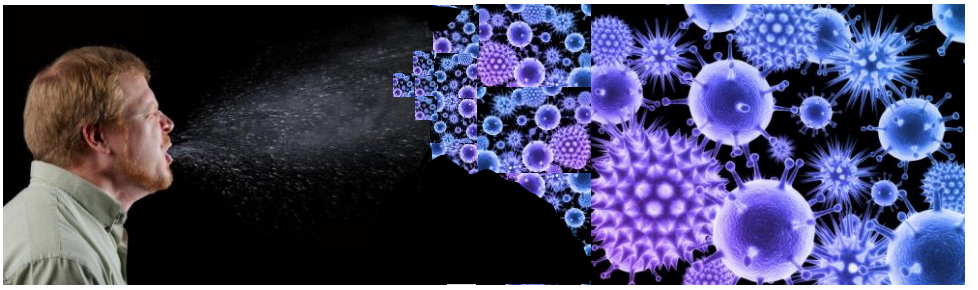
Influenza and exanthematic viruses



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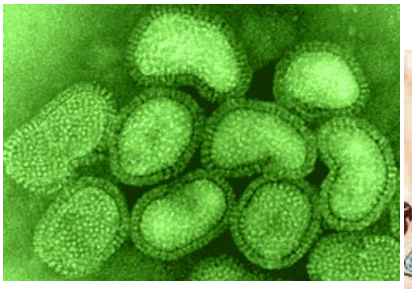
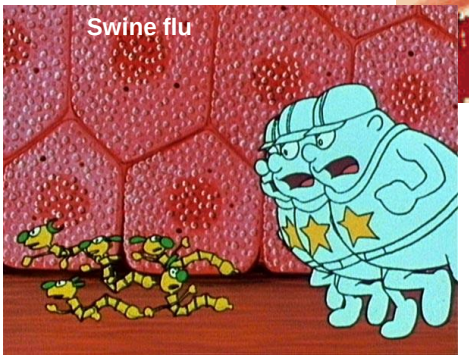
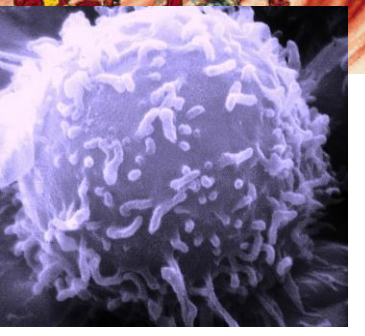
FN MOTOL

HSCT UNIT - PEDIATRICS PRAGUE CZECH REPUBLIC

Life is fight







Viruses described in immunosupressed patient

RNA viruses


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

ss RNA

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

ds RNA

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

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

Adapted ECDC Definitions of Respiratory Tract Infectious Disease (RTID)

Clinical criteria

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

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

Epidemiological Criteria

- An epidemiological link with human to human transmission

Laboratory Criteria

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

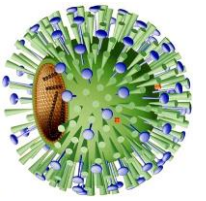
Case Classification

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

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

What is influenza?

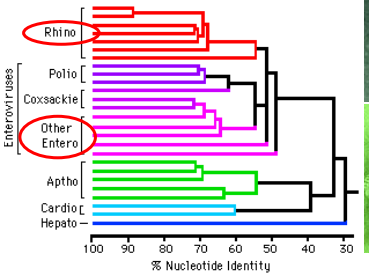
- An acute respiratory illness resulting from infection with an influenza virus (Orthomyxoviruses)
- Highly infectious and can spread rapidly from person to person
- Some strains cause more severe illness than others
- Highly infectious viral illness
- 412 BC - first mentioned by Hippocrates
- 1580 - first pandemic described
- 1580-1900 - 28 pandemics
- Virus first isolated in 1933

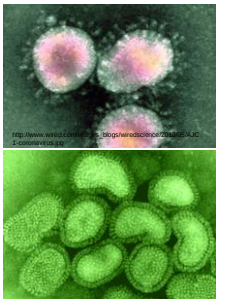


History of viral respiratory infections

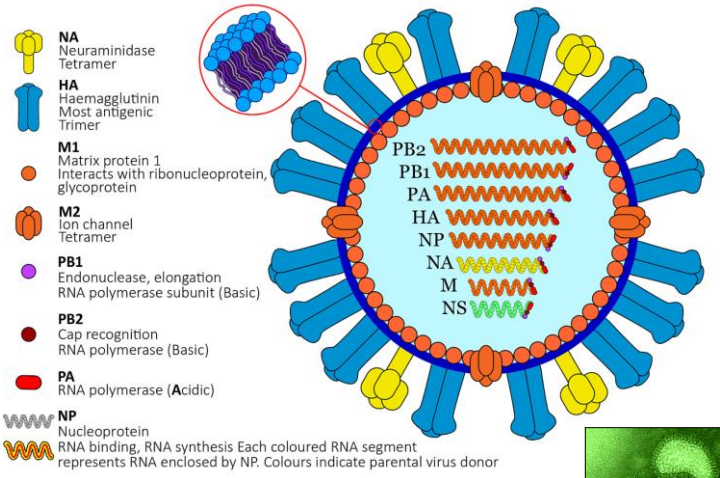
Influenza virus 1933
Coxsackive virus 1948
Echovirus 1951
Adenovirus 1953
HRV 1953
HRSV 1956
HPIV 1956
HCoV-229E 1966
HCoV-OC43 1967

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



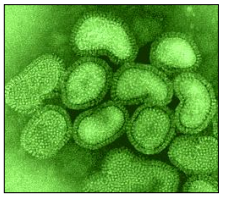


ORTHOMYXOVIRUSES



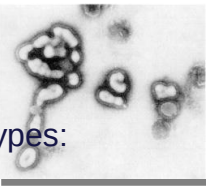
typ A, B, C : NP, M1 protein
sub-typy: HA nebo NA protein

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



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

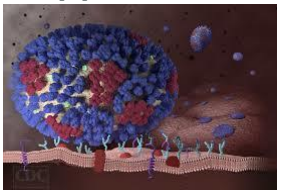
Types of influenza viruses



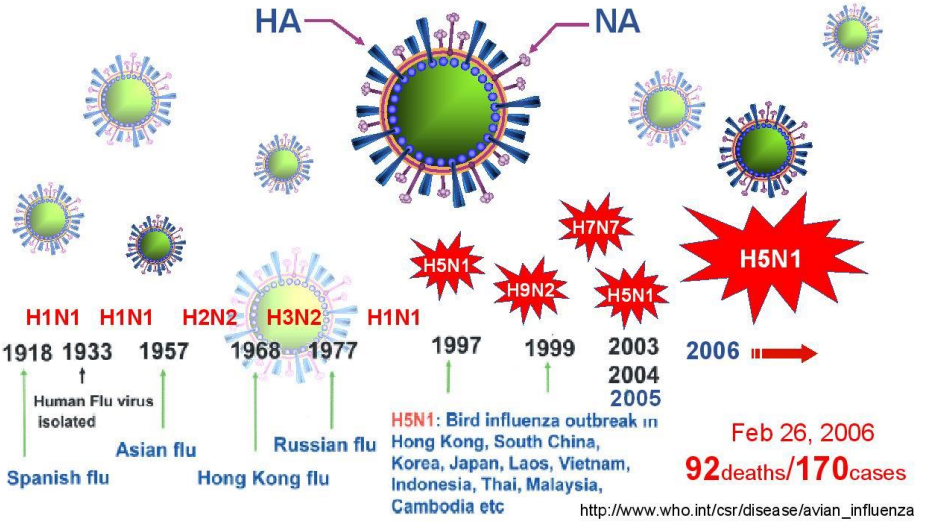
- Influenza viruses are divided into three main types: influenza A, B, and C
- **Group A** viruses
  - infect birds and other animals, as well as humans
  - source of seasonal influenza epidemics and all pandemics
  - moderate to severe illness
  - all age groups
  - humans and other animals
  - typed by NA and HA
- **Group B**
  - changes less rapidly than type A – no Ag shift
  - infects humans only, milder epidemics
  - primarily affects children
- **Group C** viruses
  - infect humans only and do not cause pandemics

