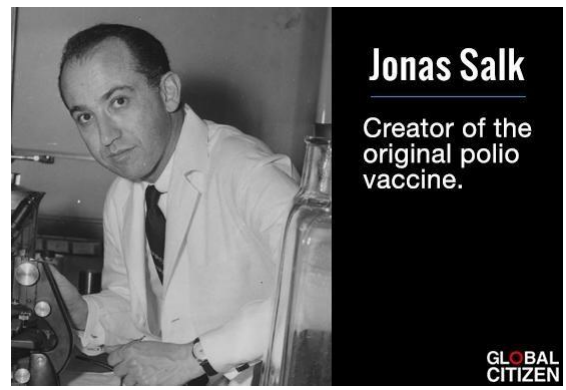
Picornaviridae – Enteroviruses - Polio

Through early morning fog I see, visions of the things to be,
the pains that are withheld for me, I realize and I can see...

Picornaviridae - Enteroviruses

- Salk vaccine - first tested in 1952 – injected inactivated (dead) poliovirus
- Sabine vaccine - oral attenuated poliovirus – trials began in 1957, licensed in 1962



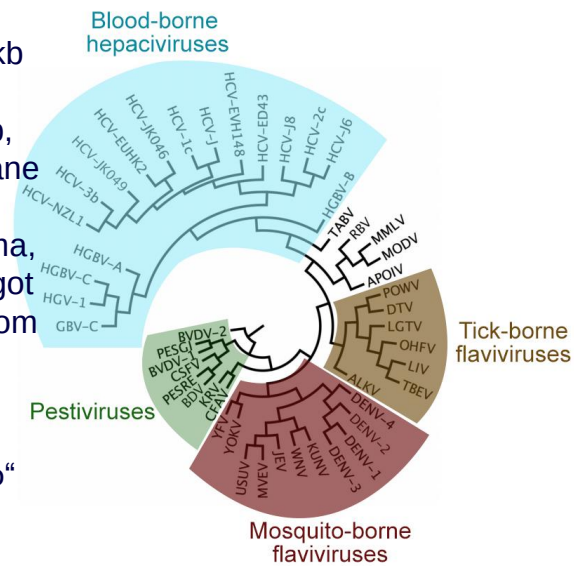


Picornaviridae - Enteroviruses

- Vaccines eradicated polio from most countries in the world, and reduced the worldwide incidence from an estimated 350,000 cases in 1988 to just 223 cases in 2012.
- In November 2013, the WHO announced a polio outbreak in Syria.

Flaviviridae

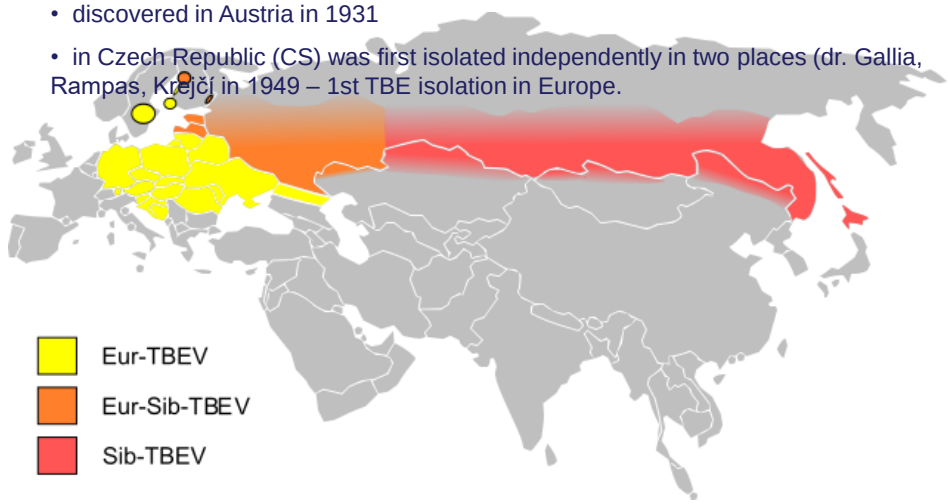
- avr. 40-60 nm
- ss (+)RNA approx. 11 kb
- virions 3 structural proteins – env. gp, core and membrane protein
- replication in cytoplasma, lipid envelope is got during budding from cytoplasmatic vesicules
- disease has often „two“ waves of clinical symptoms



https://www.utmb.edu/discoveringdenguedrugs-together/images/Flaviviridae_adj_LG.jpg

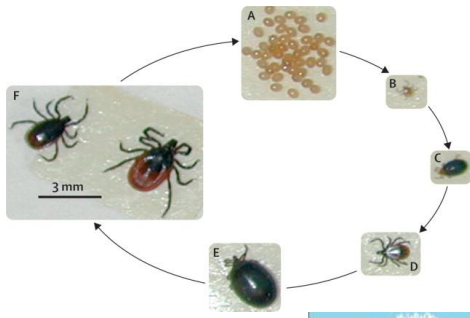
Tick Borne Encephalitis – TBE
geographical distribution

- not west from Austria
- discovered in Austria in 1931
- in Czech Republic (CS) was first isolated independently in two places (dr. Gallia, Rampas, Krejčí in 1949 – 1st TBE isolation in Europe.



http://upload.wikimedia.org/wikipedia/commons/thumb/4/41/EurAsia_TBE-belt.svg/636px-EurAsia_TBE-belt.svg.png

