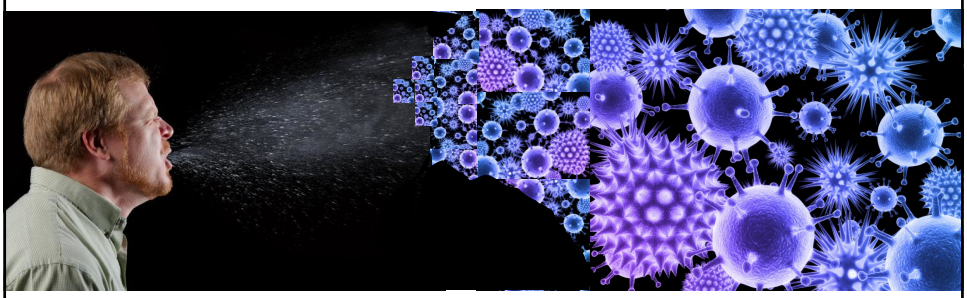
# Respiratory viruses




Petr Hubáček

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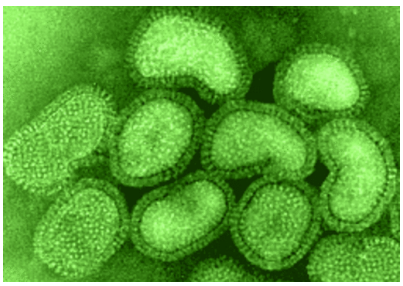
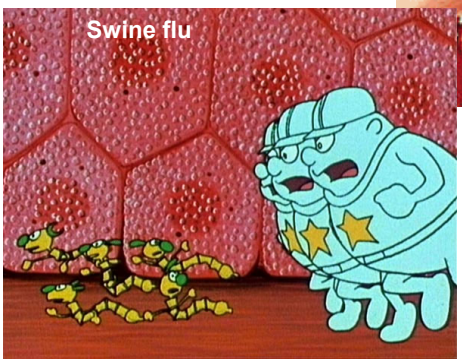
2nd Medical Faculty of Charles University and Motol University Hospital

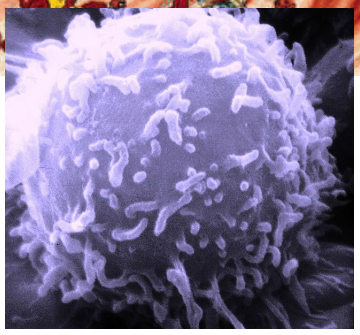

FN MOTOL

HSCT UNIT - PEDIATRICS PRAGUE CZECH REPUBLIC

# Life is fight





# RNA viruses

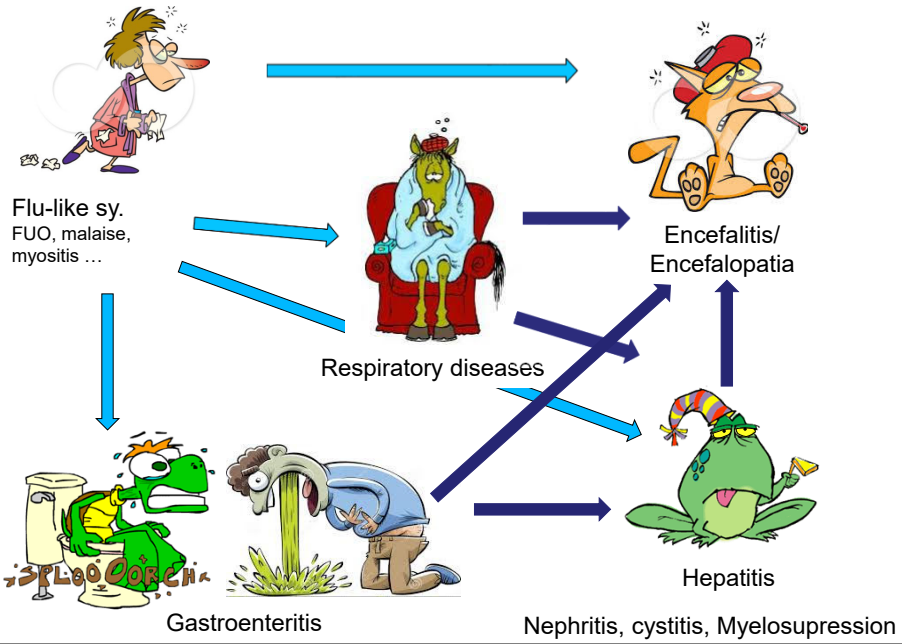
ss RNA

- ***Ortomyxoviridae*** → **Influenza A**, **Influenza B**
- ***Paramyxoviridae*** → **Paramyxovirus** → **PIV**; **Morbillivirus**; **Pneumovirus** → **RSV**, **hMPV**
- ***Coronaviridae*** → HCoV, SARS-CoV2
- ***Picornaviridae*** → **Enteroviruses**; **Rhinovirus** → **HRV**
- ***Caliciviridae*** → Human caliciviruses
- ***Astroviridae*** → Astrovirus
- ***Rhadboviridae*** → Lyssa virus
- ***Flaviviridae*** → HCV…

ds RNA

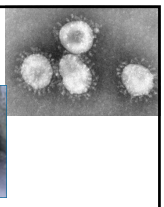
- ***Reoviridae*** → **Rotavirus**; **Orbivirus**

# Clinical consequences

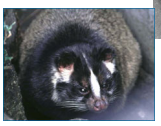


# Respiratory viruses

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

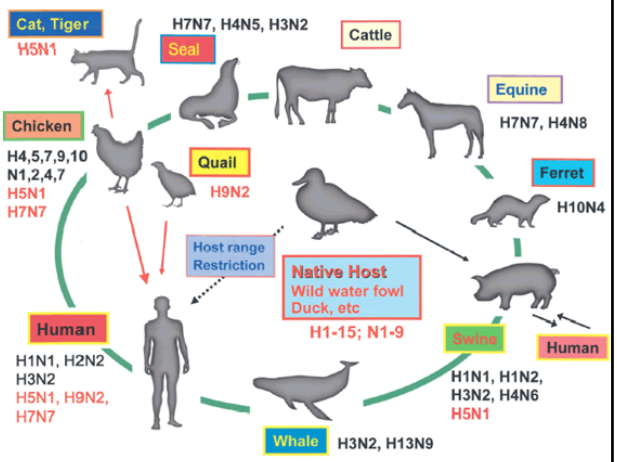


Bats – Horseshoe bat,…



Civet

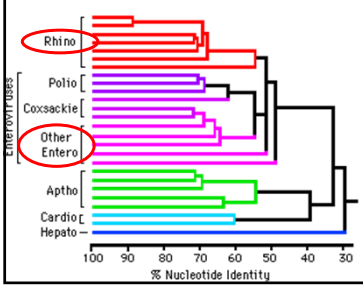
**Leads to high Frequence of recombination of new life-threatening infections**

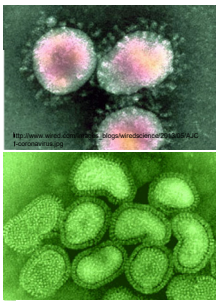


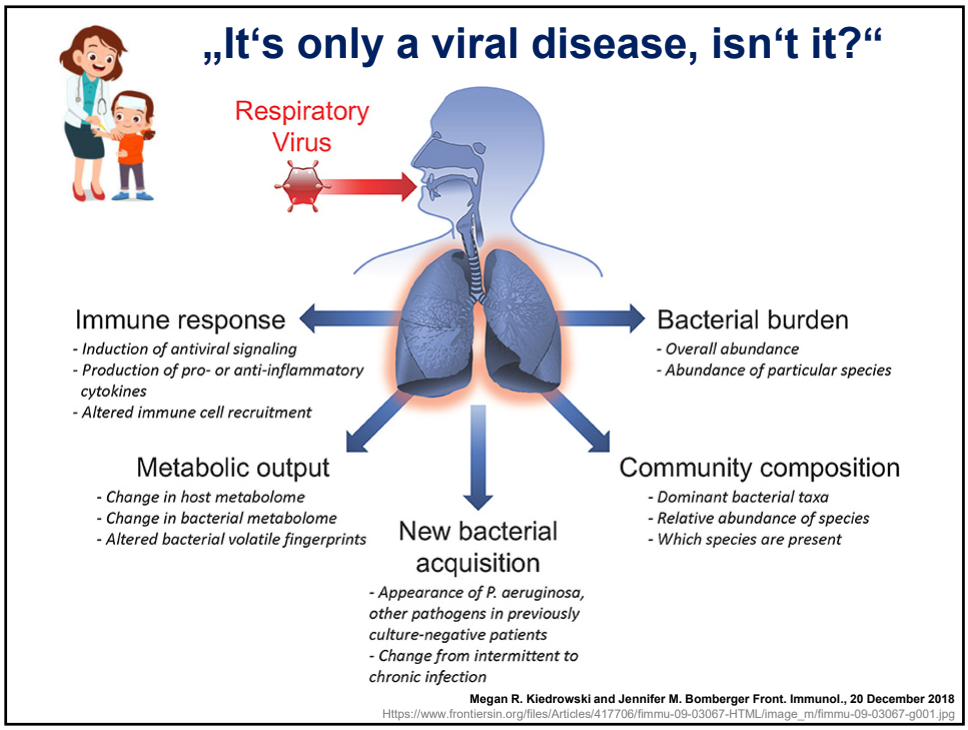

# History of viral respiratory infections


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

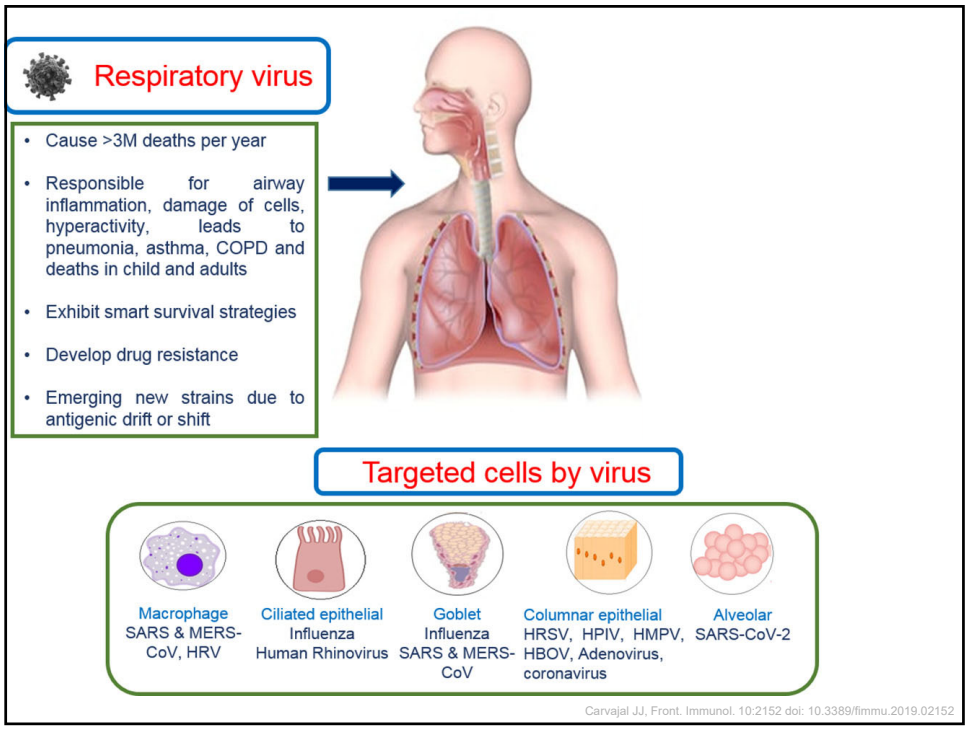
HMPV 2001
SARS-CoV 2003
HCoV-NL63 2004
HCoV-HKU1 2005
HBoV 2005
**HRV-C 2006**
**WUPyV 2007**
**KIPyV 2007**
MCV 2008
HPyV6 2010
HPyV7 2010
HPyV8-TSV 2010
HPyV9 2011
HPyV10 2012
HCoV MERS 2012






Megan R. Kiedrowski and Jennifer M. Bomberger Front. Immunol., 20 December 2018
Https://www.frontiersin.org/files/Articles/417706/fimmu-09-03067-HTML/image_m/fimmu-09-03067-g001.jpg




Carvajal JJ. Front. Immunol. 10:2152 doi: 10.3389/fimmu.2019.02152

# So - how to diagnose

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

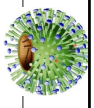
  AND
  - A clinician's judgement that the illness is due to an infection

**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)

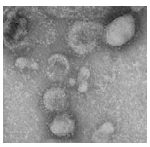


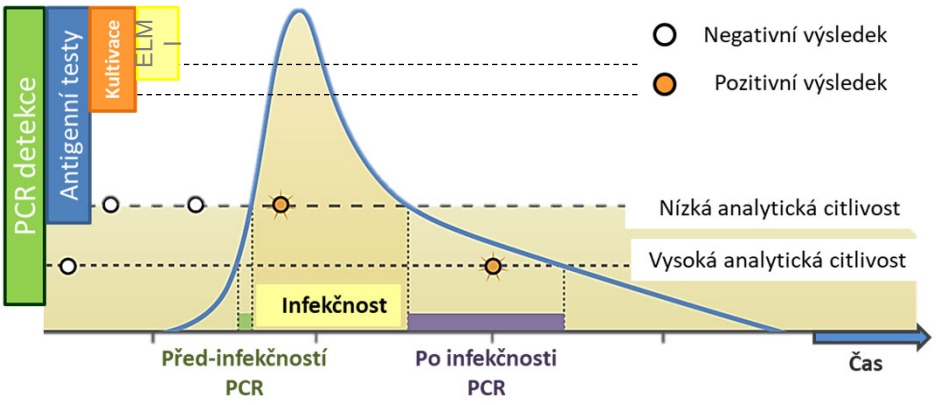
**Case Classification**

- **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

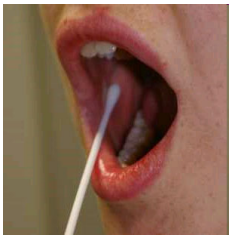
# Diagnostic windows

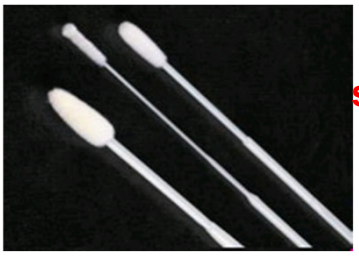




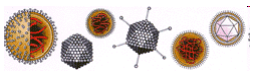

Upraveno dle Mina et al. NEJM2020

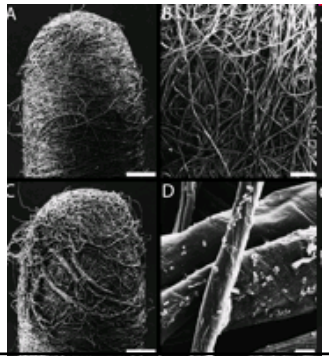
# Type of swabs

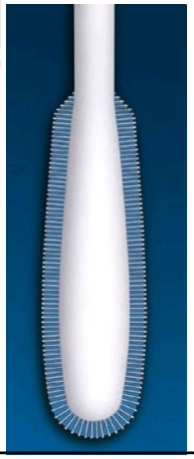




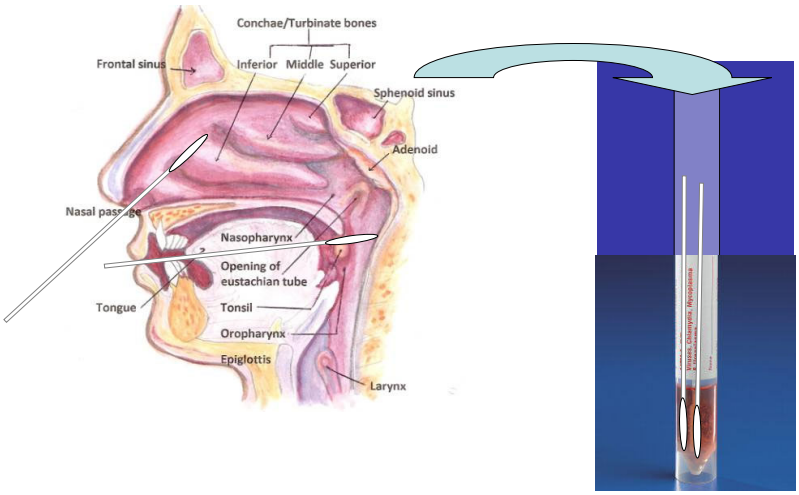
Nylon swabs







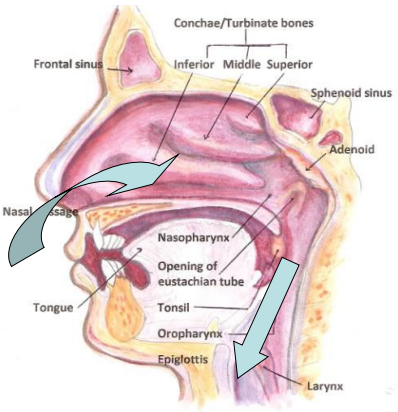
# Proper sampling of biological material



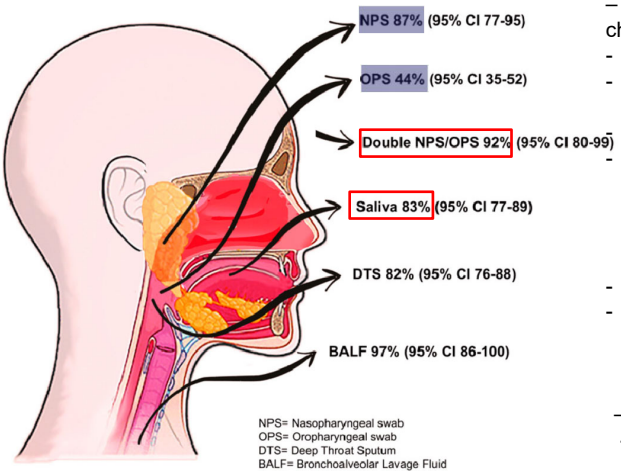

# Proper sampling of biological material

First proliferation on mucous of URT – at the locus of infection entrance.

| *Virus* | *Transmission from URT to LRT* | *Mortality* |
|---|---|---|
| **RSV** | 20-68% | 17-70% |
| **PIV** | 13-37% | 10-30% |
| **HRhV** | <10% | <10% |



# What‘s the sensitivity according to the biological material?




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

– screened 1598 studies, 33 chosen (26 quantitative)

- 1. published/accepted
- 2. patients dg or screened for COVID-19
- 3. RT-PCR
- 4. studies aimed for using of saliva, sputum, oral liquids/secrets, pharyngeal secretes for comparisson of diagbostical method
- 5. at least 2 samples
- 6. performer on proven COVID-19 patients with pair samples

**Urine**

– Ag detection -74% (Diao et al. 2020)

- amount ± $10^2$–$10^5$/ml vs. ± $10^5$–$10^{11}$/ml in NPS

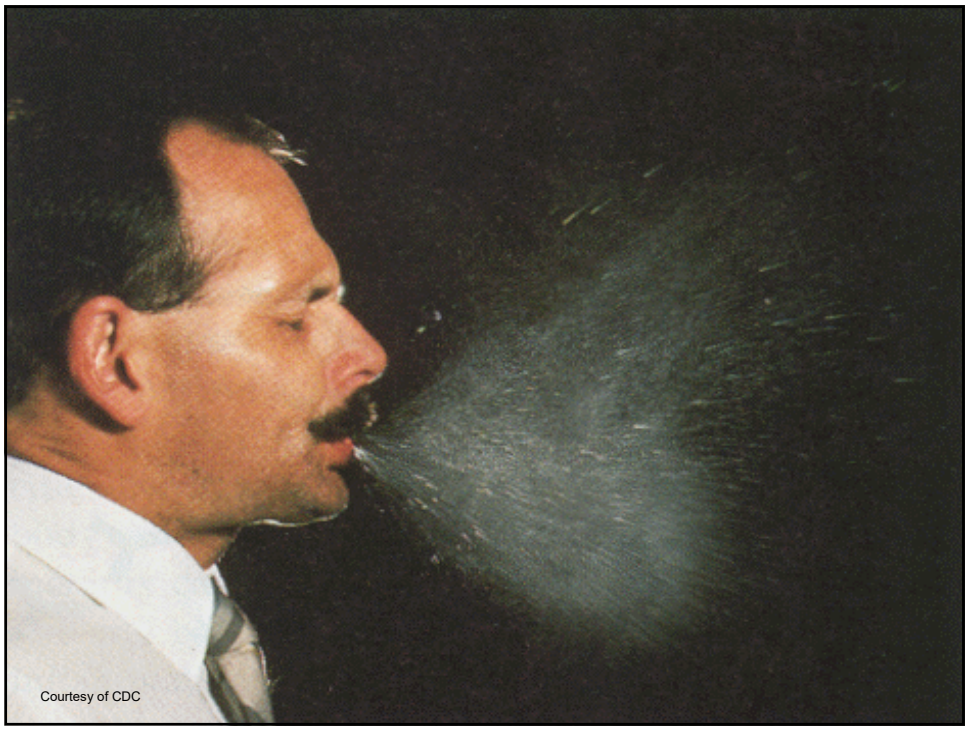
(D.L. Jones et al. Scie Total Environment 2020)

- virus in infectious

(Sun j. et al. Emerg. Microbes Infect. 2020)

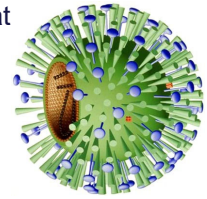
# Diagnosis

- Virus cultivation
  - Performed on tissue cultures, or chicken embryos
- Rapid tests (especially antigen detection)
- **PCR**
- Preliminary dg. – clinical picture and epidemics
- Serological detection

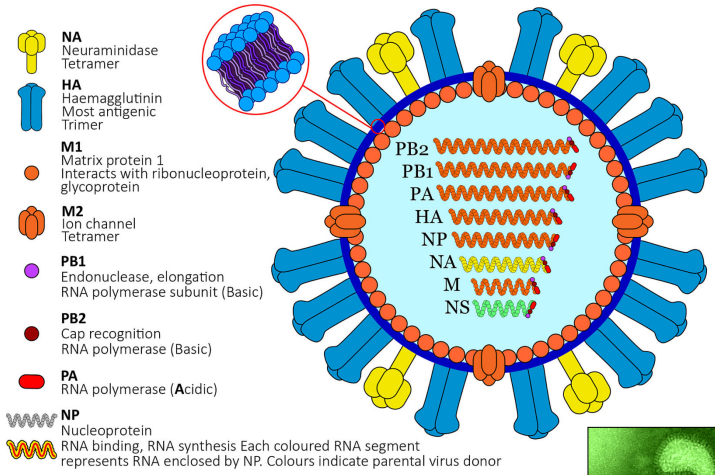



# What is influenza?

- An acute respiratory illness resulting from infection with an influenza virus (Orthomyxoviruses)
- Highly infectious and can spread rapidly from person to person
- Some strains cause more severe illness than others
- Highly infectious viral illness
- 412 BC - first mentioned by Hippocrates
- 1580 - first pandemic described
- 1580-1900 - 28 pandemics
- Name influenza came from italian „influentia“ – influence. Name was used in Italy from 16th century, because they believed that health is influenced by stars.
- Virus first isolated in 1933