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)



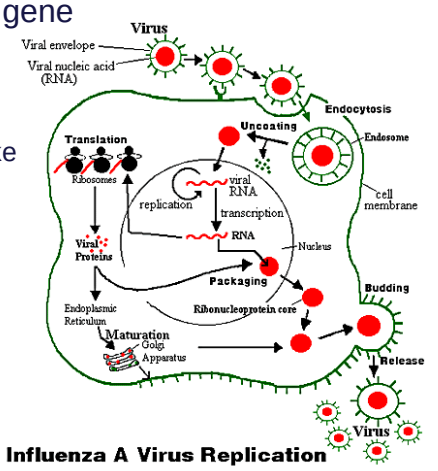
Influenza A viruses



Influenza Antigenic Changes

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

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

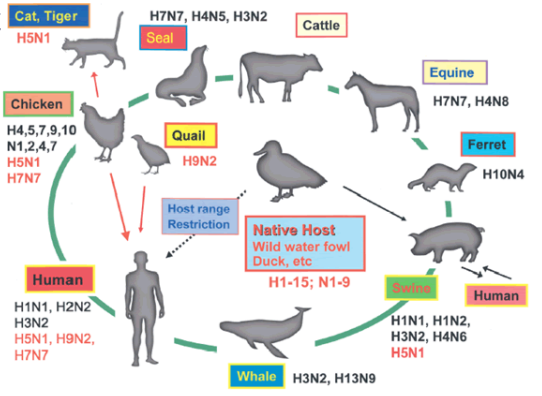


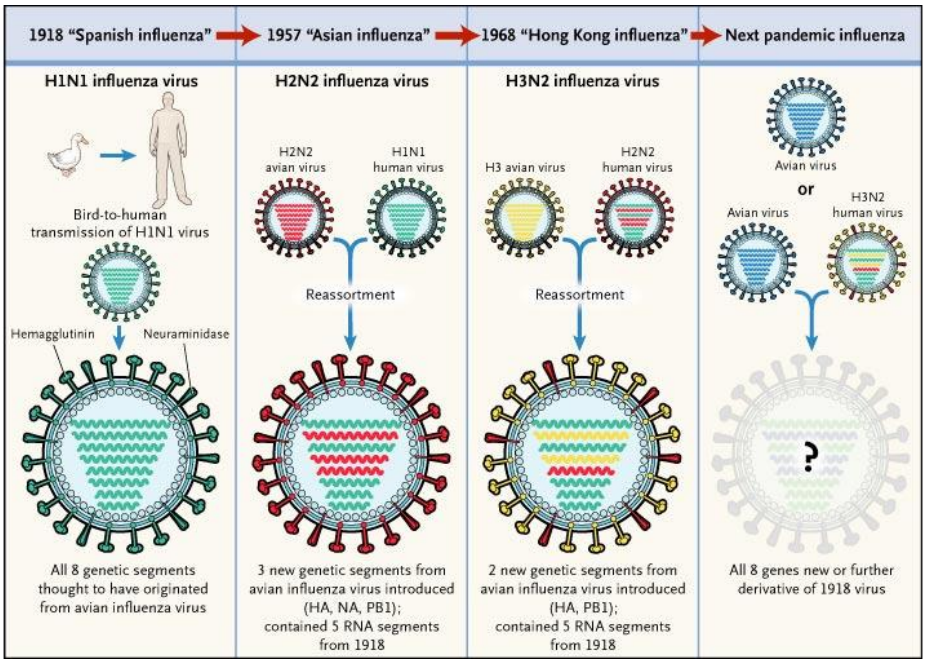
Influenza A Virus Replication

Influenza Antigenic Changes

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

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

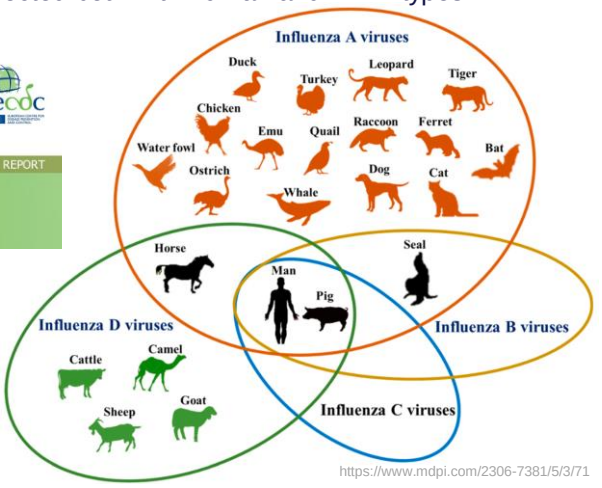




https://www.nejm.org/doi/full/10.1056/NEJMp058281

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

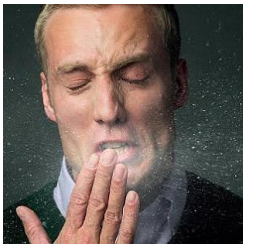
Burden of Influenza

- 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

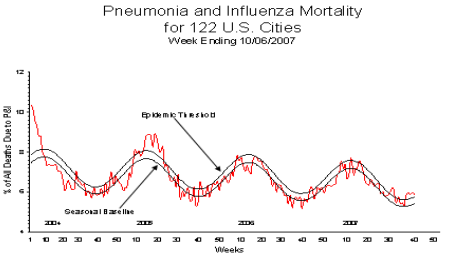
Influenza Associated Pulmonary and Circulatory Deaths, 1998

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

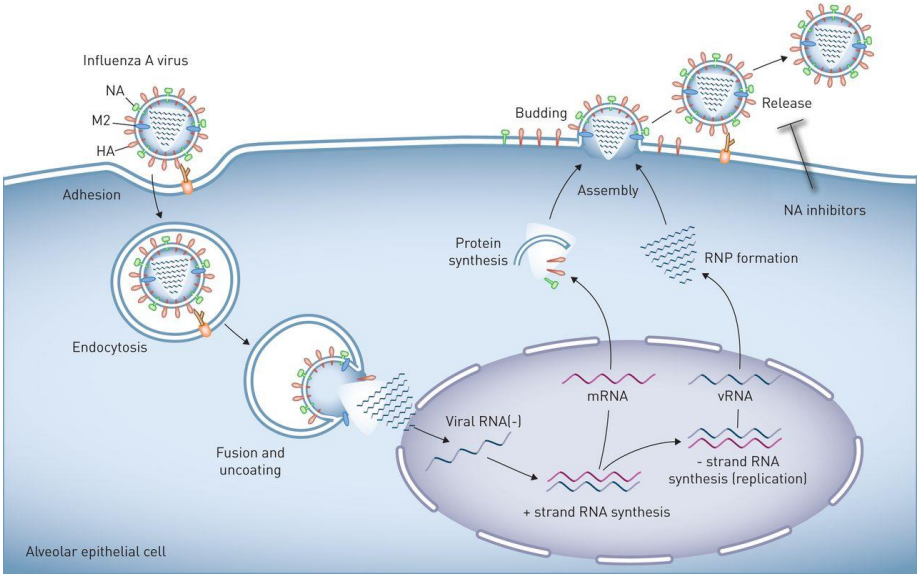
Influenza Epidemiology



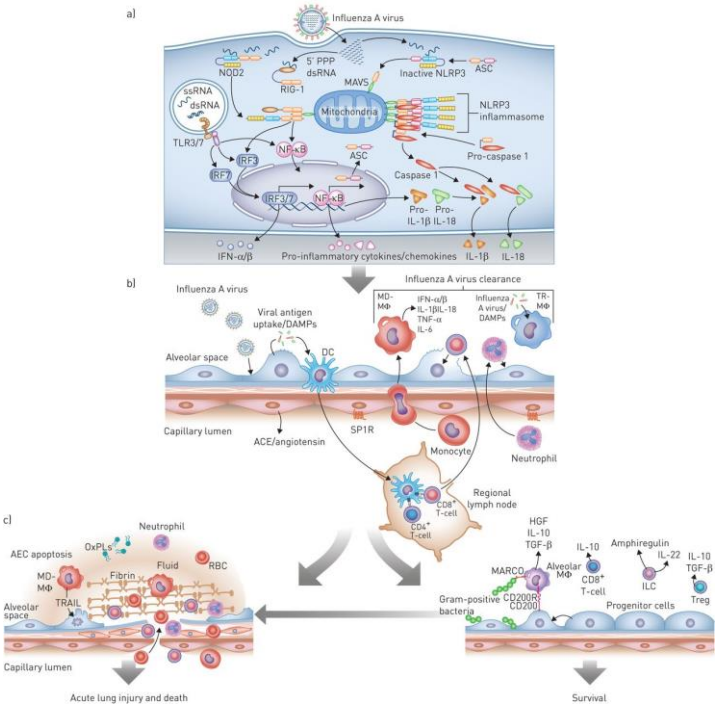
- Reservoir: Human, animals (type A only)
- Transmission: - inhaling respiratory aerosols containing the virus, produced when infected person talks, coughs, or sneezes
  100,000 - 1,000,000 virions/droplet
  » touching an infected person or an item contaminated with the virus and then touching your eyes, 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