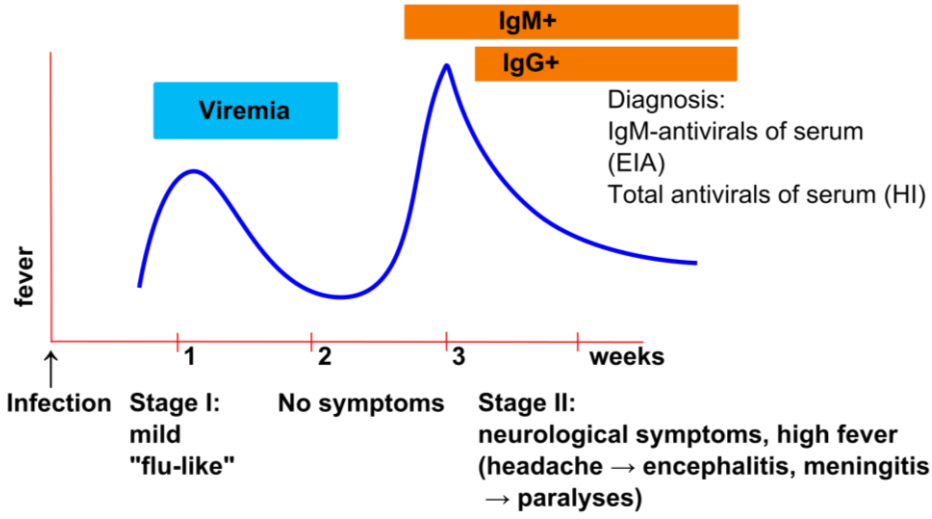
TBE
Vector



- in 1937 rusian scientest L. A. Zilber proved transmission with tick
(in russian spring-summer encefalitis)

http://www.tbe-europe.com/?iContentID=66

Tick Borne Encephalitis – TBE
symptoms and diagnosis



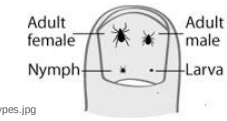
http://upload.wikimedia.org/wikipedia/commons/thumb/6/67/TBE_symptoms.svg/751px-TBE_symptoms.svg.png

- Vaccination - inactivated virus

Tick Borne Encephalitis – TBE
symptoms

- 2/3 of infections asymptomatic
- Incubation period - 8 days (range 4–28 days)
- I: nonspecific febrile illness, headache, myalgia and fatigue. -
  Up to 2/3 of patients may recover without any further illness.
- II: CNS - aseptic meningitis, encephalitis, or myelitis.
  Disease severity increases with age.

- The European subtype - milder disease, a case-fatality ratio of <2%,
  and neurologic sequelae in up to 30% of patients.
- The Far Eastern subtype – often more severe disease course,
  a case-fatality ratio of 20%–40% and higher rates of severe
  neurologic sequelae.
- The Siberian subtype - more frequently chronic or progressive
  disease and has a case-fatality ratio of 2%–3%.



http://www.tickalert.org/img/tickTypes.jpg

Vaccination - inactivated virus

http://www.ha.ax/erik/English/Nursing/Web-tours-05_files/image007.gif

Flaviviridae

Zika virus

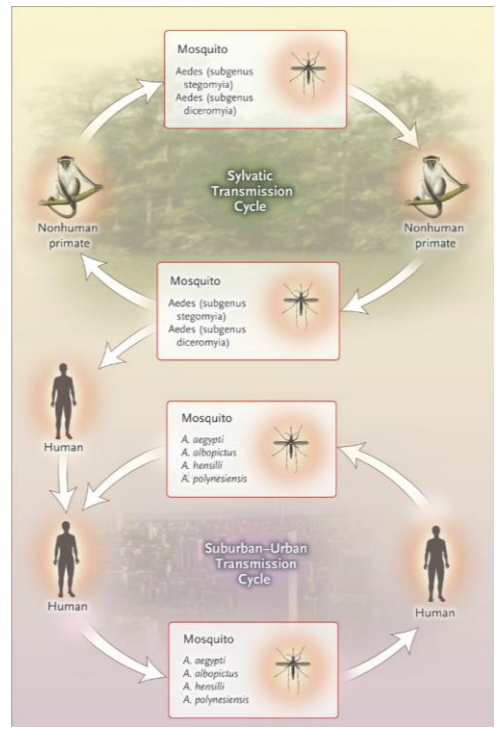
- Described in apes (Makak rhesus) in Uganda during monitoring of the yellow fever in 1947.
- In humans described for the first time in Uganda and Tanzania in 1952 v Ugandě. Subsequently recognised in Africa, Asia, and Pacific (2007-2013) and America (2015 – Brazilia and Columbia).

Flaviviridae

Zika virus

- Transmitted by mosquitos genus Aedes (especially A. aegypti) by blood.
- Transmission is described also by blood directly, perinatal transmission, amnionic fluid, CSF and sperm.

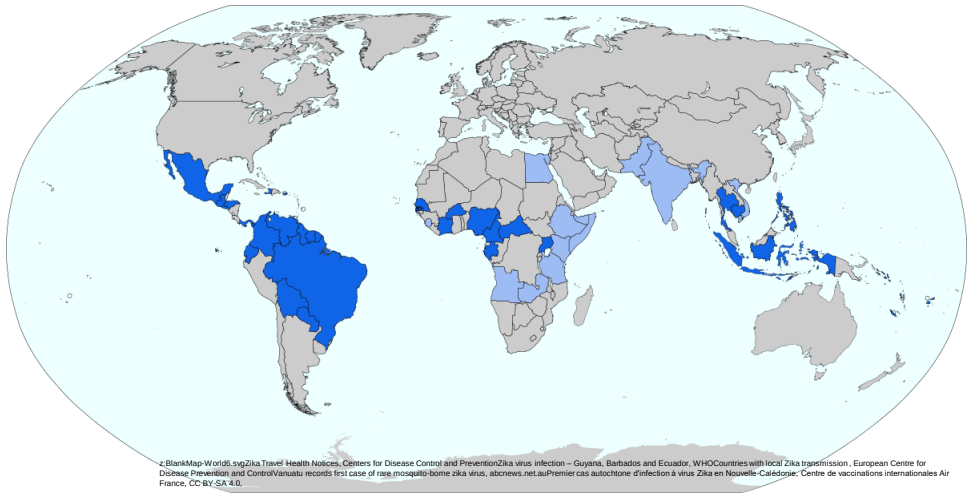
  (However, there are doubts about real presence of the virus in the sperm, or blood contamination).



