RNA viruses

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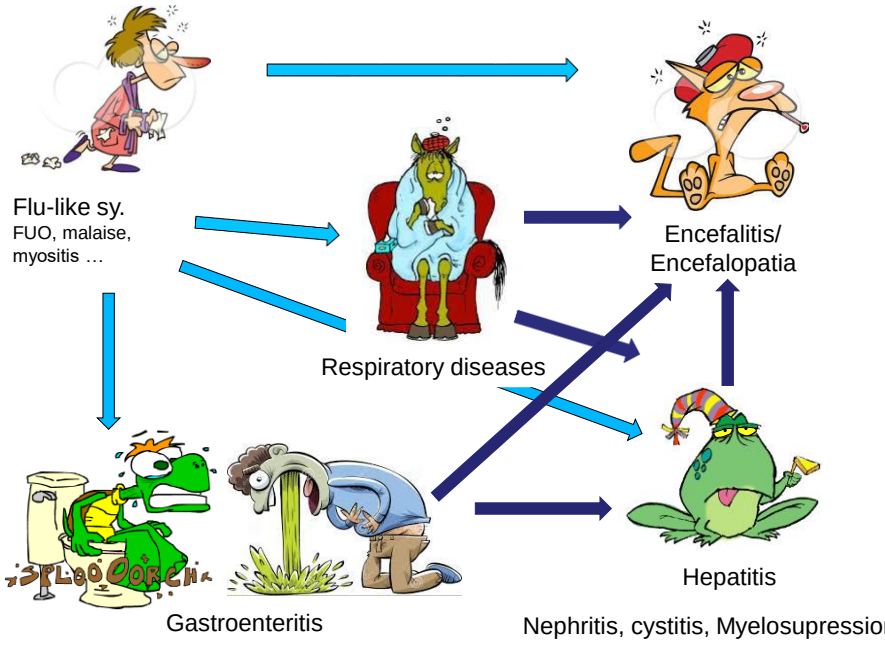
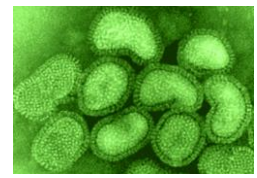
Clinical consequences



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

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,…

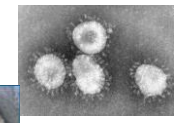
Immune related infections – HIV

GIT infections – astroviruses, caliciviruses, rotaviruses

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

Exanthematic diseases – Mumps virus, Rubella, Dengue…

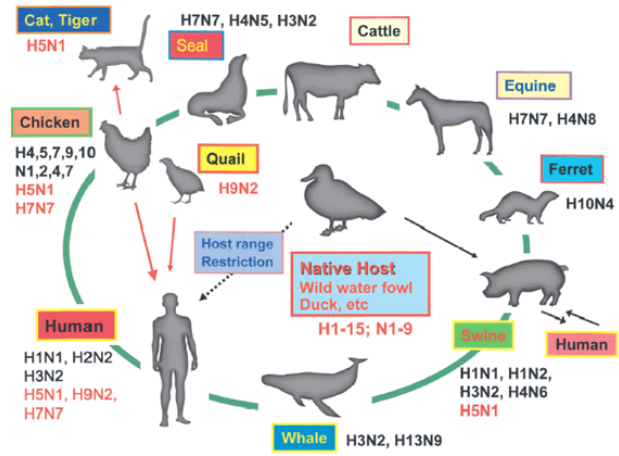
Respiratory viruses



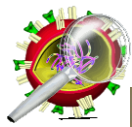
- Often zoonotic:
  - SARS – CoV
  - MERS - CoV
  - …

Bats – Horseshoe bat,…

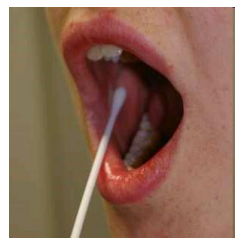
Civet

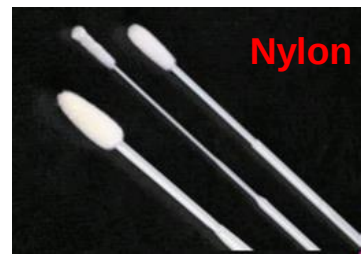


Leads to high Frequence of recombination of new life-threatening infections

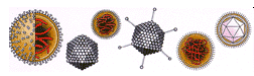


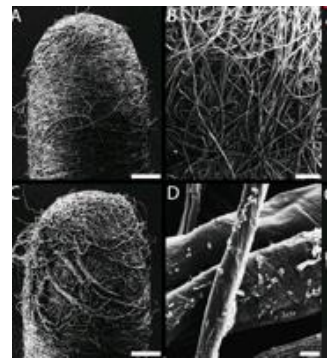
Type of biological material

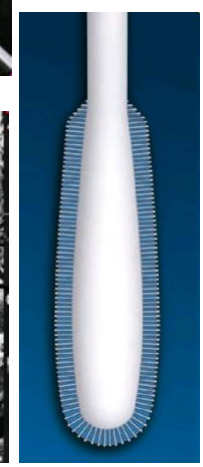




Nylon swabs







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

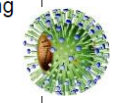
  AND
  - A clinician’s judgement that the illness is due to an infection

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

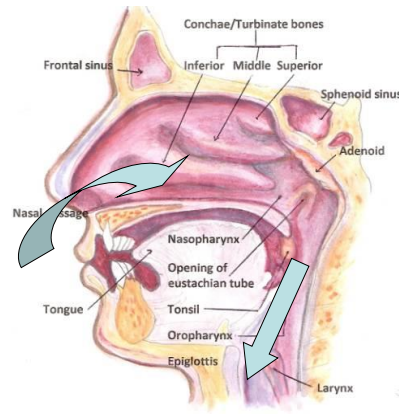
Adapted from ECDC definitions for influenza
http://ecdc.europa.eu/en/activities/surveillance/EISN/surveillance/Pages/influenza_case_definitions.aspx

What to aim during the process of dg?

Good sampling of biological material

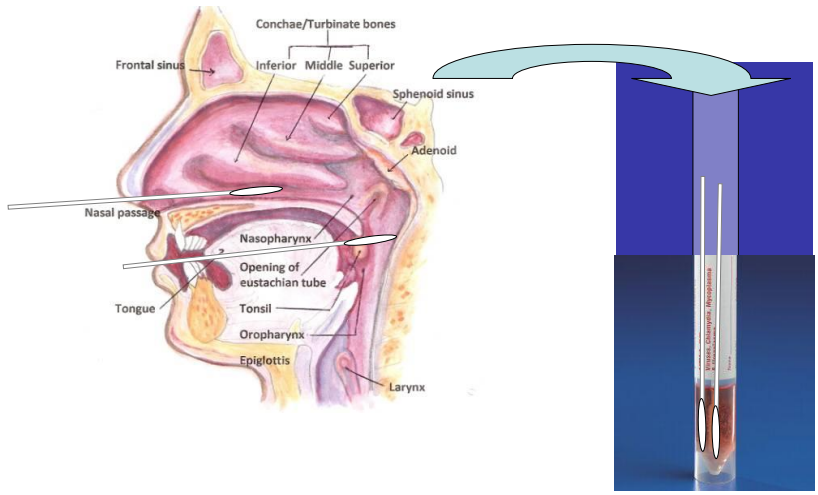
First proliferation at the mucos of upper respiratory tract.

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

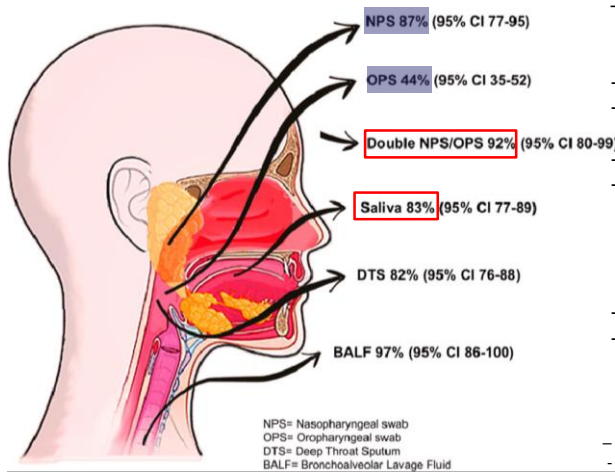


What to aim during the process of dg?

Good sampling of biological material



What about sensitivity according to the tested material?



– checked 1598 studies, 33 chosen
(26 quantitative)

- 1. published/accepted
- 2. patients with dg or screened for COVID-19
- 3. RT-PCR
- 4. studies aimed at detection in saliva, sputum, oral liquids/secretes, pharyngeal secretes for diagnostic methods comparisson
- 5. at least 2 samples
- 6. tested in proven COVID-19 patients with pair samples

Khiabani et al. Are saliva and deep throat sputum as reliable as common respiratoryspecimens for SARS-CoV-2 detection? A systematic review andmeta-analysis *American Journal of Infection Control,* DOI: 10.1016/j.ajic.2021.03.008

Urine

– Ag detection -74% (Diao et al. 2020)
- No. ± 10^2–10^5/ml vs. ± 10^5–10^{11}/ml in NPS (D.L. Jones et al. Scie Total Environment 2020)
- virus is contagious (Sun j. et al. Emerg. Microbes Infect. 2020)

Direct detection - antigen

Požadované zaškrtněte (kurzívou uveden typ vhodného 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
	Klíštová encefalitida [L]
	Influenza A a B (KFR)
	RS virus (KFR)
	Adenovirus (KFR)

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

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

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

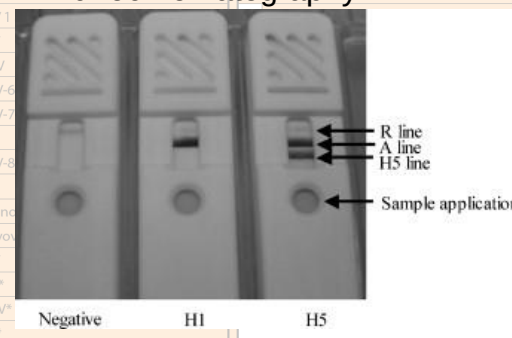
PCR PŘÍMÁ DETEKCE RNA VIRŮ — Stěr

*STATIM vyšetření a detekce označené * budou provedeny POUZE na základě výše zmíněné konzultace.*

Sdělování výsledků na l. 5380, 5381, 5382.

Example of the result

Imunochromatography

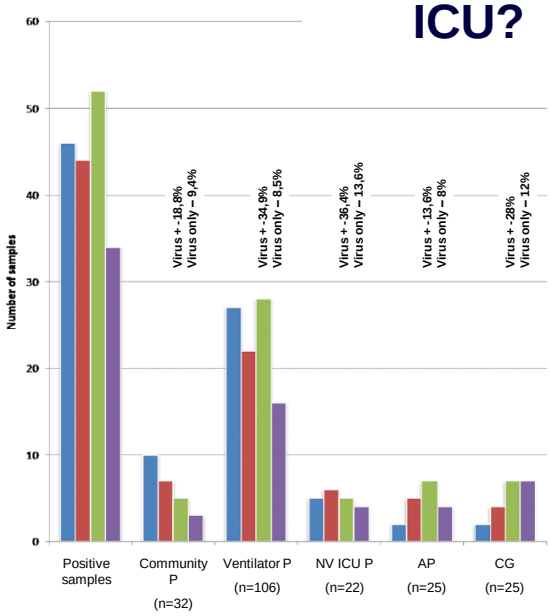


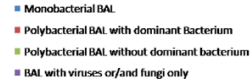
Result in ± 15 minutes.

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

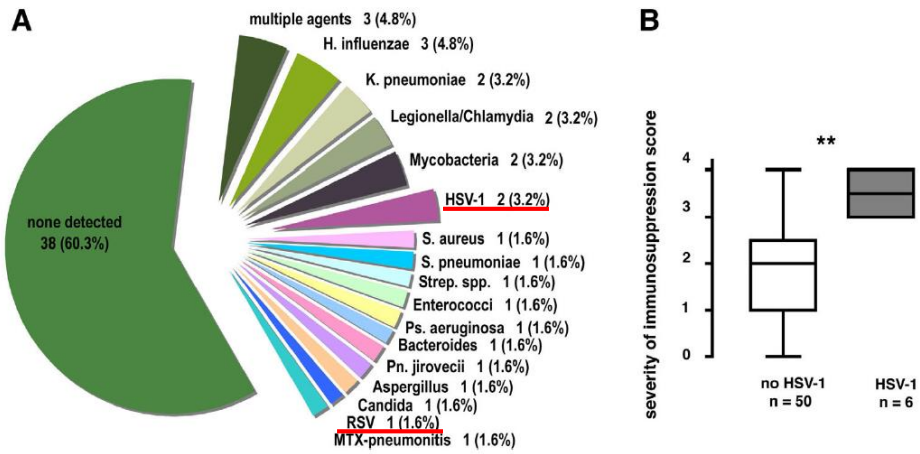


Figure 3
A: Detected primary responsible (leading) infectious agents in 63 patients with ambulatory-acquired pneumonia/pneumonitis and autoimmune disease. RSV = respiratoy syncytial virus. B: Immunosuppression scores were significantly more severe in the 6 patients with HSV-1 detection in BAL than in 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%

Viral shedding

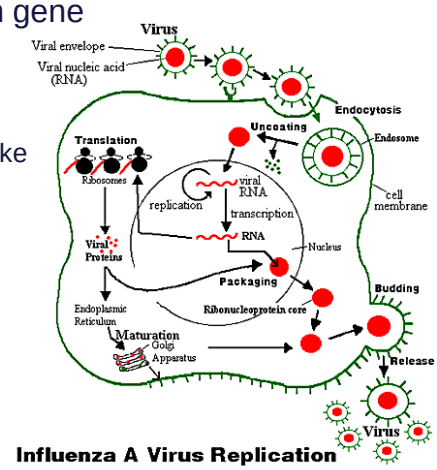
Virus	Lenth of shedding in general population (possible children/adults)	Lenth of shedding in the immunocompromised host
Influenza virus A	≤14 days/ ≤5.5 days	29.5 days to 5 months (!)
Influenza virus B	6-7 days	7.5 days (2.5-80.5)
Parainfluenza virus	PIV-1 and 2: 3-6 days PIV-3: 8 days (3-10 days)	6-42 days
RSV	± 4 days (1-12)/	Median 2-4 weeks 80 days (35-334 days)
hMPV	± 5 days	7-24 days
HRV/HEV	± 14 days (HRV-C 7 days) Adult longer then children	Mostly ≤4 weeks 5 weeks (1-49 weeks)
Coronaviry (HKU-1, 229E, OC43, NL63, SARS-CoV-2)	3-18 days, Couple of weeks to 2 months	4 weeks (1-22 weeks), in SARS-CoV-2 even 3 months

Talaat et al. JID 2013:208-1669-1678; Takeyama et al. Jmed Virol 2016, 88(6):938-946; Milano et al. Blood 2010, 115(10):2088-94; Lehners et al. PLOS One 2016, Feb. 2016; de Lima et al. Transpl Infect Dis 2014, 16(1):165-9; Gooskens et al. JID 2009, 199, 1435-1441; Pinsky et al. Emer ging Infect Diseases 2010, 16(7):1165-1167; Chen et al. J Clin Virol 2015, 64:74-82; Dennis et al. CID 2016, 62(4): 431-437; van der Hoek et al. FEMS Microbiol rev 30 (2006):760-773; Tasian et al. Pediatr Blood Cancer 2008, 50(5) 983-987; Choi et al. Blood 2011, 117(19(:5050-5056); Fields. Virology 5th ed. 2007

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

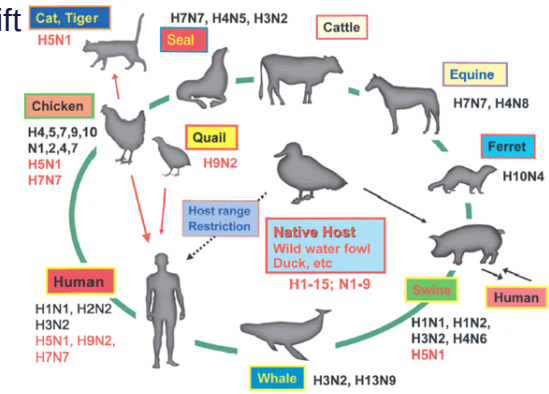


Influenza A Virus Replication

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



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VIRUS

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Health minister with virus had been in No10

Nadine Dorries in isolation after diagnosis Sixth patient dies as British cases rise to 373

Steven Swinford Deputy Political Editor
Chris Smyth Whitehall Editor
Eleni Courea Political Reporter

A health minister who has met hundreds of people in parliament in the past week and attended a reception at No10 with Boris Johnson has had coronavirus diagnosed, The Times can reveal.

Nadine Dorries, who played a role in drawing up legislation to tackle coronavirus, fell ill on Friday last week and her diagnosis was confirmed yesterday evening. She is now in isolation and understood to be recovering.

The identity of the individual who infected Ms Dorries is unknown but the minister has been working in parliament and the Department of Health and Social Care for the past week. Officials are identifying all those with whom she has been in contact since contracting the virus, including

Let them cry! Cold comfort teaches babies self-control

Rhys Blakely Science Correspondent

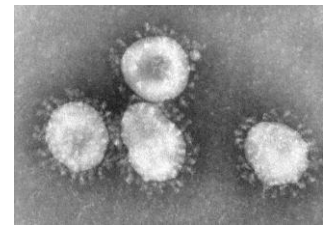
Parents who let babies "cry it out" when they refuse to sleep do no harm to the child and may be teaching them self-control, a study suggests.

New mothers and fathers often agonise over whether to comfort infants. Advocates of "attachment parenting" argue that failing to respond promptly risks damaging a child's bond with its parents. However, a study that tracked nearly 180 British mothers found that those who often or occasionally let their babies cry themselves to sleep developed just as good relationships with their children as those who did not.

Leaving babies to cry had no apparent impact on their emotional or cognitive development at 18 months. Tests indicated that it made no difference to how securely attached they felt to their mothers or how well they focused on tasks. The one effect was a little less crying at 18 months.

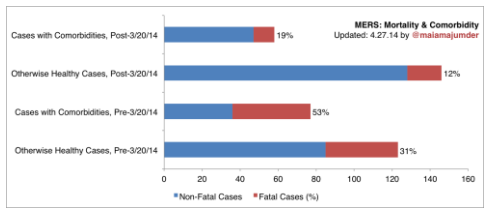
The findings might vindicate childcare authors such as Gina Ford, who has advocated letting babies learn how to settle themselves.