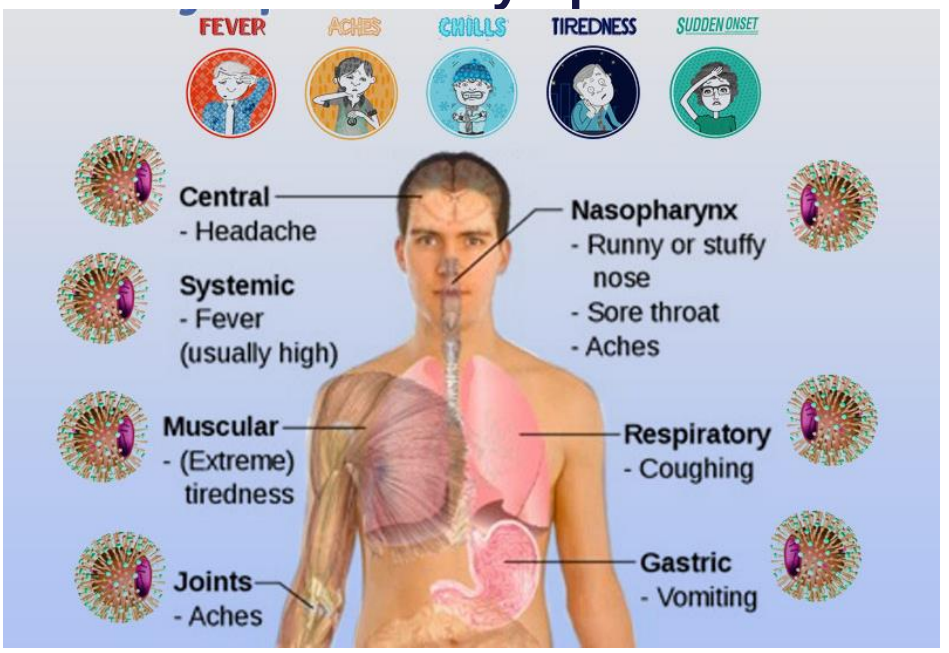


https://erj.ersjournals.com/content/45/5/1463



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

Influenza symptoms



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"

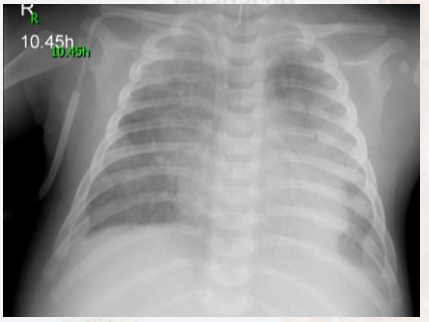
1 million deaths

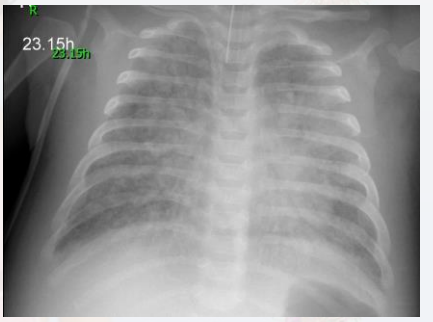
H3N2

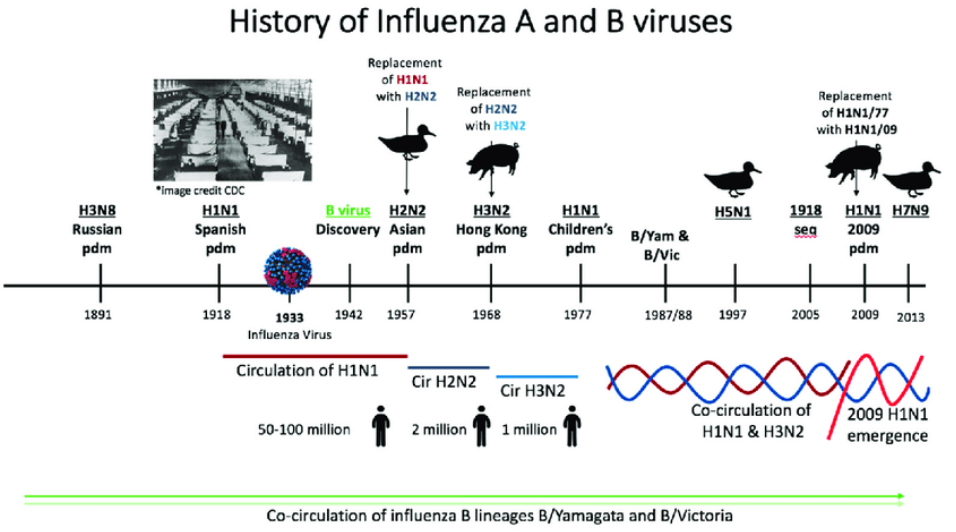
1920 1940 1960 1980 2000

Influenza symptoms

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



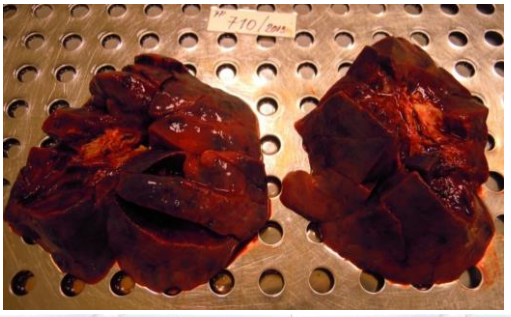




Francis, Magen & King, Morgan & Kelvin, Alyson. (2019). Back to the Future for Influenza Preimmunity—Looking Back at Influenza Virus History to Infer the Outcome of Future Infections. Viruses. 11. 122. 10.3390/v11020122.

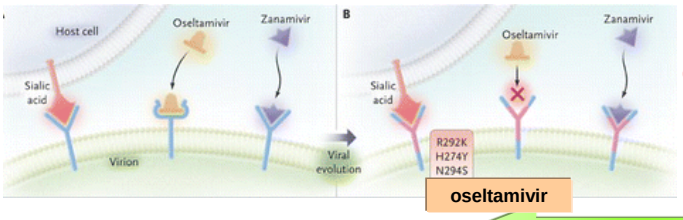
Patient 1

Influenza A virus



Macroscopic picture of influenza pneumonia.

1st proven <u>oseltamivir resistance</u> in the Czech Republic.



Resistance developed after 4 weeks of therapy.

oseltamivir

Clinical improvement

***7.1.2013 1 2 3 4 5 +12.6.2013**

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

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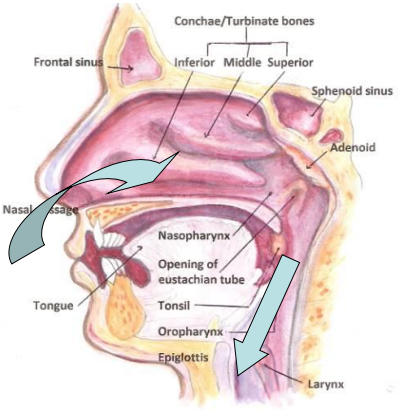
What to aim during the process of dg?