Flaviviridae

Zika virus

- Incubation period 3-12 days
- Zika fever is presented with fever, conjunctivatis, rash, pain of muscles, joints, and head, malaise lasting for about 2-7 days.



Flaviviridae

Zika virus

Microcephaly was described in infection during pregnancy during outbreak in Brasil in 2015.

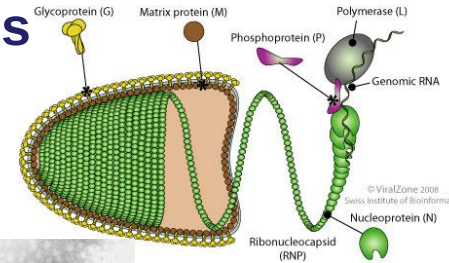
Risk of microcephaly in retrospective study from French polymesia
95 (34–191)/ 10 000 women +- 0,95%
In Brasil 29%.
(NEJM, Lancet 2016)

Described as causal pathogen in myelitis and Guillain–Barré syndrome.
(NEJM 2016)

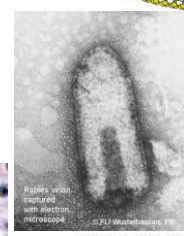
Rhabdoviridae

Lyssavirus

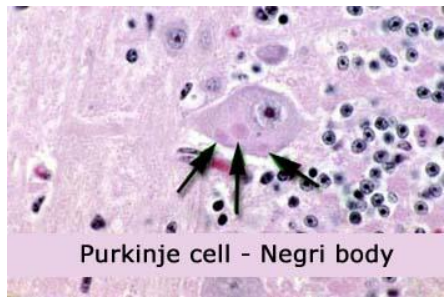
- ss (-) RNA; genome 11 kb
- enveloped
- 75 nm wide and 180 nm long
- cellular receptor: acetylcholine receptor
- Transmission: mainly from infected animals by saliva
- Clathrin mediated endocytosis
- Cytoplasmatic proliferation – **Negri bodies**



http://education.expasy.org/images/Rhabdoviridae_virion.jpg

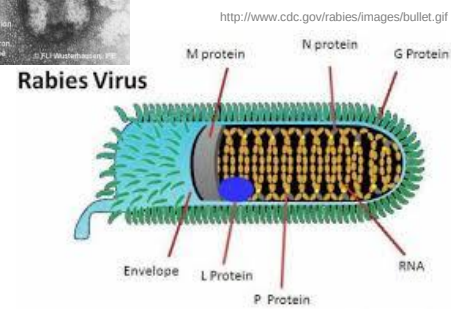


http://www.who-rabies-bulletin.org/about_rabies/Images/Virion.jpg



http://vet.uga.edu/ivcvm/courses/VPAT5316/02_neuropath/09_viral/images/f21491.jpg

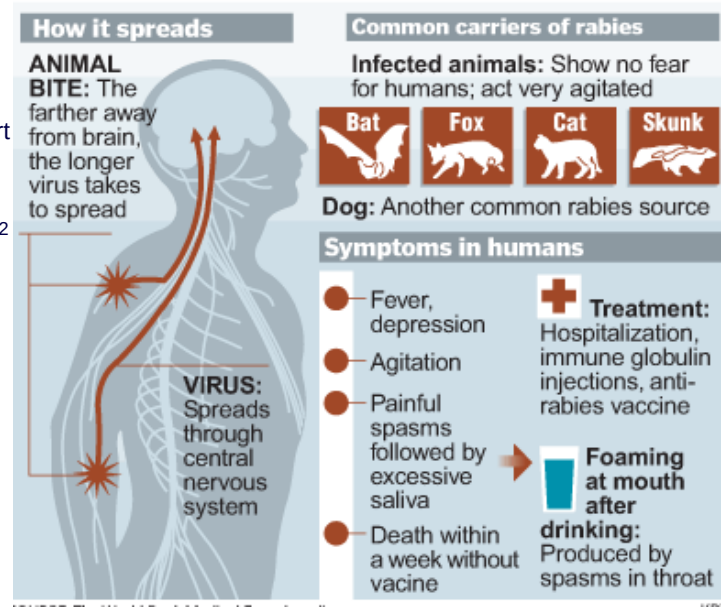
http://www.cdc.gov/rabies/images/bullet.gif



Rhabdoviridae

Lyssavirus - Rabies

- Incubation: av. 3-12 weeks
  (1 week to 15 months)
- Retrograde transport from periphery to CNS
- Prodromal phase (1-2 days), symptoms (3-4 days) after 5 days encephalitis and paralysis
- Encephalitis and/or myelitis
  (in fully developed 100%)

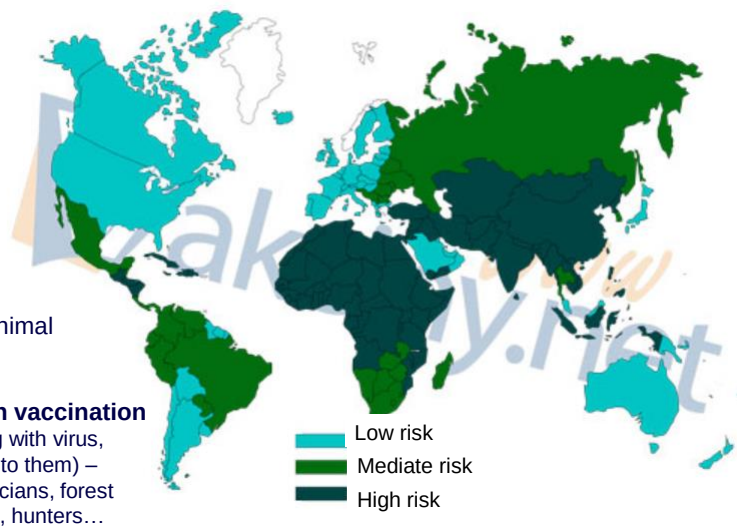


http://peterandmorrisonrabies.weebly.com/uploads/5/3/5/7/53574157/807037792.png

Rhabdoviridae

Lyssavirus - Rabies

Risk of the lyssavirus exposition in the world (WHO 2013)