Coronaviruses

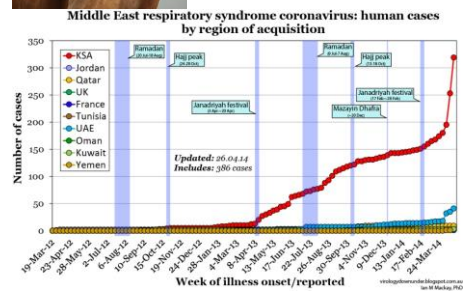


- Coronaviridae
- ss (+) RNA, 26-32 kb genone length (largest RNA)
- first identified in the mid-1960s
  - alpha – HCoV 229E and NL63
  - beta - HCoV OC43, HKU1, SARS-CoV (severe acute respiratory syndrome), and MERS-CoV (Middle East Respiratory Syndrome)
- **SARS**
  - Cellular receptor – ACE2
  - mortality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

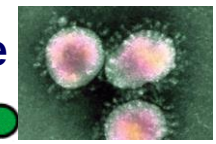
MERS - transmission through camels, their milk and cheese



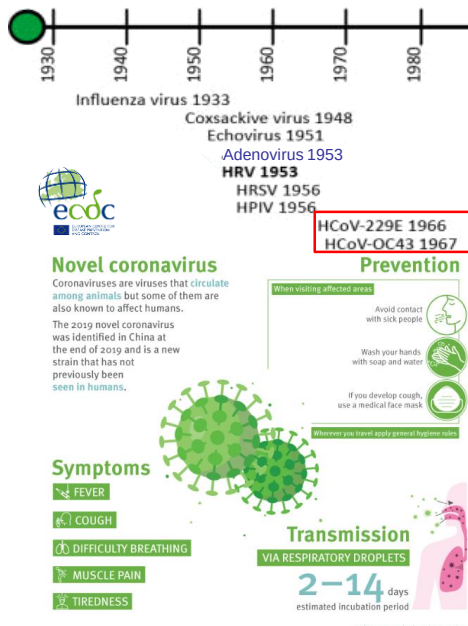
https://maimunamajumder.files.wordpress.com/2014/04/mers_comorbidity_mortality_4-271.png

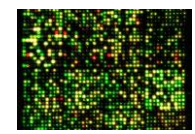


Coronaviruses are here for long time



http://www.wired.com/images_blogs/wiredscience/2013/05/AJC1-coronavirus.jpg





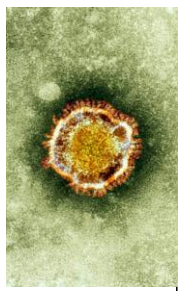
HMPV 2001
SARS-CoV 2003
HCoV-NL63 2004
HCoV-HKU1 2005
HBoV 2005
HRV-C 2006
WUPyV 2007
KIPyV 2007
MCV 2008
HPyV6 2010
HPyV7 2010
HPyV8-TSV 2010
HPyV9 2011
HPyV10 2012
HCoV MERS 2012
SARS-HCoV 2019

Luskoun ostrovní (Manis javanica)

Coronaviruses

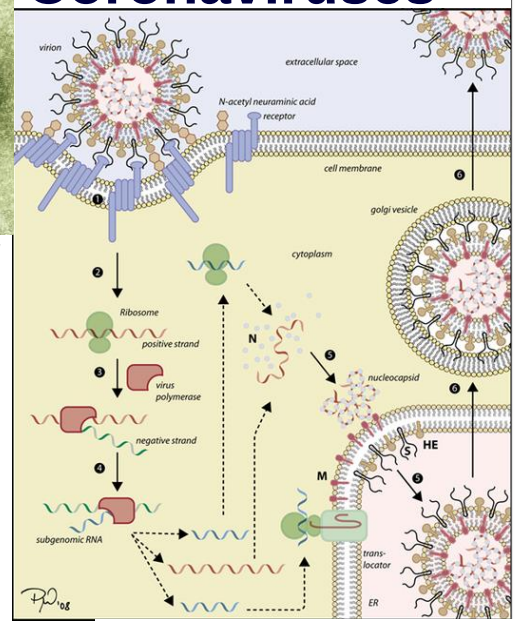
Čeleď a podčeleď	Rod	Podrod	Druh	Rok popsání	Klinické příznaky
Coronaviridae – Orthocoronavirinae	*Alphacoronavirus*	*Duvinacoronavirus*	Lidský coronavirus 229E (HCoV-229E)	1966	Lehčí respirační onemocnění typu „common cold“ s výrazným edémem sliznic. ID 2–5 dní
		Setracoronavirus	Lidský coronavirus NL63 (HCoV-NL63)	2004	Lehčí respirační onemocnění typu „common cold“ s výrazným edémem sliznic. ID 2–4 dny
	Betacoronavirus	*Embecovirus* (skupina A)	Lidský coronavirus HKU-1 (HCoV-HKU-1)	2005	Lehčí respirační onemocnění typu „common cold“ s výrazným edémem sliznic. ID 2–4 dny
			Lidský coronavirus OC43 (HCoV-OC43)	1967	Lehčí respirační onemocnění typu „common cold“ s výrazným edémem sliznic. ID 2–5 dní
		Sarbecovirus (skupina B)	Severe acute respiratory syndrome-related virus (SARS-CoV)	2003	Respirační onemocnění s těžším, život ohrožujícím průběhem. Popsaná mortalita u těžších případů je přibližně 9,6 %. ID 2–11 dní
			Severe acute respiratory syndrome-related virus 2 (SARS-CoV-2)	2019	Respirační onemocnění v celém rozsahu od asymptomatických a mírných případů (zatím popsaná přibližně polovina případů) až po život ohrožující případy. Dosud popsaná mortalita u těžších případů je přibližně 6,7 %; celkově pak přibližně 0,5–1 %. ID 2–14 dní
		Merbecovirus (skupina C)	Middle-East respiratory syndrom virus (MERS virus)	2012	Respirační onemocnění s těžším, život ohrožujícím průběhem. Popsaná mortalita u těžších případů je přibližně 35,5 % ID 2–13 dní

V tabulce vynechán Realm (*Riboviria*), Říše (*Orthornavirae*), Kmen (*Pisuviricota*), Třída (*Pisoniviricetes*), Řád (*Nidovirales*) a Podřád (*Cornidovirineae*)



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.

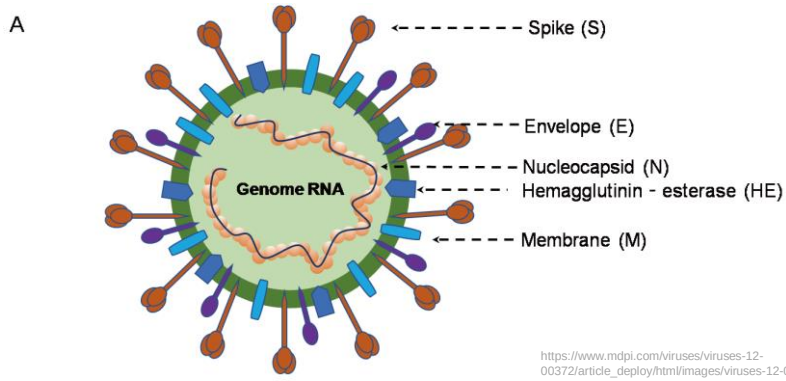
5 The protein N binds genomic RNA and the protein M is integrated into the membrane of the endoplasmatic reticulum (ER) like the envelope proteins S and HE. After binding, assembled nucleocapsids with helical twisted RNA budd into the ER lumen and are encased with its membrane.

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

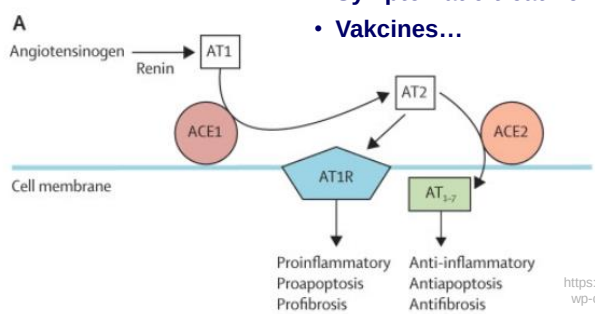
SARS-CoV-2



https://www.mdpi.com/viruses/viruses-12-00372/article_deploy/html/images/viruses-12-00372-g002.png

- **SARS-CoV (SARS)**
  - Cell receptor – ACE2
  - 8 098 infected worldwide
  - Mortality – approx. 9.5%
- Incubation period – 2-4 days
- Increased temperature – fever (>38.0°C); headache, pain of muscles, joints and orevall discomfort. In part of the patients mild, in about 10-20% diarrhoe, after 2 to 7 days possible dry cought and in most pneumonia.
- **Virostatics** (ribavirine + lopinavir/ritonavir) **Symptomatic treatment**

- **SARS-CoV-2 (COVID-19)**
  - Cell receptor – ACE2
  - So far 40 210 950 infected worldwide
  - Mortality – approx. 6.7%
- Incubation period – 2-14 days
- Increased temperature – fever (>38.0°C); headache, pain of muscles, joints and orevall discomfort. In part of the patients mild. After 7 days often worsening and development of interstitial pneumonia.
- **Virostatics** (remdesivir, favipiravir,…) **Symptomatic treatment**
- **Vakcines…**



https://www.physiciansweekly.com/wp-content/uploads/2020/04/AT1-receptor.png

SARS-CoV-2

Virus Environmental Stability

(relevance to personal safety unclear)

Half-life

(time to decrease 2-fold; not strictly constant)

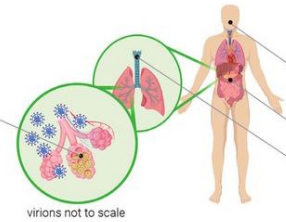
Aerosols: ≈1 hr Surfaces: ≈1-10 hr
e.g. plastic, glass, paper and metals

Based on quantifying infectious virions.
Numbers will vary between conditions and surface types.
Viral RNA observed on surfaces even after a few weeks.

Host Cells

(tentative list; number of cells per person)

Type I & II pneumocytes (~10^{11} cells)
Alveolar macrophage (~10^{10} cells)
Mucous cell in nasal cavity (~10^{9} cells)
Host cell volume: ~10^{3} μm^{3} = 10^{3} fL



Concentration

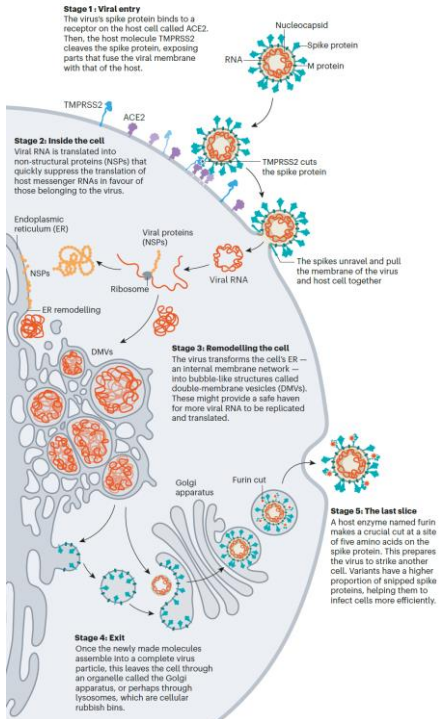
(maximal observed values following diagnosis)

Nasopharynx: 10^{6}-10^{9} RNAs/swab
Throat: 10^{4}-10^{8} RNAs/swab
Stool: 10^{4}-10^{8} RNAs/g
Sputum: 10^{6}-10^{11} RNAs/mL

RNA counts can markedly overestimate infectious virions

RNA is ussually 1000x more then infectious particles.

Bar-On eLifescience 2020
http://bit.ly/2WOeN64



Replication

Binding to ACE-2

Cleaving of the Spite protein by TMPRSS2

Ïnternalisation and subsequent translation to NS proteins

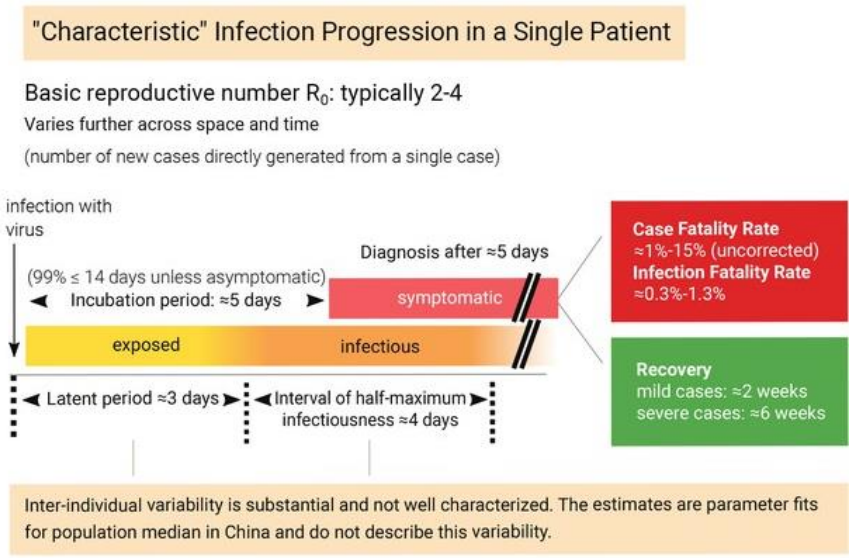
Remodelation of cellular pathways

Production of new viral particles

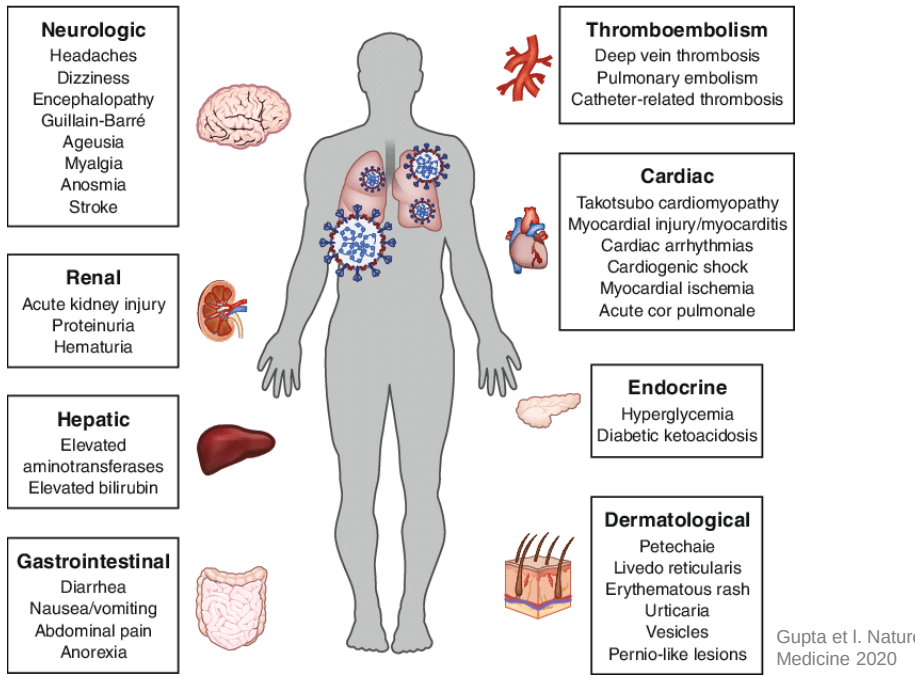
Furin cleaves 5 AA of Spike protein

Scudellari Nature 2021; 595

Patofysiology

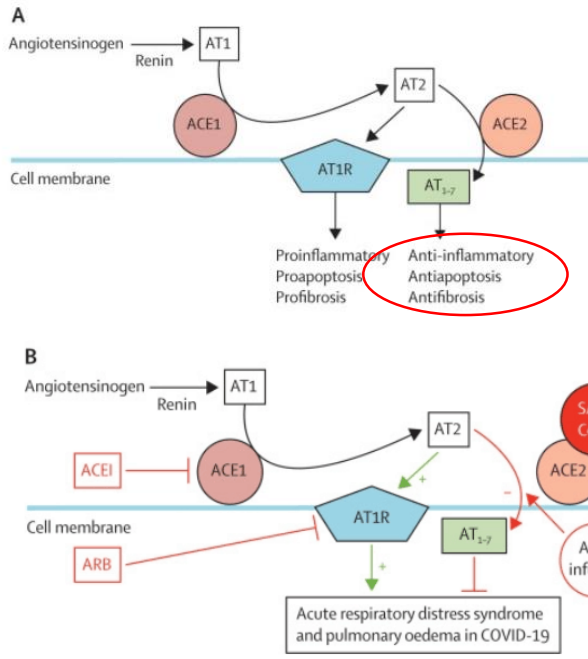


Bar-On eLifescience 2020
http://bit.ly/2WOeN64



Gupta et l. Nature Medicine 2020

1



https://www.physiciansweekly.com/wp-content/uploads/2020/04/AT1-receptor.png

1

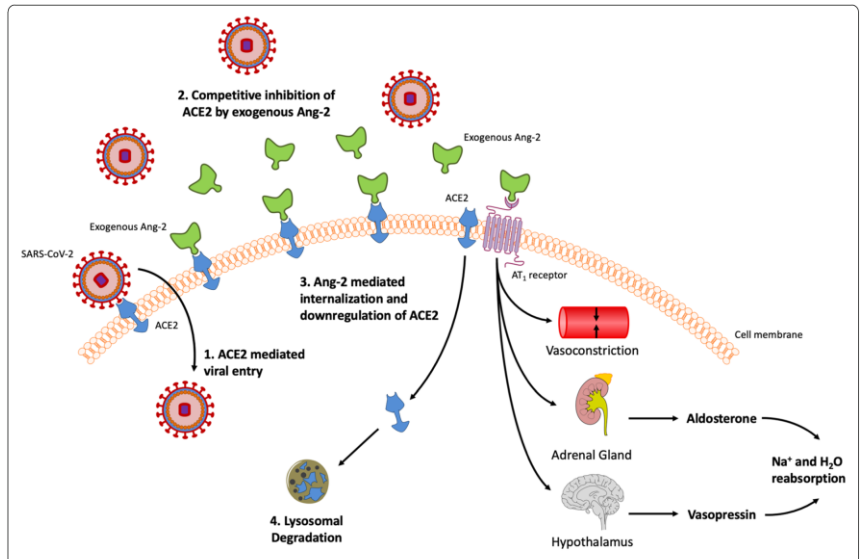
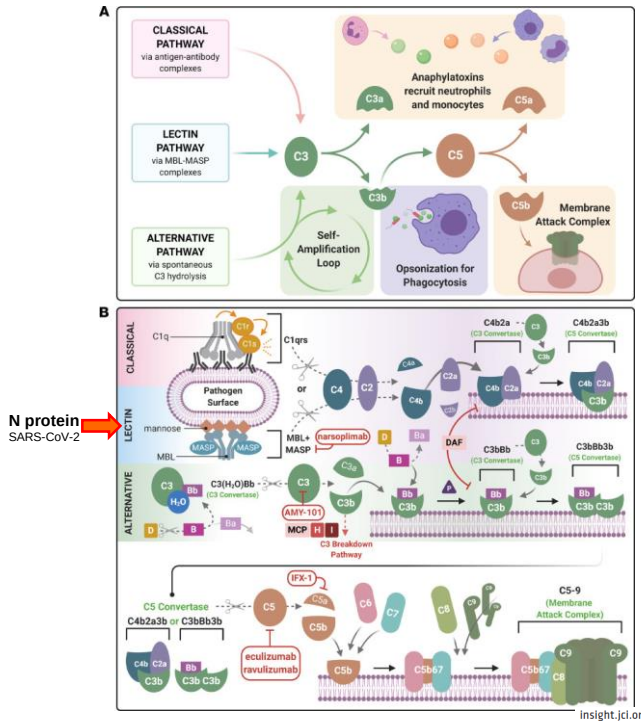