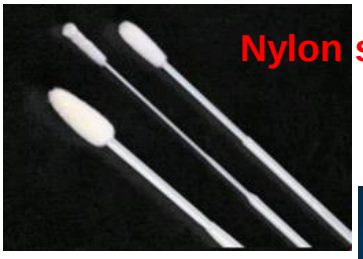
Good sampling of biological material

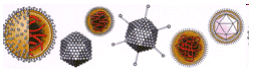
First proliferation at the mucos of upper respiratory tract.

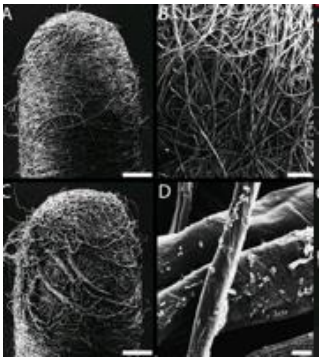
Virus	*Transmission from upper to lower RT*	*Mortality*
RSV	20-68%	17-70%
PIV	13-37%	10-30%
HRhV	<10%	<10%



Type of swabs

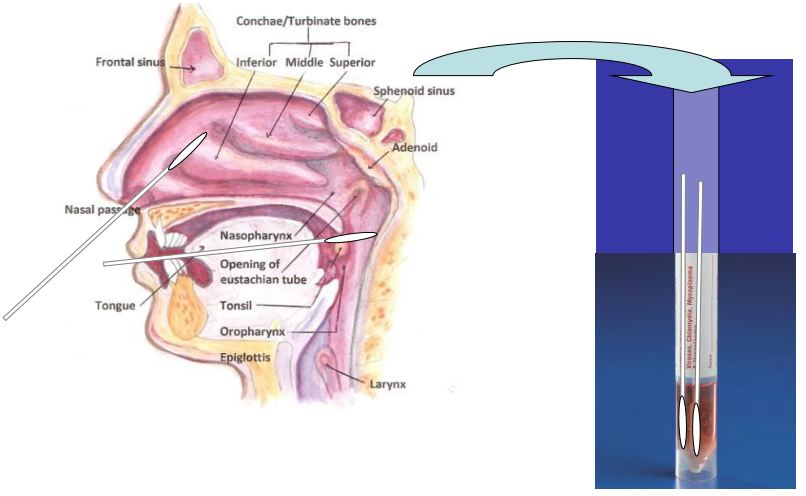






What to aim during the process of dg?

Good sampling of biological material



Diagnosis

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

- Serology

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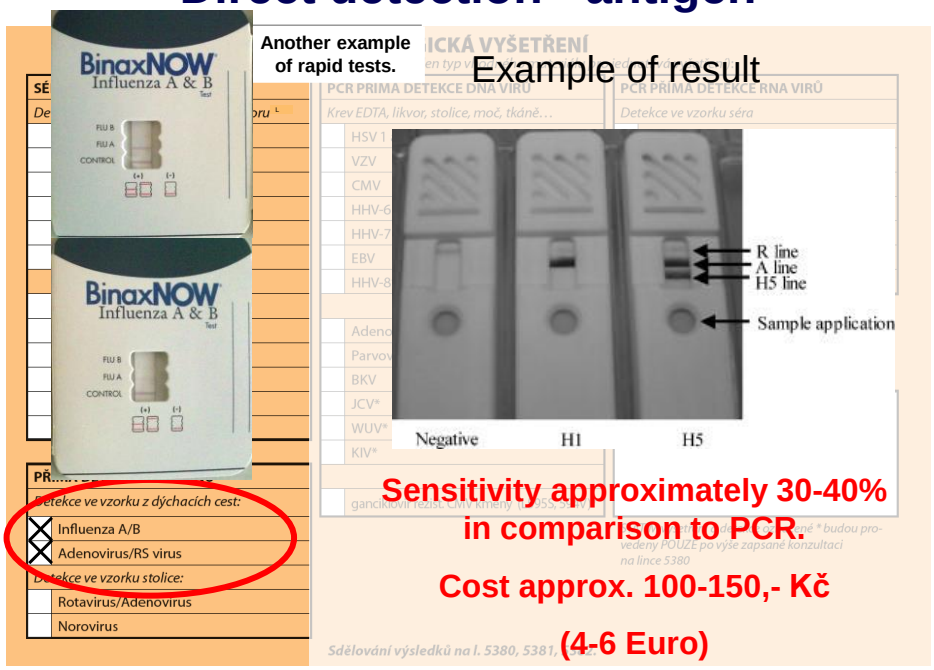
Direct detection - antigen



Another example of rapid tests.

Example of result

Sensitivity approximately 30-40% in comparison to PCR.

Cost approx. 100-150,- Kč

(4-6 Euro)

Sensitivity of antigen detection?

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

% positive Ag vs. PCR

Influenza A = 38%

Influenza B = 25%

RSV = 22%

AdV = 8.8%

Using of imunochromatografi tests

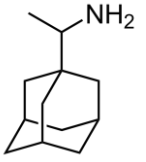
RapidVIDITEST

(RSV-Adeno, Influenza A+B)

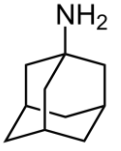
Treatment (prevention) - drugs

All virostatics have to be given early after infection

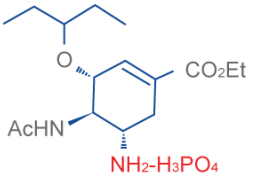
- rimantadine (M2)
  - Type A only
- amantadine (M2)
  - Type A only
- zanamivir (NA)
  - Type A and B
- oseltamivir (NA)
  - Type A and B
- peramivir (NA)
  - Type A and B



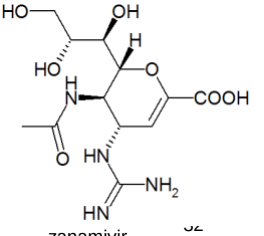
rimantadine



amantadine



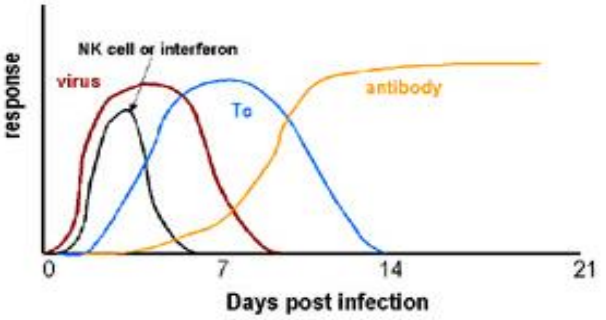
Oseltamivir Phosphate (Tamiflu)



zanamivir

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)

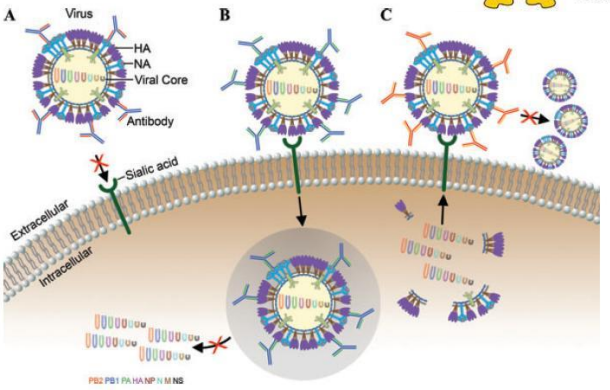
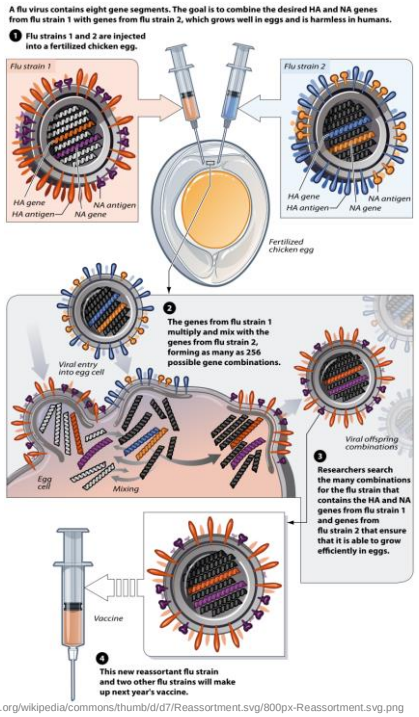


Figure 1. Mechanisms of antibody-mediated neutralization of the influenza virus. (A) Antibodies can block influenza HA1 glycoprotein binding to sialic acid residues of receptor proteins on host cells. (B) Antibodies specific to the HA2 glycoprotein of the virus can inhibit its low-pH triggered fusion 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.