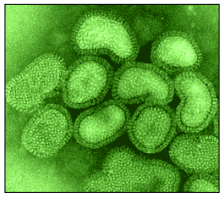
# ORTHOMYXOVIRUSES




typ A, B, C : NP, M1 protein

sub-typy: HA nebo NA protein

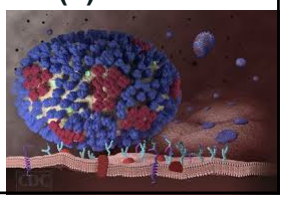
https://figshare.com/articles/Influenza_virus/6817112



http://www.uct.ac.za/depts/mmi/stannard/fluvirus.html

# Types of influenza viruses

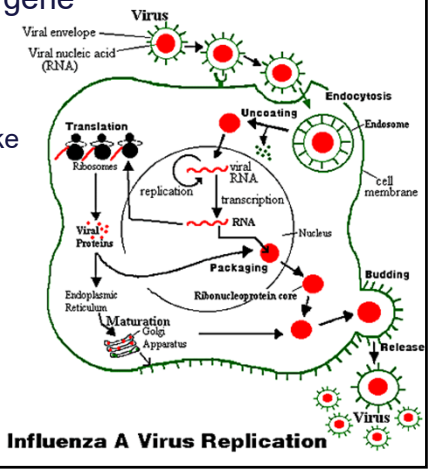
| | TYPE A | TYPE B | TYPE C |
|---|---|---|---|
| severity of illness | ++++ | ++ | + |
| animal reservoir | yes | no | no |
| human pandemics | yes | no | no |
| human epidemics | yes | yes | no (sporadic) |
| antigenic changes | shift, drift | drift | drift |
| segmented genome | yes | yes | yes |
| amantadine, rimantidine | sensitive | no effect | no effect |
| zanamivir | sensitive | sensitive | |
| surface glycoproteins | 2 | 2 | (1) |



# 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

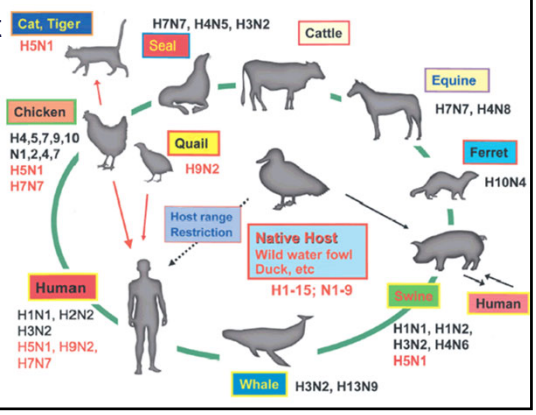


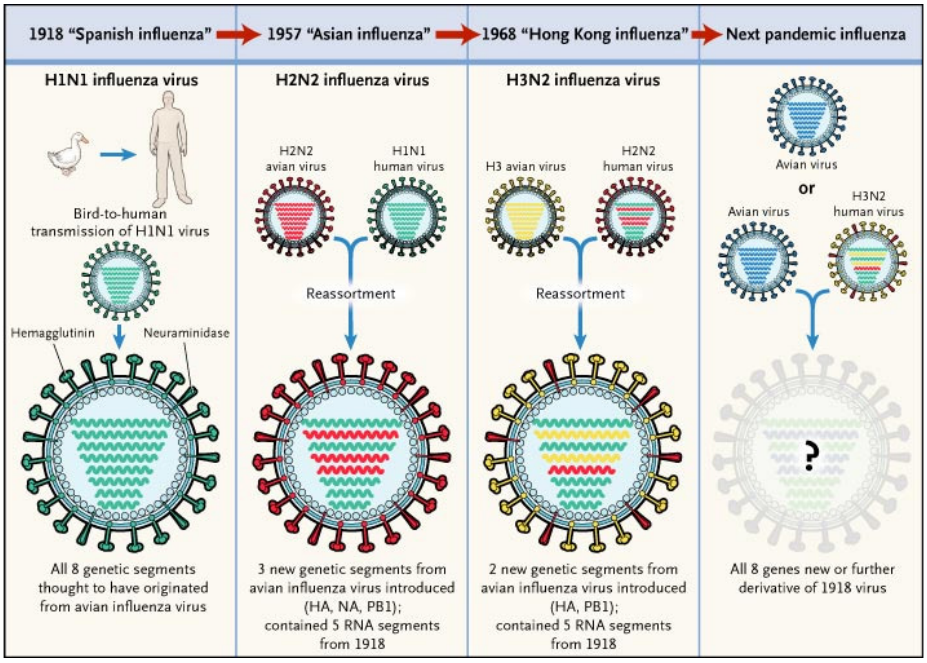
Influenza A Virus Replication

# 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

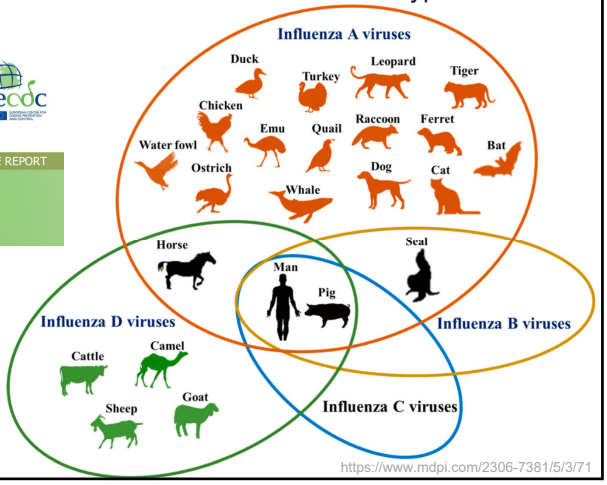





https://www.nejm.org/doi/full/10.1056/NEJMp058281

# How many HA and NA?

- 13 types HA
- 9 types NA – all circulating in birds
- Pigs – might be infected both with human and bird's types


https://www.mdpi.com/2306-7381/5/3/71

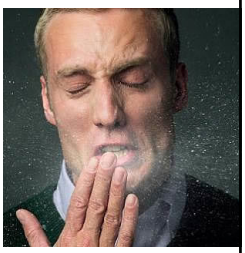
# Burden of Influenza

- 10% to 20% of the population is infected with influenza virus each year
- Average of more than 200,000 excess hospitalizations each year
  - Persons 65 and older and 2 years and younger at highest risk
- Average of 36,000 deaths each year
  - Persons 65 and older at highest risk of death

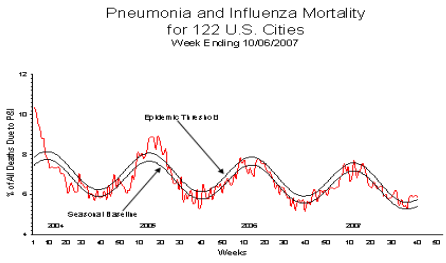
**Influenza Associated Pulmonary and Circulatory Deaths, 1998**

| Age Group (yrs) | Rate (per 100,000) | |
|---|---|---|
| 0 – 49 | 0.4 – 0.6 | |
| 50 – 64 | 7.5 | |
| ≥65 | 98.3 | (>90% mortality rate) |

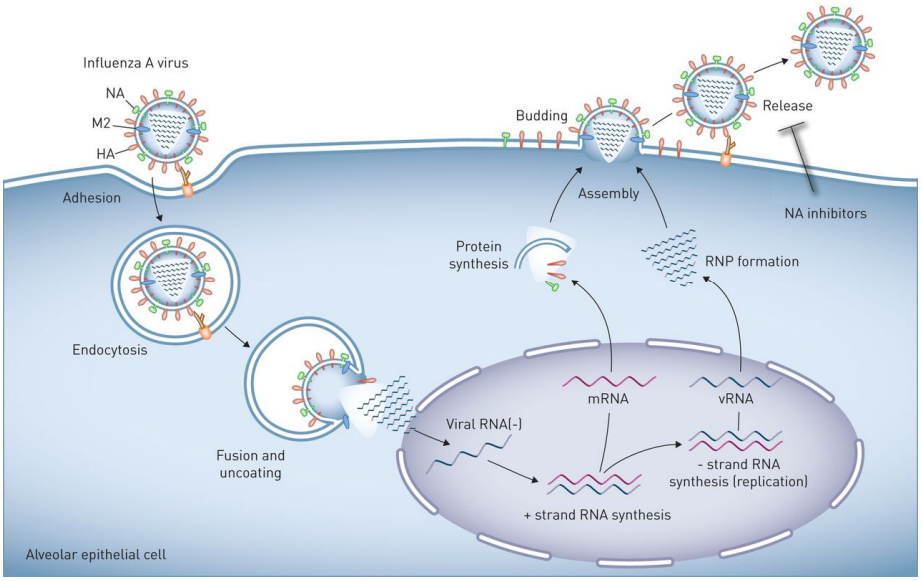
# Influenza Epidemiology



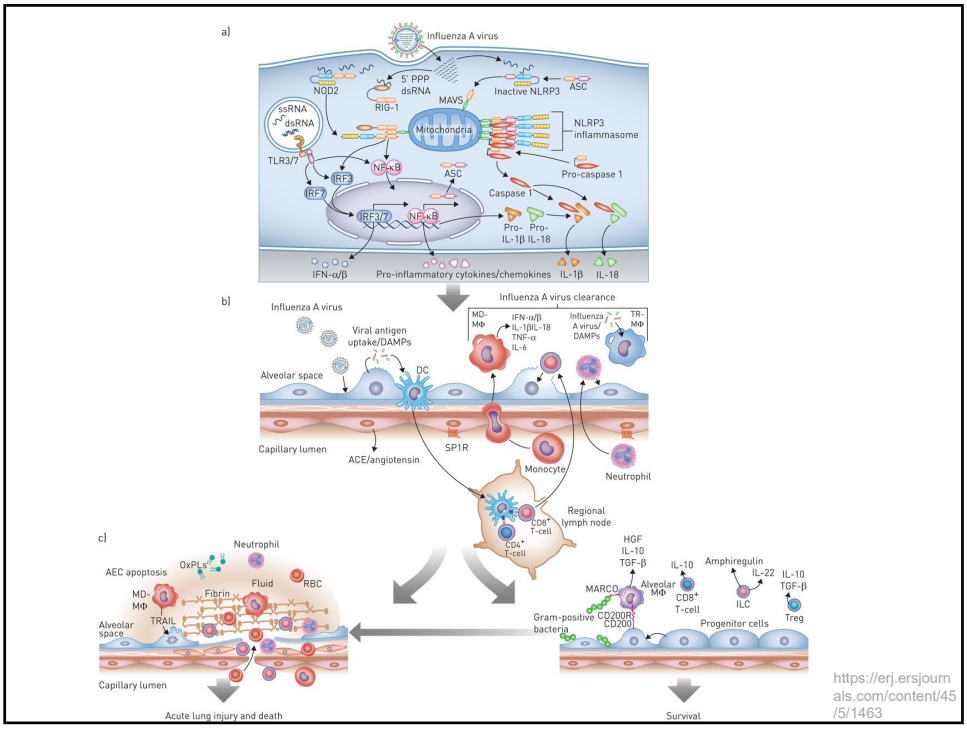
- Reservoir: Human, animals (type A only)
- Transmission: - inhaling respiratory aerosols containing the virus, produced when infected person talks, coughs, or sneezes
  100,000 - 1,000,000 virions/droplet
  - » touching an infected person or an item contaminated with the virus and then touching your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

EUROPEAN RESPIRATORY journal
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

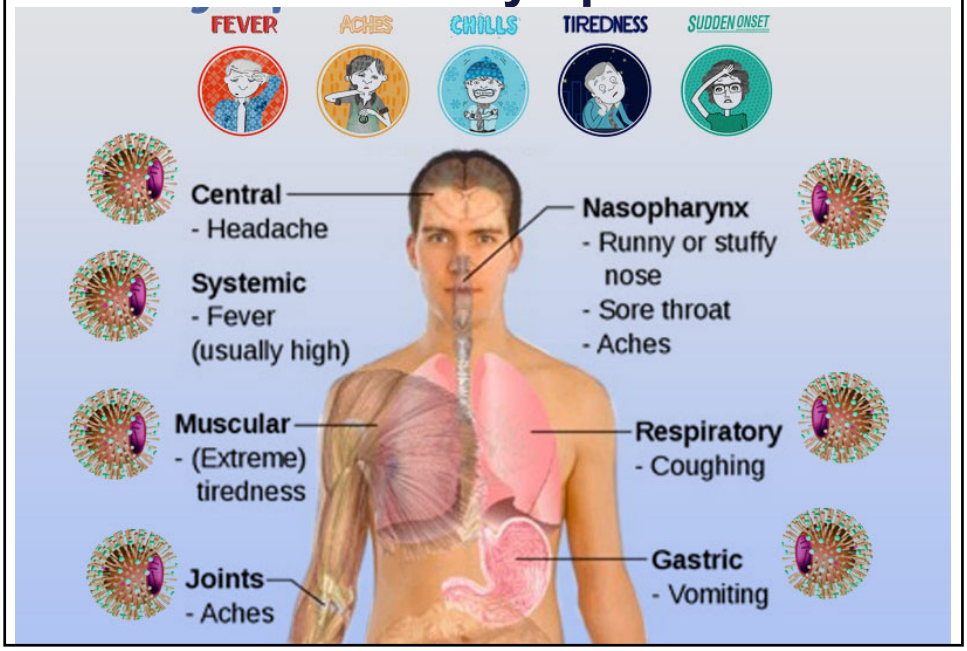


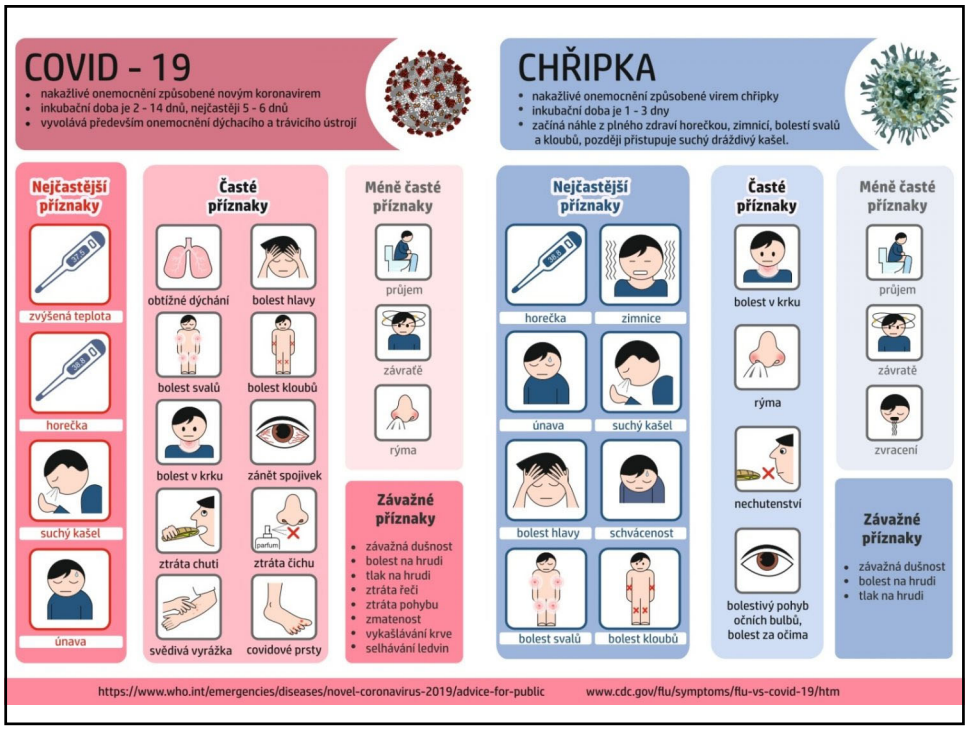

https://erj.ersjournals.com/content/45/5/1463




https://erj.ersjournals.com/content/45/5/1463

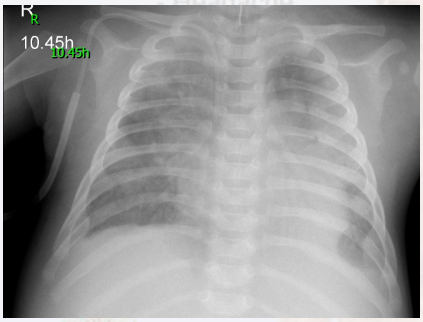
# Influenza symptoms

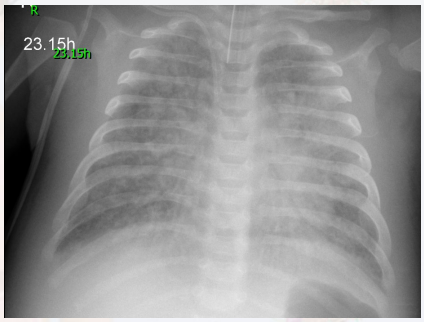


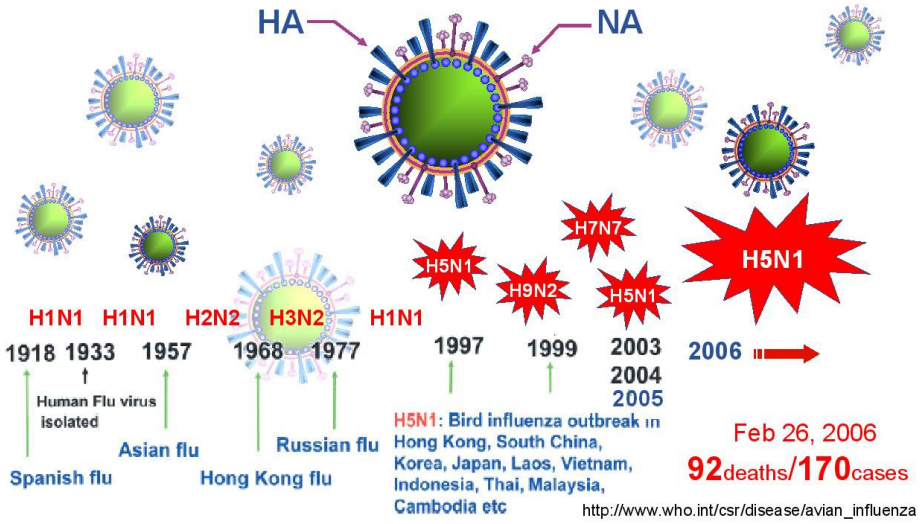
# Influenza symptoms

- **Severity**
  - Very young (neonates) or old patients
  - Immunocompromised patient
  - Lung or heart complications




# Influenza A viruses



# Pandemic influenza in the 20th Century

**1918 "Spanish Flu"** 20-40 million deaths → H1N1

**1957 "Asian Flu"** 1 million deaths → H2N2

**1968 "Hong Kong Flu"** 1 million deaths → H3N2

1920 1940 1960 1980 2000

# Influenza in „numbers"

**1500** Passing away due to influenza: approx. such number of patients in average decease every year in CR for influenza Zdroj: szu.cz

**290 000 - 650 000** humans decease every year due to influenza virus around the world Zdroj: WHO

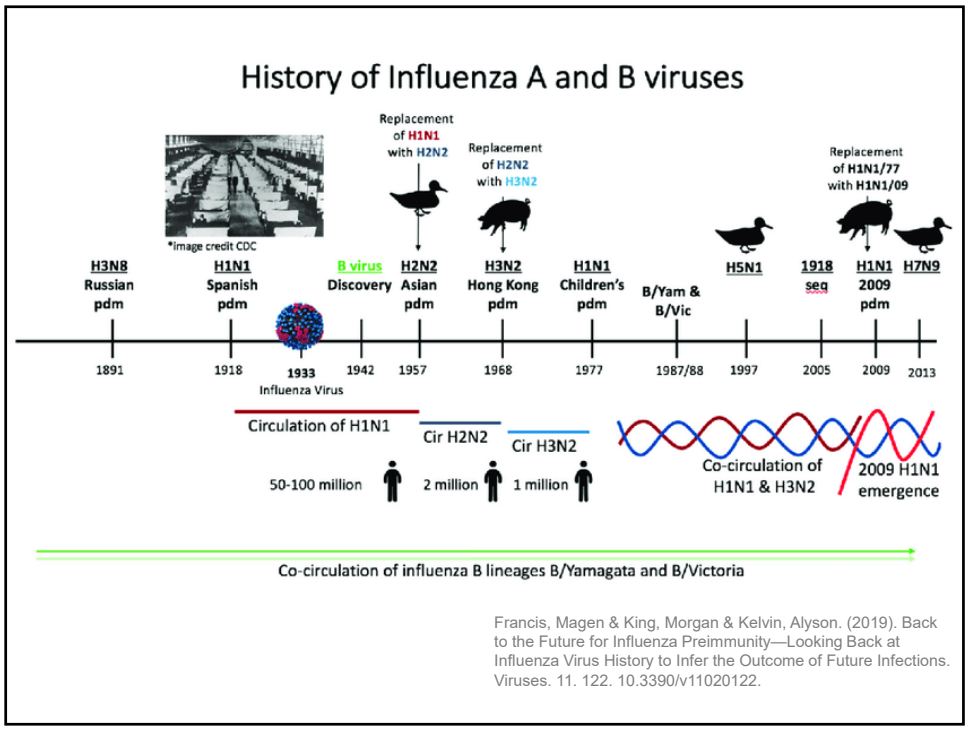
**25,4%** No. of vaccinated people in CR older 65 yrs. Zdroj: oecd.org

**6%** Jno. Of vaccinated people in general population (low in comparisson to most of the other countries)

## Recommendation of WHO:

**30%** No. of vaccinated in general population

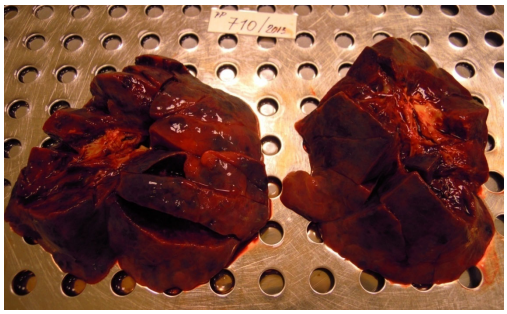
**75%** Vaccination in risk groups (persons over 65 yrs. Of age, with risk factor).




Francis, Magen & King, Morgan & Kelvin, Alyson. (2019). Back to the Future for Influenza Preimmunity—Looking Back at Influenza Virus History to Infer the Outcome of Future Infections. Viruses. 11. 122. 10.3390/v11020122.

