Influenza and exanthematic viruses

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Life is fight
Viruses described in immunosuppressed patient

**RNA viruses**

- **Orthomyxoviridae**
  - Influenza A
  - Influenza B

- **Paramyxoviridae**
  - Paramyxovirus
  - Morbillivirus
  - Pneumovirus
  - RSV
  - hMPV
  - HCoV

- **Coronaviridae**
  - Enteroviruses
  - Rhinovirus
  - Human caliciviruses
  - Influenza B

- **Picornaviridae**
  - PIV
  - Morbillivirus
  - Pneumovirus
  - RSV
  - hMPV
  - HCoV

- **Caliciviridae**
  - Human caliciviruses

- **Astroviridae**
  - Astrovirus

- **Rhabdoviridae**
  - Lyssa virus

- **Flaviviridae**
  - HCV...

- **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/publications/publications/2013/surveillance/Pages/influenza_case_definitions.aspx)

4th European Conference on Infections in Leukemia
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
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

<table>
<thead>
<tr>
<th></th>
<th>TYPE A</th>
<th>TYPE B</th>
<th>TYPE C</th>
</tr>
</thead>
<tbody>
<tr>
<td>severity of illness</td>
<td>++++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>animal reservoir</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>human pandemics</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>human epidemics</td>
<td>yes</td>
<td>yes</td>
<td>yes (sporadic)</td>
</tr>
<tr>
<td>antigenic changes</td>
<td>shift, drift</td>
<td>drift</td>
<td>drift</td>
</tr>
<tr>
<td>segmented genome</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>amantadine, rimantidine</td>
<td>sensitive</td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td>zanamivir</td>
<td>sensitive</td>
<td>sensitive</td>
<td>sensitive</td>
</tr>
<tr>
<td>surface glycopolproteins</td>
<td>2</td>
<td>2</td>
<td>(1)</td>
</tr>
</tbody>
</table>

#### Influenza A viruses

[Image of influenza A viruses with timeline and strains]

- *H1N1*, *H1N1*, *H2N2*, *H3N2*, *H1N1*, *H5N1*
- *H5N1*: Bird influenza outbreak in Hong Kong, South China, Korea, Japan, Laos, Vietnam, Indonesia, Thai, Malaysia, Cambodia etc.
- Feb 26, 2006
- 92 deaths/170 cases

[Link to WHO: http://www.who.int/csr/disease/avian_influenza]
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 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
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
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

<table>
<thead>
<tr>
<th>Age Group (yrs)</th>
<th>Rate (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 49</td>
<td>0.4 – 0.6</td>
</tr>
<tr>
<td>50 – 64</td>
<td>7.5</td>
</tr>
<tr>
<td>≥65</td>
<td>98.3 (&gt;90% mortality rate)</td>
</tr>
</tbody>
</table>

Influenza Epidemiology

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

- Central: Headache
- Systemic: Fever (usually high)
- Muscular: (Extreme) tiredness
- Joints: Aches
- Nasopharynx: Runny or stuffy nose
- Sore throat
- Aches
- Respiratory: Coughing
- Gastric: Vomiting

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

Years:
- 1920
- 1940
- 1960
- 1980
- 2000
Influenza symptoms

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

Remembrance Day
11\textsuperscript{th} November
16 millions deaths
8,538,315 soldiers

Influenza A virus

Macroscopic picture of influenza pneumonia.

1\textsuperscript{st} proven oseltamivir resistance in the Czech Republic.

Resistance developed after 4 weeks of therapy.

Clinical improvement
Complications

• **Pulmonary**
  – CROUP (YOUNG CHILDREN)
  – PRIMARY INFLUENZA VIRUS PNEUMONIA
  
  • **SECONDARY BACTERIAL INFECTION**
    – *Streptococcus pneumoniae*
    – *Staphylococcus 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

What to aim during the process of dg?

**Good sampling of biological material**

First proliferation at the mucos of upper respiratory tract.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Transmission from upper to lower RT</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV</td>
<td>20-68%</td>
<td>17-70%</td>
</tr>
<tr>
<td>PIV</td>
<td>13-37%</td>
<td>10-30%</td>
</tr>
<tr>
<td>HRhV</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>
Type of swabs

Nylon swabs

What to aim during the process of dg?

Good sampling of biological material
Diagnosis

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

Direct detection - antigen

Example of result

Sensitivity approximately 30-40% in comparison to PCR.

Cost approx. 100-150,- Kč (4-6 Euro)
Sensitivity of antigen detection?

<table>
<thead>
<tr>
<th></th>
<th>Detection Ag</th>
<th>Detection PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. tests</td>
<td>+ Discrep.</td>
</tr>
<tr>
<td>IF-A</td>
<td>256</td>
<td>19 35</td>
</tr>
<tr>
<td>IF-B</td>
<td>256</td>
<td>1 3</td>
</tr>
<tr>
<td>RSV</td>
<td>207</td>
<td>19 47+14</td>
</tr>
<tr>
<td>AdV</td>
<td>207</td>
<td>3 29</td>
</tr>
</tbody>
</table>

% 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
Recovery

• INTERFERON – side effects include
  FEVER, MYALGIA, FATIGUE, MALAISE

• CELL-MEDIATED IMMUNE RESPONSE

• 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 budding/fusion 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

![Image of Reassortment](https://upload.wikimedia.org/wikipedia/commons/thumb/d/d7/Reassortment.svg/800px-Reassortment.png)

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**Get the flu shot**

**...not the flu.**

**Optimal time for vaccination**

**HEIGHT OF FLU SEASON**

**MONTH**


**CASES**

CDC
And what about Paramyxoviruses?