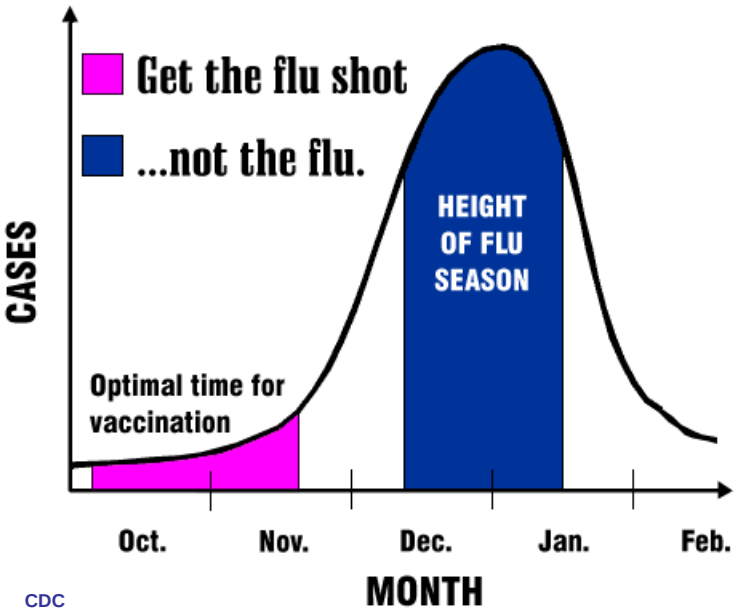
Vaccination

- inactivated
- egg grown
- sub-unit vaccine for children

- reassortant live vaccine approved 2003
  - for healthy persons (those not at risk for complications from influenza infection) ages 5-49 years



https://upload.wikimedia.org/wikipedia/commons/thumb/d/d7/Reassortment.svg/800px-Reassortment.svg.png



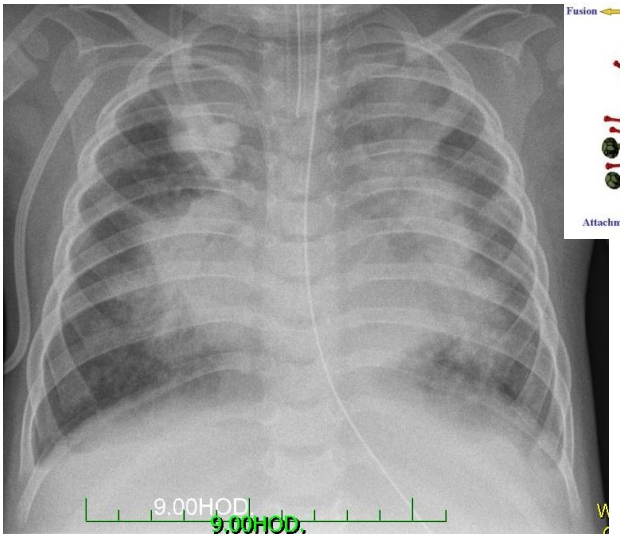
CDC

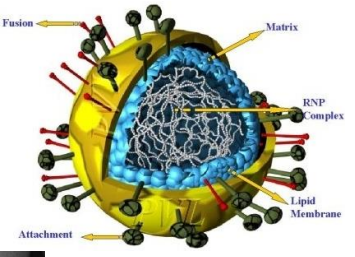
And what about Paramyxoviruses

Paramyxoviridae

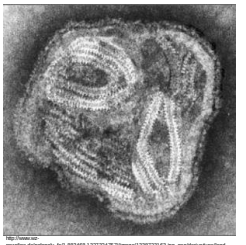
Respiratory-syntitial virus

RSV (boy treated for AML)





http://www.bushtib.com/wp-content/uploads/2010/10/dg_pmyxo.jpg

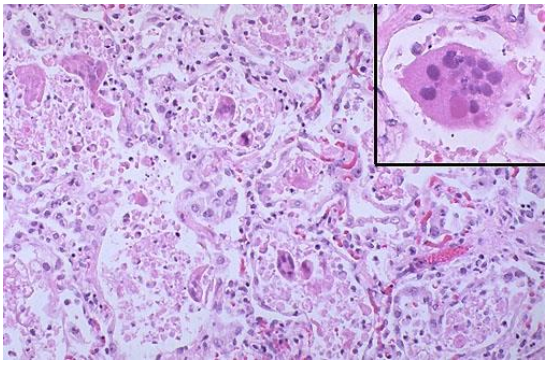


http://www.sci-newsline.de/pdcopy_fu/1.8834668.1327324757/image/1338872313.63.jpg_gender/watwes/landscape_300/1338872313.jpg

Paramyxoviridae

Pathophysiology

- Negative-strand RNA virus
- Family *Paramyxoviridae*
- RSV season late fall to early spring
- Peak in January/February
- Incubation 4-5 days
- LRI between days 5-7



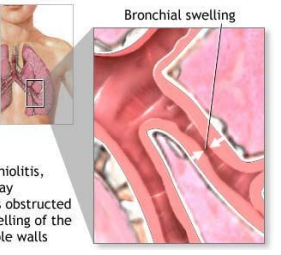
RSV in a child. Note the giant cells which are part of the viral cytopathic effect. The inset demonstrates a typical giant cell with a round, pink intracytoplasmic inclusion. RSV accounts for many cases of pneumonia in children under 2 years, and can be a cause for death in infants 1 to 6 months of age or older.

http://library.med.utah.edu/WebPath/jpeg1/LUNG158.jpg

- Most common cause of **bronchiolitis & pneumonia** in children under 1
- 25-40% of children develop bronchiolitis or pneumonia during first RSV infection
- 31/1,000 under 1 yr. are hospitalized with RSV
- 2% will die

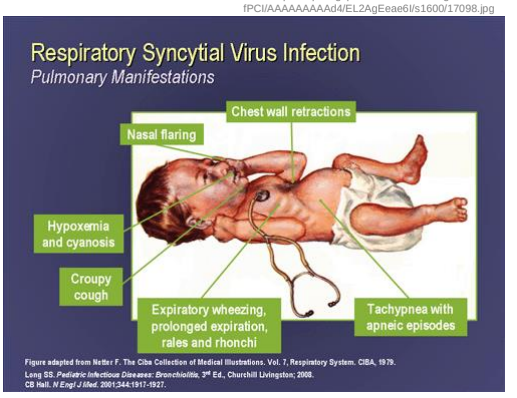
Paramyxoviridae

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



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

Severity

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

Paramyxoviridae

Inhibition of Interferons

- *Interferons believed to have antiviral properties*
- NS1 & NS2 inhibit IFN-alpha/beta
- Inhibition of IFN-gamma causes enhanced IgE production

Innate immune system

- *Activation contributes to inflammation & injury*
- RSV-F glycoprotein may inhibit T-cell activation
- RSV-infected CD8+ cells unable to release IFN-gamma

Interleukins & Chemokines

- *Infection induces expression*
- Chemokines mimic RSV glycoproteins
- Recruit monocytes, eosinophils, & neutrophils
- IL-8 levels positively associated with severity

Coinfection and Risk factors

- Rhinovirus contributes to increased severity in children with bronchiolitis
- Metapneumovirus (hMPV) enhances or mimics symptoms of RSV bronchiolitis
- 70% were coinfected w/ hMPV & required admission to PICU