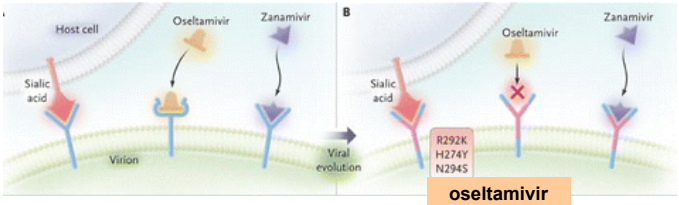
Patient 1

# Influenza A virus



**Macroscopic picture of influenza pneumonia.**

**1st proven oseltamivir resistance in the Czech Republic.**




**Resistance developed after 4 weeks of therapy.**


# Complications

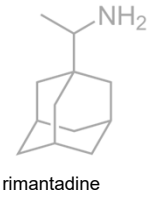
- **Pulmonary**
  - CROUP (YOUNG CHILDREN)
  - PRIMARY INFLUENZA VIRUS PNEUMONIA
  - ***SECONDARY BACTERIAL INFECTION***
    - *Streptococcus pneumoniae*
    - *Staphlyococcus aureus*
    - *Hemophilus influenzae*
- **Non-Pulmonary**
  - myositis (rare, > in children, > with type B)
  - ***cardiac complications***
  - recent studies report encephalopathy
    - studies of patients <21 yrs in Michigan - 8 cases seen last season
  - liver and CNS
    - Reye syndrome
  - peripheral nervous system
    - Guillian-Barré syndrome

38

# Treatment (prevention) - drugs

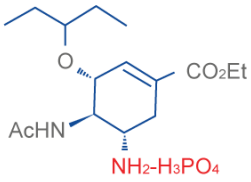
All virostatics have to be started immediatelly

- rimantadine (M2)
  - Type A only
- amantadine (M2)
  - Type A only
- oseltamivir (NA)
  - Type A and B
- zanamivir (NA)
  - Type A and B
- peramivir (NA)
  - Type A and B
- favipiravir (analogue of guanosine and adenine)

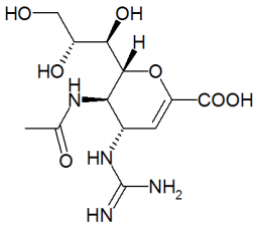



rimantadine

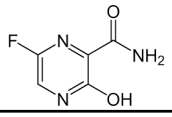

amantadine

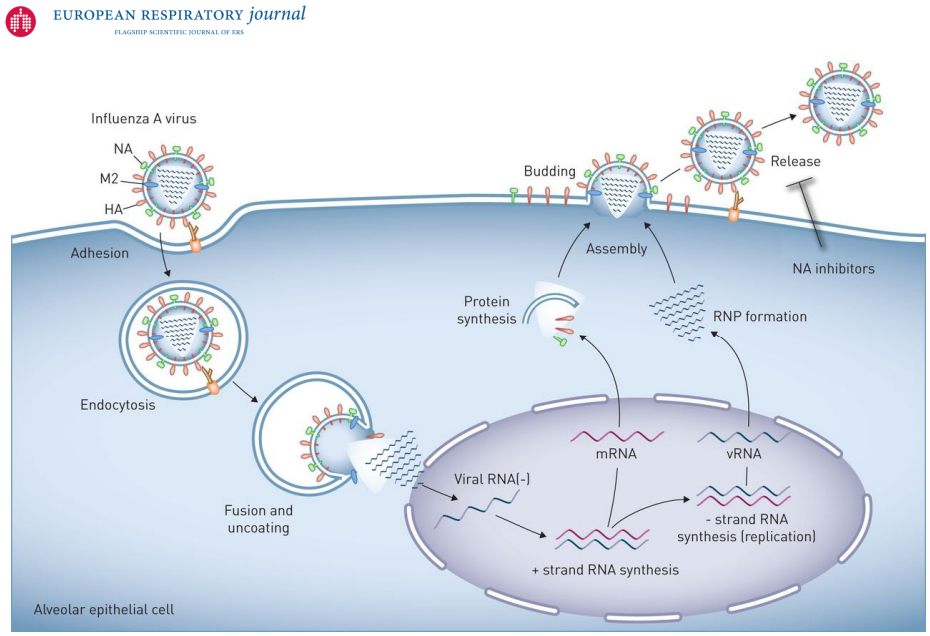



Oseltamivir Phosphate (Tamiflu)




zanamivir

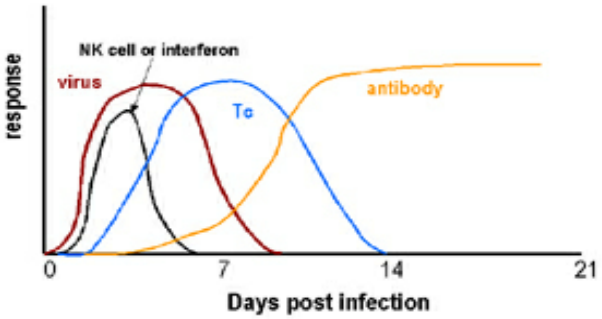



https://erj.ersjournals.com/content/45/5/1463

# Recovery

- **INTERFERON – side effects include**
  FEVER, MYALGIA, FATIGUE, MALAISE
- **CELL-MEDIATED IMMUNE RESPONSE**




Typical response to an acute virus infection

- **TISSUE REPAIR**
  can take some time

# Protection against re-infection


- IgG and IgA
  - IgG less efficient but lasts longer
- antibodies to both HA and NA important
  - antibody to HA more important (can neutralize)

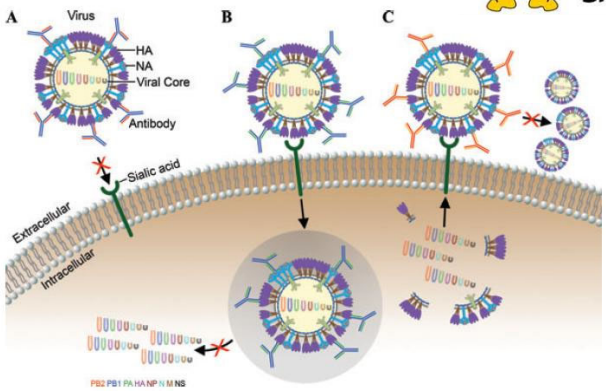
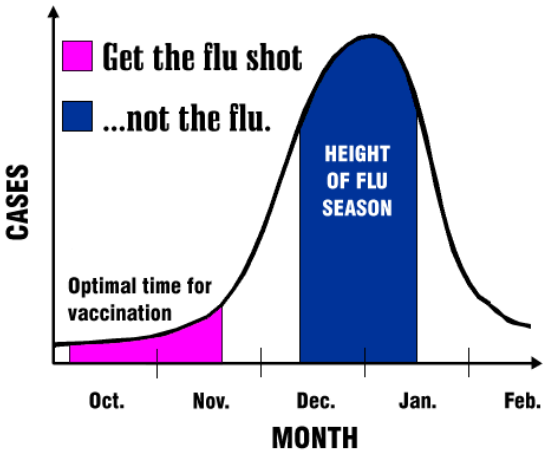



Figure 1. Mechanisms of antibody-mediated neutralization of the influenza virus. (A) Antibodies can block influenza HA1 glycoprotein binding to sialic acid residues of receptor proteins on host cells. (B) Antibodies specific to the HA2 glycoprotein of the virus can inhibit its low-pH triggered fusion activity in the endosome at the postbinding/prefusion stage, which inhibits replication of the virus. (C) Antibodies to surface neuraminidase can prevent the release of influenza virions from the infected cell surface.

# Vaccination

- Recombinant, often tetravalent
- A – H1 and H3
- B – Yamagata and Viktoria

- Intranasal vaccine




CDC

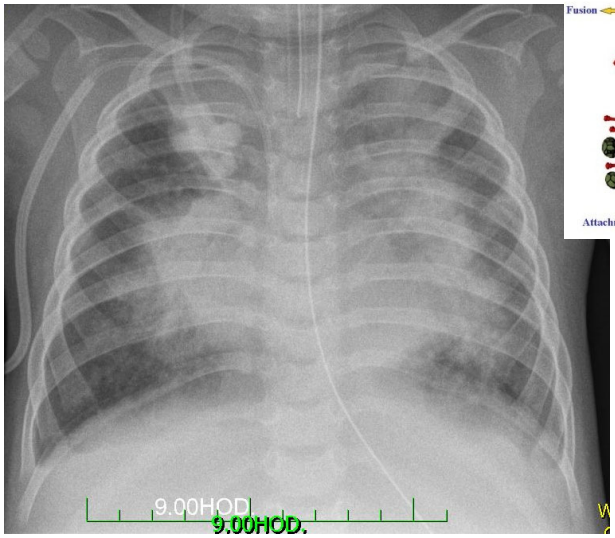
Courtesy of CDC

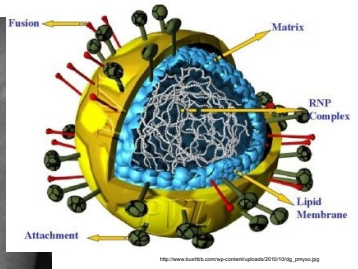
# And what about Paramyxoviruses

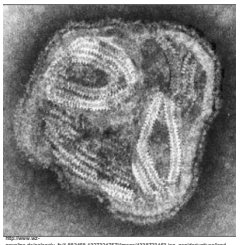
Paramyxoviridae

# Respiratory-syntitial virus

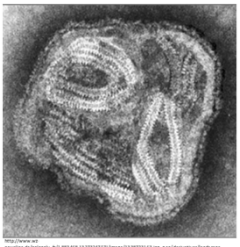
**RSV** (boy treated for AML)



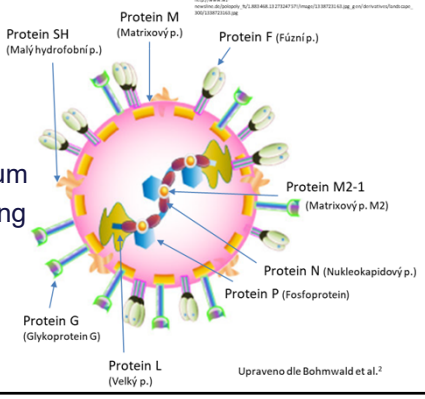



# Respiratory syntial virus



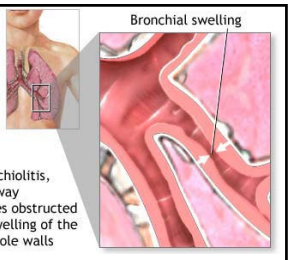
- Enveloped negative ss RNA virus
- *Pneumoviridae,* genus *Orthopneumovirus*
- 15 kb – 10 genes, 11 proteins
- 9 structural
  - 3 surface (**F, G**, SH)
  - 5 internal (L, P, N, M, M2.1, M2.2)
- A (10 genotypes) – B (13 genotypes)




- Spreading by droplets
- Proliferation in respirátory epithelium
- Frequent late Autumn to early spring
  (max. January-February)
- Incubation period 2-8 days
- Spread to LRT (bronchitis, bronchiolitis) lasts 5-7 days

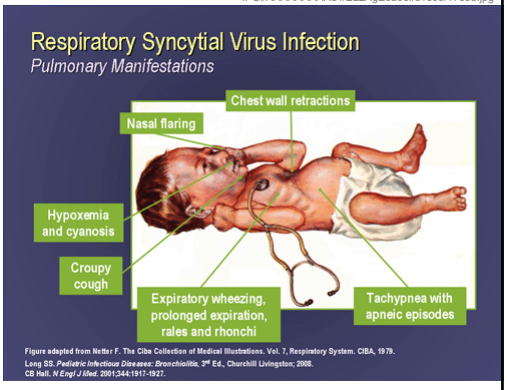
Paramyxoviridae

# Presentation




http://2.bp.blogspot.com/-1t0cvfUldKg/T4LLO2-fPCI/AAAAAAAAAd4/EL2AgEeae6I/s1600/17098.jpg

- Cold-like sx
- Audible wheezing
- SOB
- Anorexia
- Poor sleeping
- Irritability
- Vomiting
- Choking




## Severity

- Inhibition of certain interferons
- Involvement of innate immune system
- Interleukins and chemokines
- Coinfection with other respiratory viruses

http://img.medscape.com/fullsize/migrated/editorial/cmecircle/2008/18697/flash/luedtke/images/slide9.png

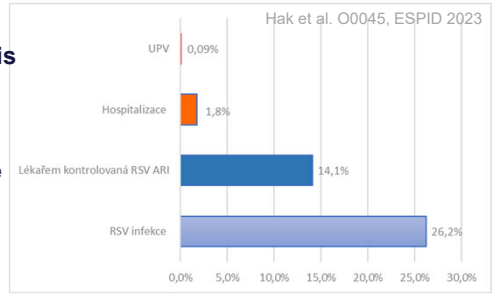
STAR WARS
RETURN OF THE JEDI

Star Wars: Return Of The Jedi - Han Solo Unfreezes, Jabba's Palace (Movie Clip) - YouTube


# RSV epidemiology

- Most frequent cause of **bronchiolitis & pneumonia in toddlers < 1 yr**
- 25-40% of kids have bronchiolitis or pneumonia within 1st RSV infection
- **10.7 milions LRTI - 0,4% decease**

(Cohen et al. Lancet Global Health 2022; 10:2:e169-e170)




**In 2015, RSV is suspected to cause woldwide :**

- 33.1 millions of acute LRT infections
- 3.2 millions of hospitalisations
- total mortality 118 200 in children < 5 yo (Shi et al. Lancet 2017; 390:946–58)
- In adults 420 000 of hospitalisation and 29 000 of deads in developer countries

- **seroprevalence at 1 year of age 60-70%** (Obando-Pacheco P, et al. J Inf Dis 2018; 217: 1356–1364)
- metaanalysis of papers from last 25 years (186 published studies; 152 209 cases of communite pneumonia in children (<18 yo) RSV (22,7%) and HRV (22,1%)

(Pratt et al. Lancet 2022; 6: 555–570.)

# Coinfection and Risk factors

## Premature delivery

- Likely to have chronic lung disease
- Hypersensitive to stimuli
- Underdeveloped airway & immunity
- Lack adult maternal levels of IgG

## Environmental & Demographics

- Male infants
- Age & birth month of infant
- Crowding & day care attendance
- Secondhand smoke

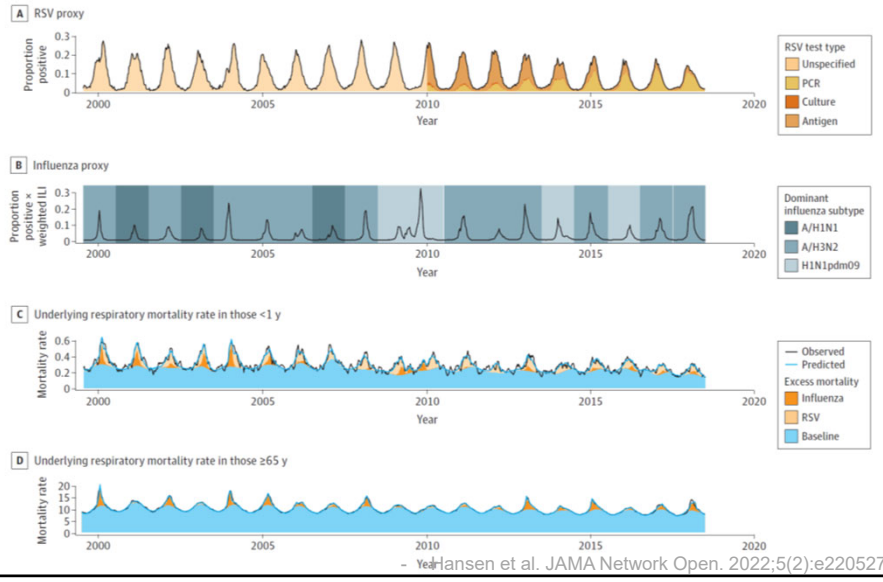
## Factors NOT Positively Correlated with RSV

- Socioeconomic status
- Malnourishment
- Breastfeeding

https://www.lancastergeneralhealth.org/health-hub-home/motherhood/your-pregnancy/differences-between-term-and-preterm-newborns

# RSV epidemiology

Figure 2. Weekly Time Series for Respiratory Syncytial Virus (RSV) and Influenza Surveillance Proxies and the Underlying Respiratory Mortality Rate per 100 000 Population in Children Younger Than 1 Year and Adults Aged 65 Years or Older




Hansen et al. JAMA Network Open. 2022;5(2):e220527.

# RSV epidemiology

Table. Estimated Mean, Annual Age-Specific Influenza and RSV Deaths and Mortality Rates per 100 000 Population, 1999-2000 to 2017-2018, US

| Underlying cause of death and age group, y | RSV deaths, No. (95% CI) | RSV mortality rate per 100 000 population (95% CI) | Influenza deaths, No. (95% CI) | Influenza mortality rate per 100 000 population (95% CI) |
|---|---|---|---|---|
| Pneumonia and influenza | | | | |
| <1 | 47 (45 to 49) | 1.2 (1.1 to 1.2) | 18 (16 to 21) | 0.5 (0.4 to 0.5) |
| 1-4 | 5 (3 to 6) | 0.0 (0.0 to 0.0) | 23 (21 to 25) | 0.1 (0.1 to 0.2) |
| 5-49 | 59 (46 to 72) | 0.0 (0.0 to 0.0) | 419 (403 to 436) | 0.2 (0.2 to 0.2) |
| 50-64 | 250 (229 to 272) | 0.5 (0.4 to 0.5) | 635 (606 to 664) | 1.1 (1.1 to 1.2) |
| ≥65 | 2655 (2506 to 2804) | 6.7 (6.3 to 7.1) | 4168 (3968 to 4367) | 10.2 (9.7 to 10.7) |
| Total | 3016 (2829 to 3203) | 1.0 (0.9 to 1.1) | 5263 (5014 to 5512) | 1.7 (1.7 to 1.8) |
| Respiratory | | | | |
| <1 | 96 (92 to 99) | 2.4 (2.3 to 2.5) | 23 (19 to 27) | 0.6 (0.5 to 0.7) |
| 1-4 | 20 (18 to 22) | 0.1 (0.1 to 0.1) | 24 (21 to 27) | 0.2 (0.1 to 0.2) |
| 5-49 | 124 (108 to 141) | 0.1 (0.1 to 0.1) | 519 (497 to 541) | 0.3 (0.3 to 0.3) |
| 50-64 | 508 (460 to 556) | 1.0 (0.9 to 1.0) | 1322 (1260 to 1384) | 2.4 (2.2 to 2.5) |
| ≥65 | 5800 (5461 to 6139) | 14.7 (13.8 to 15.5) | 8284 (7855 to 8713) | 20.5 (19.4 to 21.5) |
| Total | 6549 (6140 to 6958) | 2.2 (2.0 to 2.3) | 10 171 (9652 to 10 691) | 3.4 (3.2 to 3.5) |

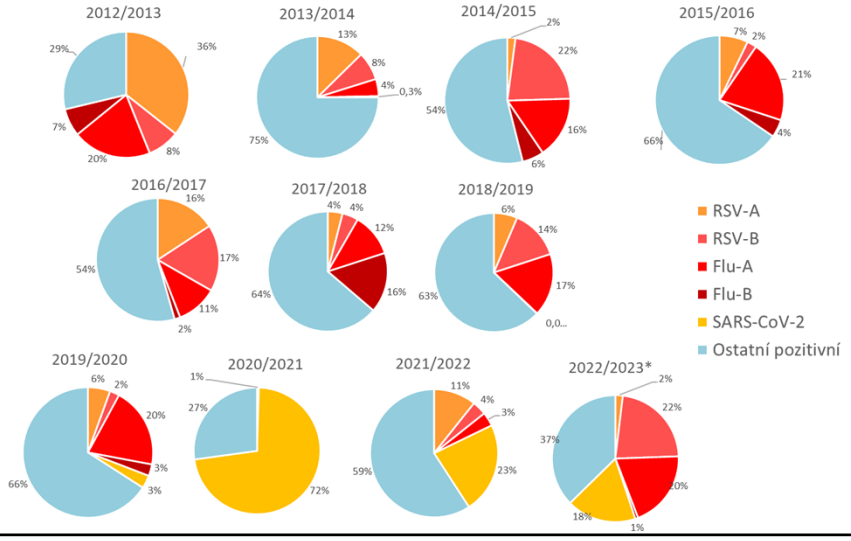
This cross-sectional study used data from 50.3 million US death certificates from 1999 to 2018 to create age-specific linear regression models and assess weekly mortality fluctuations above a seasonal baseline associated with RSV and influenza. Statistical analysis was performed for 1043 weeks from January 3, 1999, to December 29, 2018.

There were 50.3 million death certificates (50.1%women and 49.9%men; mean [SD] age at death, 72.7 [18.6] years) included in this analysis, 1.0%f or children younger than 1 year and 73.4% for adults aged 65 years or older.

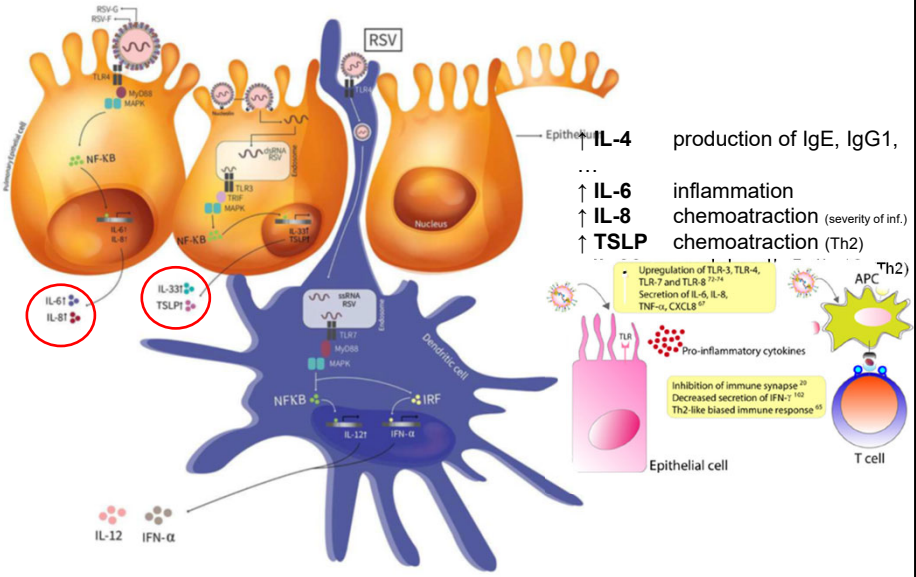
- Hansen et al. JAMA Network Open. 2022;5(2):e220527.

# RSV epidemiology

## Detection of RSV (A and B), influenza virus A and B and SARS-CoV-2 in Motol UH in respirátory seasons 2012 - January 2023.

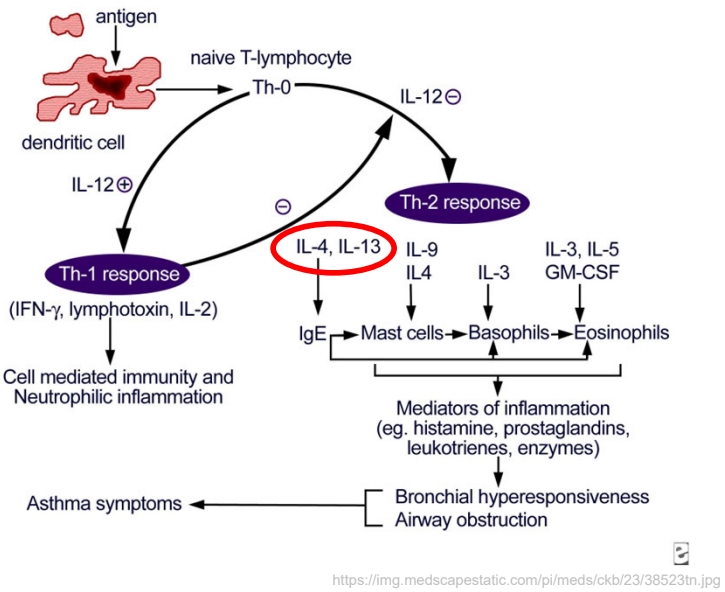


# Patophysiology of RSV




Vázquez et al. Frontiers in imunology 10.3389/fimmu.2019.01154 Bohmwald et al. Cytokines Induced by hRSV Infection, 2019

# Patophysiology of asthma




https://img.medscapestatic.com/pi/meds/ckb/23/38523tn.jpg

# Patophysiology of RSV

TABLE 1 | Effect of hRSV infection on the expression profile of cytokines in the upper and lower respiratory tract and entral nervous system.