Fig. 1 Effect of angiotensin II on the RAAS and SARS-CoV-2 binding. Angiotensin I is hydrolyzed by ACE1 to form angiotensin II, which binds to AT_1 receptors. This causes release of aldosterone from the adrenal gland, vasopressin secretion from the hypothalamus, and vasoconstriction. Vasopressin and aldosterone both lead to increased sodium and free water reabsorption in the kidney, leading to increased mean arterial pressure (MAP). Angiotensin II is then metabolized into Ang-(1–7) by ACE2. SARS-CoV-2 binds to ACE2 to gain entry into the host cell. Exogenous angiotensin II can also bind to ACE2, which can lead to competitive inhibition of the ACE2 receptor. In addition, binding of angiotensin II to AT_1 receptors leads to internalization, downregulation, and degradation of ACE2. These actions may potentially prevent SARS-CoV2 from entering the cell. Figure created with Motifolio Toolkit. Ang-2, angiotensin II; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE1, angiotensin-converting-enzyme 1; ACE2, angiotensin-converting-enzyme 2; H_2O, water; Na^+, sodium

Busse et al. Critical Care 2020

2



N protein
SARS-CoV-2

2

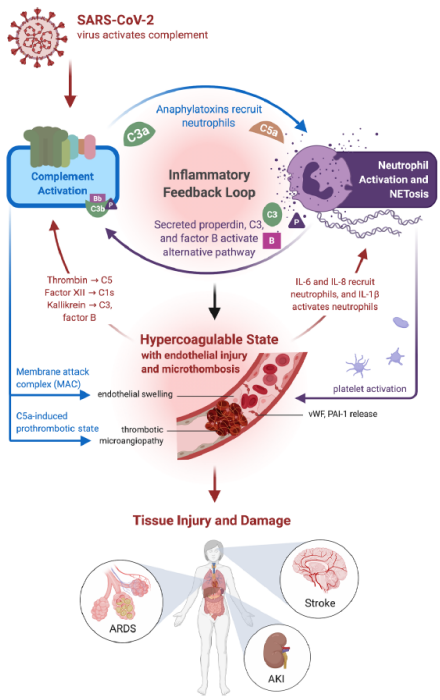
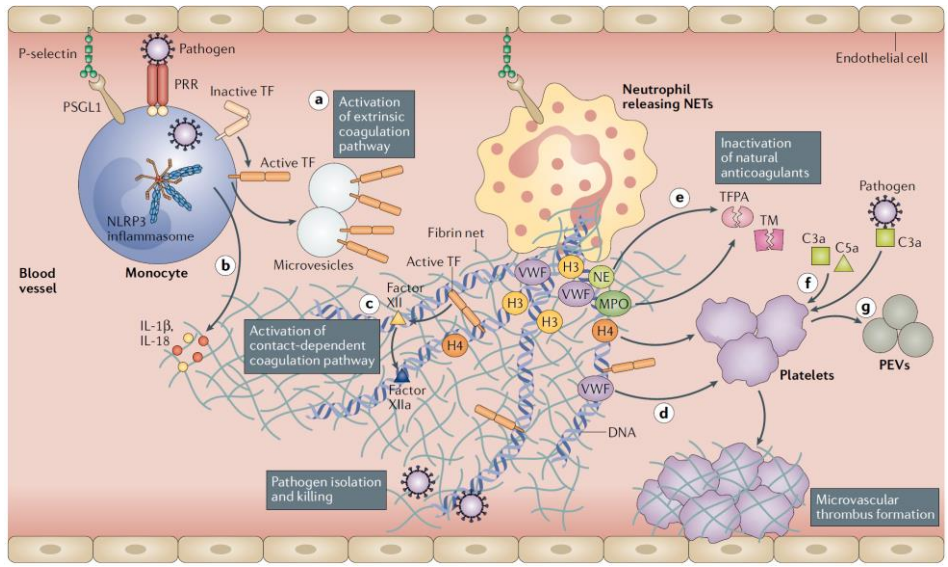


Figure 2. A summary of SARS-CoV-2 and complement activation leading to immune hyperinflammatory reactions and resulting in human pathology. Complement activation generates the proinflammatory polypeptides, C3a and C5a, and recruits neutrophils as well as monocytes. Activated neutrophils generate web-like extracellular traps (NETs), in a process known as NETosis, that contain components such as C3, properdin (P), and factor B (B) that activate the alternative complement pathway and engage an inflammatory feedback loop. Although NETs assist in host defense against pathogens, a sustained response, such as that seen in COVID-19, may incite ongoing inflammation and a hypercoagulable state. Additionally, the membrane attack complex (MAC) also induces endothelial inflammation and tissue injury, leading to the generation of IL-6 and IL-1β, which continue to propagate NETosis. Endothelial injury leads to the generation of vWF multimers. Excess ultralong vWF stabilizes factor VIII activity and prevents the binding of factor I. Endothelial damage also results in the release of plasminogen activator inhibitor-1 (PAI-1), which exacerbates thrombosis, along with C5a-induced release of tissue factor and other prothrombotic proteins. These changes then can augment a complement-coagulation pathway crosstalk, due to serine proteases, such as thrombin and kallikrein, activating the complement system in a convertase-independent manner. Such interactions among endothelial injury, hypercoagulability, and complement activation cause tissue damage, such as acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and stroke, and are often associated with a thrombotic microangiopathy.



Bonaventura et al. Nature reviews immunol 2021

2

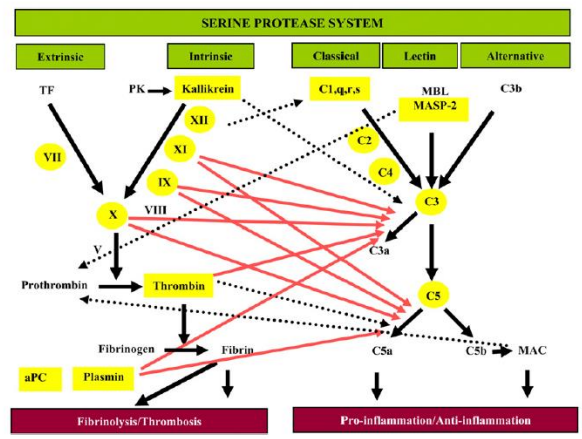
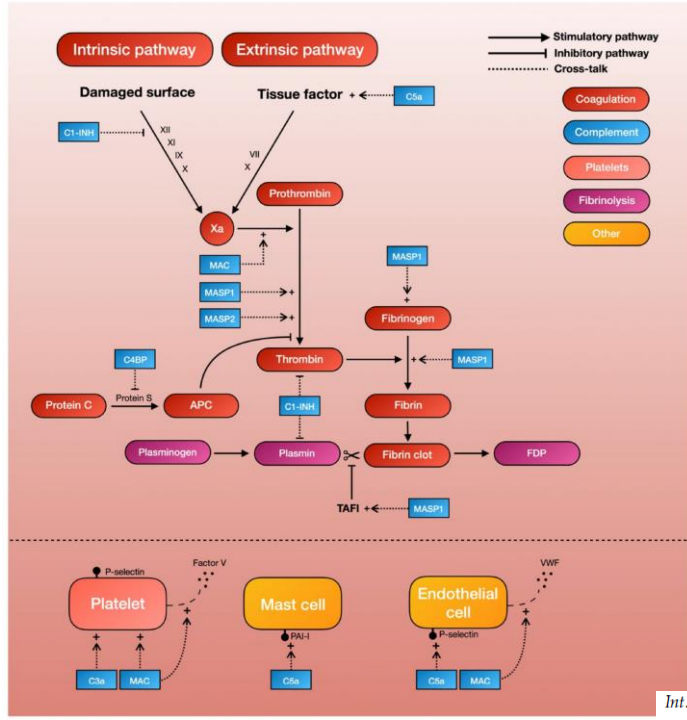


FIGURE 7. Simplified model of the serine protease system. Depiction of the complex interplay between the coagulation/fibrinolysis cascades and the complement system. The serine proteases of the complement, coagulation, and fibrinolysis systems are all highlighted in yellow. The black dotted arrow bars show previously known interactions of these systems. The red arrows identify the new paths of complement activation by the coagulation/fibrinolysis factors resulting in the generation of C3a and C5a. aPC, activated protein C; MAC, membrane attack complex; MBL, mannan-binding lectin; PK, prekallikrein.

J Immunol 2010; 185:5628-5636; Prepublished online 24 September 2010;
doi: 10.4049/jimmunol.0903678
http://www.jimmunol.org/content/185/9/5628

2



Int. J. Mol. Sci. **2020**, *21*, 1596

Patofysiology - summary

- Destruction of the tissue by viral proliferation
- Change in the renin-angiotensin aldosteron system
- Complement activation
- Thrombocytes activation
- Immune response actiovation – Mϕ, lymfocytes (cytokines, cytokine storm)
- Endothelial damage

Patofysiology - summary

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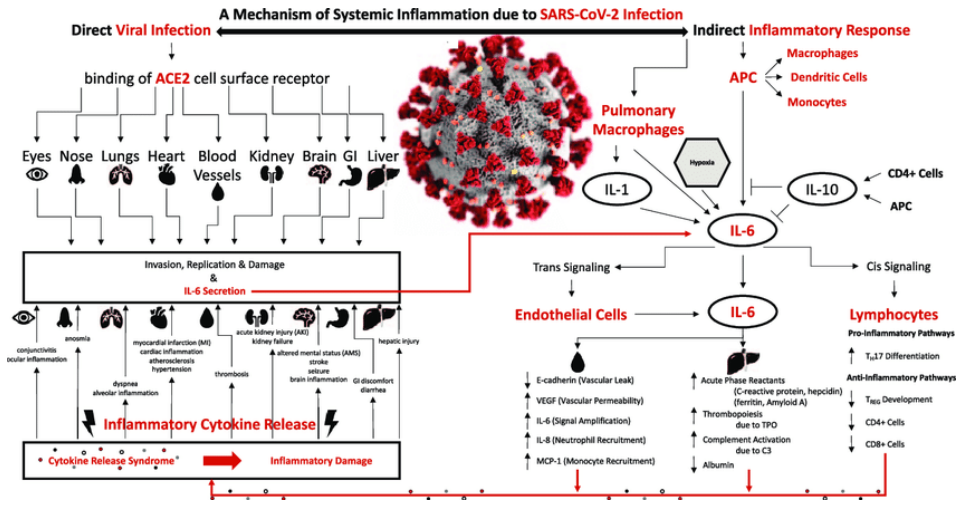
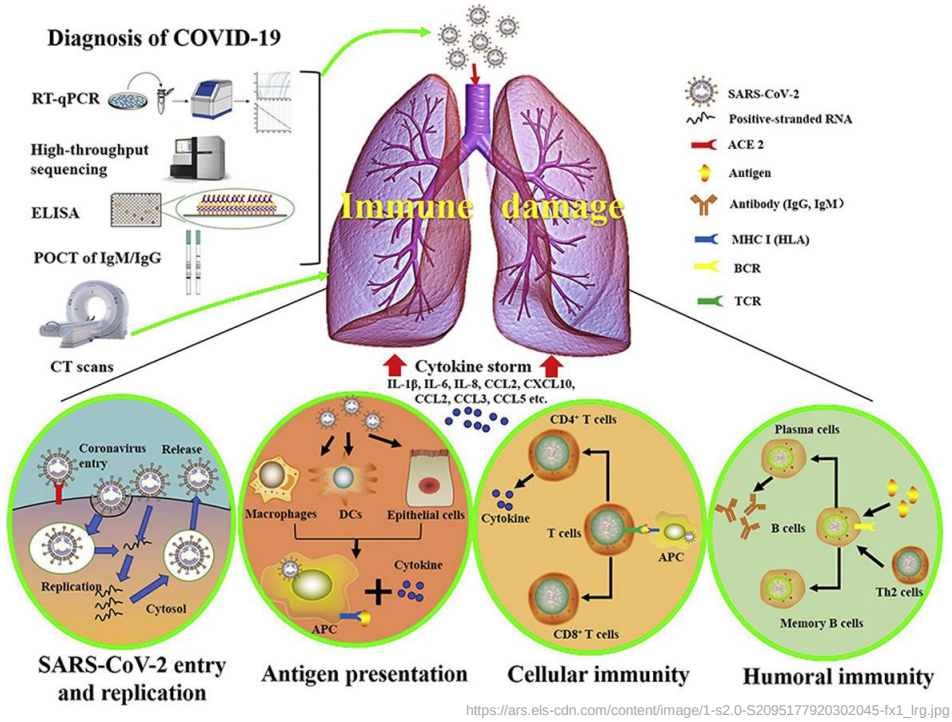
Hypercoagulation status (LMWH prevention)

Superinfection and reactiovation of latent infections

Patofysiology



Leyfman et l. SHOCK 2020



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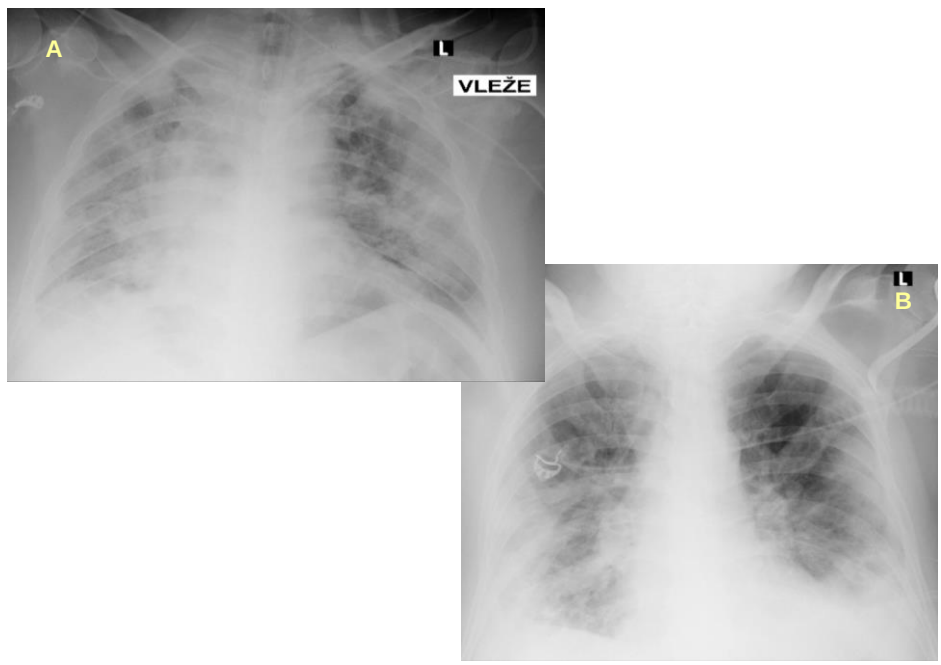
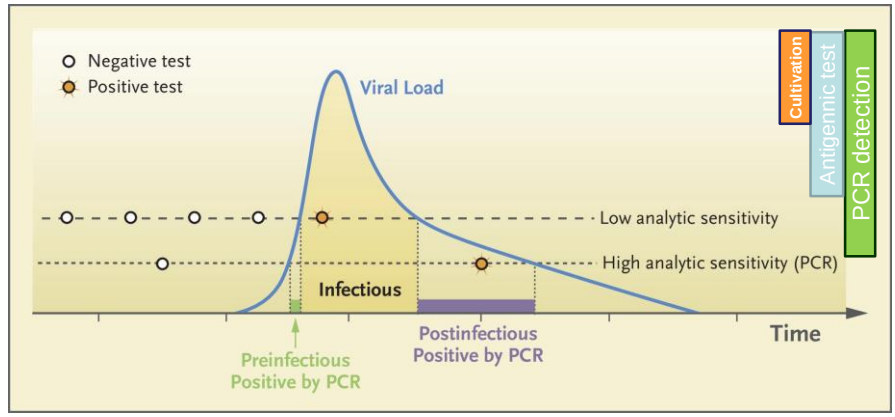
COVID-19 pneumonia (A) and subsequent HSV pneumonia (B)

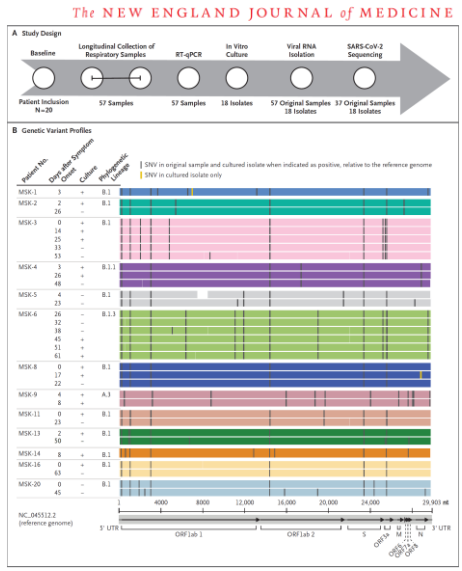


Diagnostic „window“ for different types of detection.