Premature Birth

- 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

- Socioeconomic status
- Malnourishment
- Breastfeeding

Paramyxoviridae

Prophylaxis

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

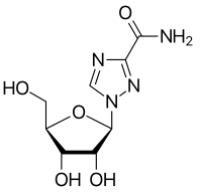
- **Palivizumab (Synagis)** – anti protein F antibody
- Given IM monthly
- Can reduce hospitalization of high risk infants by 45%
- Expensive
- Many providers reluctant to give
- Many parents unaware

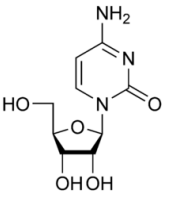
Paramyxoviridae

Treatment

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

- **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

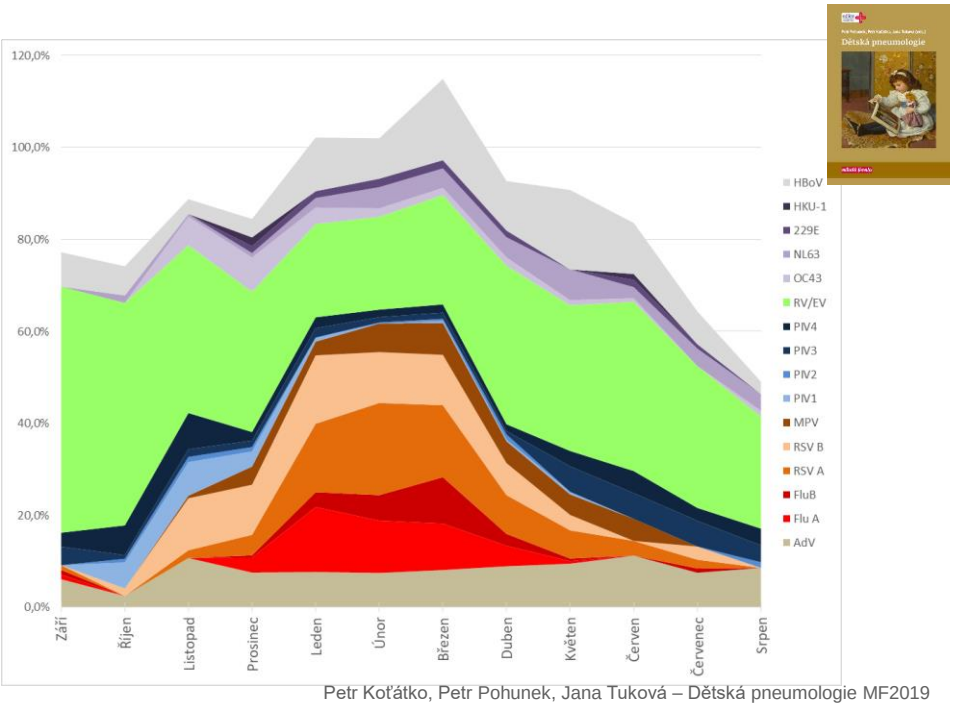
p.o. ribavirine 10-30 mg/kg/D in 3 doses

Paramyxoviridae

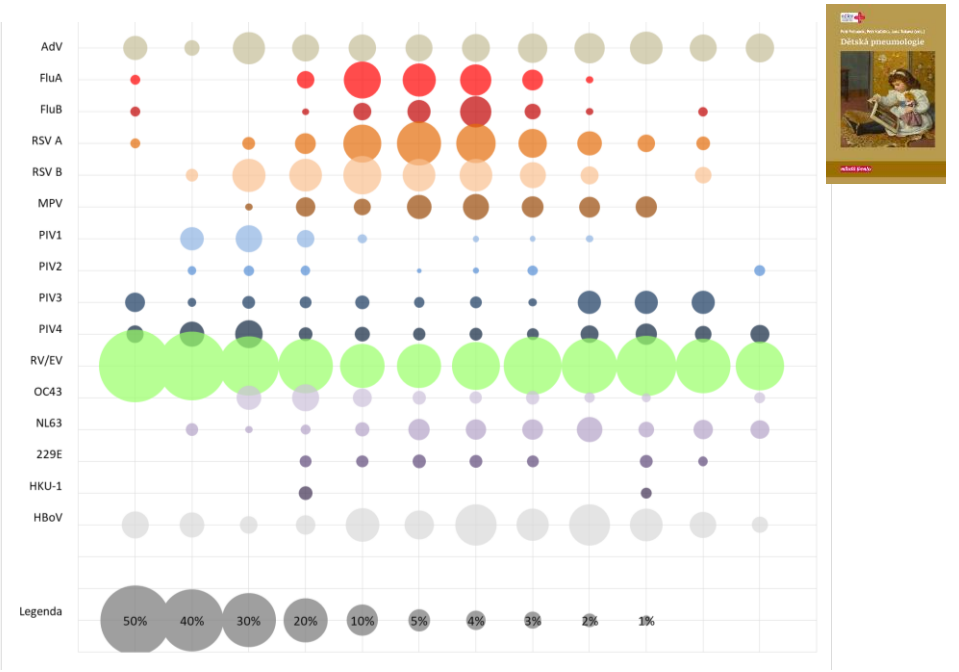
Morbidity & Mortality of RSV

- More likely to visit a specialist
- More likely to use respiratory therapy
- More likely to receive diagnostic or therapeutic procedures
- More likely to be hospitalized again
- Subsequent hospitalization will be 3x as long
- More likely to suffer recurrent infections
- Many have recurrent acute otitis media
- Many likely to be hospitalized with another episode of acute respiratory distress

- Adolescents suffer from allergic asthma, allergic rhinoconjunctivitis, & more sensitive to inhaled allergens
- More likely to have asthma, bronchial reactivity to methacholine, and reduced lung function
- RSV ind. risk factor for reduced FEV% (FEV1/FVC)

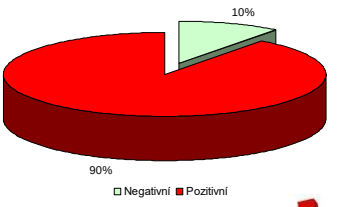


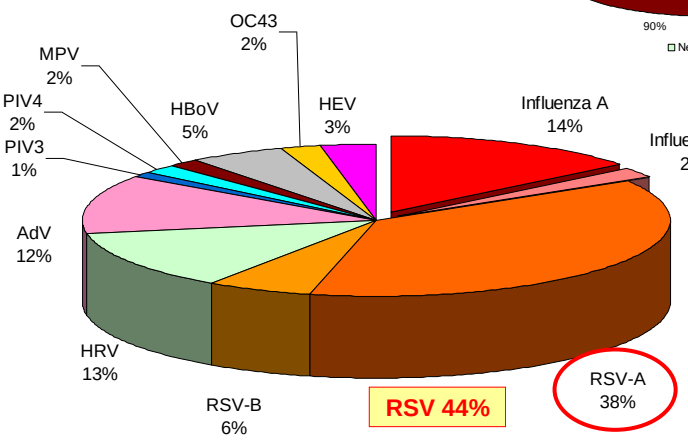
Petr Koťátko, Petr Pohunek, Jana Tuková – Dětská pneumologie MF2019



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

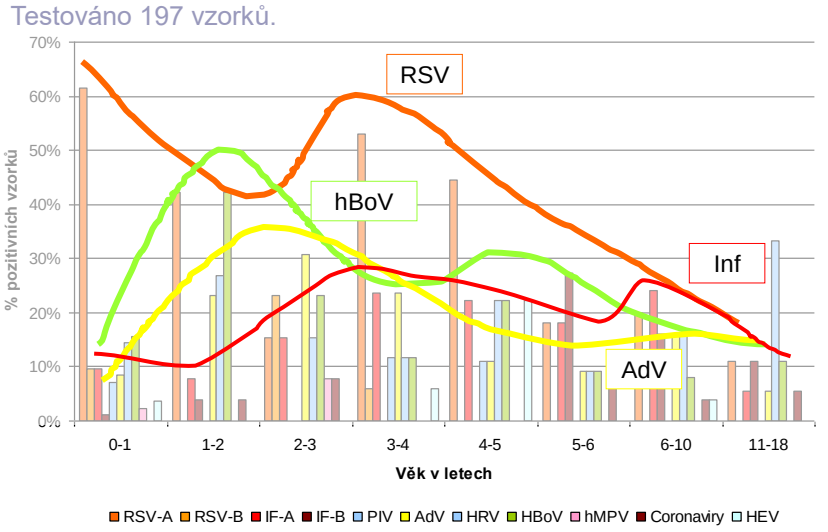
Frequency of respiratory viruses in Motol University Hospital Dept. of Paediatrics (PCR)