Zdroj: www.vakciny.net

- Prevention – animal vaccination
- **Pre-exposition vaccination** (persons working with virus, animals or close to them) – laboratory technicians, forest workers, rangers, hunters…
- **Post-exposition vaccination**

Stool samples

Most frequent viral pathogens

- Astroviruses
- Norovirus
- Rotavirus
- Adenovirus

- And others
  - Enteroviruses
  - Influenza…

- „All“ are agens of watery diarrhea together with vomitting
- Incubation period 1-4 (9) days
- Lasting 2-8 days
- Highly infectious

(norovirus 1-10 particles)

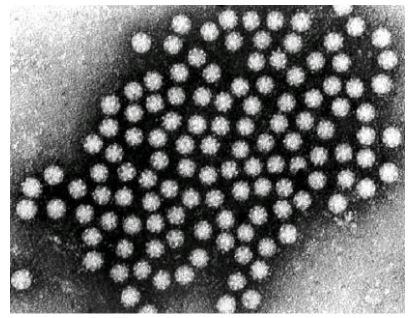
MAJOR ARTICLE

Astrovirus VA1/HMO-C: An Increasingly Recognized Neurotropic Pathogen in Immunocompromised Patients

Julianne R. Brown,[1,2] Sofia Morfopoulou,[3] Jonathan Hubb,[4] Warren A. Emmett,[3] Winnie Ip,[5] Divya Shah,[2] Tony Brooks,[6] Simon M. L. Paine,[7,9] Glenn Anderson,[7] Alex Virasami,[2] C. Y. William Tong,[4] Duncan A. Clark,[4] Vincent Plagnol,[3] Thomas S. Jacques,[7,9] Waseem Qasim,[5] Mike Hubank,[6] and Judith Breuer[1,8]

[1]Virology Department, Great Ormond Street Hospital for Children NHS Foundation Trust, [2]NIHR Biomedical Research Centre, Great Ormond Street Hospital for Children NHS Foundation Trust and University College London, [3]UCL Genetics Institute, University College London, [4]Virology Department, Barts Health NHS Trust, [5]Molecular and Cellular Immunology, [6]Molecular Haematology and Cancer Biology Unit, Institute of Child Health, University College London, [7]Department of Histopathology, Great Ormond Street Hospital for Children NHS Foundation Trust, [8]Department of Infection and Immunity, and [9]Birth Defects Research Centre, Institute of Child Health, University College London, United Kingdom

Neurotropic Pathogen HAstV VA1/HMO-C • CID 2015:60 (15 March) • 881



http://www.oardc.ohio-state.edu/lsarillab/pictures/astro%20virus%204x4.jpg

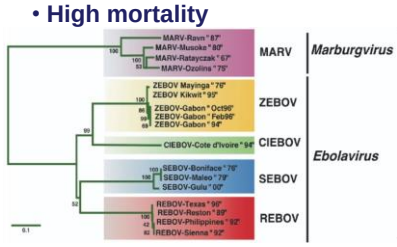
Exanthema pathogens

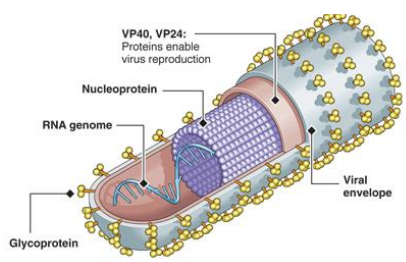
- were at lectures

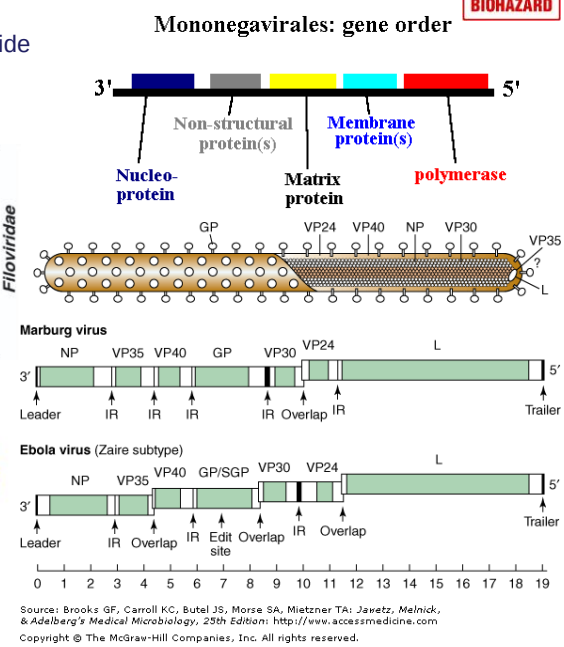
BioSafety Level 4

Filoviridae

- ss (-) RNA
- Helical nucleoprotein 13-20 nm wide
- Ebolavirus and Marburg virus
- highly infectious 1-10 virions
- **High mortality**