Mina et al. September 30, 2020 DOI: 10.1056/NEJMp2025631

Lenths of SARS-CoV-2 shedding in the hematooncological patients



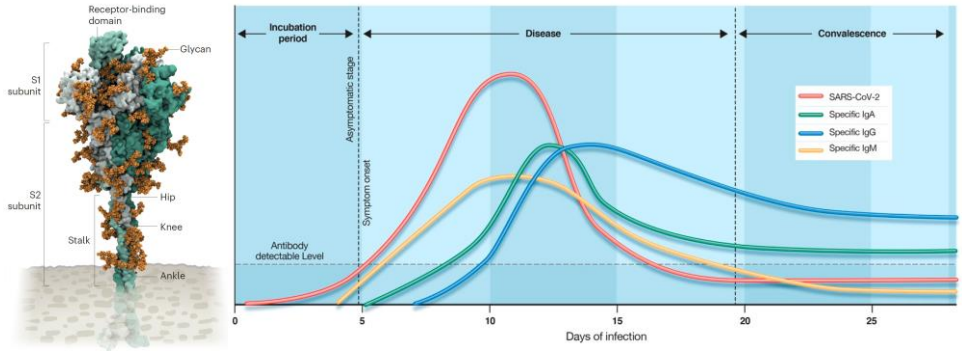
– 15 out of 20 patients had active chemotherapy
- 11 severe COVID

- viral RNA detected up to 78 days (IQR 24-64)
- First day 71% of samples cultivateable
- follow up positive in 5 patients (8, 17, 24, 26 and 61 days after beggining to the symptoms)

„Patients with profound immunosuppression after undergoing hematopoietic stem-cell transplantation or receiving cellular therapies <u>may shed viable SARS-CoV-2 for at least 2 months</u>.“

N ENGL J MED 383;26 NEJM.ORG DECEMBER 24, 2020

Antibody response



Antibodies against S1
Antibodies against RBD domain correlate to neutralisation antibodies

Antibody Response - Seroconversion

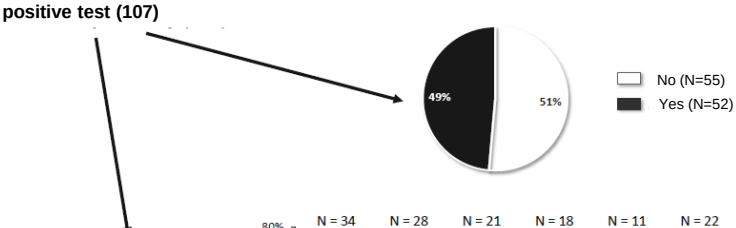
Antibodies appear in blood after: ≈10-20 days
Maintenance of antibody response:
≈2-3 years (measured for SARS-CoV-1)

Bar-On eLifescience 2020
http://bit.ly/2WOeN64
Scudellari Nature 2021; 595
https://www.mdpi.com/diagnostics/diagnostics-10-00453/article_deploy/html/images/diagnostics-10-00453-g004.png

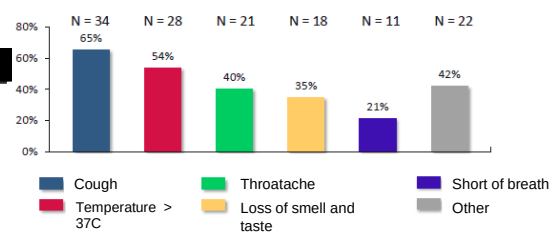
SARS-CoV-2

Presence of respiratory symptoms after 1.1.2020

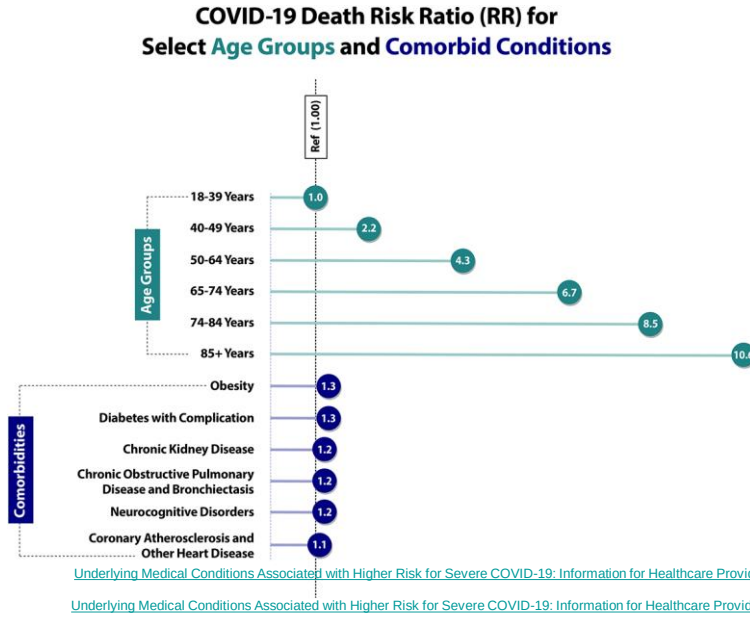
Respondents with antibody positive test (107)



Symptoms (N=52)



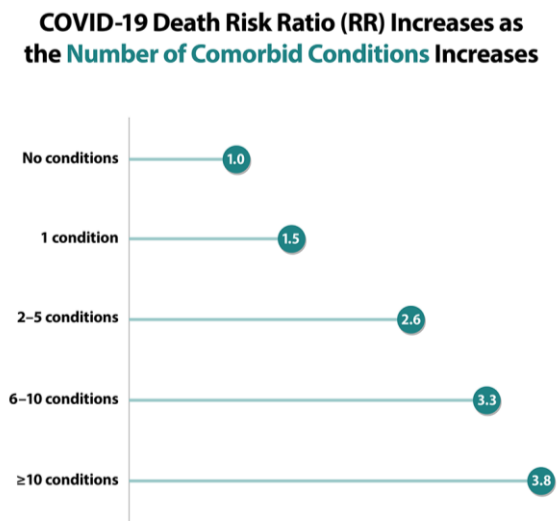
Risk groups



Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Providers (cdc.gov)

Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Providers (cdc.gov)

Risk groups



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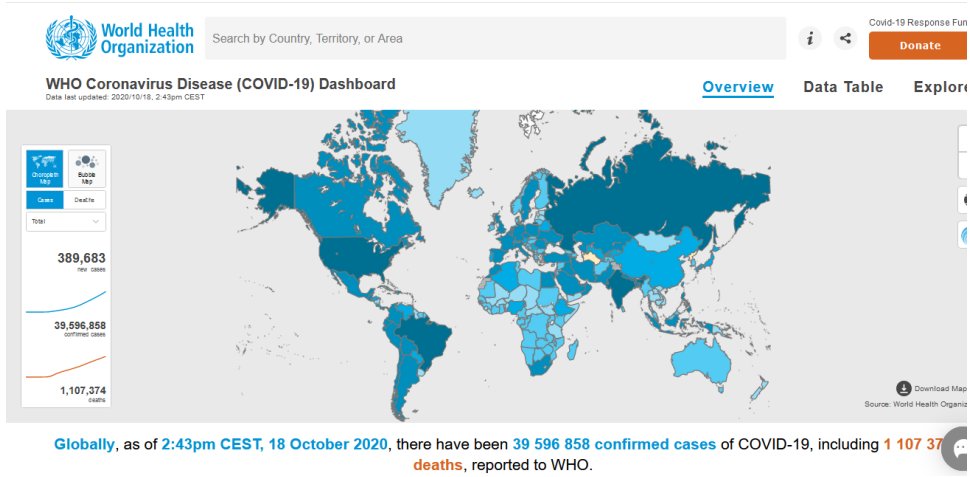
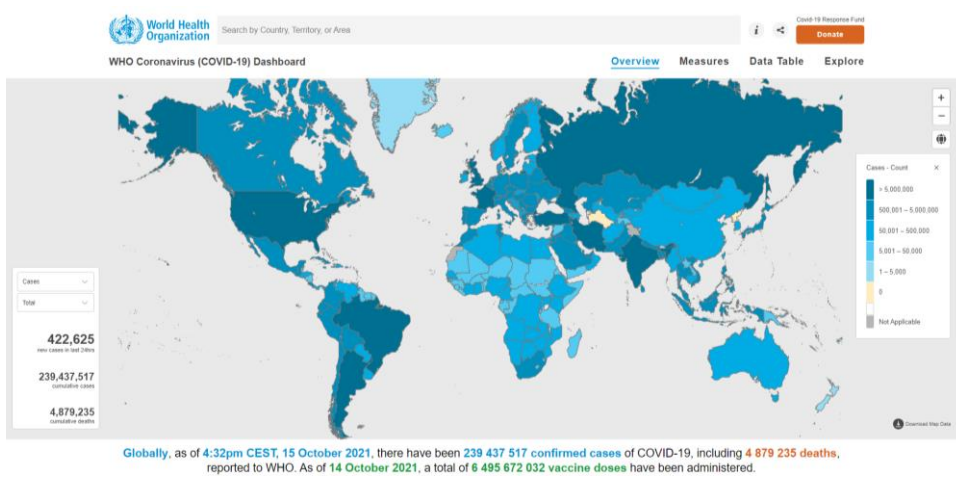
Epidemiological data



Epidemiological data



Epidemiological data

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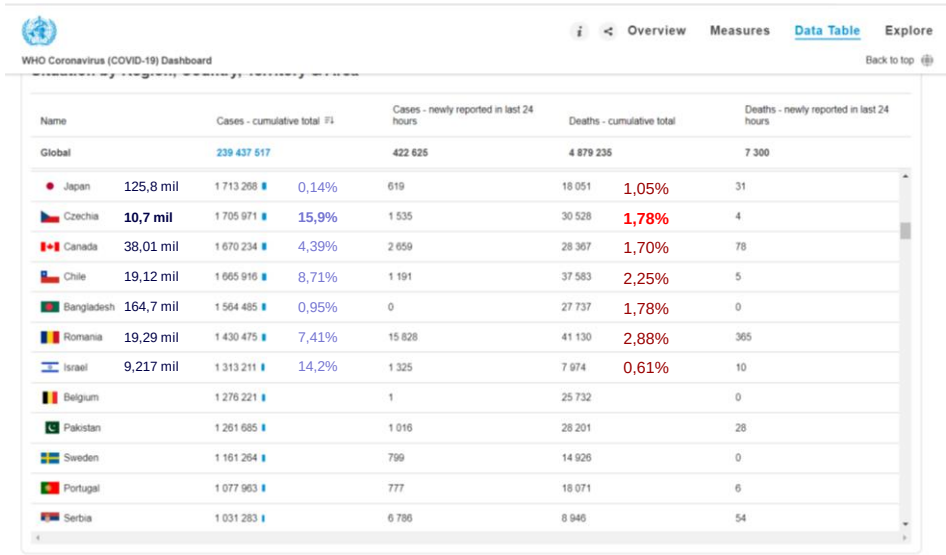


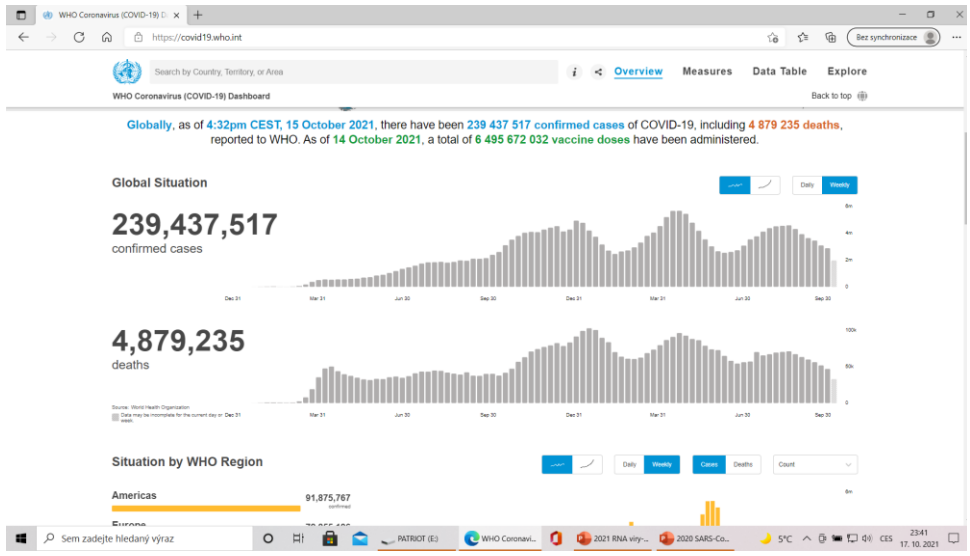
WHO Coronavirus (COVID-19) Dashboard

Overview Measures Data Table Explore

Back to top

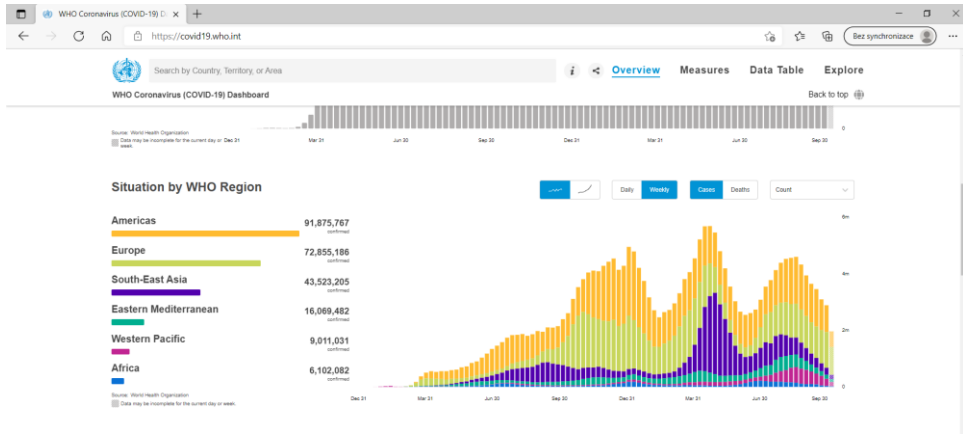
Name		Cases - cumulative total		Cases - newly reported in last 24 hours	Deaths - cumulative total		Deaths - newly reported in last 24 hours
Global		239 437 517		422 625	4 879 235		7 300
Japan	125,8 mil	1 713 268	0,14%	619	18 051	1,05%	31
Czechia	10,7 mil	1 705 971	15,9%	1 535	30 528	1,78%	4
Canada	38,01 mil	1 670 234	4,39%	2 659	28 367	1,70%	78
Chile	19,12 mil	1 665 916	8,71%	1 191	37 583	2,25%	5
Bangladesh	164,7 mil	1 564 485	0,95%	0	27 737	1,78%	0
Romania	19,29 mil	1 430 475	7,41%	15 828	41 130	2,88%	365
Israel	9,217 mil	1 313 211	14,2%	1 325	7 974	0,61%	10
Belgium		1 276 221		1	25 732		0
Pakistan		1 261 685		1 016	28 201		28
Sweden		1 161 264		799	14 926		0
Portugal		1 077 963		777	18 071		6
Serbia		1 031 283		6 786	8 946		54