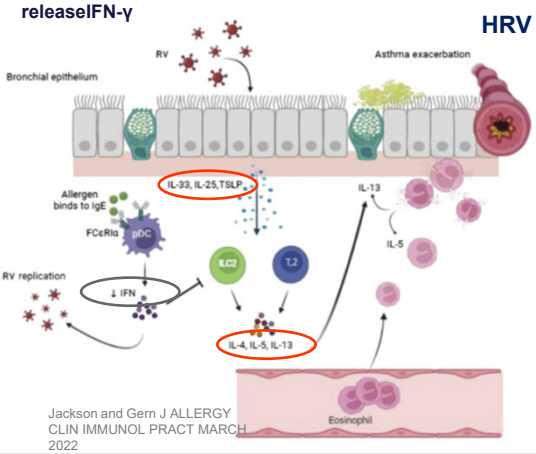
| Organism | Upper respiratory tract | Lower respiratory tract | Central nervous system |
|---|---|---|---|
| Human | | ↑IL-6 (57, 58) | ↑IL-6 (14, 15, 59) |
| | | ↑TNF-α (57, 58) | |
| | | ↑IL-4 (60–62) | |
| | ↑TNF-α (63, 64) | ↑IL-5 (60) | |
| | ↑IL-12 (65) | ↑IL-9 (60, 66) | |
| | ↑IL-23 (65) | ↓IL-10 (60–62, 67–69) | |
| | | ↑IL-13 (60–62) | |
| | | ↓IFN-γ (66) | |
| | | ↑IL-17 (70, 71) | |
| | | ↑TSLP (72) | |
| | | ↑CXCL8 (67, 58, 73) | |
| | ↑CXCL8 (74) | ↑CCL3 (57, 58, 75) | ↑CCL2 (15) |
| | ↑CCL5 (74) | ↑CCL4 (57, 58) | ↑CCL4 (15) |
| | ↑CXCL10 (74) | ↑CCL2 (57, 58) | ↑CXCL8 (15) |
| | | ↑CCL5 (57, 58, 75) | |

WILEY–Allergy

**NS1 & NS2 of RSV inhibite IFN-α/β production**
**Inhibition of IFN-γ ubsequently causes increased production of IgE**

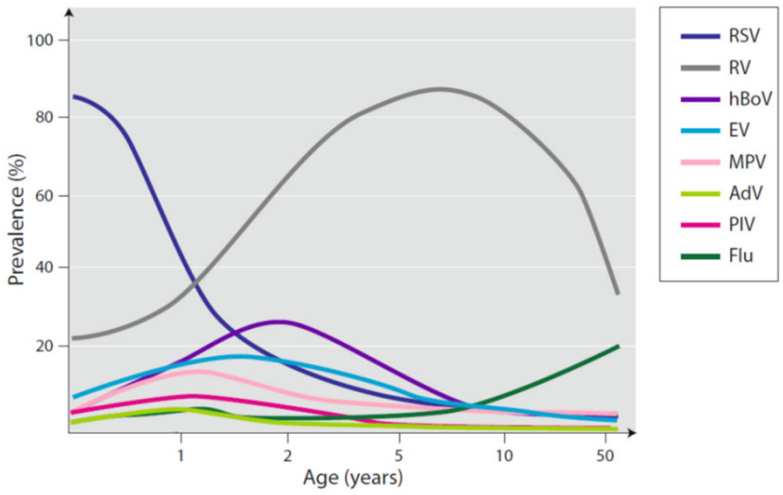
**Glycoprotein F of RSV inhibites T lymfocyte activation**
**CD8+ lymfocytes infected by RSV are not able to releaseIFN-γ**

**HRV**




Jackson and Gern J ALLERGY CLIN IMMUNOL PRACT MARCH 2022

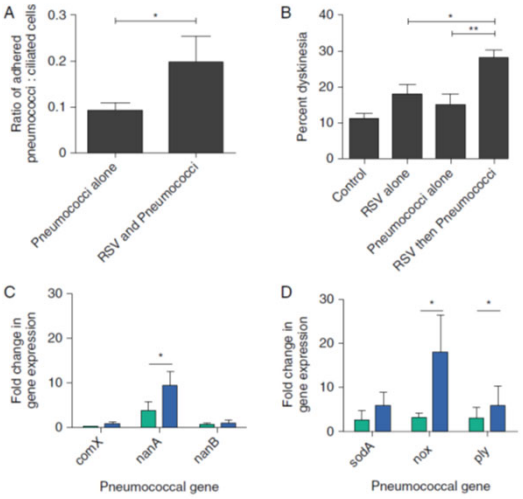
# Patophysiology of RSV




Jartti et al. Semin Immunopathol . 2020 Feb;42(1):61-74.

# RSV and *Streptococcus pneumoniae*

**G glycoprotein of RSV binds to penicillin binding protein 1a.**




G protein of RSV seems to be a receptor for *Str. pneumoniae* in infected cells and so improve invasion of the bacteria to cell.

Presence of RSV G protein lead to change of expression of 157 genes: in 99 genes was increased, in 58 decreased.

**↑pneumolysin**

Smith et al. Am J Respir Crit Care Med . 2014 Jul 15;190(2):196-207.

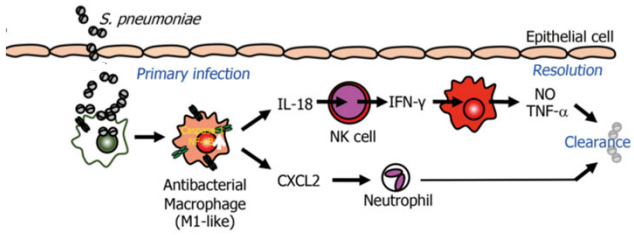
**Table 1.** Secreted Cytokine and Chemokine Concentrations in Cell Culture Supernatant after 2-Hour Exposure of *Streptococcus pneumoniae* to Mock or RSV-infected Human Ciliated Epithelial Cells

| Chemokine cytokine (pg/ml) | Mock* | | RSV* | |
|---|---|---|---|---|
| | Control† | Pneumococcus† | Control† | Pneumococcus† |
| IFN-γ | 12 (10–15) | 20 (15–20) | 17 (14–25) | **20 (19–25)** |
| IL-1β | 2 (2–4) | **4 (3–4)** | **6 (5–12)** | **5 (4–6)** |
| IL-12p70 | 2 (2–2) | **3 (3–4)** | 2 (2–3) | **4 (3–4)** |
| TNF-α | 7 (6–8) | **10 (10–15)** | 12 (9–19) | **19 (14–19)‡** |
| IL-5 | 3 (2–3) | **4 (4–4)** | **5 (4–16)** | **6 (4–6)‡** |
| IL-13 | 6 (5–7) | **10 (8–11)** | 6 (5–22) | **10 (9–11)** |
| CCL11 | 72 (68–73) | **92 (90–93)** | 68 (63–153) | **93 (93–99)** |
| CCL4 | 1 (1–1) | 2 (2–3) | 2 (2–12) | **3 (3–4)** |
| CCL17 | 35 (26–36) | **48 (48–49)** | 30 (23–89) | **52 (51–58)** |
| CCL22 | 91 (91–101) | **131 (123–138)** | 141 (122–335) | **167 (128–191)** |
| CXCL8 | 30 (26–62) | 98 (83–152) | 159 (104–1,319) | **271 (93–457)‡** |

*Definition of abbreviations*: RSV = respiratory syncytial virus; TNF = tumor necrosis factor.
Data are shown as median and interquartile range (in parentheses).
Statistical differences from the "Mock-control" sample were calculated using a paired *t* test.
Significant changes ($P < 0.05$) from the mock control are highlighted in bold.
*Primary infection (for 72 h).
†Secondary infection (for 2 h).
‡Significant difference ($P < 0.05$) between the "Mock-pneumococcus" and "RSV-pneumococcus" samples (n = 5).

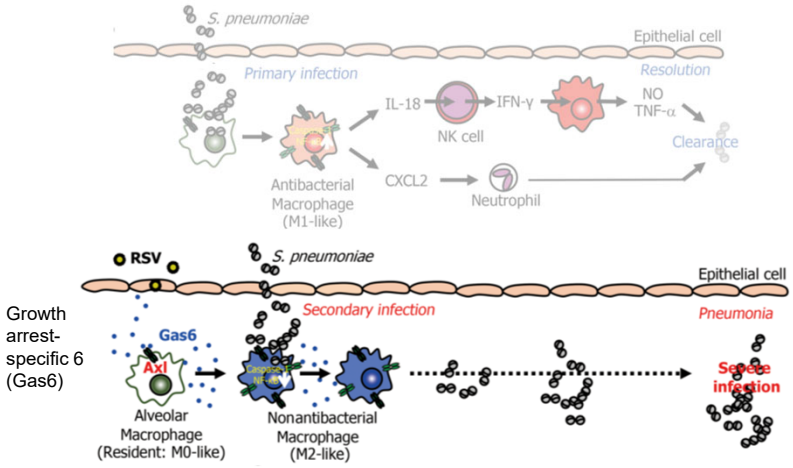
Smith et al. Am J Respir Crit Care Med . 2014 Jul

# RSV and *Streptococcus pneumoniae*




Shibata et al. J Clin Invest . 2020 Jun 1;130(6):3021-3037.

# RSV and *Streptococcus pneumoniae*



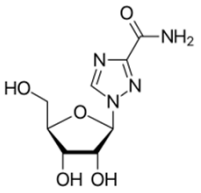

**Gas6/Axl je is involved also in development of IgA nefropathy**

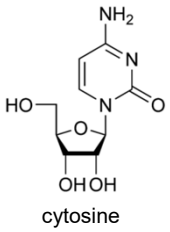
Shibata et al. J Clin Invest . 2020 Jun 1;130(6):3021-3037.

# Treatment

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

- **ribavirine in severely ill patients**




cytosine

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

REVIEW ARTICLE

CID 2013

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

Oral ribavirin for treatment of respiratory syncitial virus and parainfluenza 3 virus infections post allogeneic haematopoietic stem cell transplantation

J Casey[1], K Morris[1], M Narayana[1], M Nakagaki[2] and GA Kennedy[1,3]

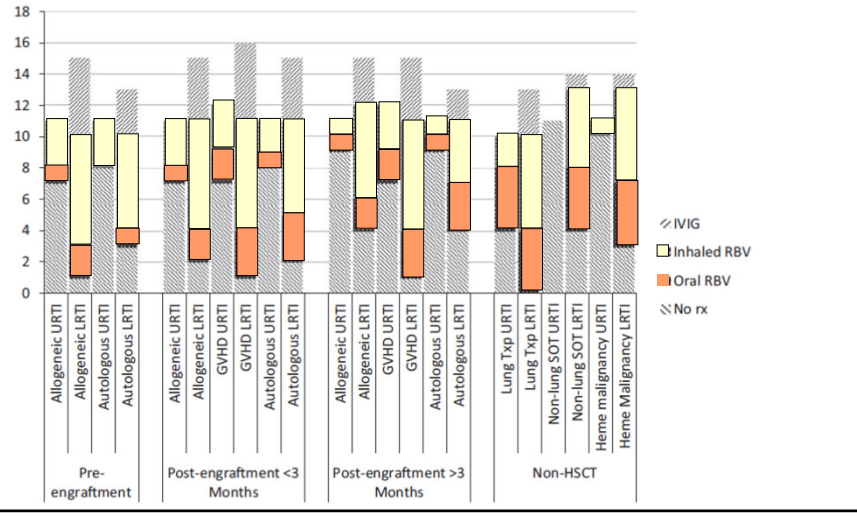
BMT 2011

**p.o. ribavirine 10-30 mg/kg/D in 3 doses**

**Current practices for treatment of respiratory syncytial virus and other non-influenza respiratory viruses in high-risk patient populations: a survey of institutions in the Midwestern Respiratory Virus Collaborative**

Beaird et al: Management of RSV in high-risk adults

*Transplant Infectious Disease* 2016: **18**: 210–215



# RSV therapy

| Virus Family | Virus | Strain | Assay Type | Nuc $EC_{50}/EC_{90}$ (μM)/[SI] | GS-5734 $EC_{50}/EC_{90}$ (μM)/[SI] |
|---|---|---|---|---|---|
| Filo- | EBOV | Rec. Mayinga-GFP | REP | 1.6/6.7/[31] | 0.066/0.203/[151] |
| | | Rec. Mayinga-Gluc | REP | 3.1/11/[16] | 0.021/0.053/[476] |
| | | Rec. Makona-ZSG | REP | 1.3/3.3/[38] | 0.014/0.045/[714] |
| | | Makona | VTR | 1.0/2.5/[50]# | 0.003/0.019/[666]‡ |
| | MARV | Rec. Bat371-Gluc | REP | NT | 0.019/0.052/[526] |
| | | Rec. Bat371-GFP | REP | 1.9/4.6/[26] | 0.014/0.047/[714] |
| Paramyxo- | NiV | Rec. M-Luc2AM | REP | 1.5/5.7/[33] | 0.045/0.126/[184] |
| | | Rec. M-GFP2AM | REP | 2.2/4.0 [22] | 0.029/0.053/[286] |
| | | M-1999 | VTR | 0.49/1.4/[102]# | 0.047/0.083/[180]‡ |
| | | B-2004 | VTR/CPE | 0.83/2.2/[60]† | 0.032/0.106/[259] |
| | HeV | 1996 | VTR/CPE | 1.0/1.8/[50]† | 0.055/0.117/[150] |
| | hPIV3 | Rec. JS-GFP | REP | 0.51/1.0/[98] | 0.018/0.35/[461] |
| | MV | Rec. $rMV^{EZ}$GFP(3) | REP | 1.0/2.6/[50] | 0.037/0.073/[224] |
| | | EZ vaccine | AG | 2.0/5.1/[25] | NT |
| | MuV | IA 2006 | AG | 9.7/26.3/[5] | 0.79/3.4/[10] |
| Pneumo- | RSV | Rec. rgRSV224 (A2) | REP | 0.63/2.2/[79] | 0.021/0.059/[395] |
| | hMPV | Rec. CAN97-83-GFP | REP | 0.73/1.7/[NT] | NT |
| Bunya- | RVFV | Rec. ZH501-GFP | REP | No inhibition | No inhibition |
| | CCHF | Rec. IbAr 10200 | AG | No inhibition | No inhibition |
| | ANDV | Chile 9717869 | AG | NT | 7.0/10.1/[1.4] |
| Arena- | LASV | Josiah | AG | No inhibition | 4.5/5.1/[2.2] |
| Rhabdo- | VSV | New Jersey | CPE | No inhibition | No inhibition |
| Flavi- | AHFV | 200300001 | CPE | 49.9/ > 150/[NT] | 4.2/17.6/[2.4] |
| | KFDV | P9605 | CPE | 46.3/ > 350/[NT] | 1.8/3.4/[5.6] |
| | TBEV | Hypr | CPE | 51.2/ > 150/[NT] | 2.1/3.5/[4.8] |
| | OHFV | Bogoluvovska | CPE | 50.6/ > 350 [NT] | 1.2/3.9/[8.3] |

**GS-5734 = remdesivir**

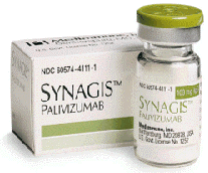
Lo et al. Scientific Reports 2017| 7:43395 | DOI: 10.1038/srep43395

Paramyxoviridae

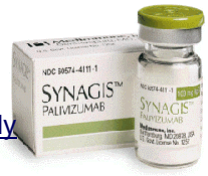
# Prophylaxis


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

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



# RSV prevention




**palivizumab (Synagis)** – anti protein F antibody

- Given i.m. monthly
- Can reduce hospitalization of high risk infants by 45%
- Expensive
- Many providers reluctant to give
- Many parents unaware
- Dosing: 15 mg/kg bw.

**nirsevimab (Beyfortus)** – antibody against F protein

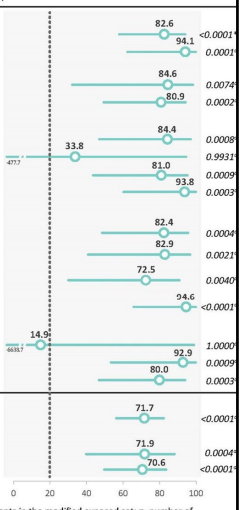
- Given i.m. 1x in 3 month
- Dosing: single amplication of 50 mg i.m. in children < 5 kg and si dose 100 mg i.m. for kids ≥ 5 kg
- Halftime approx. 69 days

# RSV prevention - vaccines

**Arexvy**
(FDA approval 18.5.2023)
**– GSK in elderly (> 60 years)**

**Figure 1.** Vaccine efficacy against first episodes of RSV-confirmed LRTD and RSV-confirmed ARI (modified exposed set)

| | RSVPreF3 OA | | | | Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | n | T (p-yr) | n/T (n/1000 p-yr) | N | n | T (p-yr) | n/T (n/1000 p-yr) | Vaccine efficacy (%) | p-value |
| **RSV-confirmed LRTD** | | | | | | | | | | |
| Overall | 12466 | 7 | 6865.9 | 1.0 | 12494 | 40 | 6857.3 | 5.8 | 82.6 | <0.0001[a] |
| Severe | 12466 | 1 | 6867.9 | 0.1 | 12494 | 17 | 6867.7 | 2.5 | 94.1 | 0.0001[a] |
| *By subtype* | | | | | | | | | | |
| RSV-A | 12466 | 2 | 6867.4 | 0.3 | 12494 | 13 | 6868.9 | 1.9 | 84.6 | 0.0074[a] |
| RSV-B | 12466 | 5 | 6866.7 | 0.7 | 12494 | 26 | 6862.3 | 3.8 | 80.9 | 0.0002[a] |
| *By age* | | | | | | | | | | |
| ≥70 yr | 5503 | 3 | 3015.0 | 1.0 | 5515 | 19 | 3020.9 | 6.3 | 84.4 | 0.0008[a] |
| ≥80 yr | 1016 | 2 | 551.4 | 3.6 | 1028 | 3 | 559.3 | 5.4 | 33.8 | 0.9931[a] |
| 60–69 yr | 6963 | 4 | 3850.8 | 1.0 | 6979 | 21 | 3836.4 | 5.5 | 81.0 | 0.0009[a] |
| 70–79 yr | 4487 | 1 | 2463.6 | 0.4 | 4487 | 16 | 2461.6 | 6.5 | 93.8 | 0.0003[a] |
| *By baseline comorbidities* | | | | | | | | | | |
| Low/medium risk[b] | 8235 | 4 | 4495.8 | 0.9 | 8367 | 23 | 4560.6 | 5.0 | 82.4 | 0.0004[a] |
| High risk[b] | 4231 | 3 | 2370.0 | 1.3 | 4127 | 17 | 2296.6 | 7.4 | 82.9 | 0.0021[a] |
| No comorbidity of interest[c] | 7529 | 6 | 4094.1 | 1.5 | 7633 | 22 | 4148.1 | 5.3 | 72.5 | 0.0040[a] |
| ≥1 comorbidity of interest[c] | 4937 | 1 | 2771.8 | 0.4 | 4861 | 18 | 2709.1 | 6.6 | 94.6 | <0.0001[a] |
| *By frailty[d]* | | | | | | | | | | |
| Frail | 189 | 1 | 95.8 | 10.4 | 177 | 1 | 92.9 | 10.8 | 14.9 | 1.0000[a] |
| Pre-frail | 4792 | 1 | 2577.6 | 0.4 | 4778 | 14 | 2545.3 | 5.5 | 92.9 | 0.0009[a] |
| Fit | 7464 | 5 | 4182.7 | 1.2 | 7519 | 25 | 4208.5 | 5.9 | 80.0 | 0.0003[a] |
| **RSV-confirmed ARI** | | | | | | | | | | |
| Overall | 12466 | 27 | 6858.7 | 3.9 | 12494 | 95 | 6837.8 | 13.9 | 71.7 | <0.0001[a] |
| *By RSV subtype* | | | | | | | | | | |
| RSV-A | 12466 | 9 | 6865.2 | 1.3 | 12494 | 32 | 6862.3 | 4.7 | 71.9 | 0.0004[a] |
| RSV-B | 12466 | 18 | 6861.7 | 2.6 | 12494 | 61 | 6849.4 | 8.9 | 70.6 | <0.0001[a] |

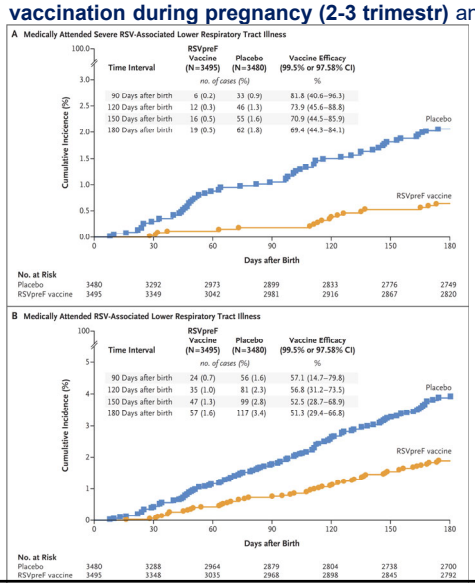



Cases reported up to the efficacy data lock point of 11 April 2022. **N**, number of participants in the modified exposed set; **n**, number of participants with ≥1 RSV-confirmed LRTD (identified by the adjudication committee) or ≥1 RSV-confirmed ARI; **T**, sum of follow-up time (from day 15 post-vaccination until first occurrence of the event, data lock point or drop-out); **p-yr**, person-years; **n/T**, incidence rate of participants reporting at least one event. Error bars represent 96.95% confidence intervals (CI) for primary objective (RSV-confirmed LRTD, overall) and 95% CI for other endpoints. [a]Two-sided exact p-value conditional to number of cases comparing incidence rates; [b]Two-sided exact nominal p-value conditional to number of cases comparing incidence rates. [b]Charlson comorbidity index: low/medium risk, participants with baseline comorbidity score ≤3; high risk, participants with baseline comorbidity score >3. [c]Comorbidities of interest included chronic obstructive pulmonary disease, asthma, any chronic respiratory/pulmonary disease, chronic heart failure, diabetes mellitus type 1 or type 2 and advanced liver or renal disease. [d]Frailty status assessed using a gait speed test: frail, participants with a walking speed <0.4 m/s or not able to perform the test; pre-frail, participants with a walking speed of 0.4–0.99 m/s; fit, participants with a walking speed ≥1 m/s. Note: RSV subtype was unknown for 1 RSV-confirmed LRTD and 2 RSV-confirmed ARI episodes.

https://www.gsk.com/en-gb/media/press-releases/gsk-s-older-adult-respiratory-syncytial-virus-rsv-vaccine-