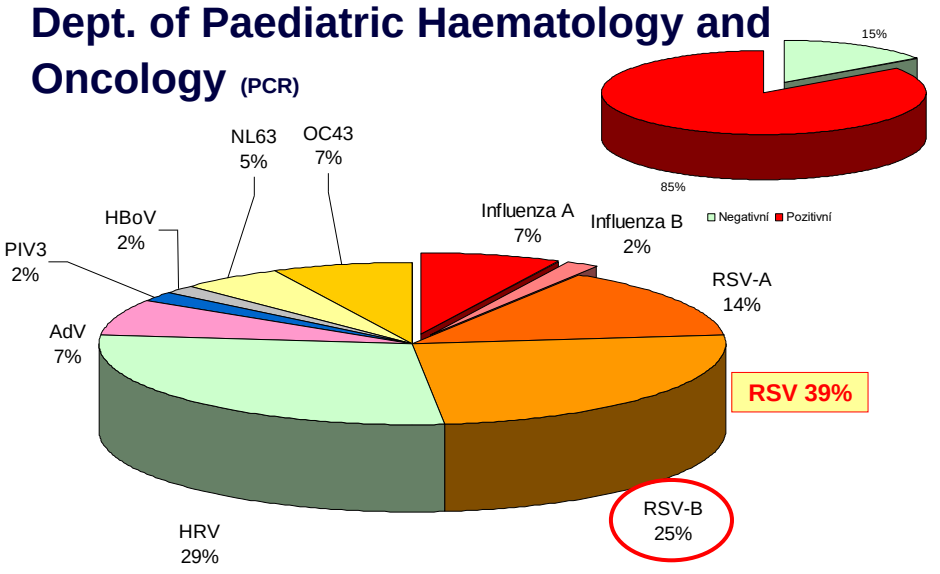


Flu in 16% only

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!

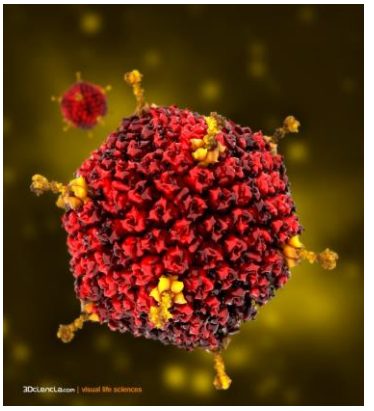
It is true also for commercial kits e.g. There is evidence that Anyplex RV16 detects only **10 out of 60 described serotypes.**

Most frequently detected,

but not the only!!!!

PCR negativity does not

neccesary omits AdV infection.



REVIEW ARTICLE

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

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

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

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

Viral exanthematic diseases

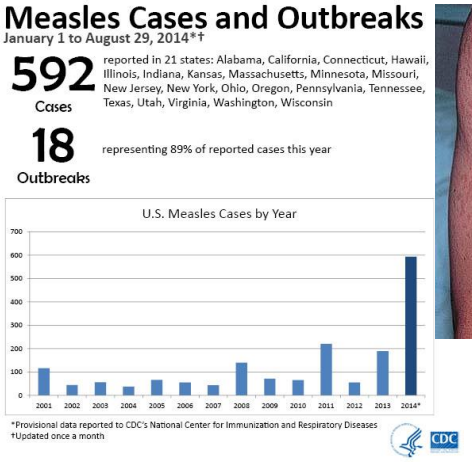
Childhood exanthema diseases

Classical name	„systematic exant. name“	Pathogen
Measles (rubeola)	1st childhood disease	morbillivirus
Scarlet fever	2nd childhood disease	Streptococcus pyogenes
Rubella (German measles)	3rd childhood disease	Rubivirus
Filatov-Duke‘s disease (pseudoscarlantina)	4th childhood disease	Coxackie and Echoviruses
Erythema infectiosum	5th childhood disease	Parvovirus B19
Exanthema subitum – Roseola infantum	6th childhood disease	HHV-6 and HHV-7

Chicken pox - VZV

Paramyxoviridae

Measles



Estimated cases – 20,000,000 / year.
Estimated kills - 164,000 people in world/year.

Paramyxoviridae

Measles

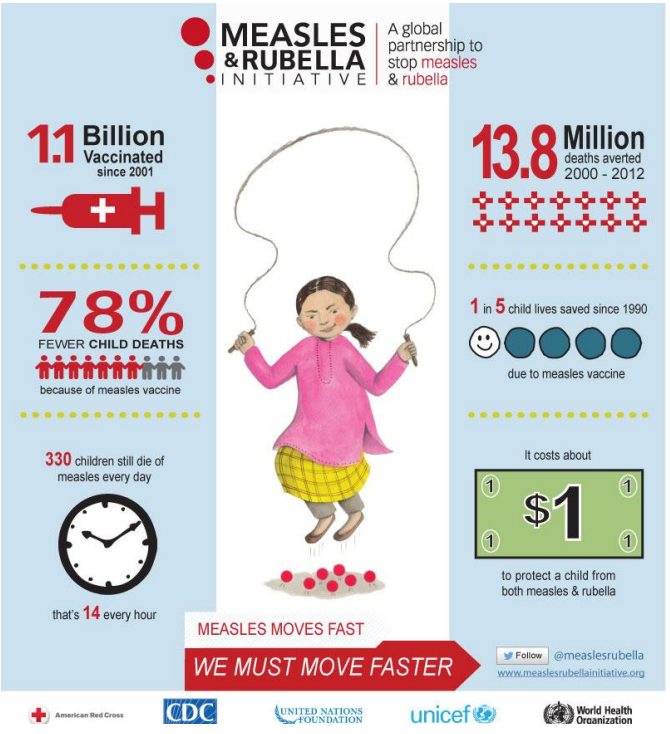
- Respiratory disease caused by a morbillivirus
- Measles virus normally grows in the cells that line the back of the throat and lungs
- ss (-) RNA virus of genome length 15-16 kb, coding 8 proteins
- spherical symetry of capsid and diameter of 100-300 nm
- incubation period 8-12 days

Symptoms
Measles causes fever, runny nose, cough and a rash all over the body. Rash starts at head and neck and spreads from this areas to whole body.

Complications
About 1 / 10 children gets an ear infection, and up to 1 out of 20 gets pneumonia. About 1 out of 1,000 gets encephalitis, and 1-2 out of 1,000 die.

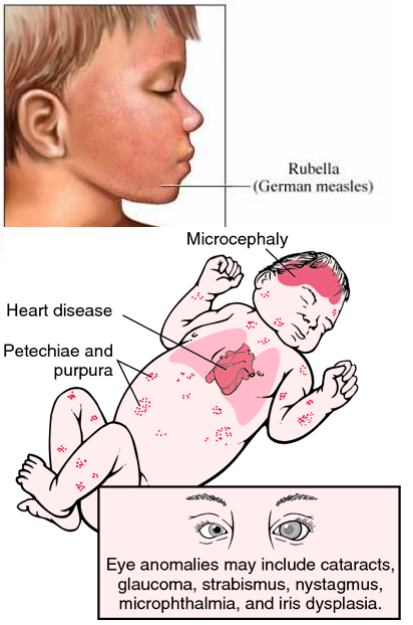
Transmission
Spreads through the air by breathing, coughing or sneezing.
It is so contagious that any child who is exposed to it and is not immune will probably get the disease.

There is vaccination against measles.



Togaviridae

Rubella - German measles



- Rubivirus (RNA)
- incubation period avr. 18 days (12-23)
- viraemia 5th-7th day after exposition with subsequent speading to the organs

Togaviridae

Rubella - German measles

The infection is usually mild with fever and rash. In pregnancy the virus can cause serious birth defects.