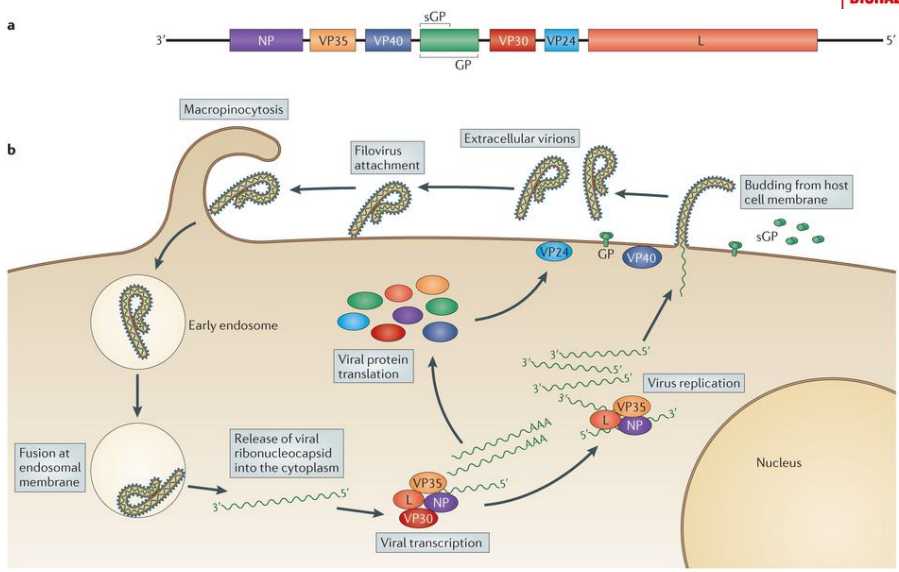




Source: Brooks GF, Carroll KC, Butel JS, Morse SA, Mietzner TA: *Jawetz, Melnick, & Adelberg's Medical Microbiology, 25th Edition*: http://www.accessmedicine.com

BioSafety Level 4

Filoviridae

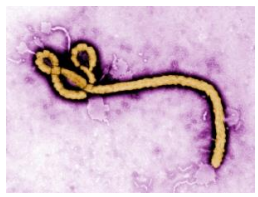


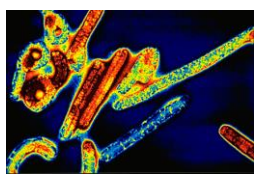
Nature Reviews | Microbiology

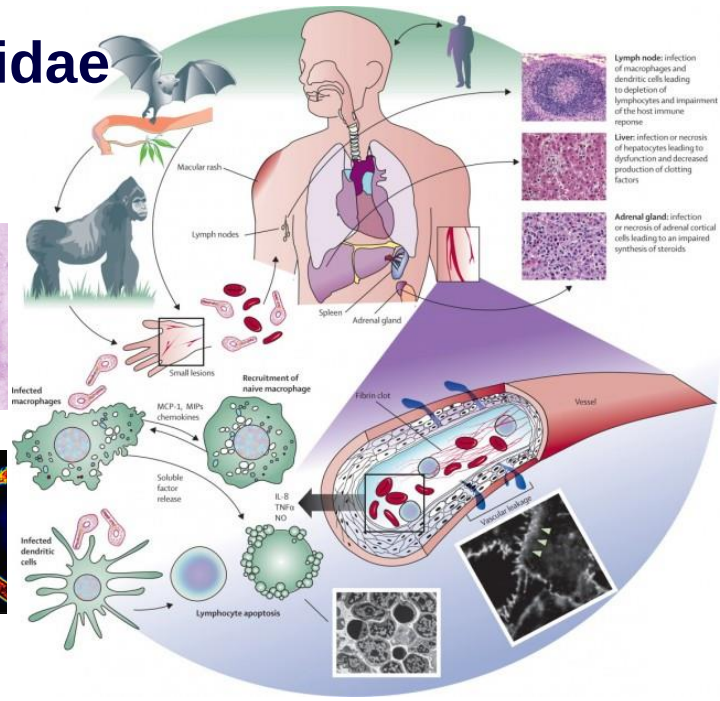
http://www.nature.com/nrmicro/journal/v13/n11/images/nrmicro3524-f1.jpg

BioSafety Level 4

Filoviridae







BioSafety Level 4

Filoviridae

Ebola virus disease

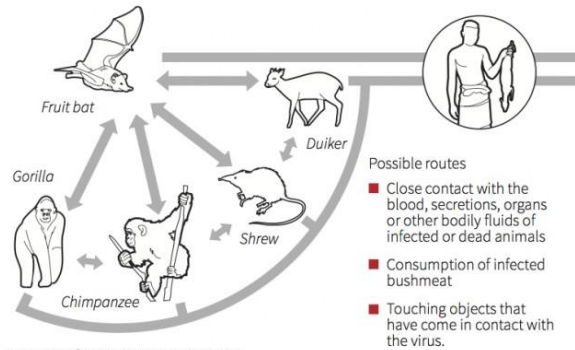
Mortality rate 25-90%

Ebola, which first appeared in outbreaks in Sudan and DR Congo in 1976, is a severe and often fatal disease with no known specific treatment or vaccine. It has since killed more than 1,500 people in parts of Africa.

SOURCE
In Africa, particular species of fruit bats are considered possible natural hosts for Ebola virus.

TRANSMISSION
Infected bats are thought to transmit the disease to humans, or indirectly through other animals which are hunted for their meat.

DAMAGE
Incubation period is from two to 21 days. Death from the disease is often caused by multiple organ failure and tissue death.



Possible routes
- Close contact with the blood, secretions, organs or other bodily fluids of infected or dead animals
- Consumption of infected bushmeat
- Touching objects that have come in contact with the virus.