Epidemiological data

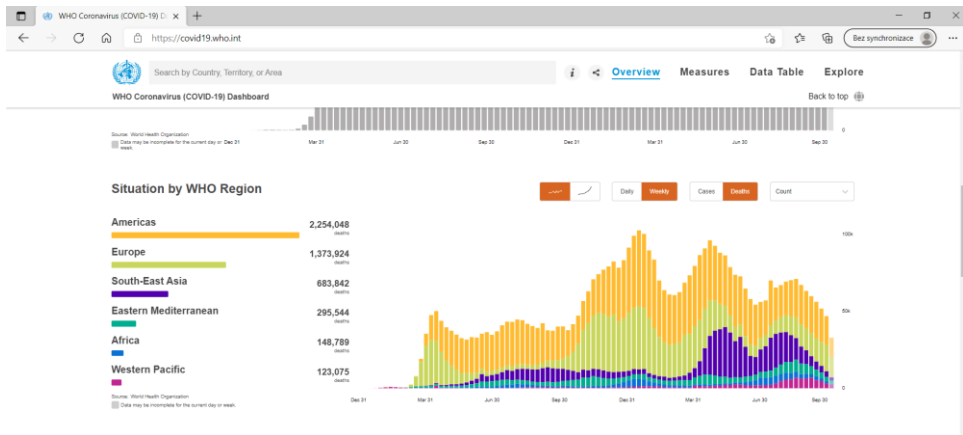


Mortality 2,04%

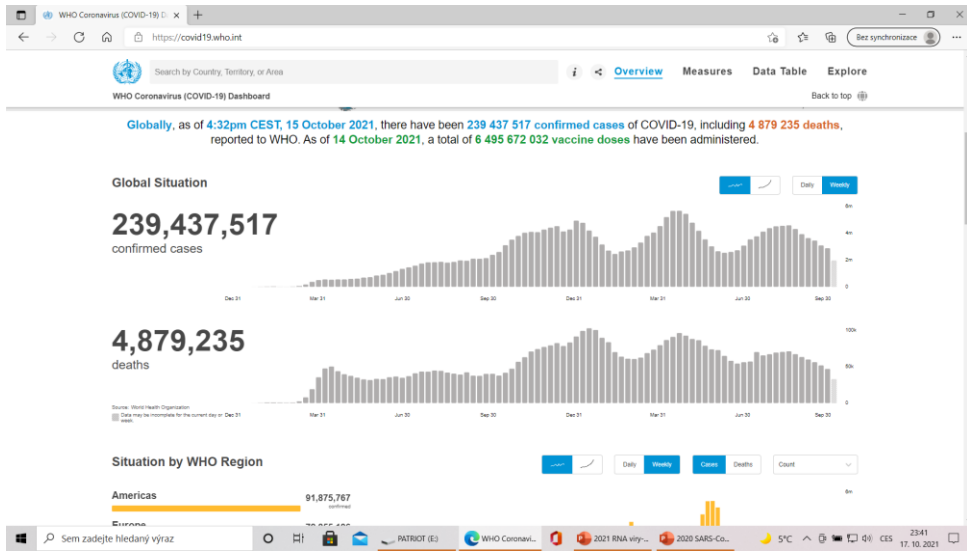
Epidemiological data



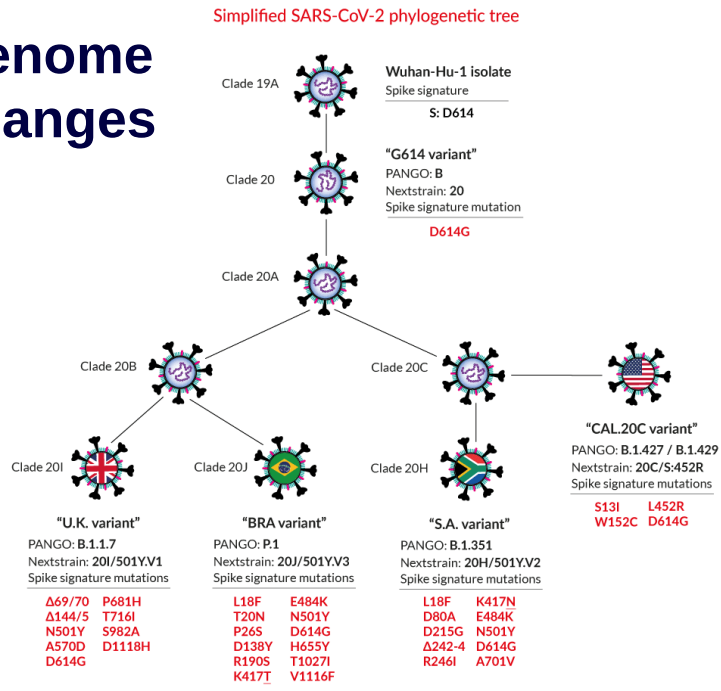
Epidemiological data



Epidemiological data

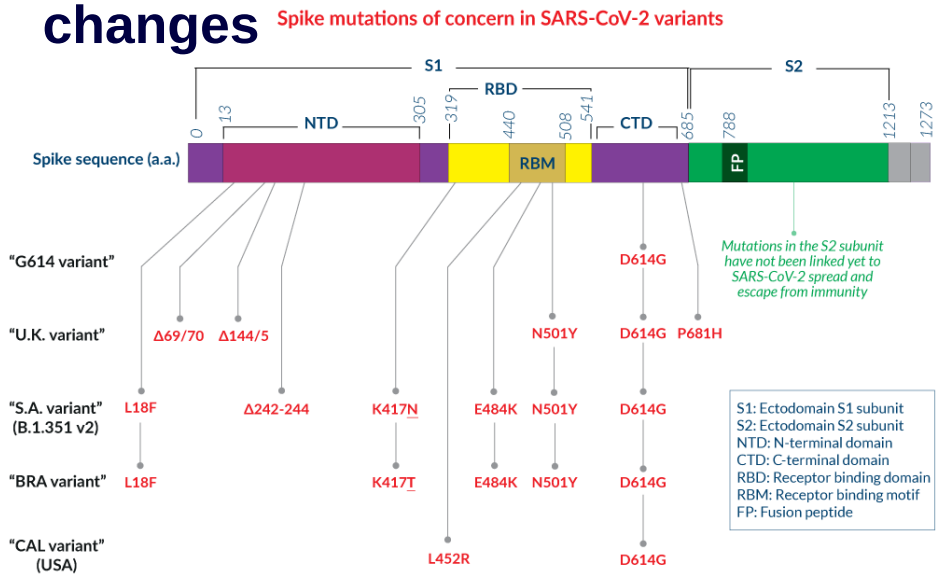


Genome changes



https://www.invivogen.com/sites/default/files/pictures/sars2-tree-invivogen.png

Genome changes



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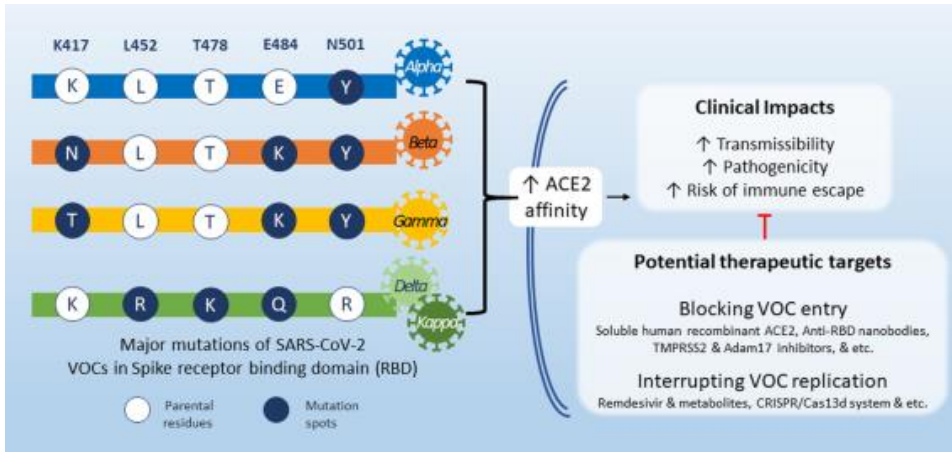
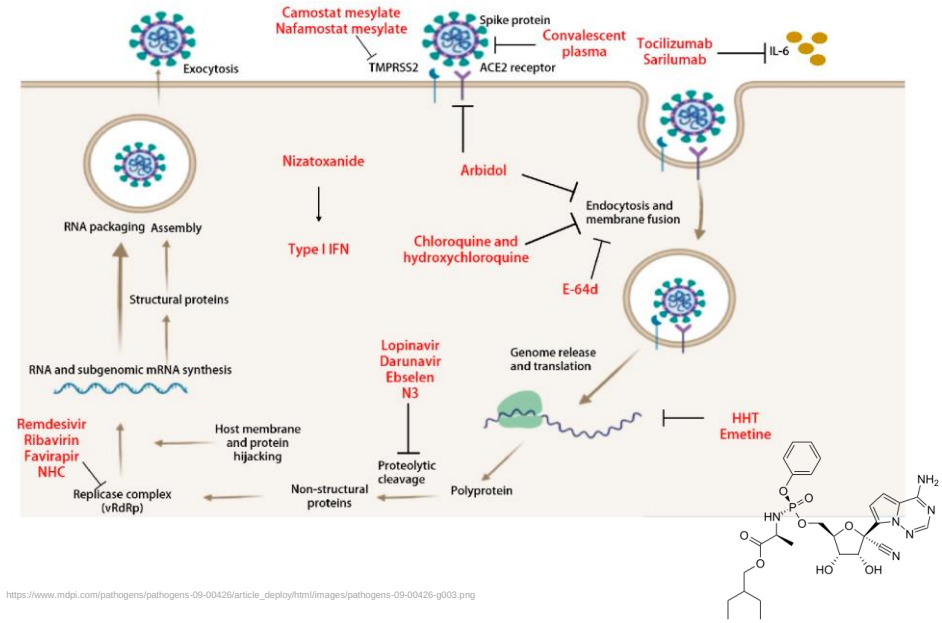
Genome changes



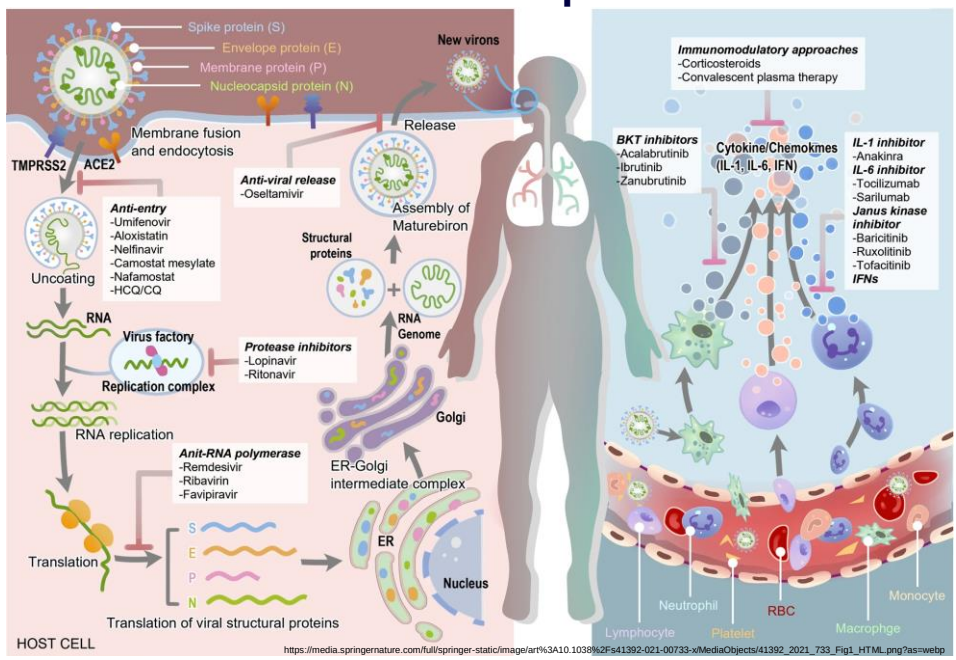
https://www.invivogen.com/sites/default/files/pictures/sars2-tree-invivogen.png

Possible treatment options



https://www.mdpi.com/pathogens/pathogens-09-00426/article_deploy/html/images/pathogens-09-00426-g003.png

Treatment options



https://media.springernature.com/full/springer-static/image/art%3A10.1038%2Fs41392-021-00733-x/MediaObjects/41392_2021_733_Fig1_HTML.png?as=webp

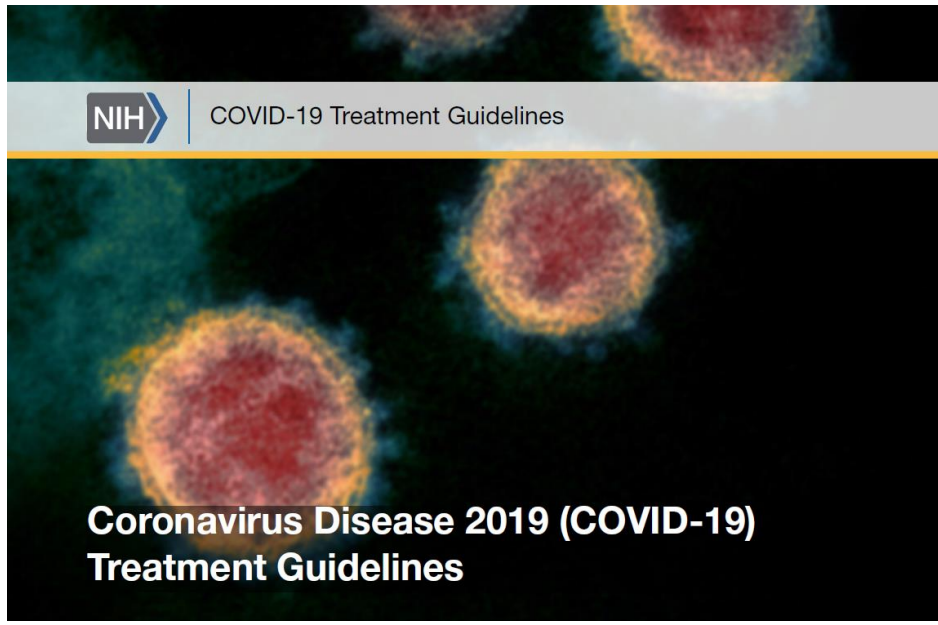


Figure 2. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[b] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone** (when combination with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIII)** For recently hospitalized[c] patients with rapidly increasing oxygen needs and systemic inflammation: • Add either **baricitinib (BIIa)** or **IV tocilizumab (BIIa)** to one of the two options above[d] • If neither baricitinib nor IV tocilizumab is available or feasible to use, **tofacitinib** can be used instead of baricitinib **(BIIa)** or **IV sarilumab** can be used instead of IV tocilizumab **(BIIa)**.
Hospitalized and Requires IMV or ECMO	• **Dexamethasone (AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** • If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

[a] Corticosteroids prescribed for an underlying condition should be continued.
[b] If patients progress to requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, complete remdesivir course.
[c] For example, within 3 days of hospital admission.
[d] Drugs are listed alphabetically and not in order of preference. As there are no studies directly comparing baricitinib and tocilizumab for treatment of COVID-19, there is insufficient evidence to recommend one drug over the other. Treatment decisions should be determined by local guidance, drug availability, and patient comorbidities.

Key: ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IMV = invasive mechanical ventilation; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

Figure 1. Therapeutic Management of NonHospitalized Adults With COVID-19

All outpatients with COVID-19 who enter the health care system should have in-person or telehealth follow-up visits. Symptomatic treatments, including hydration, antipyretics, analgesics, and antitussives, can be initiated as needed.

Patients should be counseled about symptoms that warrant re-evaluation by a health care provider (e.g., new onset dyspnea, worsening dyspnea [particularly dyspnea that occurs while the patient is resting or that interferes with daily activities], mental status changes). Home resources should be assessed before patients are discharged from a clinic, urgent care center, ED, or hospital; outpatients should have access to housing, proper nutrition, a caregiver, and a device that is suitable for telehealth. If patients are discharged while they are still receiving oxygen supplementation, they should receive oximetry monitoring and close follow-up soon after discharge.

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Not Requiring Hospitalization or Supplemental Oxygen, As Determined by a Health Care Provider in ED or an In-Person or Telehealth Visit	Anti-SARS-CoV-2 monoclonal antibody products are recommended for outpatients with mild to moderate COVID-19 who are at high risk of disease progression, as defined by the EUA criteria (treatments are listed in alphabetical order):[a] • **Bamlanivimab plus etesevimab**; *or* • **Casirivimab plus imdevimab**; *or* • **Sotrovimab** The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in the absence of another indication **(AIII)**.[b]
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone (AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but who still require oxygen*[c]	There is insufficient evidence to recommend either for or against the continued use of remdesivir, dexamethasone, and/or baricitinib. Review the text below when considering the use of any of these agents after hospital discharge.
Discharged From ED Despite New or Increasing Need for Supplemental Oxygen *When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured*[d]	The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use should not exceed 10 days) with careful monitoring for adverse events **(BIII)**. There is insufficient evidence to recommend either for or against the use of remdesivir. When considering the use of remdesivir, review the text below for further discussion. The Panel **recommends against** the use of **baricitinib** in this setting, except in a clinical trial **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

[a] In laboratory studies, some SARS-CoV-2 variants of concern or variants being monitored harbor certain mutations that are associated with reduced susceptibility to certain agents. Some regimens may be preferred in certain settings based on the degree of reduced susceptibility and the prevalence of these variants in a given region. See Anti-SARS-CoV-2 Monoclonal Antibodies and The Panel's Statement on Bamlanivimab Plus Etesevimab for more information. Updates on the distribution of bamlanivimab plus etesevimab are available on the HHS Bamlanivimab/Etesevimab website.
[b] There is currently a lack of safety and efficacy data on the use of these agents in outpatients with COVID-19; using systemic glucocorticoids in this setting may cause harm.
[c] These individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person clinic visits.
[d] In cases where resources (e.g., inpatient beds, staff members) are scarce, it may be necessary to discharge an adult patient and provide an advanced level of home care, including supplemental oxygen (whether patients are receiving oxygen at home for the first time or are increasing their baseline oxygen requirements), pulse oximetry, and close follow-up through visiting nurse services, telehealth, or in-person clinic visits.

Key: ED – emergency department; EUA – Emergency Use Authorization; HHS – Department of Health and Human Services; the Panel – the COVID-19 Treatment Guidelines Panel; PO = orally

Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19

Last Updated: July 8, 2021

Summary Recommendations

Remdesivir is the only Food and Drug Administration-approved drug for the treatment of COVID-19. In this section, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations for using antiviral drugs to treat COVID-19 based on the available data. **As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.** For more information on these antiviral agents, see Table 2e.

Remdesivir

- See Therapeutic Management of Hospitalized Adults with COVID-19 for recommendations on using remdesivir with or without dexamethasone.

Ivermectin

- There is insufficient evidence for the Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.

Nitazoxanide

- The Panel **recommends against** the use of **nitazoxanide** for the treatment of COVID-19, except in a clinical trial **(BIIa)**.

Hydroxychloroquine or Chloroquine and/or Azithromycin

- The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** and/or **azithromycin** for the treatment of COVID-19 in hospitalized patients **(AI)** and in nonhospitalized patients **(AIIa)**.

Lopinavir/Ritonavir and Other HIV Protease Inhibitors

- The Panel **recommends against** the use of **lopinavir/ritonavir** and **other HIV protease inhibitors** for the treatment of COVID-19 in hospitalized patients **(AI)** and in nonhospitalized patients **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

The Possible Role of Vitamin D in Suppressing Cytokine Storm and Associated Mortality in COVID-19 Patients

Ali Daneshkhah[1], Vasundhara Agrawal[1], Adam Eshein[1], Hariharan Subramanian[1], Hemant K. Roy [2], and Vadim Backman[1*]

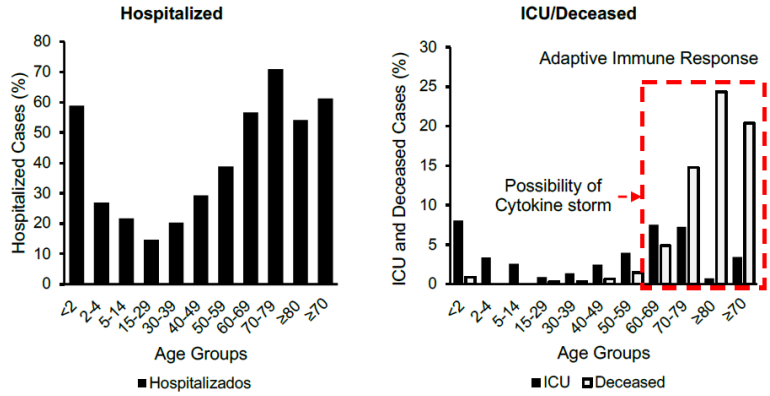


Figure 7 Age distribution of the a) hospitalized, b) admitted to ICU or deceased in Spain based on data from 145,429 cases[26].

