Influenza
Contents

• virology
• epidemiology
• clinical manifestation
• 1918 and today - should we be afraid of the avian flu?
• diagnosis
• drug therapy
• vaccination
Virology

- what kind of virus is Influenza taxonomically anyway?

- what category does Hepatitis B, C and Herpes simplex 1 belong to

- Trick question:
  - do you know a double-strand RNA virus?
  - what kind of obstacles might it face in a human cell trying to replicate
  - how would it overcome those?
Influenza-Virus A, B und C

- hemagglutinin: H1-H16
- neuraminidase N1-N9
- nomenclature:
  type/(host)/place/clade/year(HxNx)
  A/Moscow/10/99 (H1N1)
  A/Swine/Iowa/15/30 (H1N1)
Influenza-Replication

hemagglutinin mediates binding, cell tropism

RNA-replication: high rate of errors, high rate of genetic variants

neuraminidase mediates
Influenza - sources of genetic variation

- **antigenic drift**
  - random point mutations

- **antigenic shift**
  - genetic reassortment (frequent), recombination (rare), acquisition of new genes, e.g. other types of hemagglutinin
Influenza A - genetic reassortment

simultaneous infection

exchange of genetic segments
Influenza A-hosts

- aquatic birds (mostly apathogenic)
- seals
- domestic birds
- swine
- humans
- ....
Influenza Transmission

- Transmission is generally very effective, mainly by droplets, direct contact (hands), less often by aerosol
Influenza - Clinical Timeline

- Upper respiratory disease
- Headache, myalgia, malaise

Temperature (°C) over time (days):
Influenza Complications

• Most common: pneumonia
  - total ca. 2%
  - with immunosuppression, eg. after BM-Tx >50%!

• very rare
  - myocarditis
  - encephalitis
Influenza and Pneumonia

• What are the different types of pneumonia in Influenza?

• what clinical characteristics do they have?
Morbidity and Mortality

- Attack rates in pandemics up to 80%
  - Pandemic H3N2 1968/69/70 in Germany ca. 60% (= ca. 39 Millionen)
- Attack rates in severe epidemics 20-30%
- Attack rates in less severe epidemics 10%
  - Epidemic 1995/96 in Deutschland ca. 8,5 Millionen
- Germany 2002 - 2003:
  - 16-20.000 deaths (excess mortality)
  - 30.000 excess hospitalizations
Mortality Influenza

- Mortality due to Influenza remains high and is still rising
- Rise in mortality due to Influenza (and RSV) between 1976/7 and 1998/99 in the US:
  - rise in deaths from 2000 to 14,000 per year
  - rise in mortality nearly completely due to H3N2
  - nearly exclusively in patients >65y (rapidly expanding segment of population)

Thompson et al. JAMA 2003, 289,179ff
Influenza- Diagnosis

• Clinical diagnosis „Influenza“
  – Fever, cough, myalgia
  – PPV during epidemic  ~70 - 85%
  – PPV with circulating virus  ~30 - 40%

• Laboratory
  culture (gold standard, slow: 3-10 days
  DFA  2-4h
  RT-PCR  2-4h
  Elisa (rapid tests)  30min
Influenza Rapid Test

- Sensitivity ~70-75%
- Specificity ~90-95%

- how does this translate to true positives, false positives, false negatives in a situation with a prevalence of
  - 50% (epidemic)
  - 10% (influenza season)
  - <1% (out of season)

- what are the diagnostic characteristics of actual HIV1/2 Elisa or rapid tests?
Influenza Immunity

- natural infection -> type specific antibodies, protection from severe disease with same type (lifelong?)
- vaccination (inactivated virus, split virus) -> short lived and very narrow protection against vaccine strain
- yearly vaccination with current strains necessary
Influenza-Pandemics since 1700

- 1729 Russland ?
- 1732 USA ??
- 1781 China ?
- 1830 China ?
- 1833 Russland ?
- 1889 Usbekistan (H2N2)
- 1918 "Spanisch " (H1N1)
- 1957 "Asiatisch" (H2N2)
- 1968 "Hong-Kong" (H3N2)
- 1976 "Schweinegrippe" USA (H1N1)
Influenza 1729 - 1889
Influenza 1918

• First outbreak 1918 in Ft. Riley, Kansas

• rapid expansion within USA, transported with troop ships over the atlantic

• two waves, first milder, second more severe (beginning in August 1918)
Influenza 1918
Influenza- Mortality by age
Influenza 1918 - Outcome

• 22 ? -40 -100 ? Mio. deaths worldwide
• Germany 460.000 -700.000 deaths
• 80% of all deaths of US-soldiers in WW I due to Influenza
• most probably important influence on outcome of WW I and postwar negotiations
Why did the 1918 virus hit so hard?