Targets in the body
- Hepatocytes, functional cells of the liver
- Endothelial cells, which form the linings of the blood vessels
- Phagocytes, blood cells that absorb foreign particles

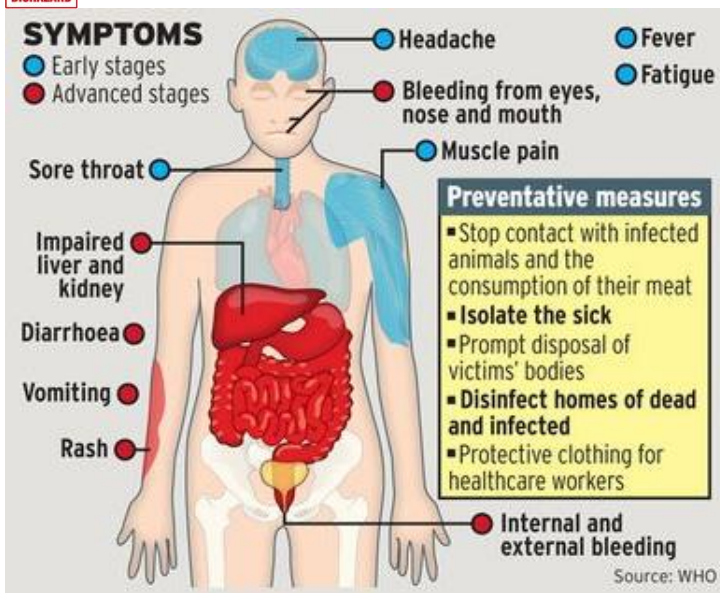
Symptoms
- Fever
- Sore throat
- Severe headache
- Muscle pain
- Intense weakness
- Vomiting
- Diarrhea
- Impaired liver and kidney function
- Internal and external bleeding

Note: List of animals is not exhaustive.
Sources: Centers for Disease Control and Prevention; World Health Organisation

G.Cabrera, 28/03/2014 http://blog.thomsonreuters.com/index.php/ebola-virus-disease-graphic-of-the-day/ REUTERS

BioSafety Level 4

Filoviridae



Therapy:

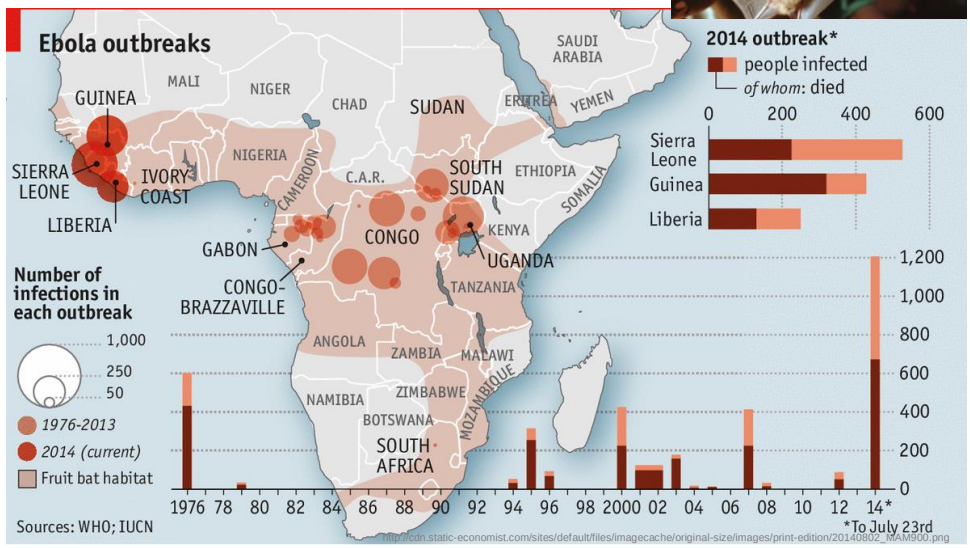
study only

ZMapp – 3 Ab

at the moment not available!!!!

BioSafety Level 4

Filoviridae



http://cdn.static-economist.com/sites/default/files/imagecache/original-size/images/print-edition/20140802_MAM900.png

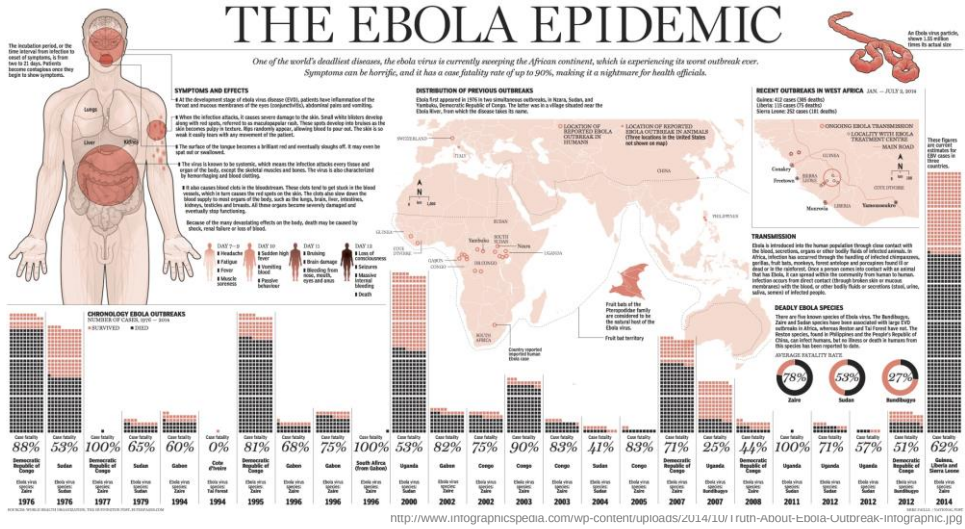
BioSafety Level 4

Filoviridae

2014 EBoV in West Africa (13th April 2016)

-Ebola outbreak: Total Cases: **28,652**

Laboratory-Confirmed Cases: **15,261** **Total deaths: 11,235**



http://www.infographicspedia.com/wp-content/uploads/2014/10/Truth-About-Ebola-Outbreak-Infographic.jpg