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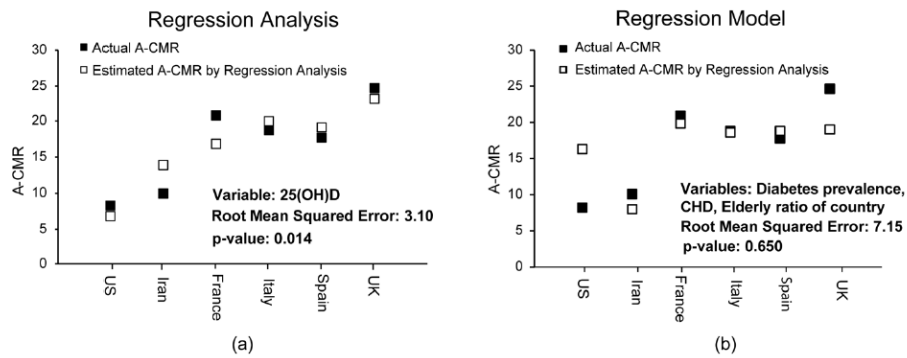

Figure 6 Regression analysis based on (a) 25(OH)D, (b) Diabetes prevelance among men and women (age standardized), elderly ratio (≥70 yo) in the country, CHD death rate per 100, 000 (age standardized)

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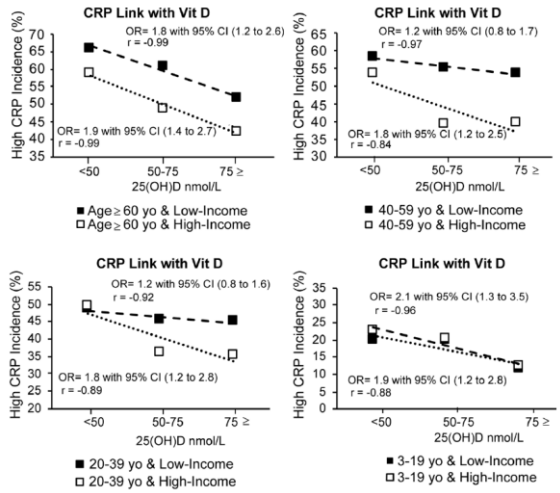
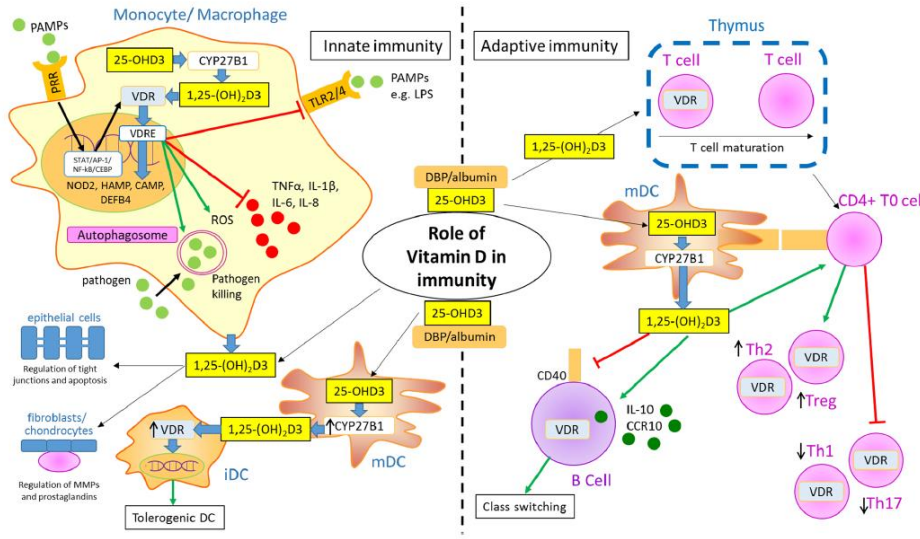




S.R. Harrison et al. Calcified Tissue International (2020) 106:58–75

Nucleotide based vaccine candidates

Genomic RNA

0 5000 10000 15000 20000 25000 28000 bp

ORF1a ORF1b ORF3a E ORF6 S ORF7a ORF8 M N

DNA sequence of S,M and N genes as vaccine target

mRNA -1273 and BNT162 encoding S protein

Subunit vaccine candidates

Membrane protein (M)

Envelope small membrane protein (E)

Hemagglutinin Estrase (HE)

Spike Glycoprotein (S)

Nucleoprotein (N)

Inactivated vaccines candidates

Inactivated or whole killed virus (WKV)

Viral vector based vaccine candidates

Coronavirus proteins/glycoproteins expressed by attenuated adenovirus/poxvirus/ newcastle disease virus

Attenuated vaccines candidates

Gene deletion of various essential genes (S,N,E genes), Nonstructural proteins (nsp) encoding genes

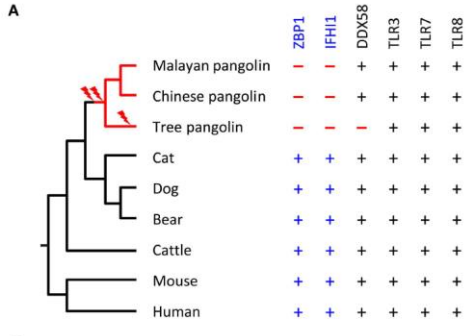
frontiers in Immunology

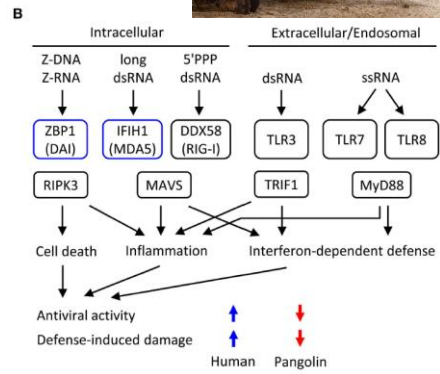
Pangolins Lack IFIH1/MDA5, a Cytoplasmic RNA Sensor That Initiates Innate Immune Defense Upon Coronavirus Infection

ORIGINAL RESEARCH
published: 08 May 2020
doi: 10.3389/fimmu.2020.00939

*Heinz Fischer[1], Erwin Tschachler[2] and Leopold Eckhart[2]**

FIGURE 3 | Evolution of RNA sensor genes and possible implications on antiviral responses in pangolins. **(A)** Phylogenetic tree of mammals and comparison of presence (+) or absence (–) of RNA sensor genes. Evolutionary gene loss (indicated by lightning bolt symbols) was inferred from the species distribution of the genes. Species: Malayan pangolin (*Manis javanica*), Chinese pangolin (*Manis pentadactyla*), tree pangolin (*Manis tricuspis*), cat (*Felis catus*), dog (*Canis lupus familiaris*), bear (*Ursus arctos horribilis*), cattle (*Bos taurus*), mouse (*Mus musculus*), human (*Homo sapiens*). **(B)** Schematic overview of innate immune sensors of viral RNA and signaling in mammals. Only RNA sensors investigated in this study are shown. The schematic includes the hypothesis about IFIH1 and ZBP1-dependent differences in the antiviral activity and defense-induced damage to the host. The directions of the colored arrows indicate the effects of the presence or absence of RNA sensors. 5′PPP, triphosphorylated at the 5′-end; ds, double-stranded; ss, single-stranded.

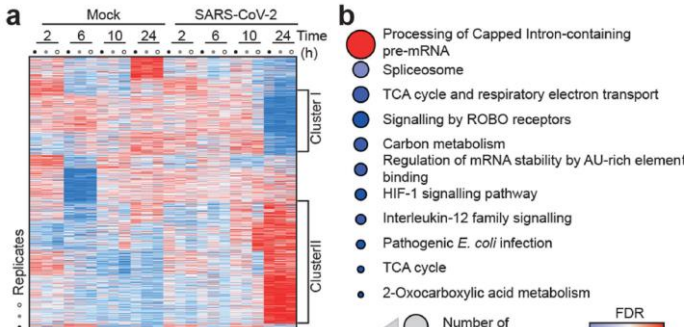




Article

Proteomics of SARS-CoV-2-infected host cells reveals therapy targets

https://doi.org/10.1038/s41586-020-2332-7
Received: 27 February 2020
Accepted: 6 May 2020
Published online: 14 May 2020



These analyses revealed that SARS-CoV-2 reshapes central cellular pathways, such as translation, splicing, carbon metabolism and nucleic acid metabolism. Small molecule inhibitors targeting these pathways prevented viral replication in cells. Our results reveal the cellular infection profile of SARS-CoV-2 and led to the identification of drugs inhibiting viral replication. We anticipate our results to guide efforts to understand the molecular mechanisms underlying host cell modulation upon SARS-CoV-2 infection. Furthermore, our findings provide insight for the development of the therapy options for COVID-19.

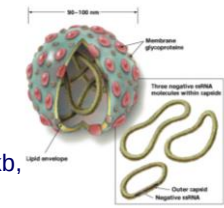
REVIEW ARTICLE

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

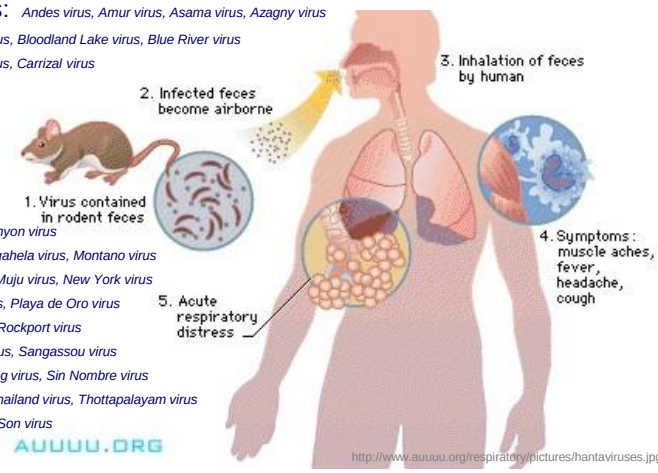
Hantaviruses



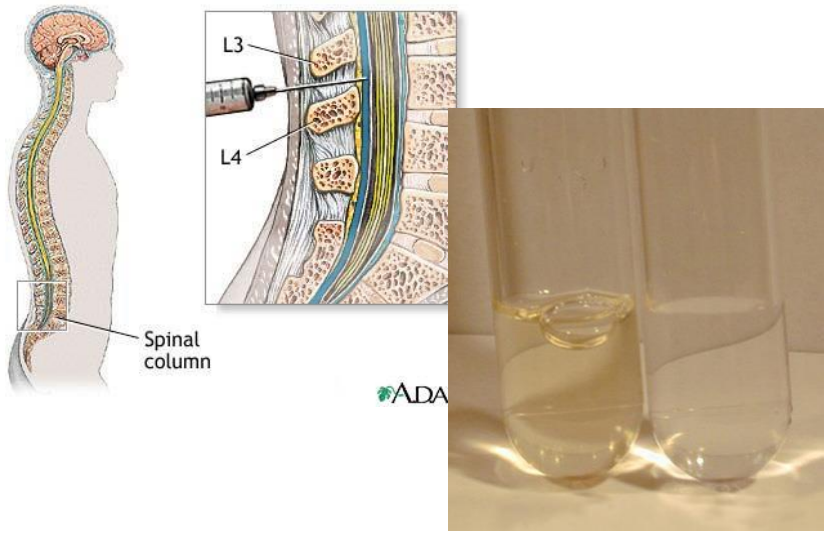
- Bunyaviridae
- ss(-) RNA - 3 segments (small ~ 1.7-2 kb, medium ± 3.7 kb, large ± 6.5 kb)
- enveloped 120-160 nm in diameter
- Incubation period – 2-4 weeks
- The described in 1951, where a hantavirus caused hemorrhagic fever with renal syndrome (HFRS) in North and South Korea.
- Transmitted from rodens, 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 prowazeki (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

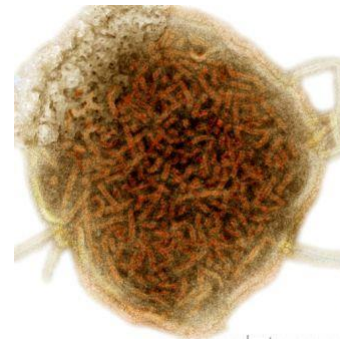
Virus vztekliny

http://www.stanford.edu/group/virus/rhabdo/2004tischoff/changrabies.gif

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

Most frequently detected viruses according to the clinical symptoms

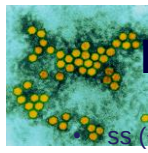
Clinical presentation	Possible aetiological agent
Cranial nerve abnormalities	HSV, EBV, listeria, tuberculous meningitis, syphilis, Lyme disease, *Cryptococcus neoformans*
Cerebellar ataxia	VZV, EBV, mumps virus, trypanosomiasis
Dementia	HIV, measles virus, syphilis, human transmissible spongiform encephalopathies
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/67302/250wm/C0023030-Mumps_virus,_TEM-SPL.jpg

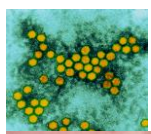
Thompson et al. Arch Dis Child 2012;97:150-161.

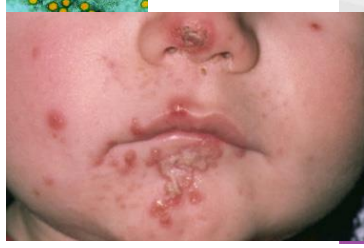


Picornaviridae - Enteroviruses

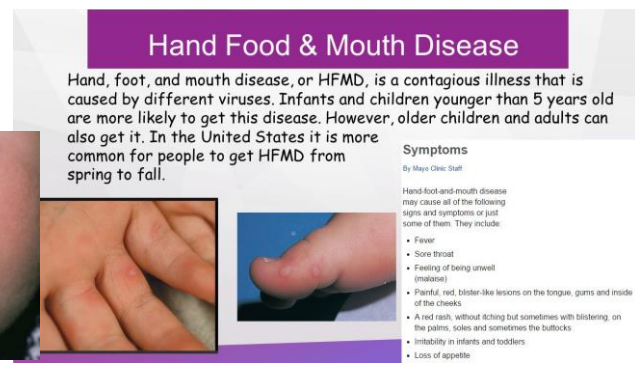
ss (+) RNA, genome 7.2-8.5 kb

- 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

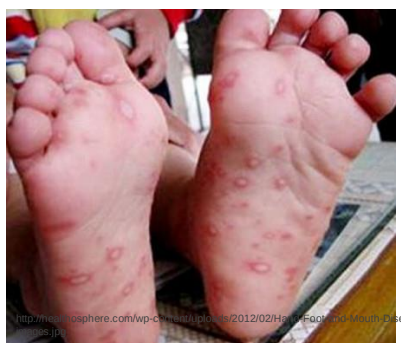




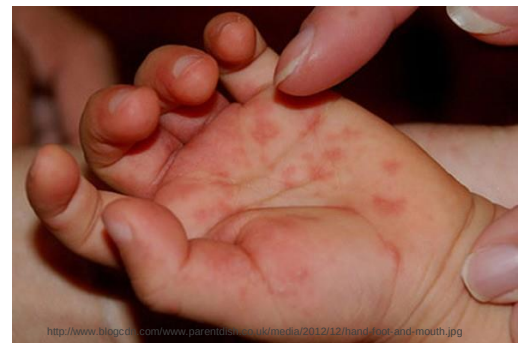
http://www.nhs.uk/tools/documents/visual_guides_v2/data/baby_rashes/images/slideshow_6.jpg



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



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



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

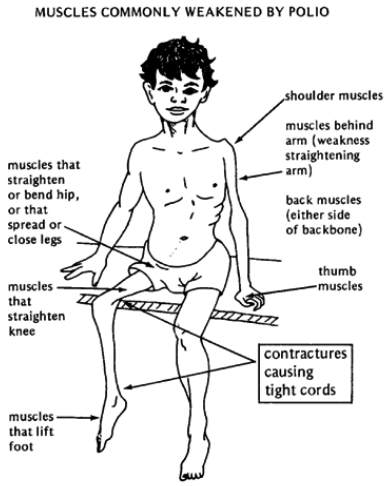
http://healthosphere.com/wp-content/uploads/2012/02/Hand-Foot-and-Mouth-Disease1.jpg

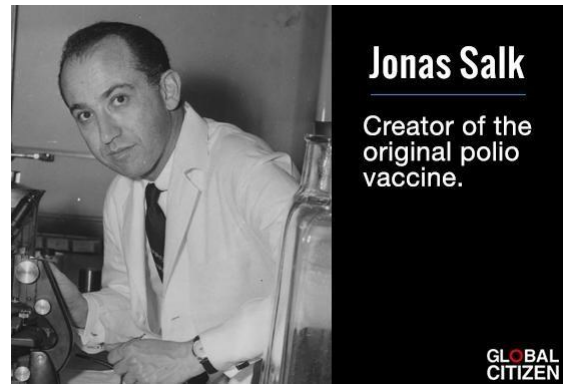
Picornaviridae – Enteroviruses - Polio

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





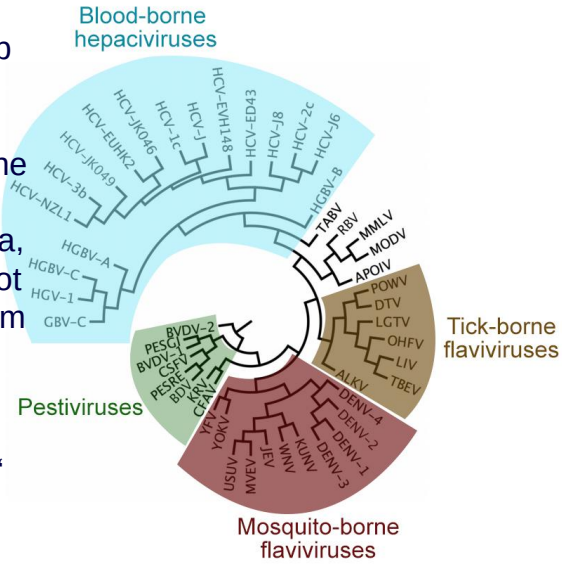
Picornaviridae - Enteroviruses

- 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

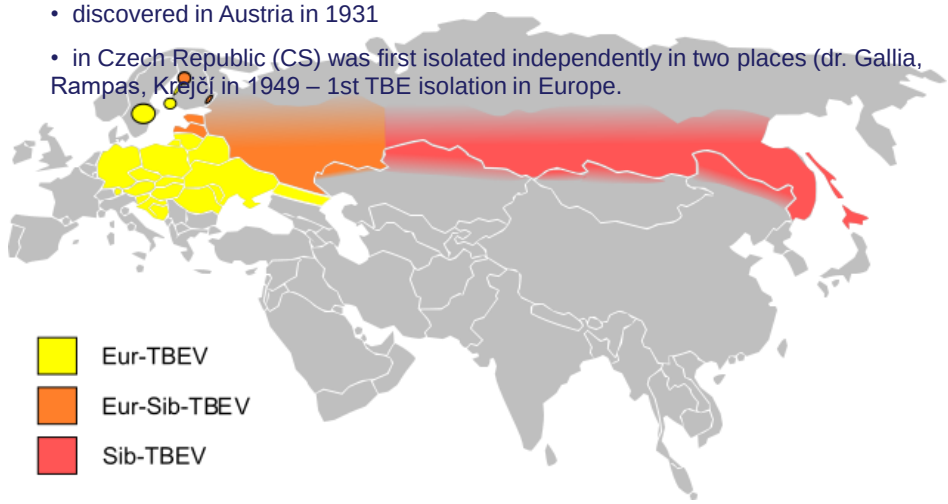
- disease has often „two“ waves of clinical symptoms



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

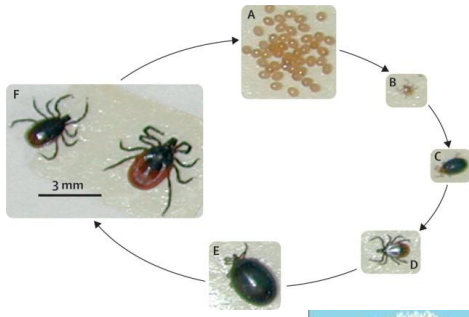
Tick Borne Encephalitis – TBE
geographical distribution