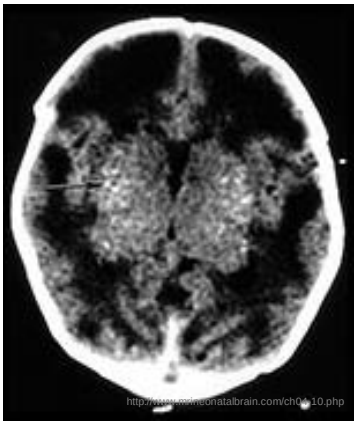
Symptoms: in children: Rash that starts on the face and spreads to the rest of the body, Low fever. Usually a mild disease
These symptoms last 2 or 3 days.
Older children and adults: swollen glands and symptoms cold-like sy. before the rash.
Aching joints occur in many cases, especially among young women.
About ½ of the people do not have symptoms.
In rare cases, serious problems can occur. These include brain infections and bleeding problems.

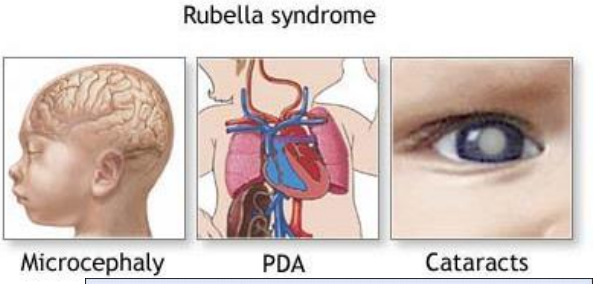
In pregnancy: miscarriage or birth defects like deafness, intellectual disability, and heart defects. 85% of babies born to mothers who had rubella in the first 3 months of her pregnancy will have a birth defect.
Spreading: through coughs or sneezes; most contagious when the person has a rash. But it can spread up to 7 days before the rash appears. People without symptoms can still spread rubella.

The MMR vaccine protects against rubella.

Togaviridae

Rubella - German measles





Box 1: Clinical features of congenital rubella syndrome

Classic triad

- *Congenital heart disease* (e.g., patent ductus arteriosis, pulmonary artery stenosis, pulmonary valvular stenosis)
- *Ocular defects* (e.g., congenital cateracts, microphthalmos, pigmentary retinopathy, congenital glaucoma)
- *Hearing loss*

Congenital rubella syndrome is usually associated with a failure to thrive and developmental delay as well as microcephaly. Other common presentations at birth include:
- purpuric rash
- hepatosplenomegaly
- meningoencephalitis
- radiolucent bone
- hepatitis
- thrombocytopenia

http://www.cmaj.ca/content/172/13/1678/F1.expansion.html

Infection between 8th-10th week of gestation leads to development of congenital rubella syndrome in 90%.

Congenital infections with Venezuelan Equine Encephalitis Virus are symptomatically similar.

Rubella and measles

Details e.g. also in:

http://ecdc.europa.eu/en/publications/Publications/systematic-review-incubation-period-shedding-children.pdf

Parvovirus B19

Described in Australia in 1975 by Yvonne Cossart, in microtitration plate „B19“.

Proliferation in erythroid cells of bone marrow (dysregulation of cell cycle through NS1 protein.

Transmission by droplets, mainly. Incubation: 2 weeks (4-28 day) lasting for a week.

Erythema infectiosum („slapped cheek“) – „Fifths disease“.

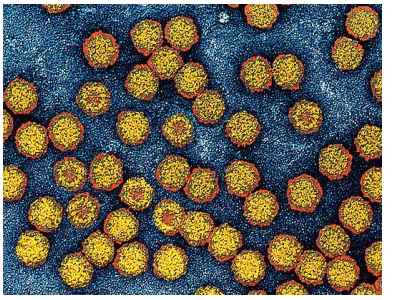
Teenage - "Papular Purpuric Gloves and Socks Syndrome".

Adults – urticas; Pregnant hydrops foetalis

Immunosupressed patients - „pure red cell aplasia“.

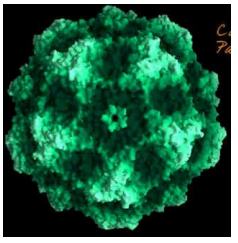
http://snotty-noses.com/illnesses/parvovirus.html

Described possible related complication of B19 infection is myocarditis.



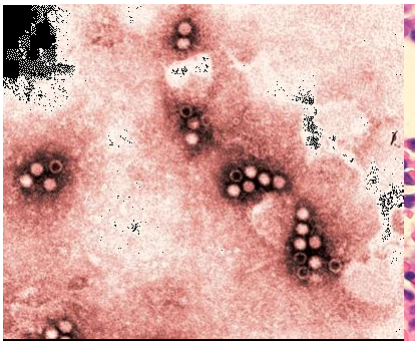
http://www.sciencephoto.com/images/download_lo_res.html?id=770500728

Parvovirus B19



http://fai.unne.edu.ar/biologia/virologia/images/virolo6.jpg

- small ss DNA +/-
- Capsid 20-26 nm, genome: 5 kbp
- E.g. Aplastic anaemia…



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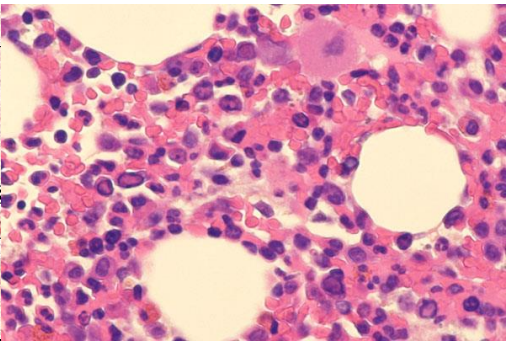
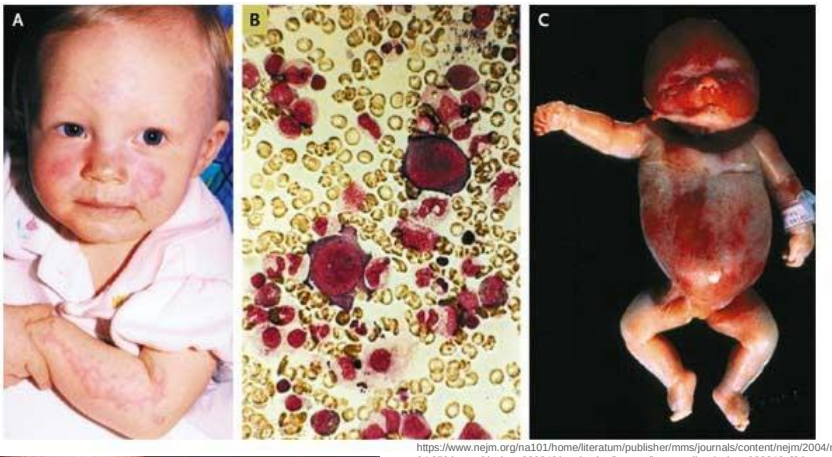
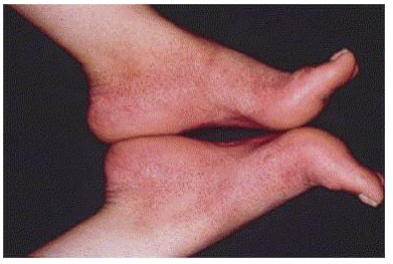


http://www.yamagiku.co.jp/pathology/image/210/1.jpg



https://www.nejm.org/na101/home/literatum/publisher/mms/journals/content/nejm/2004/nejm_2004.350.issue-6/nejmra030840/production/images/img_medium/nejmra030840_f3.jpeg



https://ars.els-cdn.com/content/image/1-s2.0-S0190962299700277-gr2.jpg

Human herpesvirus 6

Previously two variants of HHV-6.
Recently 2 distinct viral species

HHV-6 A

Unknown

„Orphan virus“

Rash during sixth disease
Fitzpatrick's Dermatology

HHV-6 B

Immunocompetent host

- **Sixth disease**
- **Febrile seizures**
- **Encephalitis**

Immunocompromised host

- **Encephalitis**
- **Myelosupression**
- Hepatitis
- Pneumonitis
- Pericarditis
- **Delayed engraftment after HSCT**


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