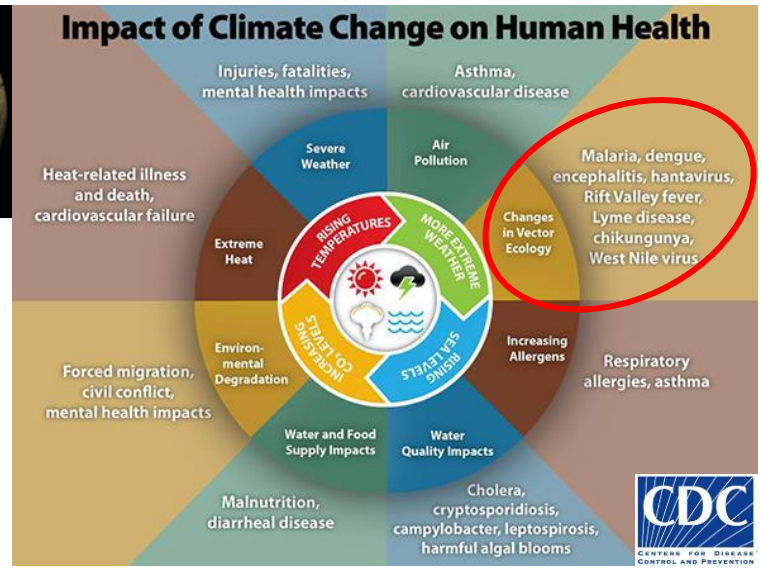
BioSafety Level 4

Filoviridae

- Double gloves
- Boot covers that are waterproof and go to at least mid-calf or leg covers
- Single use fluid resistant or imperable gown that extends to at least mid-calf or coverall without intergraded hood.
- Respirators, including either N95 respirators or powered air purifying respirator (PAPR)
- Single-use, full-face shield that is disposable
- Surgical hoods to ensure complete coverage of the head and neck
- Apron that is waterproof and covers the torso to the level of the mid-calf should be used if Ebola patients have vomiting or diarrhea

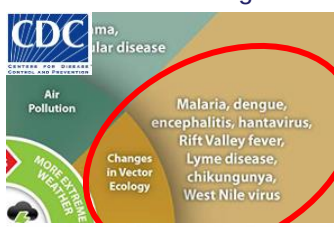
Why we observe emerging viruses?

1. Climate changes



Why we observe emerging viruses?

1. Climate changes



Barmah Forest virus, BFV
Eastern equine encephalitis virus, EEEV
Middelburg virus, MIDV
Ndumu virus, NDUV
Bebaru virus, BEBV[3]
Chikungunya virus, CHIKV[3]
Mayaro virus (–Una virus), MAYV–UNAV[3]
O'nyong'nyong virus, ONNV[3]
Ross River Virus, RRV[3]
Semliki forest virus, SFV[3]
Venezuelan Equine Encephalitis virus, VEEV[4]
Cabassou virus, CABV[4]
Everglades virus, EVEV[4]
Mosso das Pedras virus, MDPV[4]
Mucambo virus, MUCV[4]
Rio Negro virus (RNV)[4]
Western Equine Encephalitis Virus, WEEV[5]
Aura Virus, AURAV[5]
Sindbis Virus ,SINV[5]
Babanki Virus, SINV–B[5]
Kyzylagach virus, SINV–K[5]
Ockelbo Virus, SINV–O[5]
Whataroa virus, WHAV[5]
Highlands J virus, HJV[5]
Buggy Creek Virus, BCV[5]
Fort Morgan Virus, FMV[5]
Tonate virus, TONV

Why we observe emerging viruses?

2. Changes in human behaving and travelling

- E.g. expansion of Peoples Republic China activities in Africa

- Fly time

  Amsterdam – Sydney shortest trip 27 hours and 20 minutes – less then 2 days…

- ….

Why we observe emerging viruses?

2. Changes in behaving of the people and travelling

Refugees crisis Epidemiological diseases

- Vaccination absence, or low frequency vaccination

World Health Organization

Polio outbreak in the Middle East - update

Ongoing transmission in the Syrian Arab Republic with international spread

As of 20 March 2014, in the Syrian Arab Republic a total of 37 WPV1 cases have been reported: 25 cases by the Syrian Arab Republic Ministry of Health, and 12 cases from contested areas (Aleppo, Edleb and Deir Al Zour) not yet reflected in official figures. The most recent case had onset of paralysis on 17 December 2013, from Edleb.

Circulating vaccine-derived poliovirus – Lao People's Democratic Republic (29.1.2016)

Circulating vaccine-derived poliovirus – Myanmar (21.12.2015)

Circulating vaccine-derived poliovirus – Lao People's Democratic Republic (15.12.2015, 26.11.2015, 12.10.2015)

Circulating vaccine-derived poliovirus – Ukraine (1.9..2015)

Poliovirus in Madagascar (24.7.2015)

Poliovirus in South Sudan and Madagascar (14.11.2014)

Poliovirus in Cameroon – update (6.9.2014)

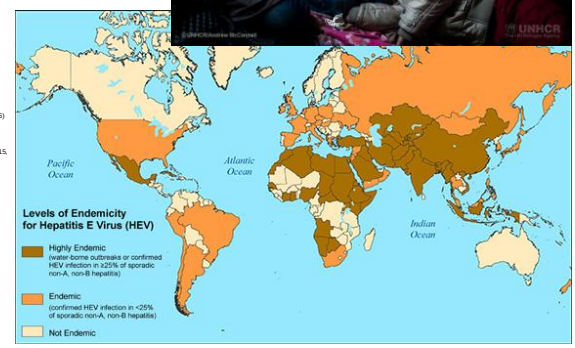
Update on polio in Equatorial Guinea (17.7.2014)

Update on polio in central Africa (25.7.2014)

Detection of poliovirus in sewage, Brazil (23.6.2014)

Update on polio in central Africa - polio confirmed in Equatorial Guinea, linked to outbreak in Cameroon (17.4.2014)

....