- 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

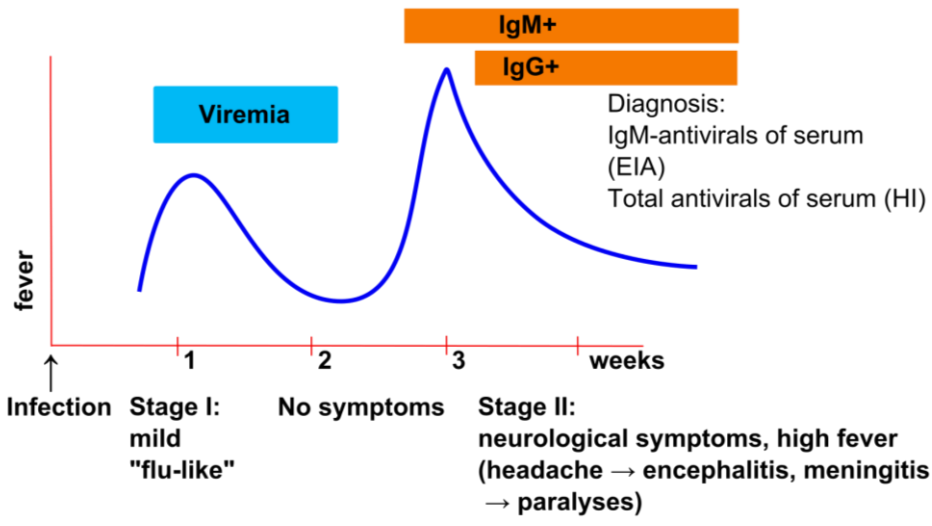
TBE
Vector



- 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



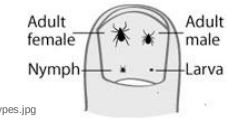
http://upload.wikimedia.org/wikipedia/commons/thumb/6/67/TBE_symptoms.svg/751px-TBE_symptoms.svg.png

- 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

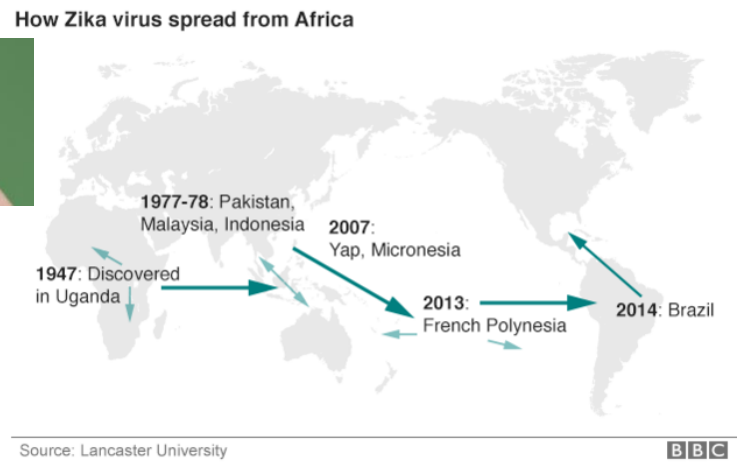
Vaccination - inactivated virus

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

Flaviviridae

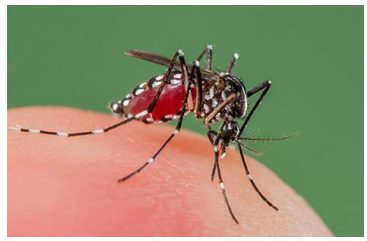
Zika virus

- 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).



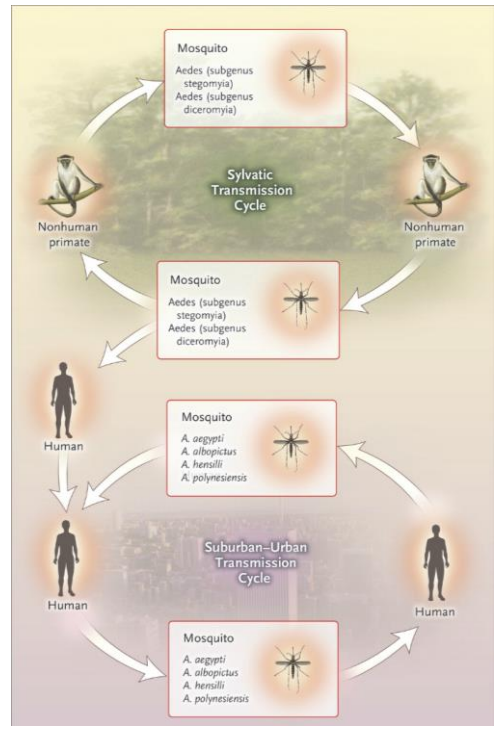
Flaviviridae

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.

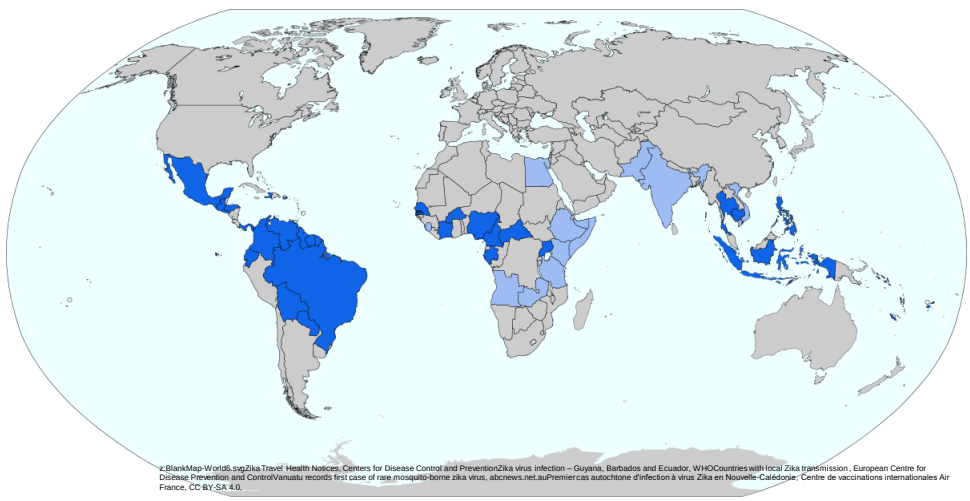
  (However, there are doubts about real presence of the virus in the sperm, or blood contamination).



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

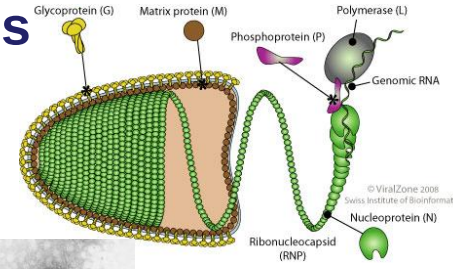
Zika virus

- 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)

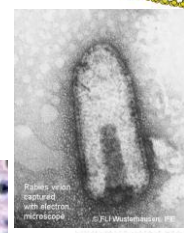
Rhabdoviridae

Lyssavirus

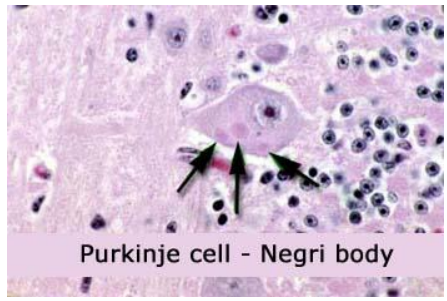
- ss (-) RNA; genome 11 kb
- enveloped
- 75 nm wide and 180 nm long
- cellular receptor: acetylcholine receptor
- Transmission: mainly from infected animals by saliva
- Clathrin mediated endocytosis
- Cytoplasmatic proliferation – **Negri bodies**



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

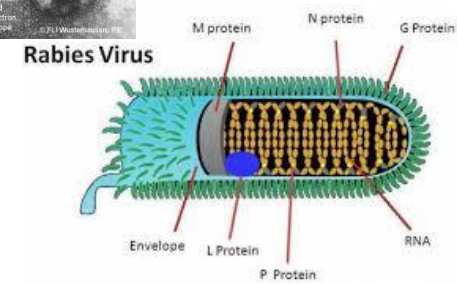


http://www.who-rabies-bulletin.org/about_rabies/Images/Virion.jpg



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

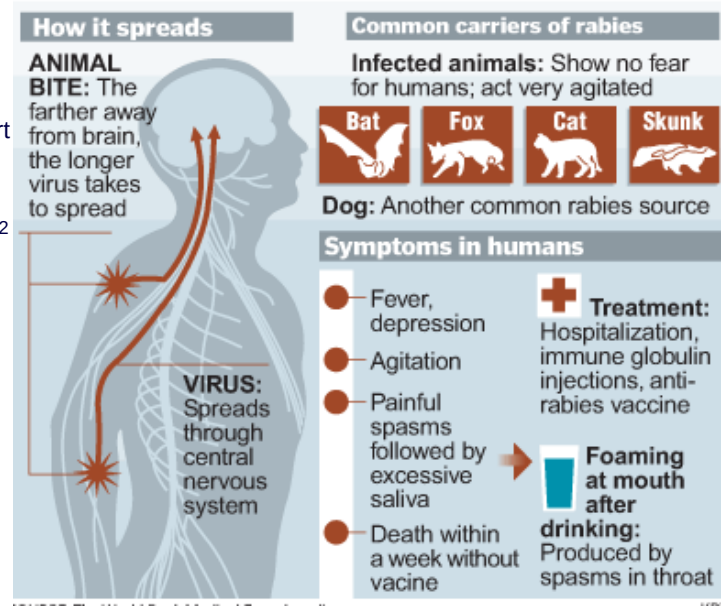
http://www.cdc.gov/rabies/images/bullet.gif



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%)

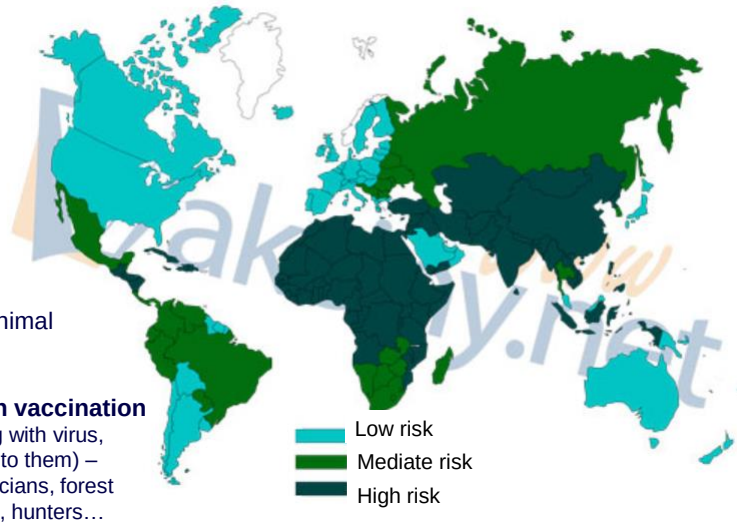


http://peterandmorrisonrabies.weebly.com/uploads/5/3/5/7/53574157/807037792.png

Rhabdoviridae

Lyssavirus - Rabies

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



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

Zdroj: www.vakciny.net

Diarrhea disease

Around the world, there is approx. 1.7 billions of diarrheal disease in kids every year.
About 525 000 children bellow 5 yrs. of age decease every year. (zdroj: WHO)

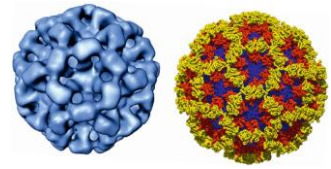
Most frequent viral pathogens

- Astroviruses
- Caliciviruses (Norovirus, Sapovirus)
- 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)



	Noroviry	Sapoviry	Rotaviry	Adenoviry (sérotyp 40, 41 a 52)	Astroviry
čeleď	*Caliciviridae*	*Caliciviridae*	*Reoviridae*	*Adenoviridae*	*Astroviridae*
genom a jeho délka	+ss RNA ~ 7,7 kb	+ss RNA 7,1–7,7 kb	segmentovaný ds RNA ~ 18 kb	ds DNA ~ 34 kb	+ss RNA ~ 6,8 kb
velikost virové partikule	35 nm	30–38 nm	70 nm	70–100 nm	28–30 nm
% výskytu	18 % ze všech průjmových onemocnění	celosvětově 2,2–12,7 % průjmových onemocnění	28 % průjmových onemocnění dětí	~ 12 % dětí < 5 let	přibližně 1 % průjmových onemocnění
infekciozita	~ 20 v. partikulí	~ 1000 genomových kopií	< 100 v. partikulí	< 150 PFU	< 100 v. partikulí
inkubační doba (dny)	1,2 (10–51 h)	1–4	2,0 (1–3)	5–8	4,5
rizikový věk	děti < 5 let věku	děti < 5 let věku, zejména novorozenci a imunosuprimovaní pacienti	děti < 2 let věku	děti < 5 let věku	děti < 3 let věku
typické příznaky	gastroenteritis s častým zvracením, vodnatý průjem	gastroenteritida se zvracením, vodnatý průjem	gastroenteritida se zvracením, vodnatý průjem	gastroenteritida, nauzea, horečka	mírnější gastroenteritida, subfebrilie, bolesti hlavy
průjem	~ 87%	88 %	93 %	100 % (u AdV infekcí s gastroenteritidou)	73%
zvracení	25–100 %	49 %	50 % (80 % nauzea)	56 %	46 %
horečka	2–47 %	23 %	35 %	60 %	46 %
bolest břicha	4–76 %	?	90 %	5 %	36 %
délka obtíží	1–3 dny	5–7 dní	3–7 dní	1–2 týdny	5 dní
další možné komplikace	neurologické (encefalopatie, křeče), nekrotizující enterokolitida, exacerbace Crohnovy nemoci	–	neurologické (2–5 %) (benigní křeče až fatální encefalitida)	hepatitida, pankreatitida	neurologické, včetně encefalitidy
sezonalita	říjen–březen	listopad–březen	prosinec–květen	není známa	říjen–únor
dopady	18 % všech průjmových onemocnění, 212 000 úmrtí ve světě/rok	–	215 000 úmrtí ve světě /rok; 5 úmrtí / 100 000 dětí < 5 let	~ 2 % průjmových onemocnění u dětí	–
možnost prevence	–	–	živá p. o. vakcína	–	–

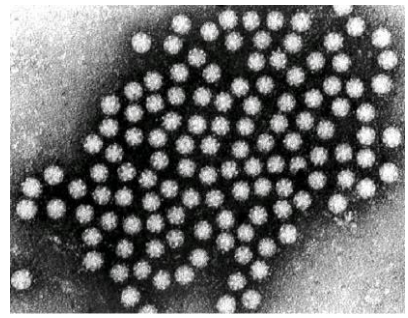
MAJOR ARTICLE

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]

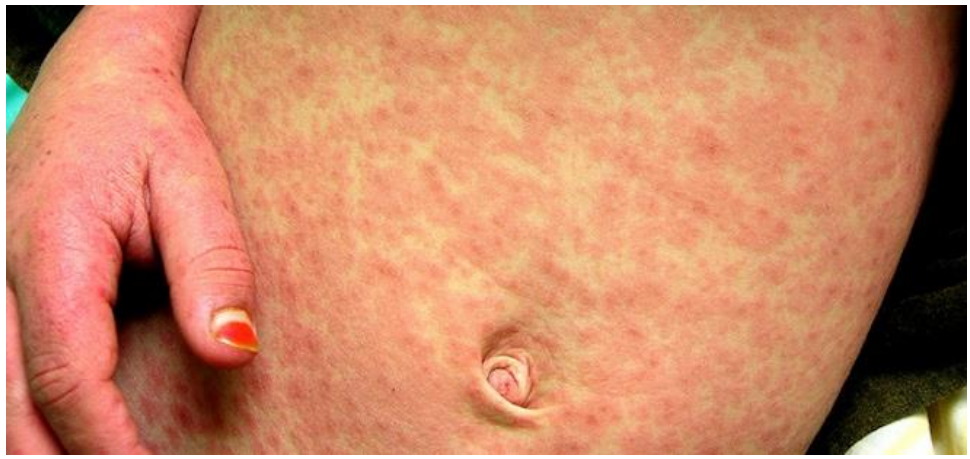
[1]Virology Department, Great Ormond Street Hospital for Children NHS Foundation Trust, [2]NIHR Biomedical Research Centre, Great Ormond Street Hospital for Children NHS Foundation Trust and University College London, [3]UCL Genetics Institute, University College London, [4]Virology Department, Barts 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/lsailflab/pictures/astro%20virus%204x4.jpg