# RSV prevention - vaccines

**Protein vaccine Pfizer** (FDA 18.5.2023 approved) –
**vaccination during pregnancy (2-3 trimestr)** and for elderly




The NEW ENGLAND JOURNAL of MEDICINE

Kapmann et al. N Engl J Med 2023 ;388:1451-64.
DOI: 10.1056/NEJMoa2216480

# RSV prevention - vaccines

**Protein vaccine Pfizer** (FDA 18.5.2023 approved) –
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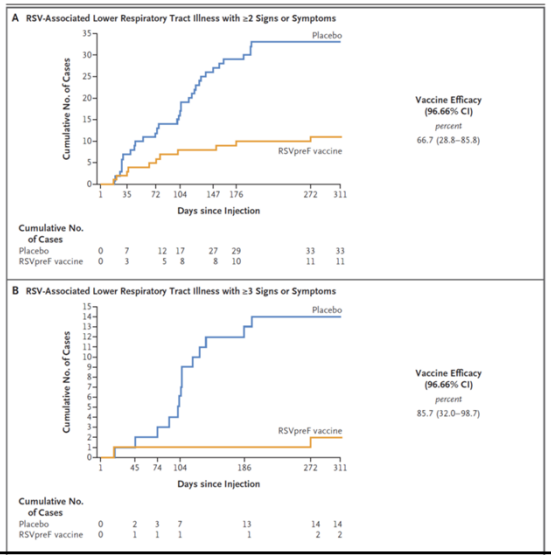
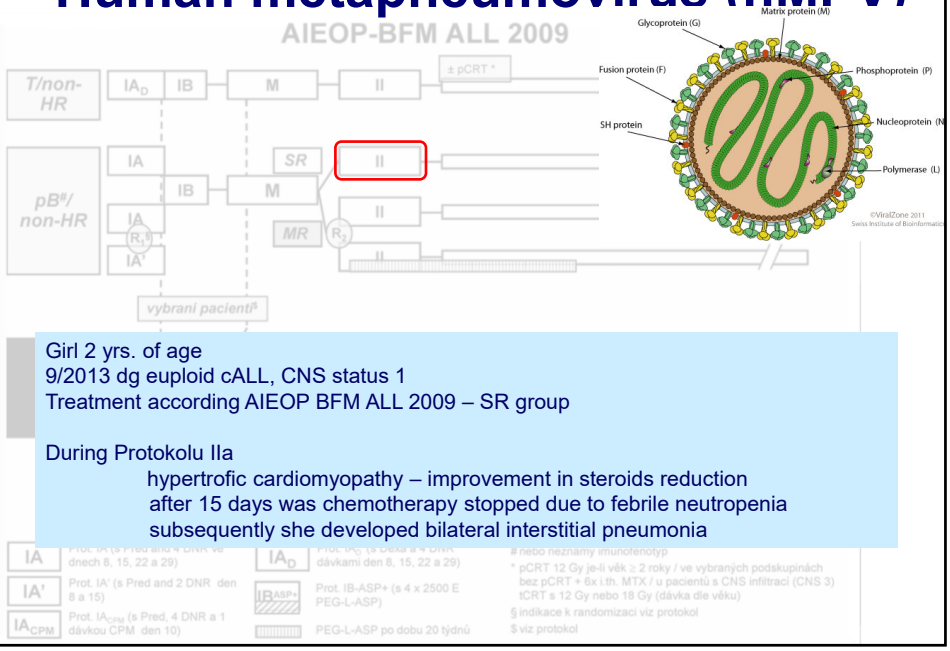



The NEW ENGLAND JOURNAL of MEDICINE

Walsh et al. N Engl J Med 2023 ;388:1465-77.
DOI: 10.1056/NEJMoa2213836

Paramyxoviridae

# Human metapneumovirus (hMPV)

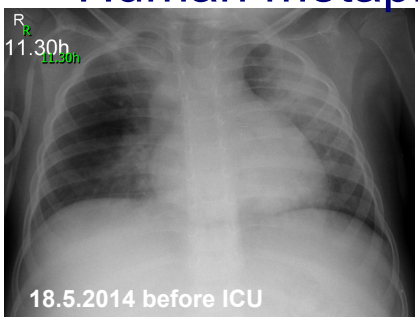


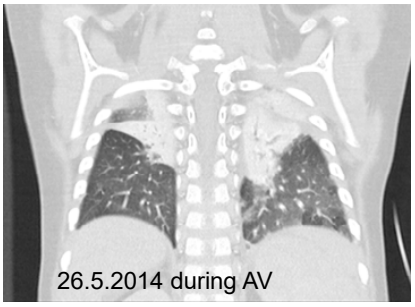

Girl 2 yrs. of age
9/2013 dg euploid cALL, CNS status 1
Treatment according AIEOP BFM ALL 2009 – SR group

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

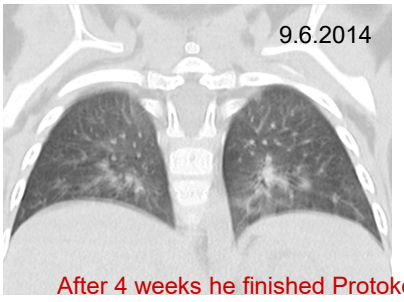
Paramyxoviridae

# Human metapneumovirus (hMPV)

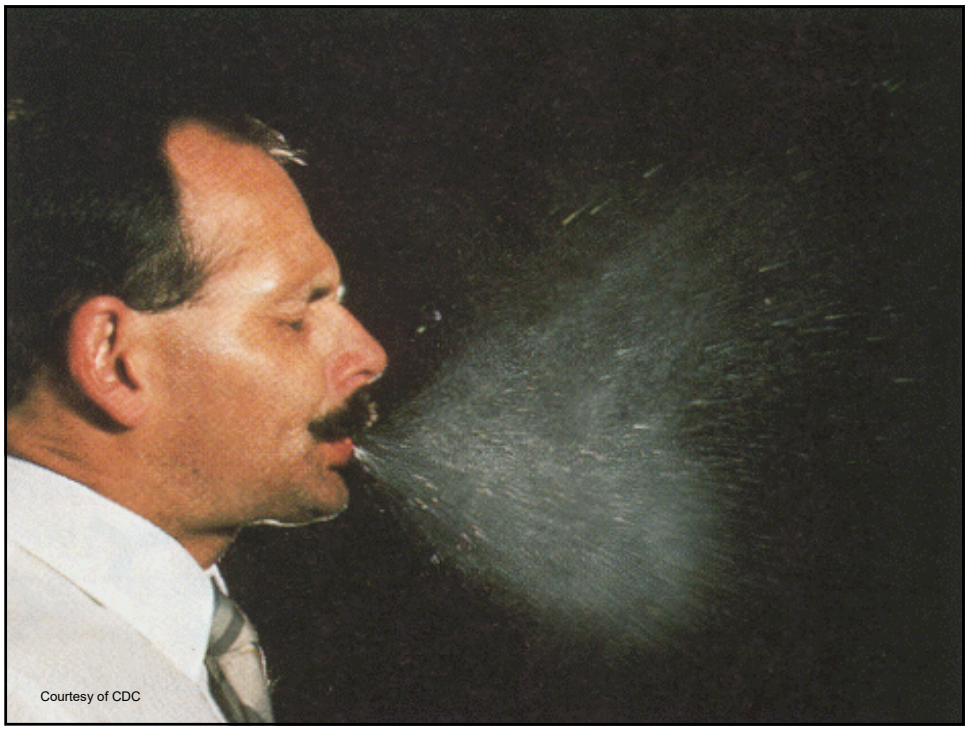


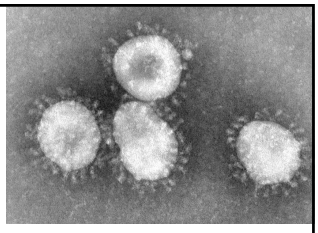

- 9.5.2014 positive NF swab for hMPV
- Treatment:
  - IVIG (substitution 0.3 g/kg - 4 doses)
  - ribavirine 6 mg/kg á 8 hod p.o. 5 weeks
- Respiratory failure with 8 days of AV ($FiO_2$ 1,0)
- hMPV confirmed for ET tube
- hMPV positivity 4 weeks
- Control CT after 10 days of AV - regression




After 4 weeks he finished Protokol IIa.

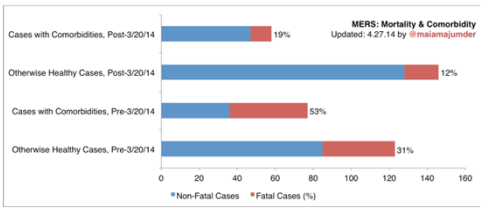



# Coronaviruses

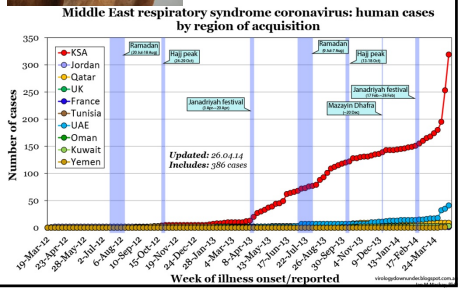


- Coronaviridae
- ss (+) RNA, 26-32 kb genone length (largest RNA)
- first identified in the mid-1960s
  - alpha – HCoV 229E and NL63
  - beta - HCoV OC43, HKU1, SARS-CoV (severe acute respiratory syndrome), and MERS-CoV (Middle East Respiratory Syndrome)
- **SARS**
  - Cellular receptor – ACE2
  - mortality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

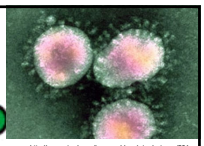
MERS - transmission through camels, their milk and cheese



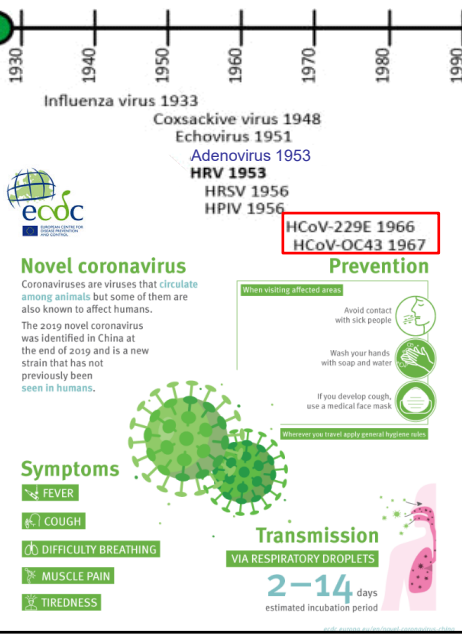

https://maimunamajumder.files.wordpress.com/2014/04/mers_comorbidity_mortality_4-271.png

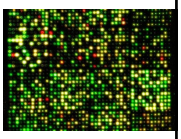


# Coronaviruses are known for decades



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



*Luskoun ostrovní (Manis javanica)*

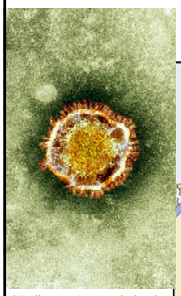
# Coronaviruses

| Virus | Receptor | References |
|---|---|---|
| Alphacoronaviruses | | |
| HCoV-229E | APN | [115] |
| HCoV-NL63 | ACE2 | [116] |
| TGEV | APN | [117] |
| PEDV | APN | [118] |
| FIPV | APN | [119] |
| CCoV | APN | [120] |
| Betacoronaviruses | | |
| MHV | mCEACAM | [121, 122] |
| BCoV | *N*-acetyl-9-*O*-acetylneuraminic acid | [123] |
| SARS-CoV | ACE2 | [124] |
| MERS-CoV | DPP4 | [100] |

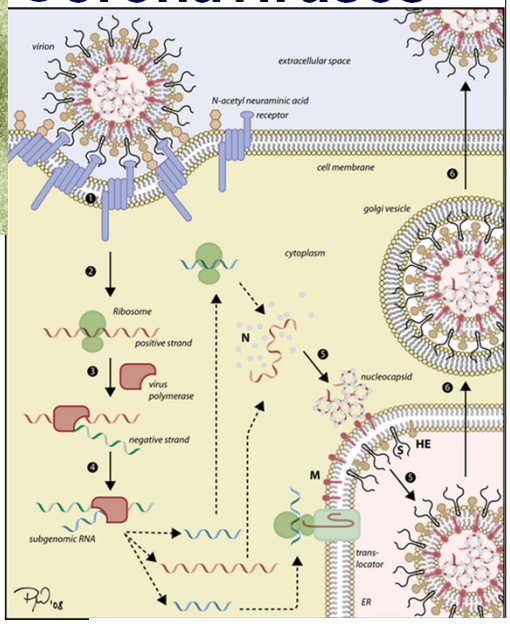
*APN* aminopeptidase N, *ACE2* angiotensin-converting enzyme 2, *mCEACAM* murine carcinoembryonic antigen-related adhesion molecule 1, *DPP4* dipeptidyl peptidase 4, *HCoV* human coronavirus, *TGEV* transmissible gastroenteritis virus, *PEDV* porcine epidemic diarrhea virus, *FIPV* feline infectious peritonitis virus, *CCoV* canine coronavirus, *MHV* murine hepatitis virus, *BCoV* bovine coronavirus, *SARS-CoV* severe acute respiratory syndrome coronavirus, *MERS-CoV* Middle East respiratory syndrome coronavirus

Coronaviruses. 2015; 1282: 1–23.

# Coronaviruses



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




**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.

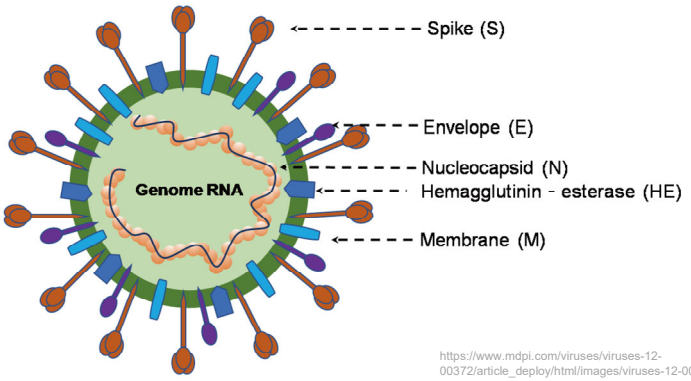
**6** These viral progeny are finally transported by golgi vesicles to the cell membrane and are exocytosed into the extracellular space.

*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

A




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

B


| | |
|---|---|
| Confirmed cases | 37 109 851 |
| Confirmed deaths | 1 070 355 |
| Countries, areas or territories with | 235 |

Last update: 11 October 2020, 02:00 CEST

# SARS-CoV-2

**Virus Environmental Stability**

(relevance to personal safety unclear)

Half-life

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

Aerosols: ≈1 hr

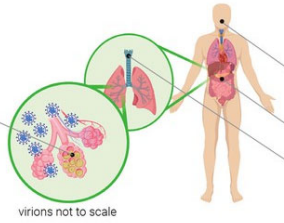
Surfaces: ≈1-10 hr
e.g. plastic, glass, paper and metals

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



virions not to scale

**Concentration**

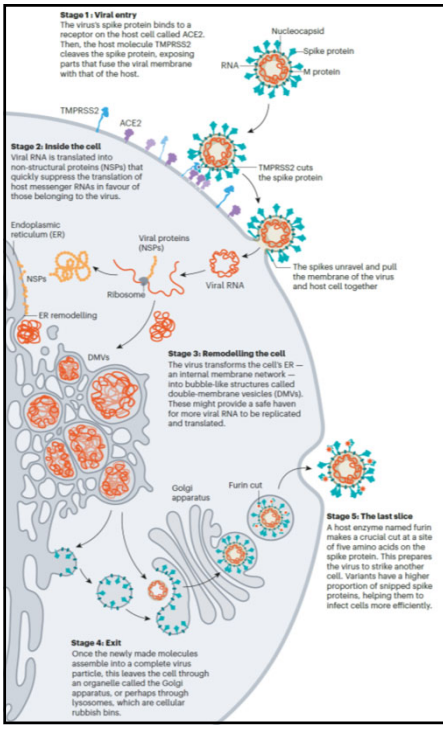
(maximal observed values following diagnosis)

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 je zpravidla 1000x víc než infekčních virových partikulí.**

Bar-On eLifescience 2020




# Replication

Binding to ACE-2

Cleavage of spike protein by TMPRSS2

Ïnternalisation and subsequent transcription of NS proteins

Remodelation of cellular metabolism

Production of new particles

Furin cuts 5 AA of spike protein

Scudellari Nature 2021; 595

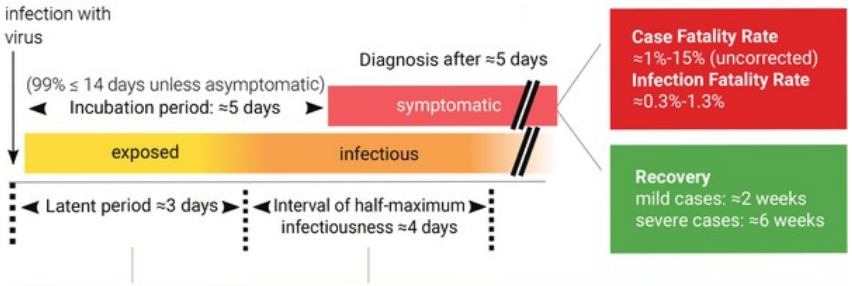
# Patophysiology

"Characteristic" Infection Progression in a Single Patient

Basic reproductive number $R_0$: typically 2-4

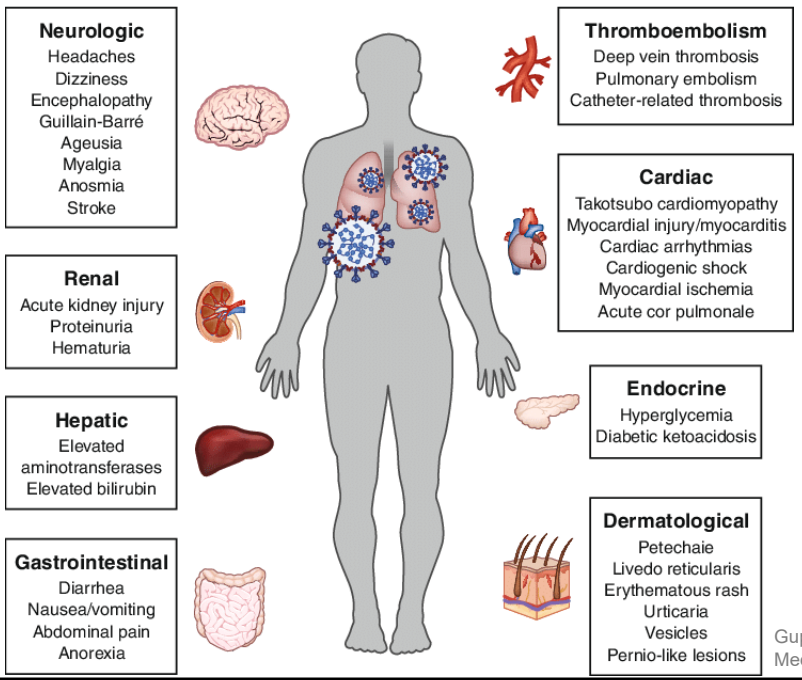
Varies further across space and time

(number of new cases directly generated from a single case)



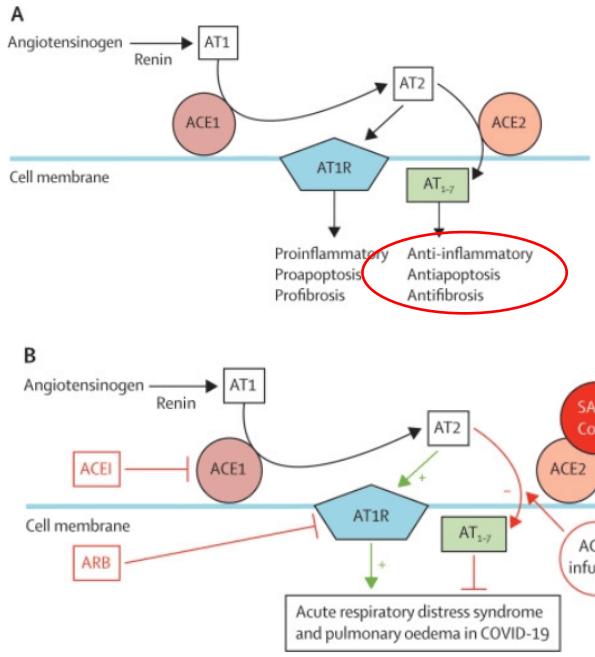

Inter-individual variability is substantial and not well characterized. The estimates are parameter fits for population median in China and do not describe this variability.

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




Gupta et l. Nature Medicine 2020

1




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

1

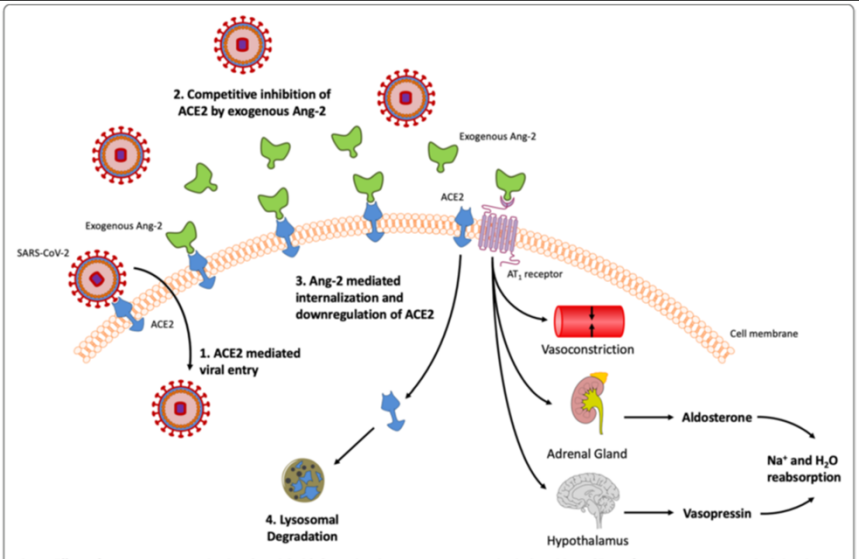
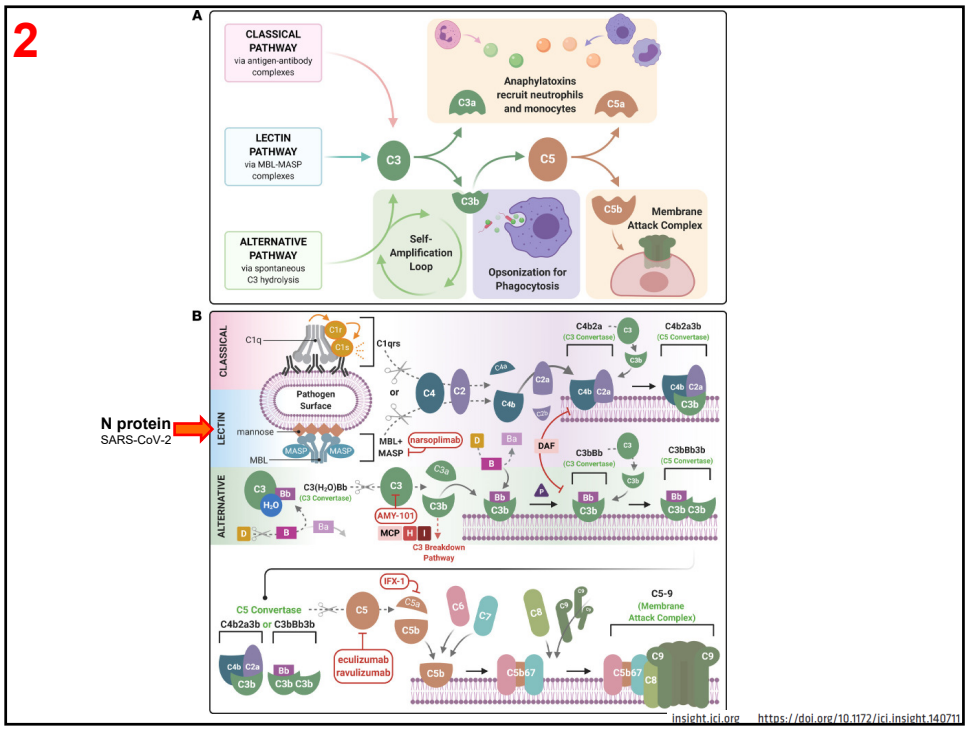