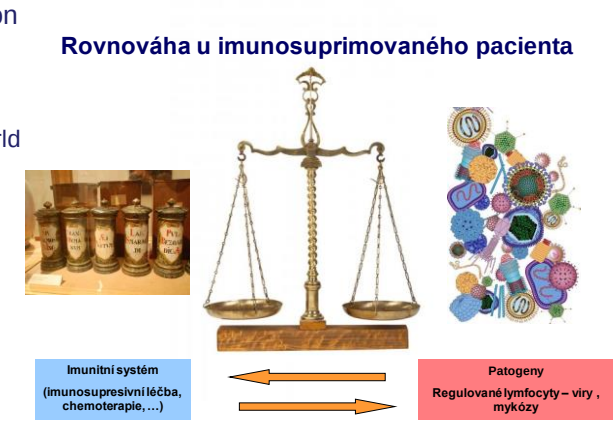


Why we observe emerging viruses?

3. More immunosupression

- from 2008 WHO recognized 100 800 solid organ transplants in 104 countries per year (approx. 90% world population).
  - 69 400 kidney (46% from living donors)
  - 20 200 liver (14.6% from living donors)
  - 5 400 heart
  - 3 400 lungs
  - 2400 pancreas

  Approx. 110 000 HSCT per year.
- More monoclonal antibodies (anti-CD20, CD52, TNF-α…) …



Steroids more then > 2 mg/kg – highly lymphotoxic (used e.g. in NHL, ALL…)

Why we observe emerging viruses?

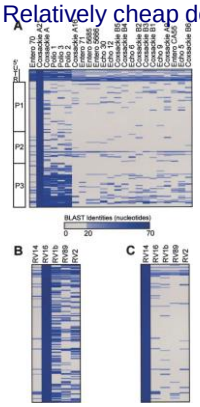
4. Better detection (even in new) – treatment – resistance

Molecular-biological techniques

Direct and relative cheap detection based on NA

Reasonable time for detection of the agens

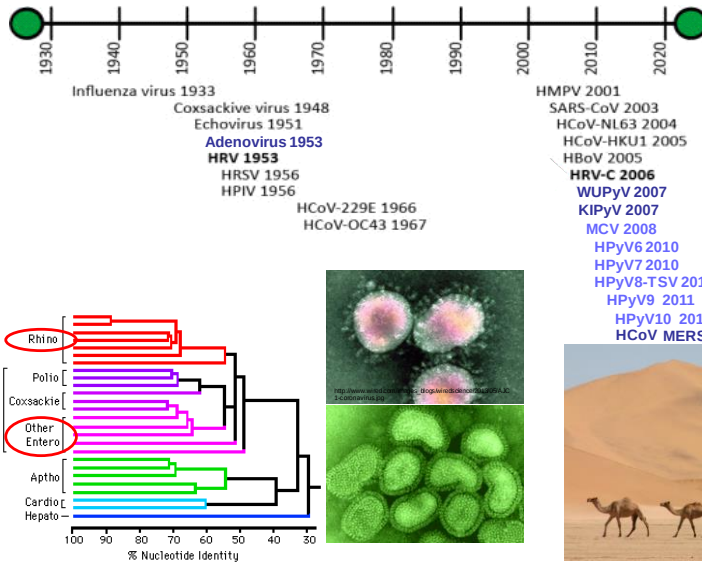
Relatively cheap detection of new viruses



CHIP technique was used in new WUV and KIV polyomavirus detection in 2007, which were detected in respiratory tract.

Why we observe emerging viruses?

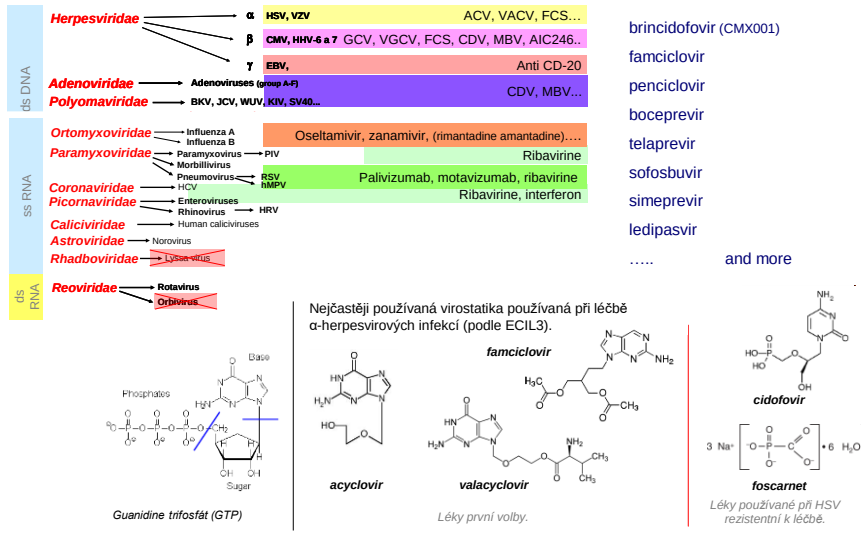
4. Better detection – treatment – resistance



Why to act?

4. Better detction – treatment – resistance

Virostatic therapy



Guanidine trifosfát (GTP)

Nejčastěji používaná virostatika používaná při léčbě α-herpesvirových infekcí (podle ECIL3).

Léky první volby.

Léky používané při HSV rezistentní k léčbě.


Thank you for your attention
Petr.Hubacek@Lfmotol.cuni.cz