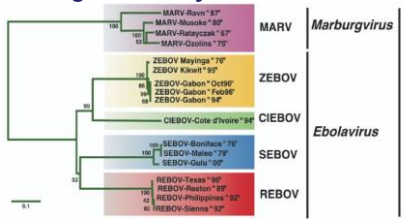
Exanthema pathogens
- were at lectures

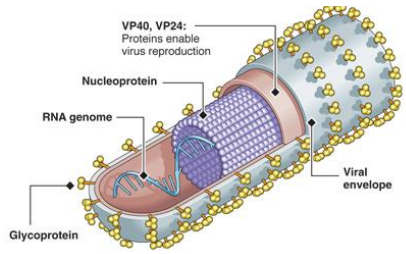


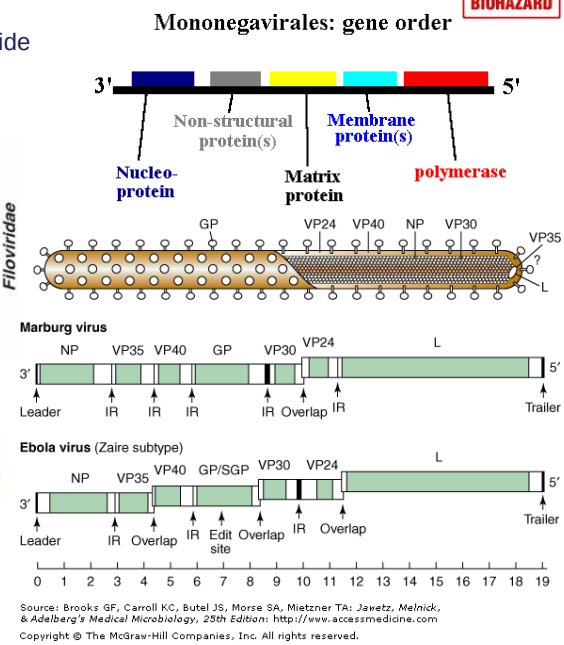
BioSafety Level 4

Filoviridae

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

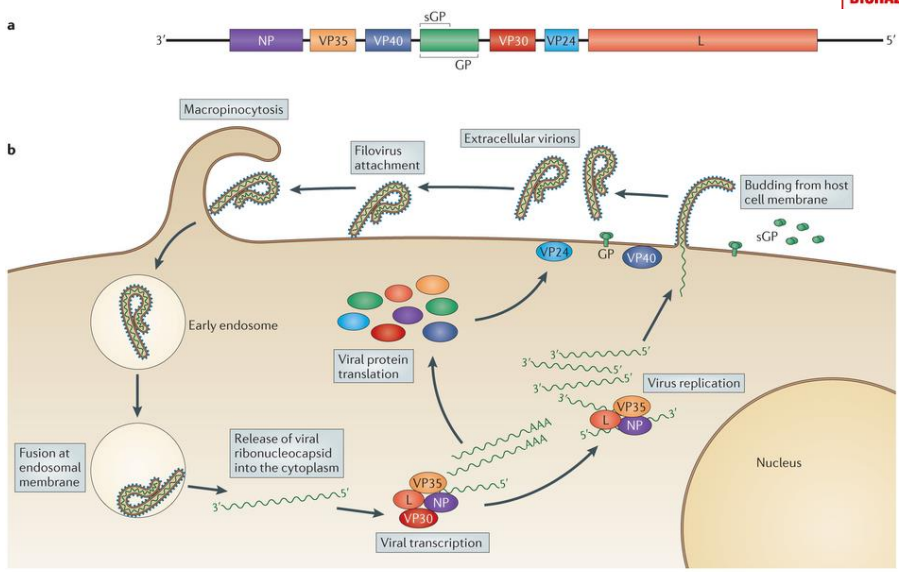






BioSafety Level 4

Filoviridae

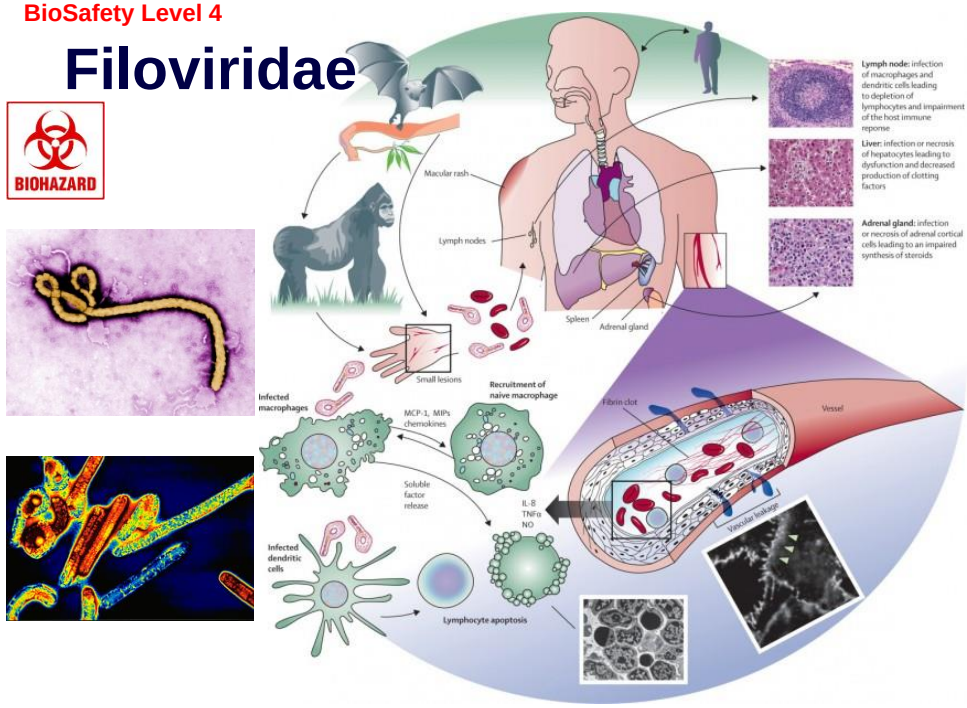


Nature Reviews | Microbiology

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

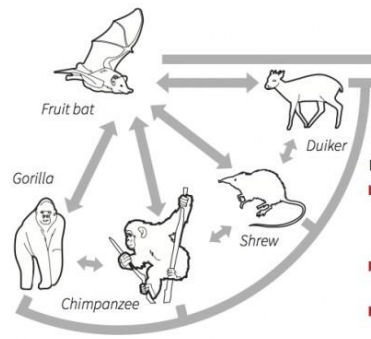
In Africa, particular species of fruit bats are considered possible natural hosts for Ebola virus.

TRANSMISSION

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

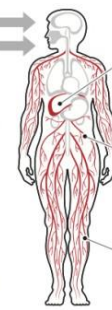
DAMAGE

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

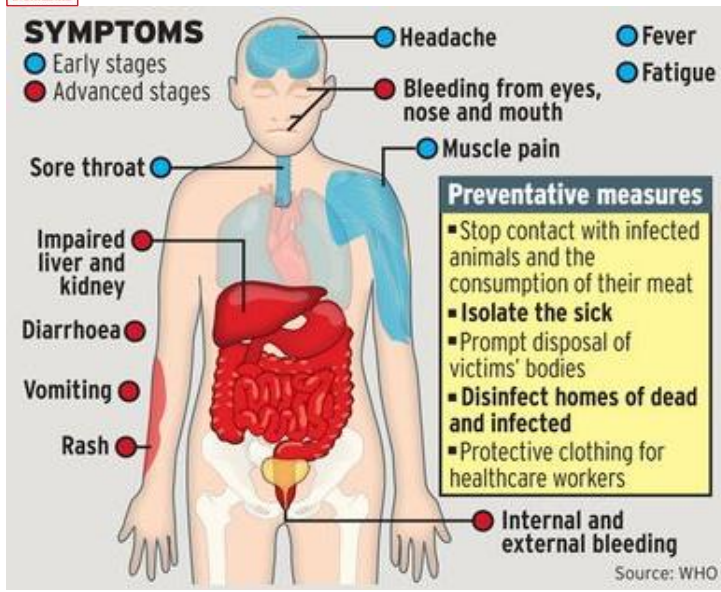
Note: List of animals is not exhaustive.

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:

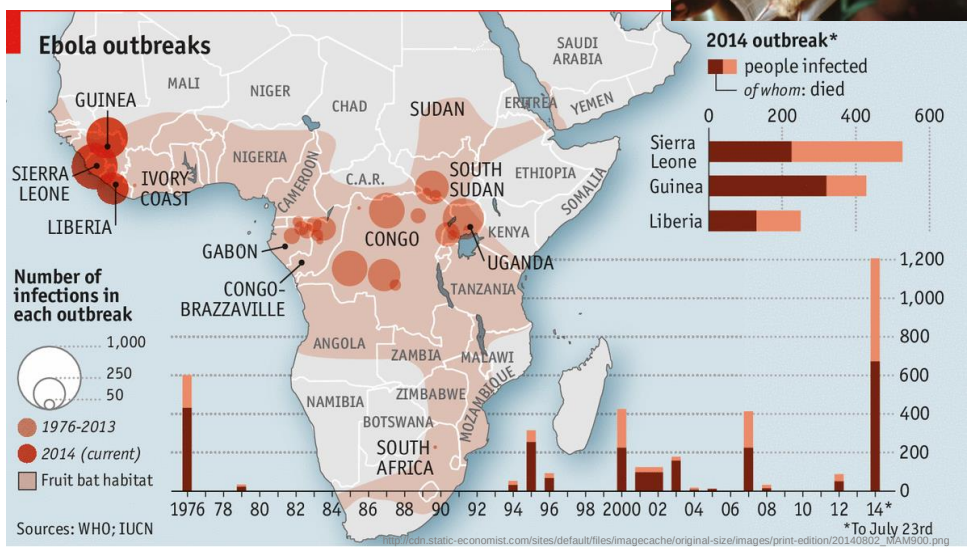
study only

ZMapp – 3 Ab

at the moment
not available!!!!

BioSafety Level 4

Filoviridae



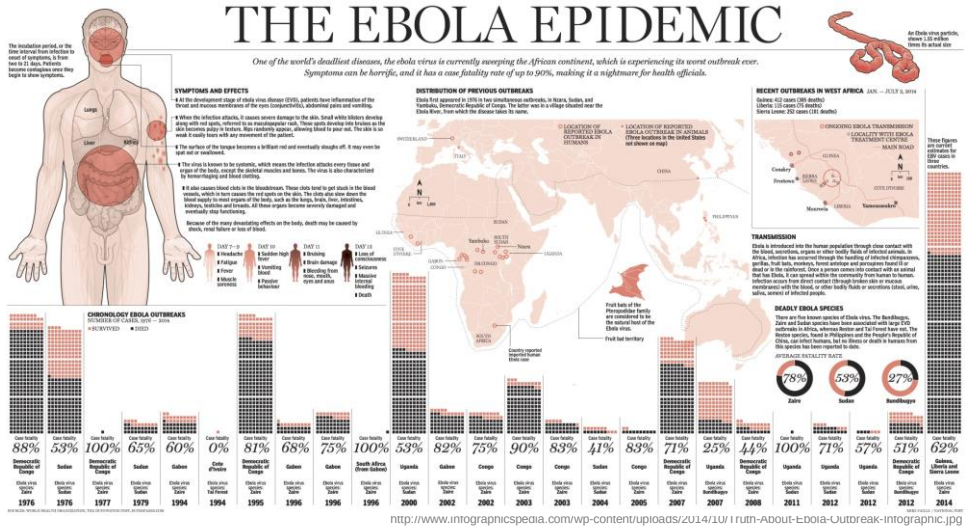
BioSafety Level 4

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

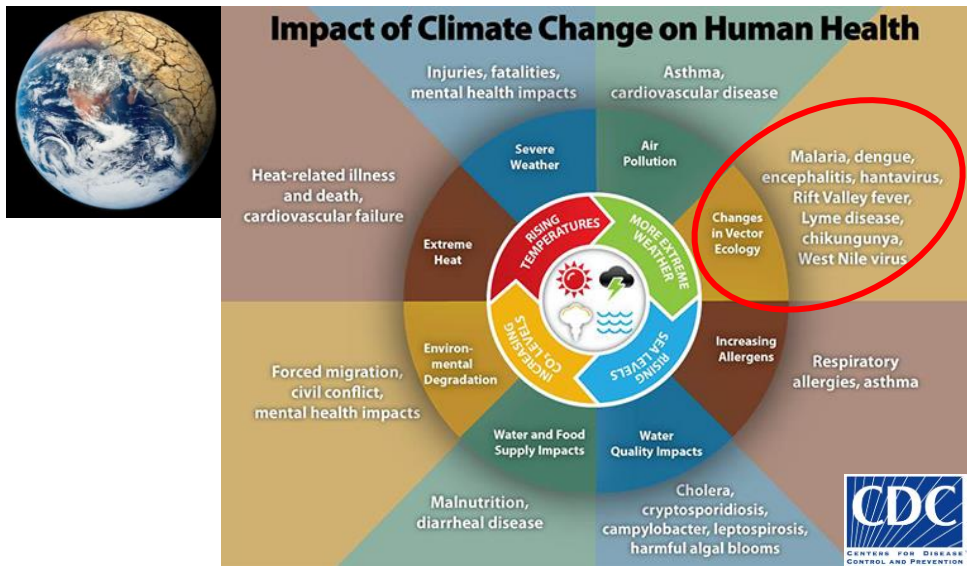
BioSafety Level 4

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

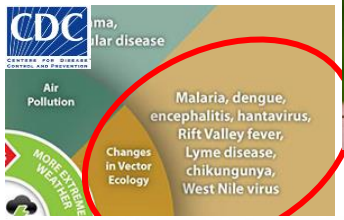
Why we observe emerging viruses?

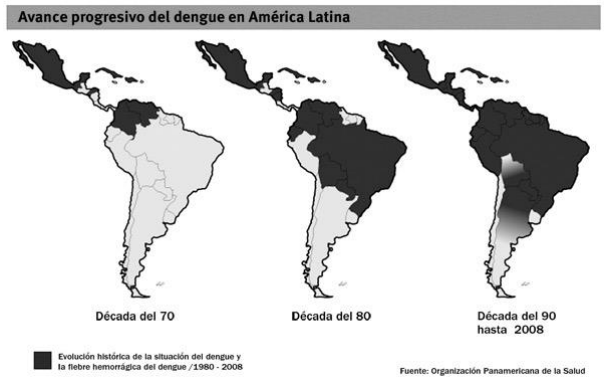
1. Climate changes



Why we observe emerging viruses?

1. Climate changes



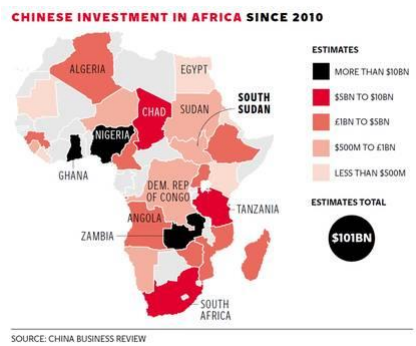


Barman Forest virus, BFV
Eastern equine encephalitis virus, EEEV
Middelburg virus, MIDV
Ndumu virus, NDUV
Bebaru virus, BEBV[3]
Chikungunya virus, CHIKV[3]
Mayaro virus (–Una virus), MAYV–UNAV[3]
O'nyong'nyong virus, ONNV[3]
Ross River Virus, RRV[3]
Semliki forest virus, SFV[3]
Venezuelan Equine Encephalitis 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

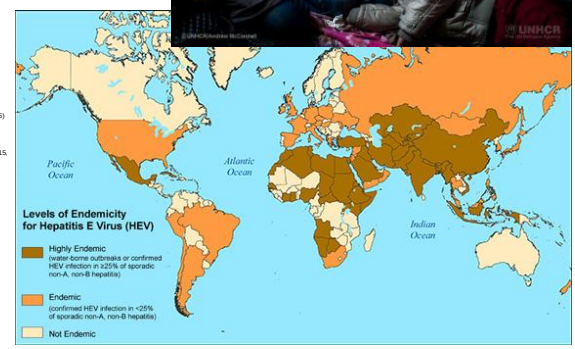
World Health Organization

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)



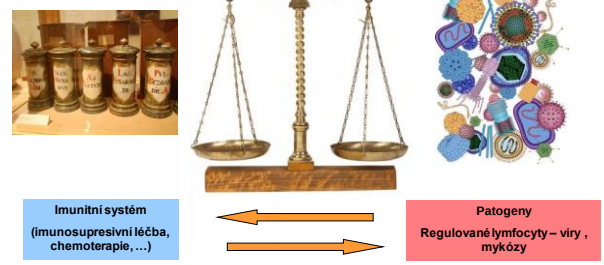
Why we observe emerging viruses?

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…) …

Rovnováha u imunosuprimovaného pacienta



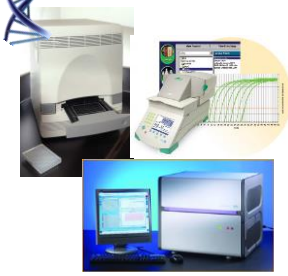
Steroids more then > 2 mg/kg – highly lymphotoxic (used e.g. in NHL, ALL…)

Why we observe emerging viruses?

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

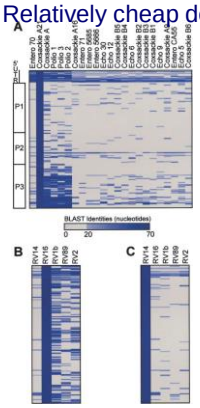
Molecular-biological techniques

Direct and relative cheap detection based on NA



Reasonable time for detection of the agens

Relatively cheap detection of new viruses



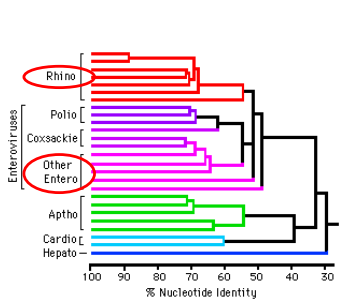
CHIP technique was used in new WUV and KIV polyomavirus detection in 2007, which were detected in respiratory tract.

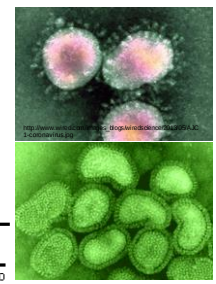
Why we observe emerging viruses?

4. Better detection – treatment – resistance

Influenza virus 1933
Coxsackive virus 1948
Echovirus 1951
Adenovirus 1953
HRV 1953
HRSV 1956
HPIV 1956
HCoV-229E 1966
HCoV-OC43 1967

HMPV 2001
SARS-CoV 2003
HCoV-NL63 2004
HCoV-HKU1 2005
HBoV 2005
HRV-C 2006
WUPyV 2007
KIPyV 2007
MCV 2008
HPyV6 2010
HPyV7 2010
HPyV8-TSV 2010
HPyV9 2011
HPyV10 2012
HCoV MERS 2012

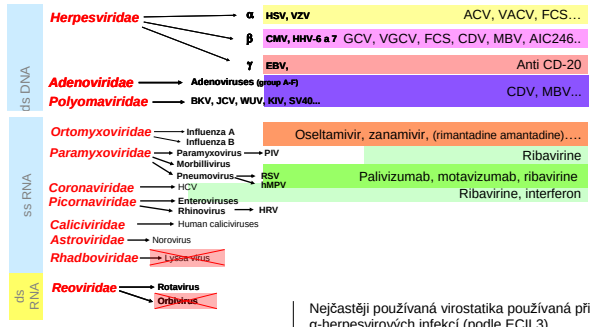




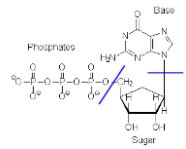
Why to act?

4. Better detction – <u>treatment</u> – resistance

Virostatic therapy

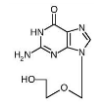


brincidofovir (CMX001)
famciclovir
penciclovir
boceprevir
telaprevir
sofosbuvir
simeprevir
ledipasvir
….. and more

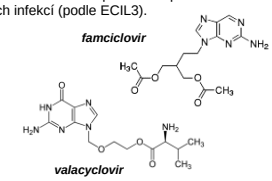


Guanidine trifosfát (GTP)

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



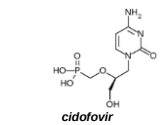
acyclovir



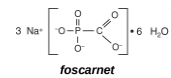
famciclovir

valacyclovir

Léky první volby.



cidofovir



foscarnet

Léky používané při HSV rezistentní k léčbě.