**Fig. 1** Effect of angiotensin II on the RAAS and SARS-CoV-2 binding. Angiotensin I is hydrolyzed by ACE1 to form angiotensin II, which binds to $AT_1$ receptors. This causes release of aldosterone from the adrenal gland, vasopressin secretion from the hypothalamus, and vasoconstriction. Vasopressin 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



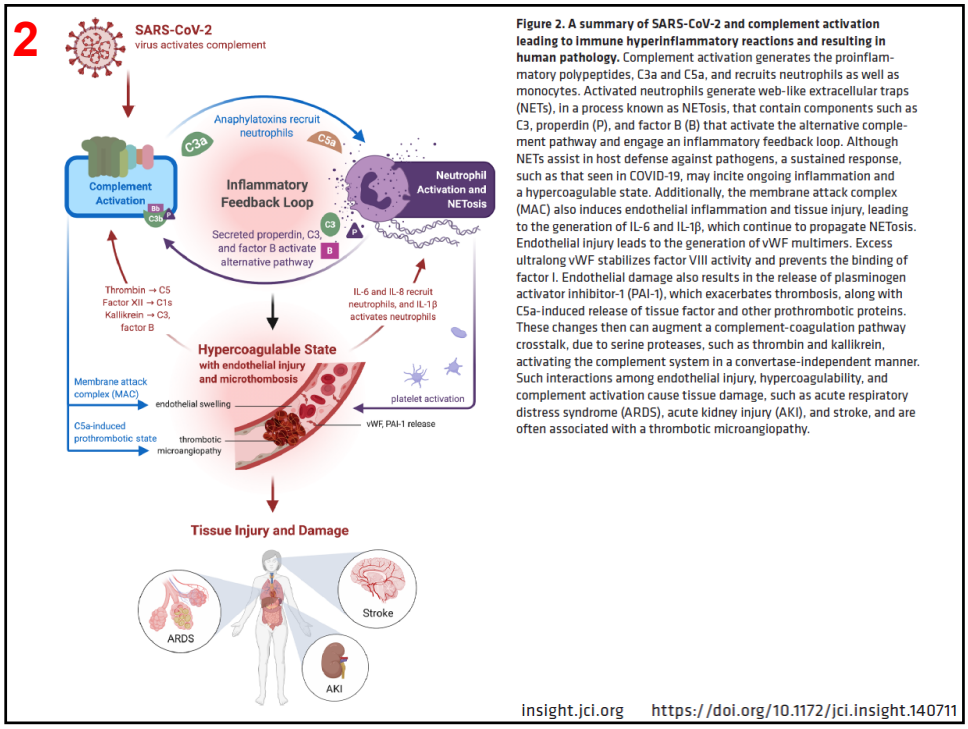
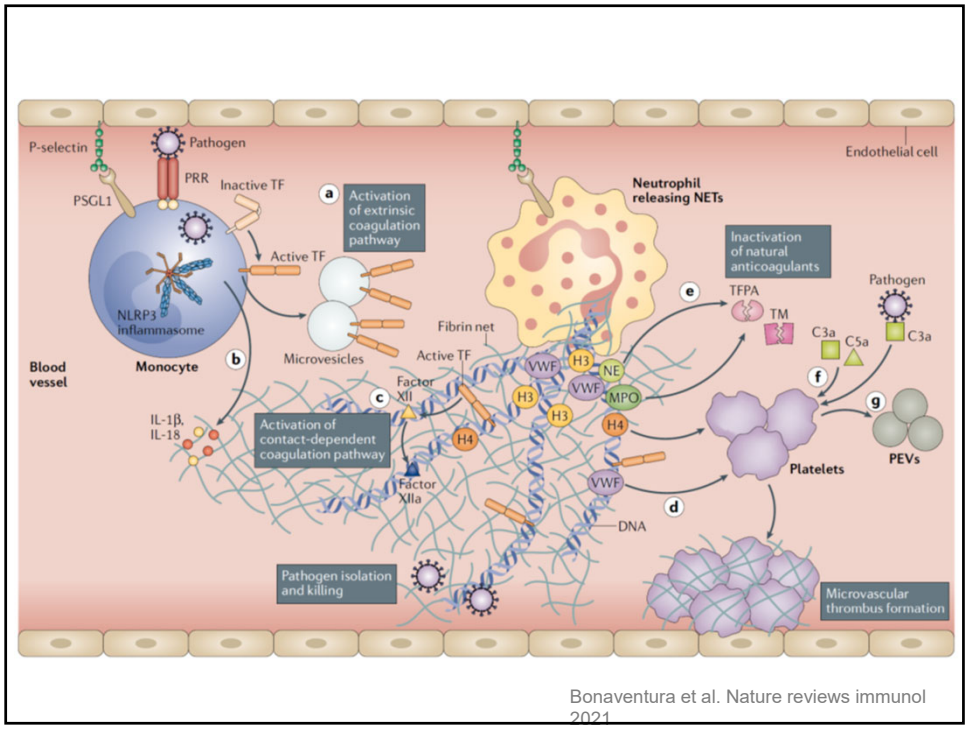
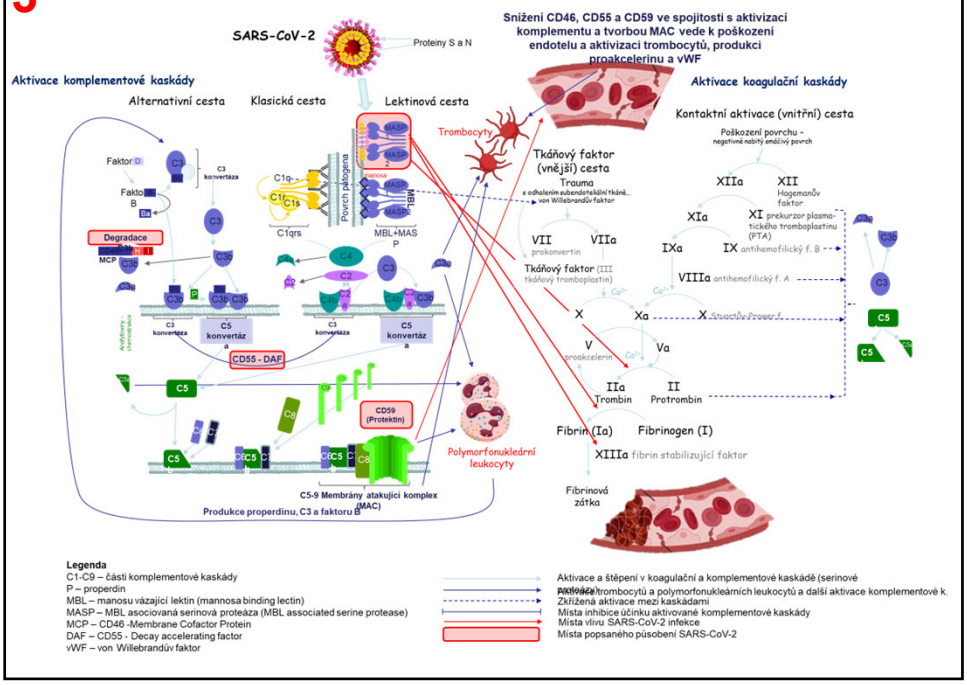




**Figure 2. A summary of SARS-CoV-2 and complement activation leading to immune hyperinflammatory reactions and resulting in human pathology.** Complement activation generates the proinflammatory polypeptides, C3a and C5a, and recruits neutrophils as well as monocytes. Activated neutrophils generate 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.



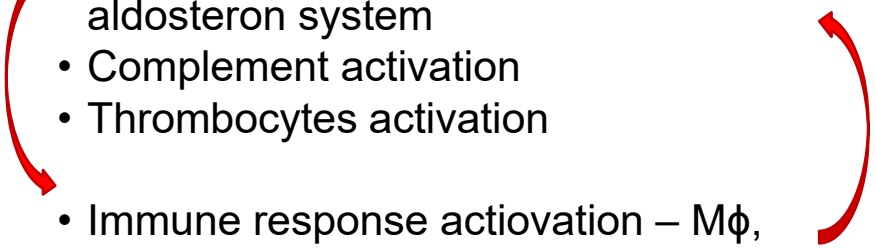

Bonaventura et al. Nature reviews immunol 2021

3



## 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

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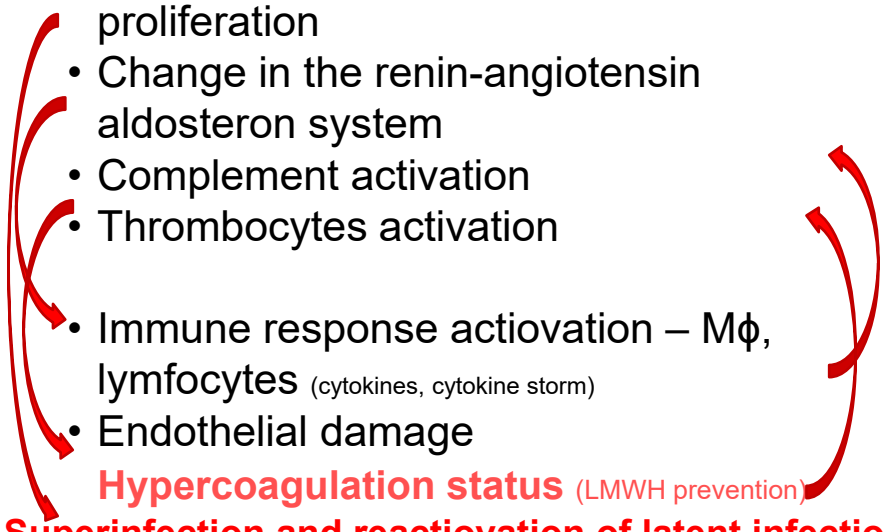
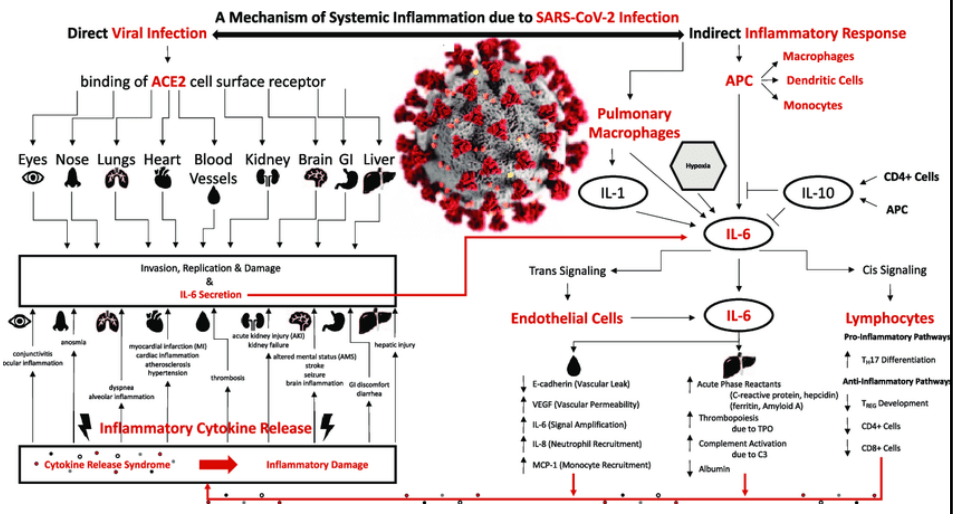
- Complement activation
- Thrombocytes activation
- Immune response actiovation – Mϕ, lymfocytes (cytokines, cytokine storm)
- Endothelial damage

**Hypercoagulation status** (LMWH prevention)

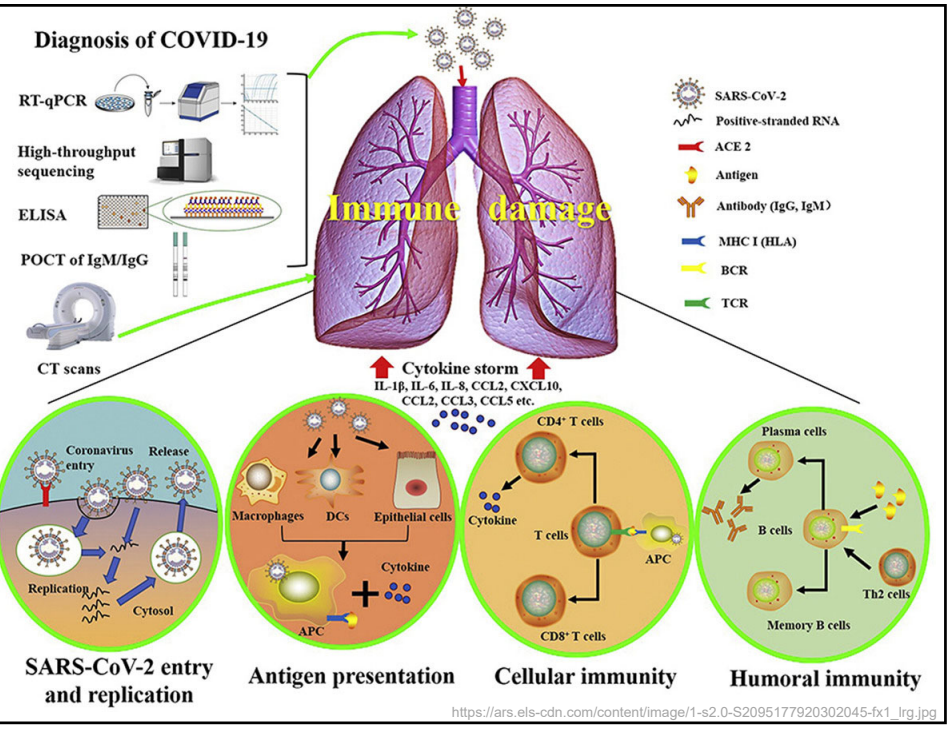
**Superinfection and reactiovation of latent infections**



# Patofysiology

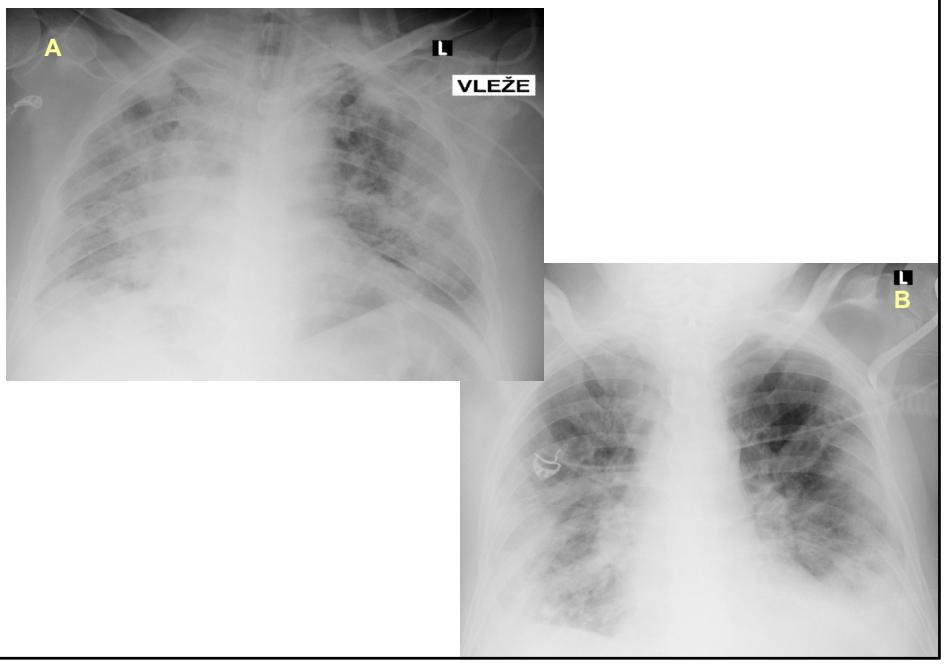



Leyfman et l. SHOCK 2020

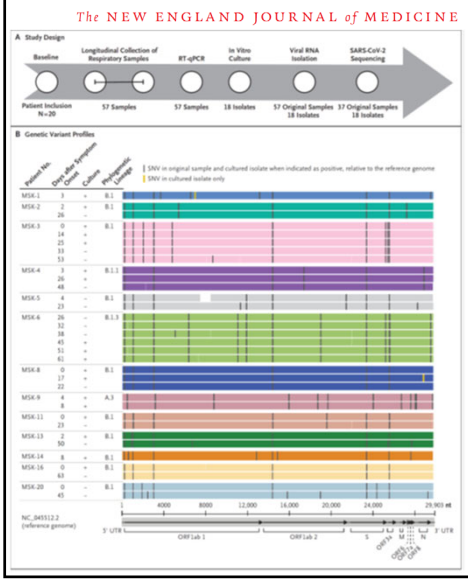



https://ars.els-cdn.com/content/image/1-s2.0-S2095177920302045-fx1_lrg.jpg

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




# 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 may shed viable SARS-CoV-2 for at least 2 months."**

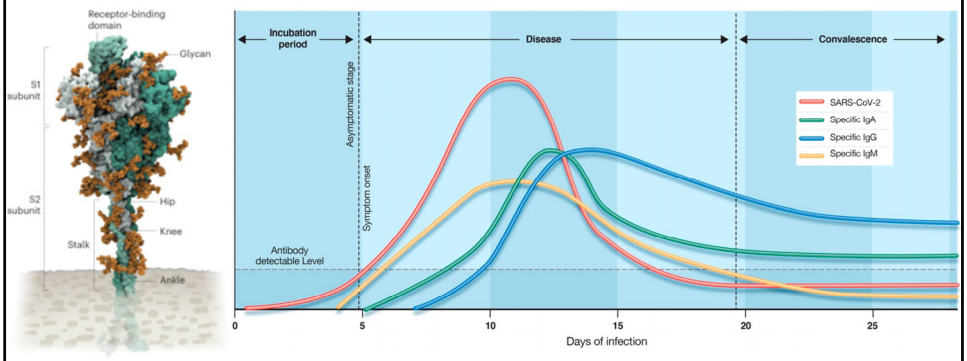
N ENGL J MED 383;26 NEJM.ORG DECEMBER 24, 2020

# 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<br>PIV-3: 8 days (3-10 days) | 6-42 days |
| RSV | ± 4 days (1-12)/ | Median 2-4 weeks<br>80 days (35-334 days) |
| hMPV | ± 5 days | 7-24 days |
| HRV/HEV | ± 14 days (HRV-C 7 days)<br>Adult longer then children | Mostly ≤4 weeks<br>5 weeks (1-49 weeks) |
| Coronaviry<br>(HKU-1, 229E, OC43, NL63, SARS-CoV-2) | 3-18 days,<br>Couple of weeks to 2 months | 4 weeks (1-22 weeks),<br>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*

# Antibody response




Antibodies against S1
Antibodies against RBD domain correlate to neutralisation antibodies

Antibody Response - Seroconversion

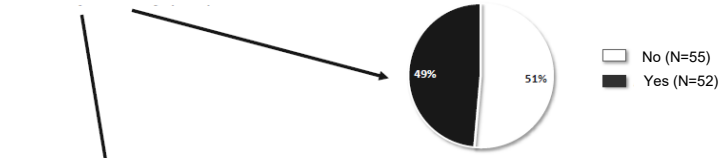
Antibodies appear in blood after: ≈10-20 days
Maintenance of antibody response:
≈2-3 years (measured for SARS-CoV-1)

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

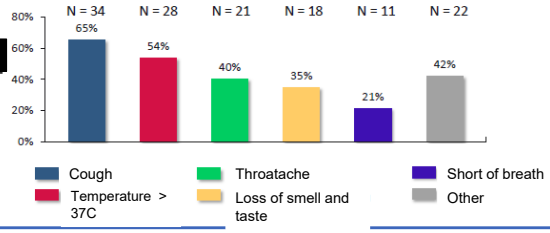
# SARS-CoV-2

## Presence of respiratory symptoms after 1.1.2020

**Respondents with antibody positive test (107)**




**Symptoms (N=52)**




Evropská unie
Evropský sociální fond
Operační program Zaměstnanost

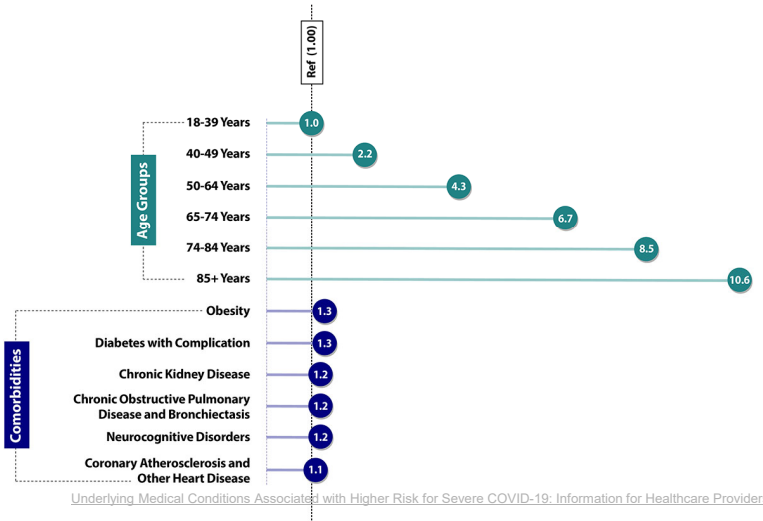
NÁRODNÍ SCREENINGOVÉ CENTRUM

ÚZIS

MINISTERSTVO ZDRAVOTNICTVÍ ČESKÉ REPUBLIKY

# Risk groups

**COVID-19 Death Risk Ratio (RR) for Select Age Groups and Comorbid Conditions**

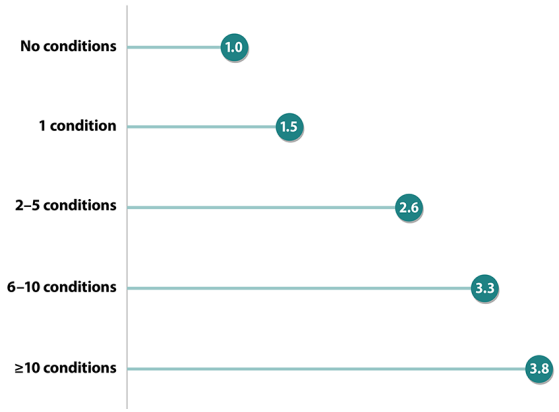



Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Providers (cdc.gov)