Paramyxoviridae

Respiratory-syntitial virus

RSV (boy treated for AML)
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

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

Presentation

- 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

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.
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
Paramyxoviridae

**Coinfection and Risk factors**

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

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**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

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**Factors NOT Positively Correlated**

- Socioeconomic status
- Malnourishment
- Breastfeeding
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

Treatment

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

- **ribavirine in severely ill patients**

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

p.o. ribavirine 10-30 mg/kg/D in 3 doses
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)
Frequency of respiratory viruses in Motol University Hospital Dept. of Paediatrics (PCR)

- Influenza A: 14%
- Influenza B: 2%
- HRV: 13%
- HEV: 3%
- AdV: 12%
- OC43: 2%
- PIV3: 1%
- PIV4: 2%
- HBoV: 5%
- MPV: 2%
- RSV-A: 38%
- RSV-B: 6%
- RSV-A: 38%

Flu in 16% only
Frequency of respiratory viruses in Motol University Hospital (PCR)

Testováno 197 vzorků.

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 neccessary omits AdV infection.

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

Childhood exanthema diseases

<table>
<thead>
<tr>
<th>Classical name</th>
<th>&quot;systematic exant. name&quot;</th>
<th>Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles (rubeola)</td>
<td>1st childhood disease</td>
<td>morbillivirus</td>
</tr>
<tr>
<td>Scarlet fever</td>
<td>2nd childhood disease</td>
<td>Streptococcus pyogenes</td>
</tr>
<tr>
<td>Rubella (German measles)</td>
<td>3rd childhood disease</td>
<td>Rubivirus</td>
</tr>
<tr>
<td>Filatov-Duke’s disease</td>
<td>4th childhood disease</td>
<td>Coxackie and Echoviruses</td>
</tr>
<tr>
<td>Erythema infectiosum</td>
<td>5th childhood disease</td>
<td>Parvovirus B19</td>
</tr>
<tr>
<td>Exanthema subitum – Roseola infantum</td>
<td>6th childhood disease</td>
<td>HHV-6 and HHV-7</td>
</tr>
</tbody>
</table>

Chicken pox - VZV

Paramyxoviridae

Measles

Measles Cases and Outbreaks

January 1 to August 29, 2014

592 Cases
18 Outbreaks

Representing 89% of reported cases this year

Estimated cases ~ 20,000,000 / year.
Estimated kills - 164,000 people in world/year.
**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 symmetry 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.**
Rubella - German measles

**WHAT IS RUBELLA?**

- An infection that affects your skin and lymph nodes.
- Can be known as "German measles".
- "The Scarlet Sneeze".
- A rash that normally spreads from your face and anywhere below.

- Rubivirus (RNA)
- Incubation period avr. 18 days (12-23)
- Viraemia 5th-7th day after exposition with subsequent spreading to the organs.

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.
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 - German measles

Rubella syndrome

Microcephaly  PDA  Cataracts

Box 1: Clinical features of congenital rubella syndrome

- Congenital heart disease (e.g., patent ductus arteriosus, pulmonary artery stenosis, pulmonary valve stenosis)
- Occular defects (e.g., congenital cataracts, 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
- Radioulnar bone
- Hepatitis
- Thrombocytopenia

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

Rubella and measles

Details e.g. also in:

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“) – „Fifth disease“.

Teenage - „Papular Purpuric Gloves and Socks Syndrome“.

Adults – urticas; Pregnant hydrops foetalis

Immunosupressed patients - „pure red cell aplasia“.

Described possible related complication of B19 infection is myocarditis.

Parvovirus B19

• small ss DNA +/-
• Capsid 20-26 nm, genome: 5 kbp
• E.g. Aplastic anaemia…
Human herpesvirus 6

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

<table>
<thead>
<tr>
<th>HHV-6 A</th>
<th>HHV-6 B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>Immunocompetent host</td>
</tr>
<tr>
<td>„Orphan virus“</td>
<td>- Sixth disease</td>
</tr>
<tr>
<td></td>
<td>- Febrile seizures</td>
</tr>
<tr>
<td></td>
<td>- Encephalitis</td>
</tr>
<tr>
<td>Immunocompromised host</td>
<td></td>
</tr>
<tr>
<td>- Encephalitis</td>
<td></td>
</tr>
<tr>
<td>- Myelosuppression</td>
<td></td>
</tr>
<tr>
<td>- Hepatitis</td>
<td></td>
</tr>
<tr>
<td>- Pneumonitis</td>
<td></td>
</tr>
<tr>
<td>- Pericarditis</td>
<td></td>
</tr>
<tr>
<td>- Delayed engraftment after HSCT</td>
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</tr>
</tbody>
</table>
Thank you for your attention

Petr.Hubacek@Lfmotol.cuni.cz