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

# Risk groups

**COVID-19 Death Risk Ratio (RR) Increases as the Number of Comorbid Conditions Increases**




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

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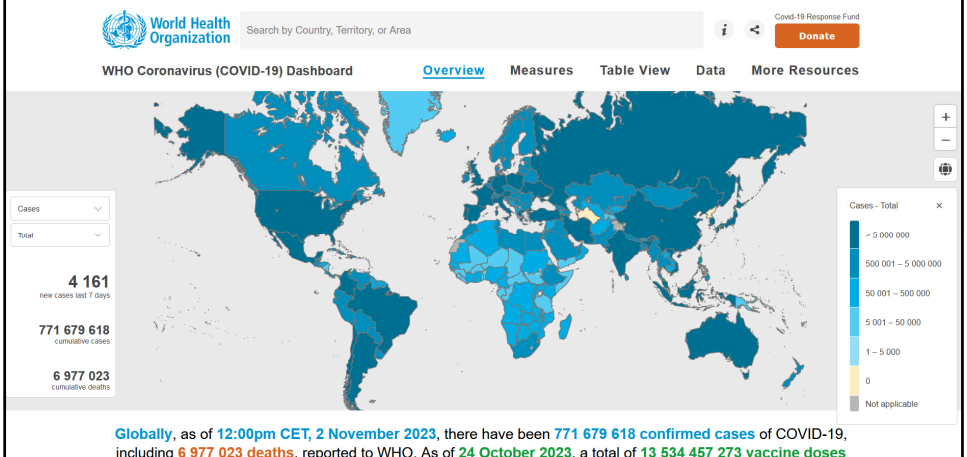
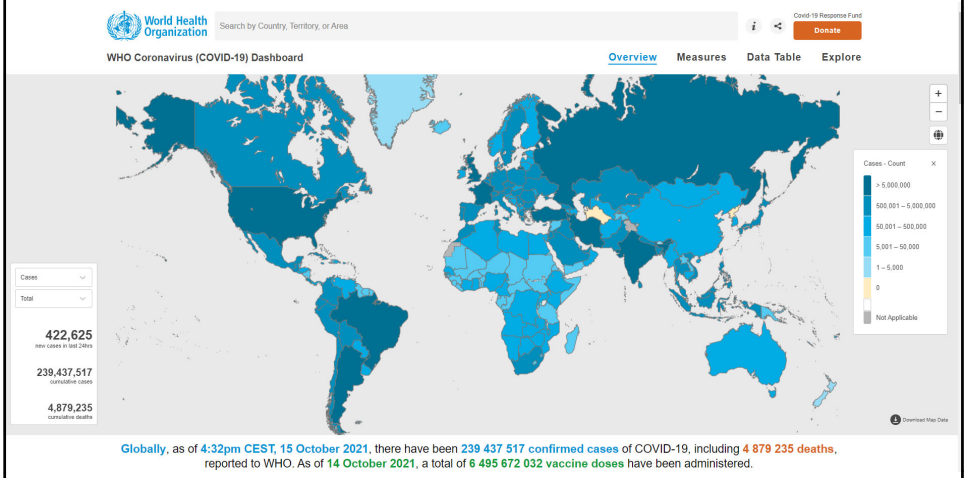
# Epidemiology




**Globally**, as of **12:00pm CET, 2 November 2023**, there have been **771 679 618 confirmed cases** of COVID-19, including **6 977 023 deaths**, reported to WHO. As of **24 October 2023**, a total of **13 534 457 273 vaccine doses**

# Epidemiology

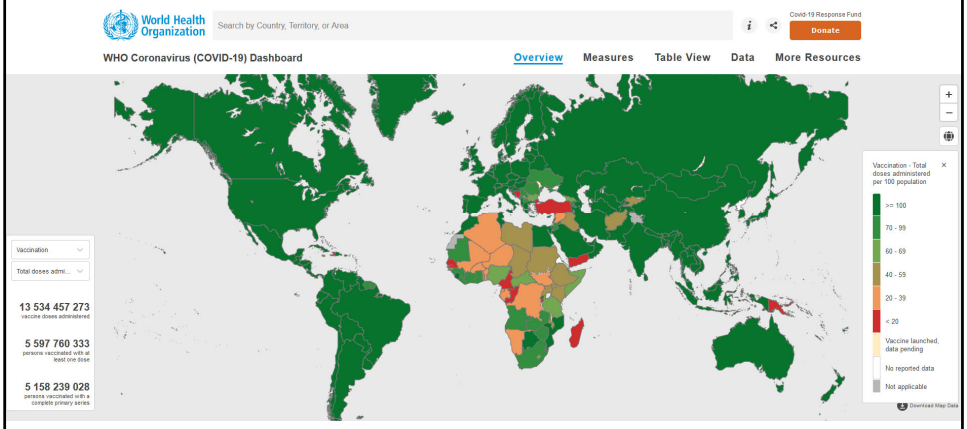



Globally, as of 4:32pm CEST, 15 October 2021, there have been 239 437 517 confirmed cases of COVID-19, including 4 879 235 deaths, reported to WHO. As of 14 October 2021, a total of 6 495 672 032 vaccine doses have been administered.

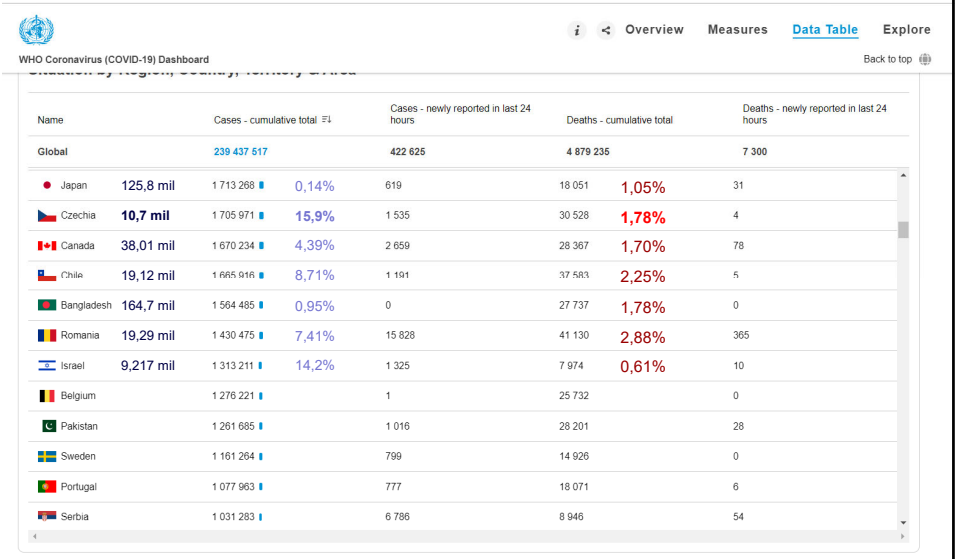
# Epidemiology


Globally, as of 12:00pm CET, 2 November 2023, there have been 771 679 618 confirmed cases of COVID-19, including 6 977 023 deaths, reported to WHO. As of 24 October 2023, a total of 13 534 457 273 vaccine doses

# Epidemiology




# Epidemiology



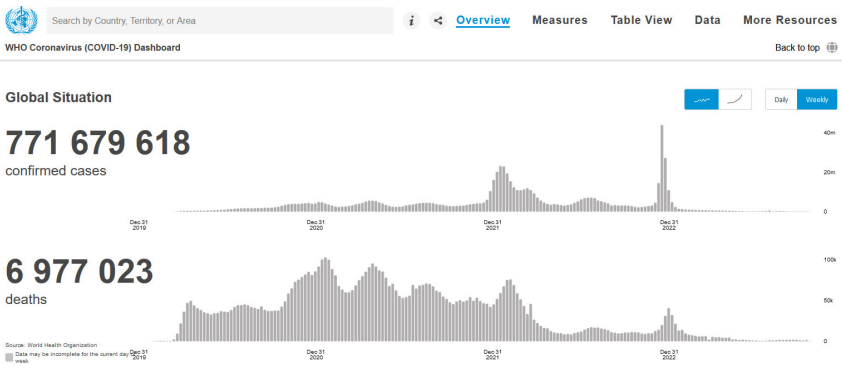

| Name | | Cases - cumulative total | | Cases - newly reported in last 24 hours | Deaths - cumulative total | | Deaths - newly reported in last 24 hours |
|---|---|---|---|---|---|---|---|
| Global | | 239 437 517 | | 422 625 | 4 879 235 | | 7 300 |
| Japan | 125,8 mil | 1 713 268 | 0,14% | 619 | 18 051 | 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 |

# Epidemiology

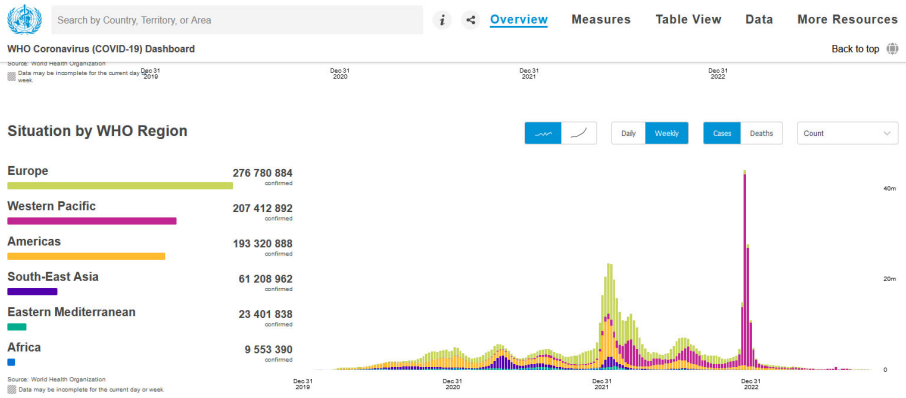
**Situation by Region, Country, Territory & Area**

| Name | | Cases - cumulative total | Cases - newly reported in last 7 days | | Deaths - cumulative total | Deaths - newly reported in last 7 days | | Vaccines - Total doses administered per 100 population | Vaccines - Persons vaccinated with a complete primary series per 100 population | Vaccines - Persons vaccinated with at least one booster or additional dose 100 population |
|---|---|---|---|---|---|---|---|---|---|---|
| **Global** | | **771,679,618** | **4,161** | | **6,977,023** | **63** | | **173.64** | **66.18** | **31.91** |
| Malaysia | 33,57 mil | 5 131 899 | | 15,29% | 37 202 | | 0,72% | 224,96 | 85,11 | 50,49 |
| Israel | 9,217 mil | 4 840 714 | | 52,51% | 12 697 | | 0,26% | 207 | 71,75 | 50,27 |
| Belgium | 11,59 mil | 4 817 196 | | 41,56% | 34 339 | | 0,71% | 252,7 | 78,84 | 62,37 |
| Thailand | 71,6 mil | 4 758 125 | 206 | 6,65% | 34 487 | 2 | 0,72% | 199,63 | 77,64 | 39,37 |
| Canada | 38,01 mil | 4 716 205 | | 12,41% | 53 297 | | 0,13% | 258,59 | 82,96 | 52,4 |
| Czechia | **10,51 mil** | 4 665 557 | 1 361 | **44,39%** | 42 917 | 9 | **0,09%** | 174,1 | 65,5 | 41,52 |
| Peru | 33,72 mil | 4 522 474 | | 13,41% | 221 727 | | 4,90% | 271,73 | 86,91 | 67,16 |

# Epidemiology

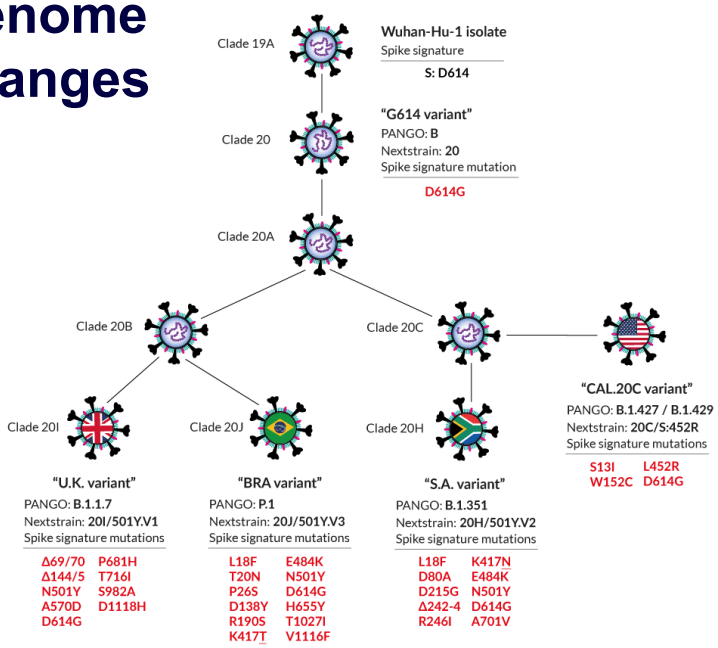


# Epidemiology




# Genome changes

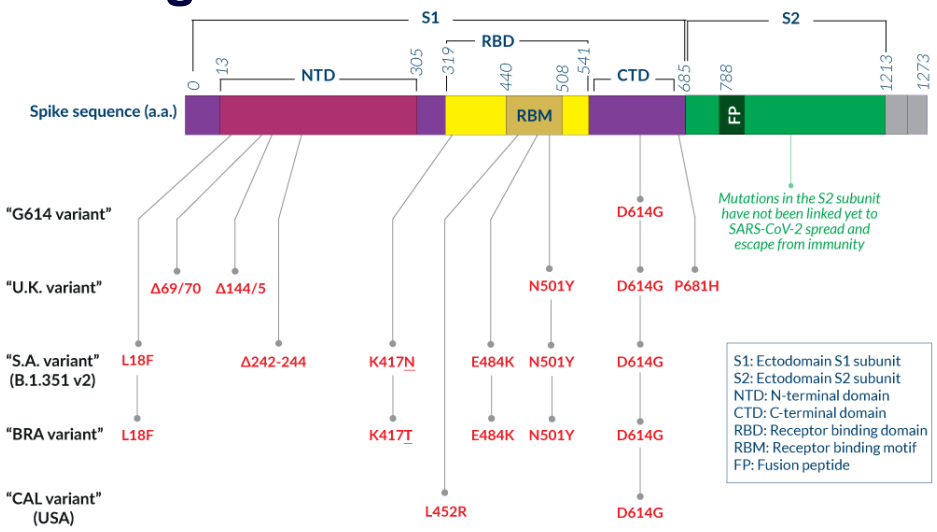
Simplified SARS-CoV-2 phylogenetic tree




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

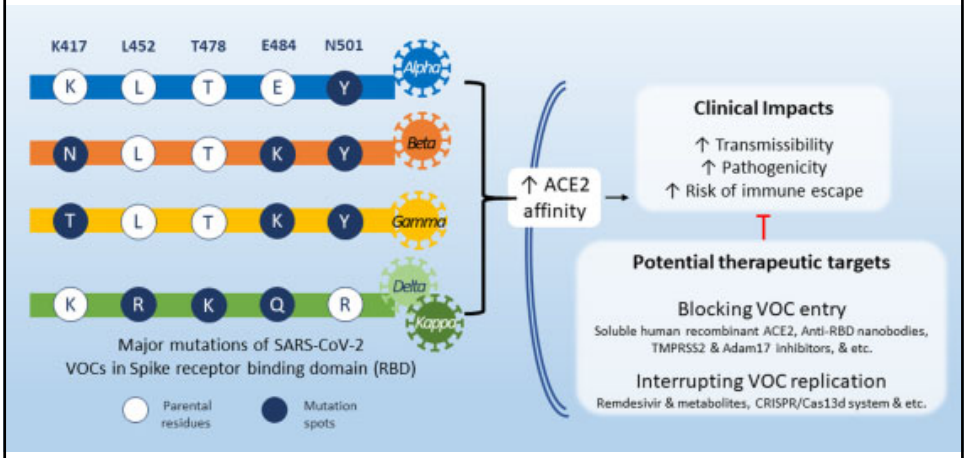
# Genome changes

Spike mutations of concern in SARS-CoV-2 variants



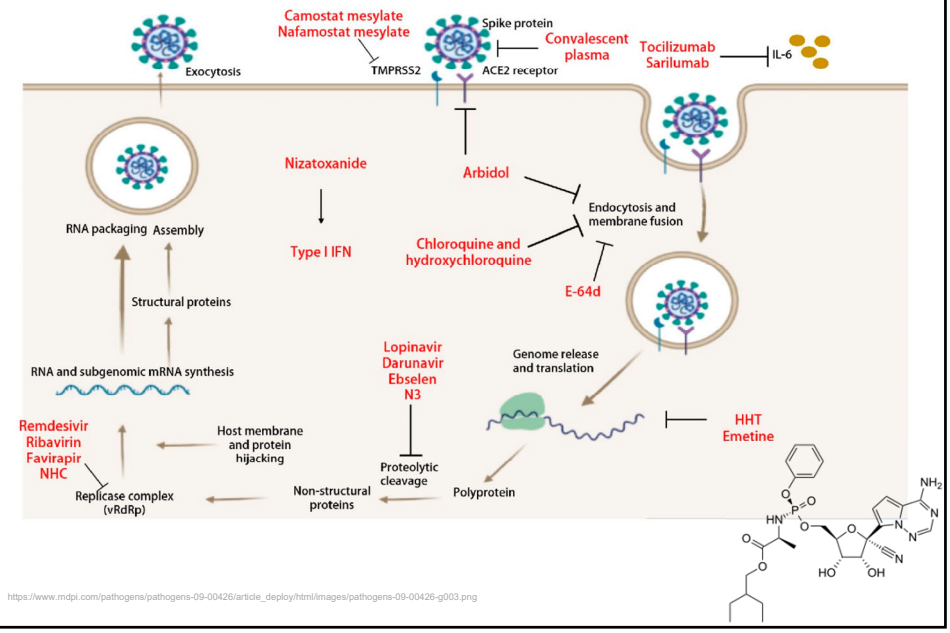

https://www.invivogen.com/sites/default/files/pictures/sars2-tree-invivogen.png

# Genome changes

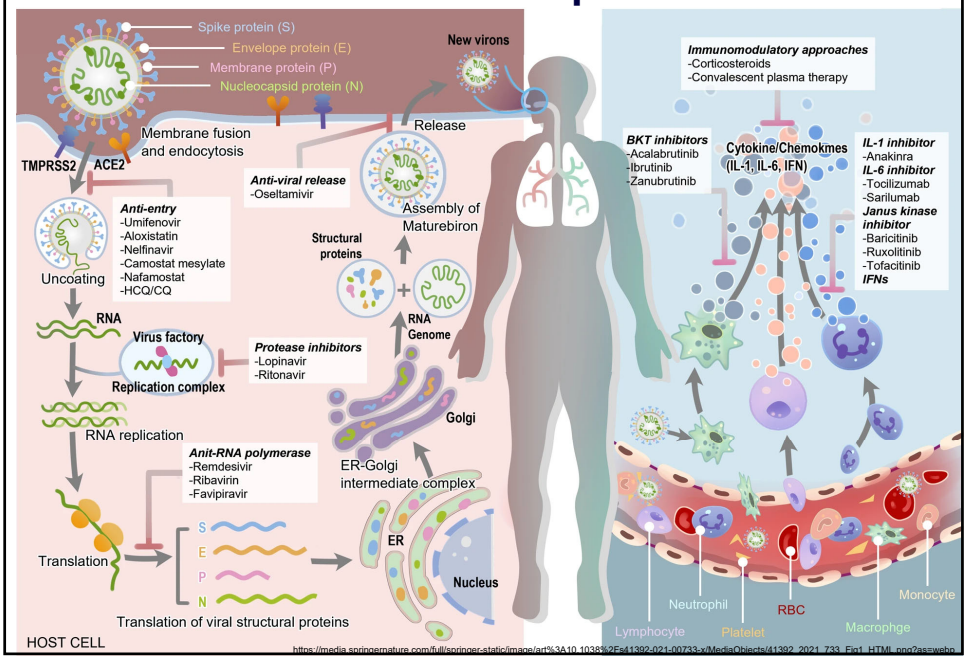



https://www.invivogen.com/sites/default/files/pictures/sars2-tree-invivogen.png

# Possible treatment options




# Treatment options



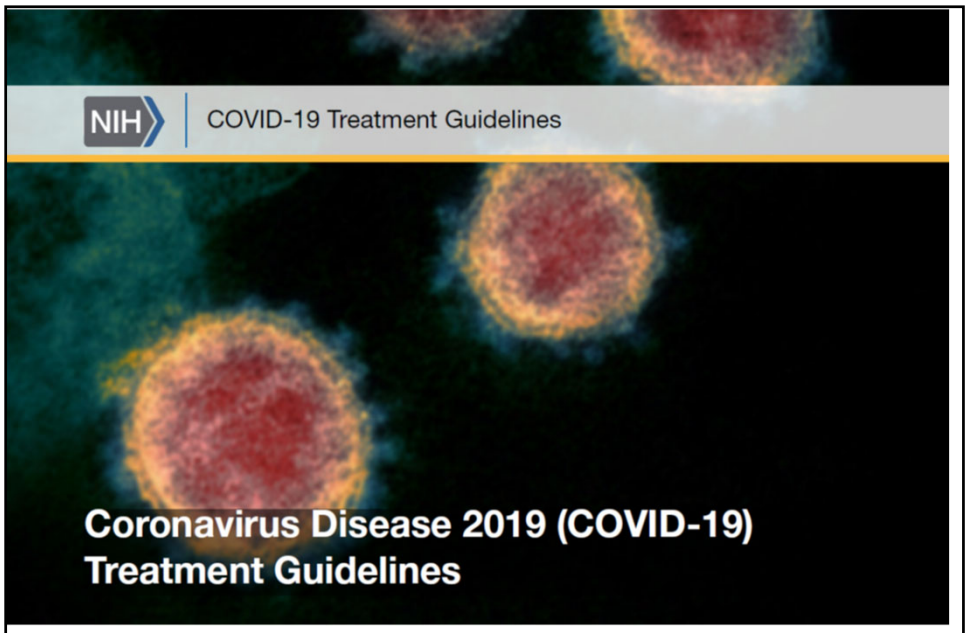



Figure 2. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

| 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]<br>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:<br>• **Remdesivir**[b] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)**<br>• **Dexamethasone plus remdesivir**[b] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)**<br>• **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:<br>• **Dexamethasone (AI)**<br>• **Dexamethasone plus remdesivir**[b] **(BIII)**<br>For recently hospitalized[c] patients with rapidly increasing oxygen needs and systemic inflammation:<br>• Add either **baricitinib (BIIa)** or **IV tocilizumab (BIIa)** to one of the two options above[d]<br>• 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)**<br>For patients who are within 24 hours of admission to the ICU:<br>• **Dexamethasone plus IV tocilizumab (BIIa)**<br>• 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]<br>• **Bamlanivimab plus etesevimab**; *or*<br>• **Casirivimab plus imdevimab**; *or*<br>• **Sotrovimab**<br>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**<br>*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**<br>*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)**.<br>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.<br>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*]

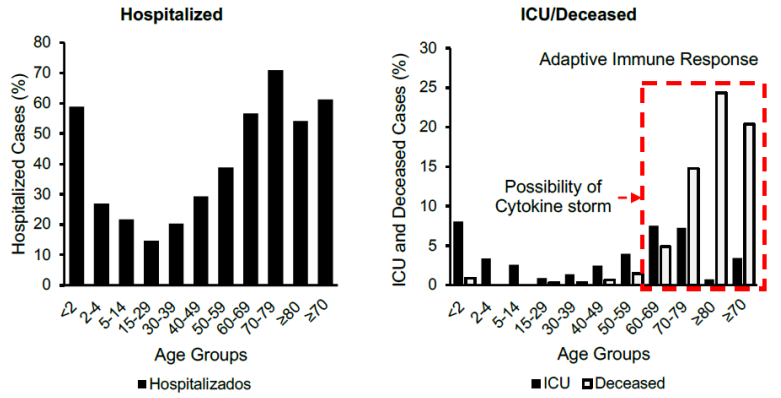



**Figure 7** Age distribution of the a) hospitalized, b) admitted to ICU or deceased in Spain based on data from 145,429 cases[26].

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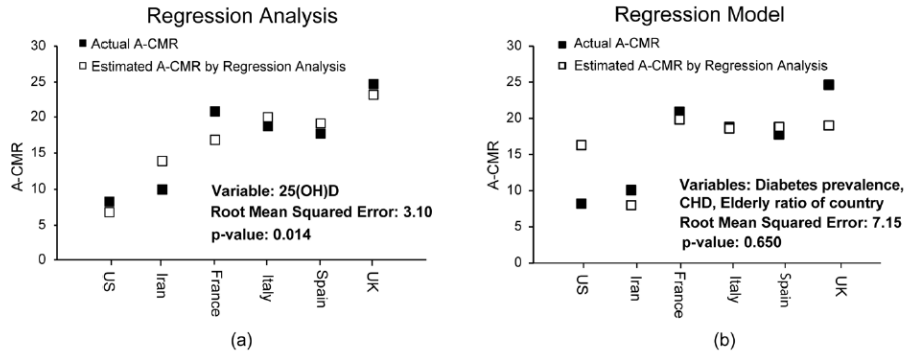


**Figure 6** Regression analysis based on (a) 25(OH)D, (b) Diabetes prevelance among men and women (age standardized), elderly ratio (≥70 yo) in the country, CHD death rate per 100, 000 (age standardized)

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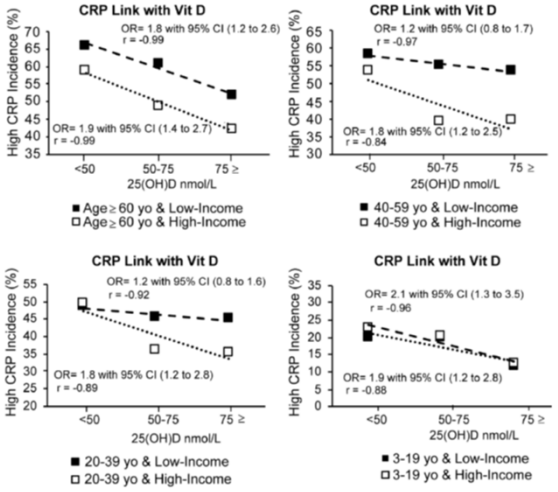
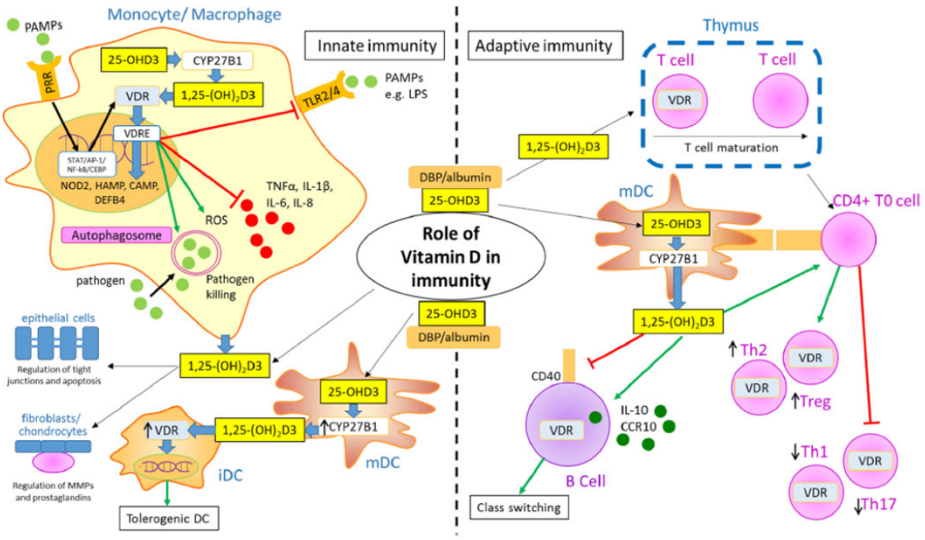
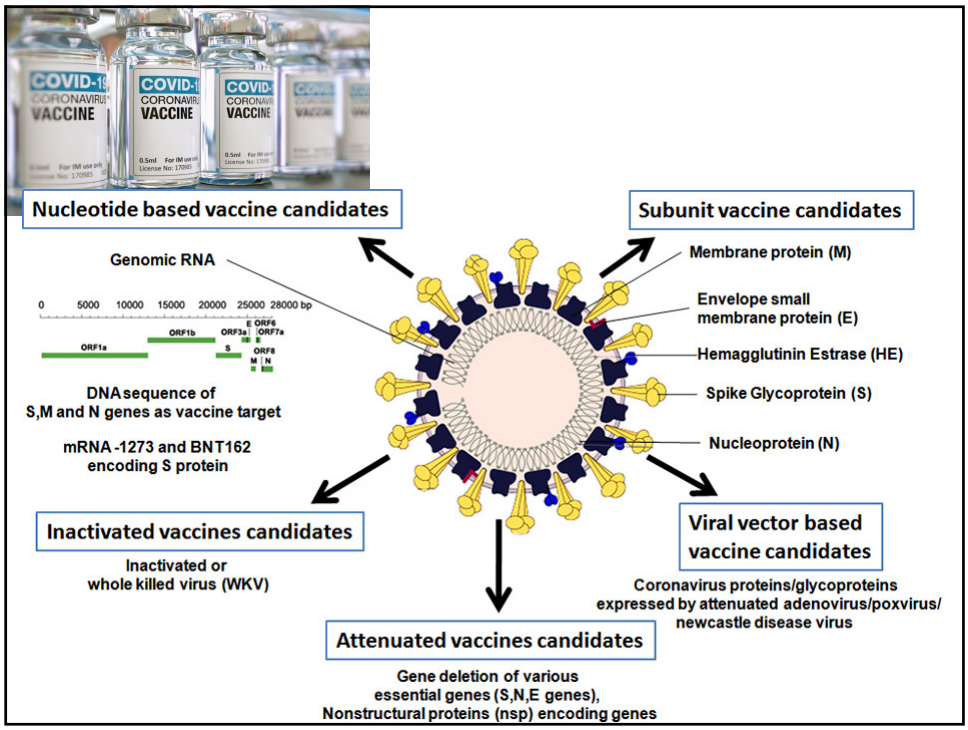
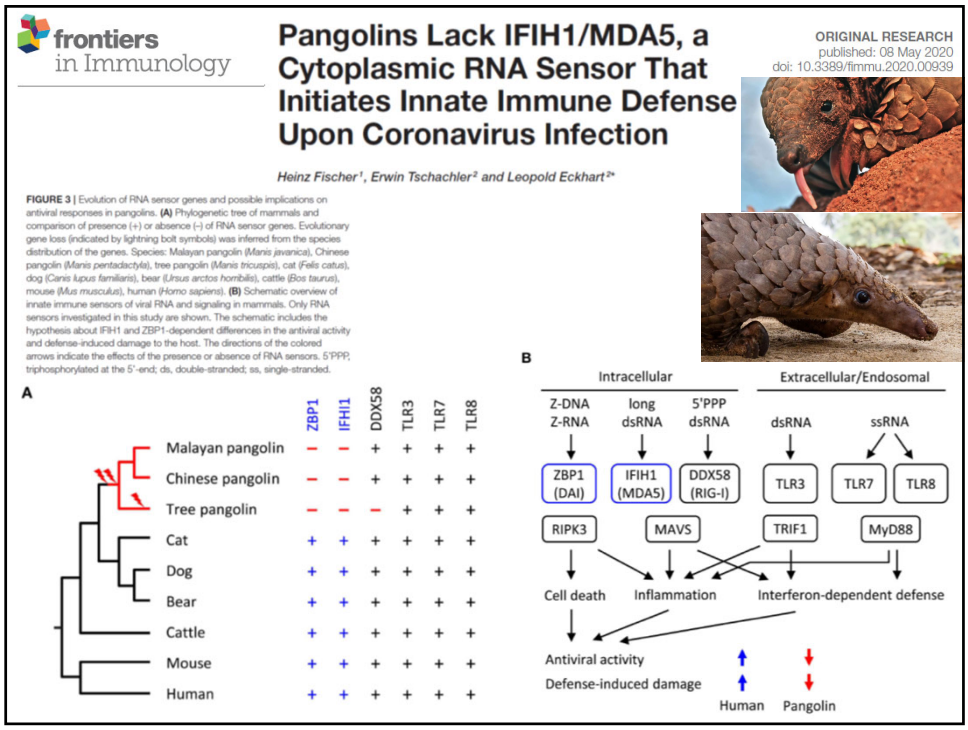



S.R. Harrison et al. Calcified Tissue International (2020) 106:58–75

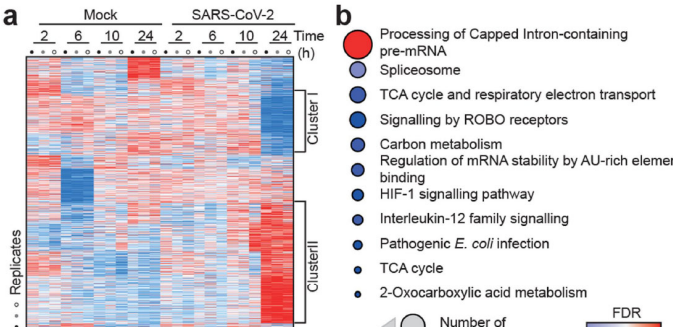

COVID-19
CORONAVIRUS
VACCINE
Nucleotide based vaccine candidates
Subunit vaccine candidates
Genomic RNA
0 5000 10000 15000 20000 25000 28000 bp
ORF1a
ORF1b
ORF3a
E
S
ORF6
ORF7a
ORF8
M
N
DNA sequence of
S,M and N genes as vaccine target
mRNA-1273 and BNT162
encoding S protein
Membrane protein (M)
Envelope 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.
A
ZBP1 IFIH1 DDX58 TLR3 TLR7 TLR8
Malayan pangolin – – + + + +
Chinese pangolin – – + + + +
Tree pangolin – – – + + +
Cat + + + + + +
Dog + + + + + +
Bear + + + + + +
Cattle + + + + + +
Mouse + + + + + +
Human + + + + + +
B
Intracellular
Extracellular/Endosomal
Z-DNA
Z-RNA
long
dsRNA
5'PPP
dsRNA
dsRNA
ssRNA
ZBP1
(DAI)
IFIH1
(MDA5)
DDX58
(RIG-I)
TLR3
TLR7
TLR8
RIPK3
MAVS
TRIF1
MyD88
Cell death
Inflammation
Interferon-dependent defense
Antiviral activity
Defense-induced damage
Human
Pangolin

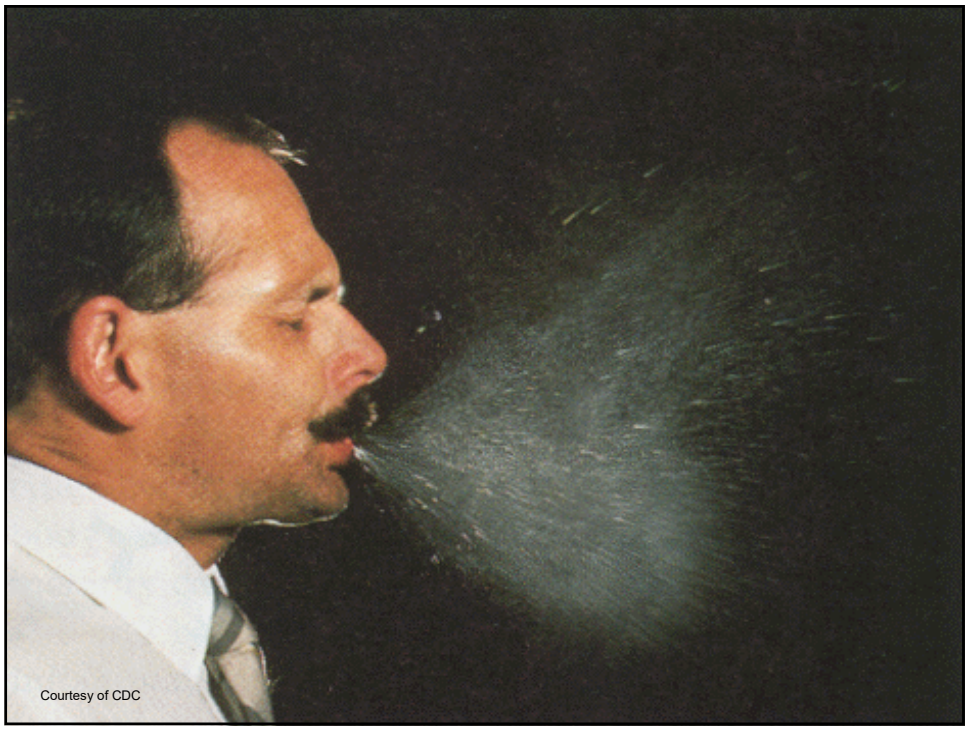
Article

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

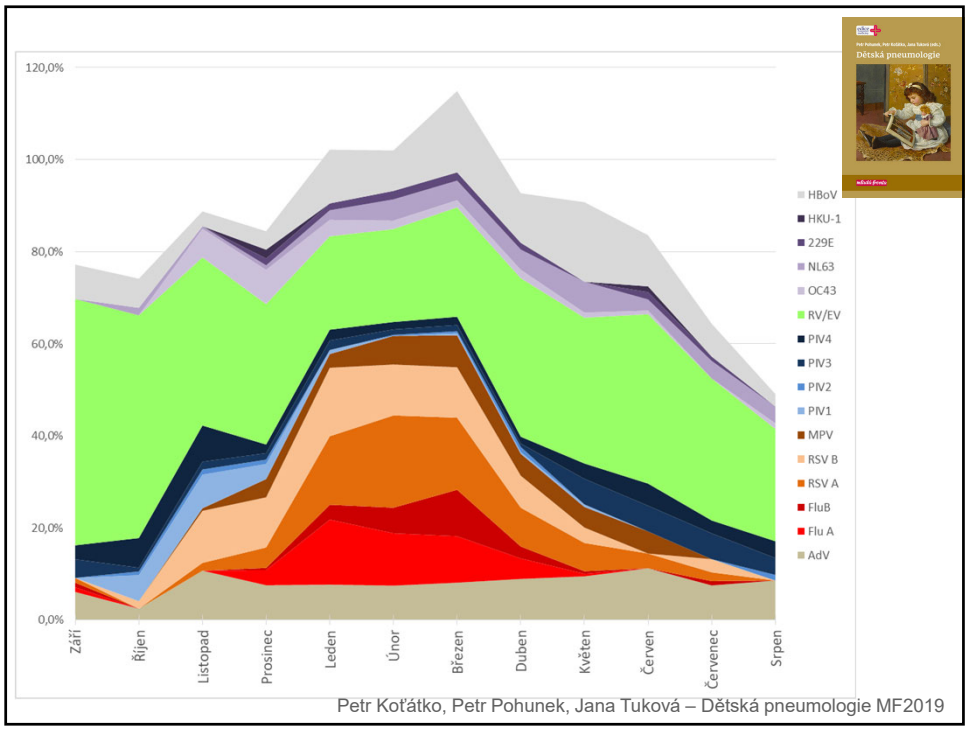
https://doi.org/10.1038/s41586-020-2332-7
Received: 27 February 2020
Accepted: 6 May 2020
Published online: 14 May 2020



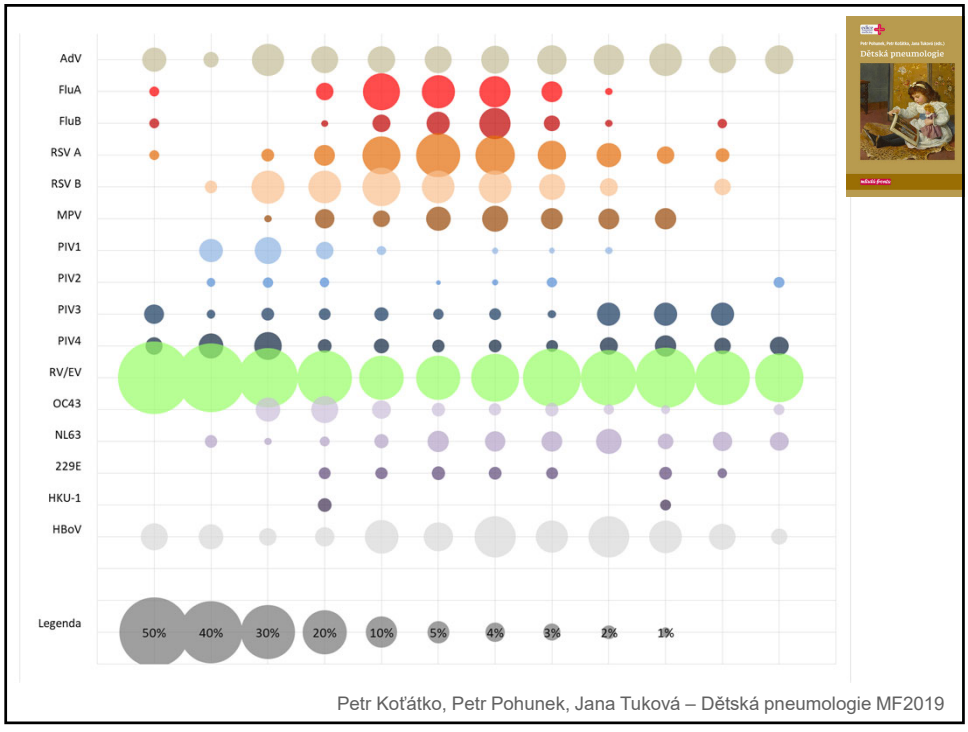

**These analyses revealed that SARS-CoV-2 reshapes central cellular pathways, such as translation, splicing, carbon metabolism and nucleic acid metabolism. Small molecule inhibitors targeting these pathways prevented viral replication in cells. Our results reveal the cellular infection profile of SARS-CoV-2 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.**



Courtesy of CDC

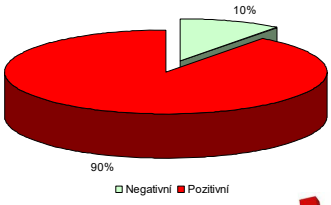


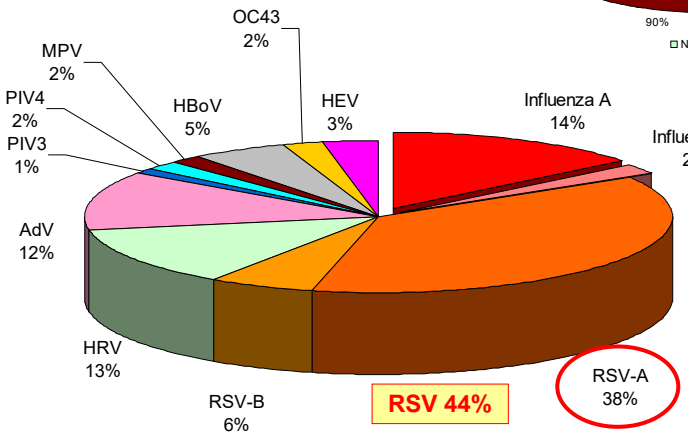

Petr Koťátko, Petr Pohunek, Jana Tuková – Dětská pneumologie MF2019




Petr Koťátko, Petr Pohunek, Jana Tuková – Dětská pneumologie MF2019

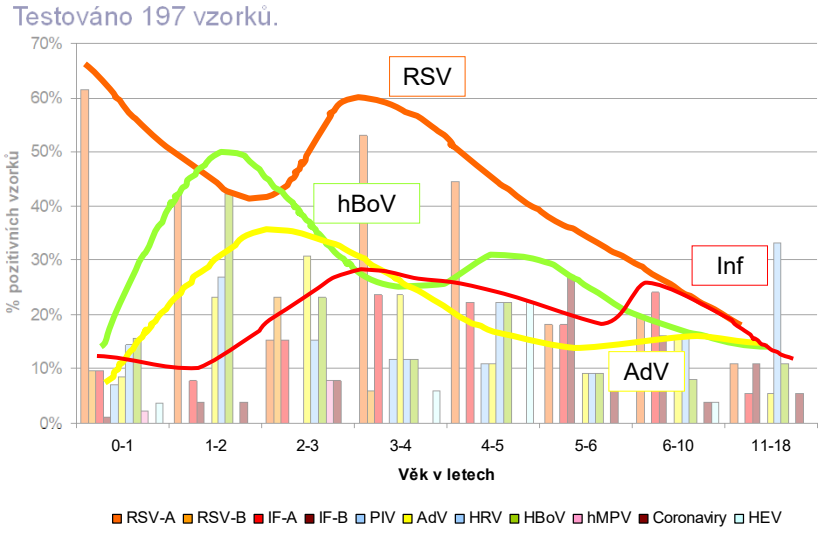
# Frequency of respiratory viruses in Motol University Hospital Dept. of Paediatrics (PCR)




**Flu in 16% only**

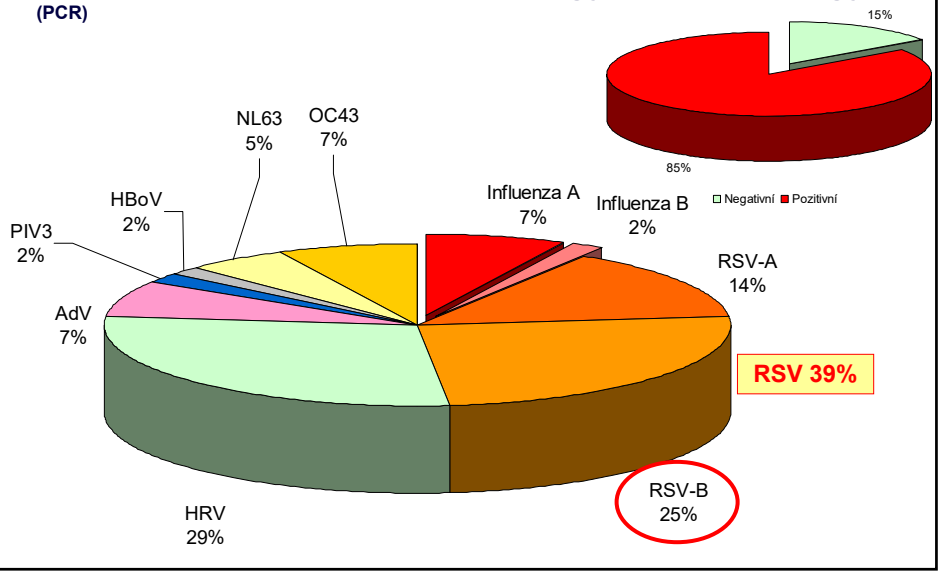
# Frequency of respiratory viruses in Motol University Hospital (PCR)



## Frequency of respiratory viruses in Motol University Hospital

## Dept. of Paediatric Haematology and Oncology

**(PCR)**




## CAVE

**Every detection technique has limits!**

**Even molecular-biological = PCR!**

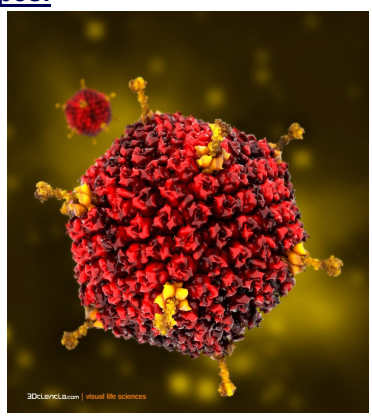
It is true also for commercial kits e.g. There is evidence that Anyplex RV16 detects only **10 out of 60 described serotypes.**

**Most frequently detected,**

**but not the only!!!!**

**PCR negativity does not**

**neccesary omits AdV infection.**



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