• Questions
  – where did the virus originate and how did it jump to humans?
  – what is the reason for the high mortality

• Problem
  – no original virus stored

• initially search for remaining virus in permafrost conserved victims in Alaska 1951 (US Army; A. McKee, J. Hultin)
Reconstruction of the 1918 Virus

• 1997 reconstruction of the HA-gene from lung tissue of Influenza victims in tissue archives (J. Taubenberger, A. Reid)

• only short RNA fragments, incomplete gene
Archeology of the 1918 Virus - I
(K. Duncan, J. Oxford)
Archeology of the 1918 Virus -II
(J. Taubenberger/ J. Hultin)

1997 excavation of four influenza victims in Brevig Mission, Alaska. Isolation of Influenza RNA from one Inuit woman.
Reconstruction of the 1918 Virus

- 1998 - 2001 characterization of parts of hemagglutinin, neuraminidase and two nonstructural gene segments

- 2004: identification of the last 3 genes

- construction of a recombinant virus with 1918-hemagglutinin gene

J. Taubenberger, A. Reid, Y. Kawaoka, Tumpey, 1998-2005
The 1918 Virus - final answers

• Origin of the virus
  – the virus has directly jumped from an avian host to humans, without reassortment with other mammalian viruses (probably originated in the early 20th century)
  – first clear evidence of direct change of species from aquatic birds to humans - consequences for the current avian flu epidemics?

• High synergy of the genes of the 1918 virus with high viral titers and high mortality in the mouse model - a pathogen to be worked with only in a S4-environment

Tumpey Characterization of the reconstructed 1918 Spanish influenza pandemic virus. Science 2005, 310, 77-80
Avian Flu - H5N1 and others

• H5N1 highly pathogenic for domestic birds
• first epidemic: Pennsylvania 1983-4, culling of 17 Mio. birds, direct cost 400 Mio US $
• H5N1: first cases in humans (Hongkong 1997),
• H7Nx - weniger pathogen bei Vögeln wie bei Menschen
## Avian Flu - human cases*

<table>
<thead>
<tr>
<th>Stamm</th>
<th>Date</th>
<th>Country</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>H5N1</td>
<td>1997/98</td>
<td>HK</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>H7N7</td>
<td>Feb 03</td>
<td>NL</td>
<td>83</td>
<td>1</td>
</tr>
<tr>
<td>H7N2</td>
<td>3.-4. 04</td>
<td>CAN/US</td>
<td>3</td>
<td></td>
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<tr>
<td>H5N1</td>
<td>2003-8</td>
<td>SA, SEA**, Asia, Africa, Europe</td>
<td>383</td>
<td>241</td>
</tr>
</tbody>
</table>

*WHO, 25.5.2008, ** cases in Thailand, Vietnam, Cambodia, Indonesia, China, Lao, Myanmar
Avian Flu - Clinical Manifestation

- incubation time 2-4 Tage (after contact to poultry)
- fever, cough, dyspnoea (early!)
- uncommon: classic upper respiratory disease
- abdominal pain, diarrhoea, nausea

- bilateral pulmonary infiltrates, rapid progression to respiratory failure

- Lymphopenia, thrombocytopenia, elevated ALT and AST

- Mortality 60%, median time to death 12 d

WHO, NEJM 2005
Influenza - Prevention and Therapy

• Vaccination, vaccination, vaccination

• Drugs
  - Amantadine, Rimantadine
  - Neuraminidase-inhibitors
Who should get a flu shot?

- everybody with a higher risk for complications....
  - > 50 y
  - chronic lung- or heart disease
  - chronic metabolic disease
  - children treated with ASS
  - pregnant women with second or third trimester in influenza season
  - ...

- everybody with a high risk of transmission
  - health personnel
  - persons with contact to high risk patients
  - ..
Efficacy of vaccine

- healthy young adults (< 65y)
  - efficacy 75-80% (prevention of infection)
  - lower reduction of clinical influenza (15% - 25%)
- children 1-15 y
  - efficacy 77-80% (prevention of infection)
  - relevant reduction of clinical influenza (50-75%)
- older adults (>65y.)
  - efficacy 40-70% (prevention of infection)
  - reduction of clinical influenza 60-70%
  - reduction of hospitalization and pneumonia 30-70%
- Vaccination cost saving in all but healthy adults (16-64y)
Why vaccinate medical personnel?

• Dramatic Reduction in clinical disease
• Dramatic reduction of transmission to family members
• Dramatic reduction in patient mortality

• Which of these are true?
Drug therapy in Influenza

• Early drug therapy
  - amantadine and rimantadine
  - inhibition ion channel of M-protein (only influenza A)
  - rapid evolution of resistance, high prevalence of resistance in circulating strains (H3N2 > 99%)

• Newer developments:
  - specific inhibitors of neuraminidase
  - zanamivir (inhalative) and oseltamivir (oral)
  - good efficacy
  - development of resistance initially very low
Efficacy of NA-inhibitors

- prophylaxis
  - 90% reduction of clinical illness, 80% reduction of infection

- symptoms of influenza
  - reduction of duration (by 1.3 d)
  - lower symptom scores

- complications:
  - otitis media in children: reduction from 21 to 12%
  - antibiotic use: reduction from 3.4 to 0.4%
  - hospitalization: reduction from 1.7 to 0.7%

Kaiser L et al., Arch Int Med 2003
## Efficacy NA- inhibitors I I

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>high risk patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>placebo n=1063</td>
<td>n=1350</td>
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<tr>
<td>bronchitis</td>
<td>87 (8%)</td>
<td>53 (4%)</td>
</tr>
<tr>
<td>pneumonia</td>
<td>19 (2%)</td>
<td>9 (1%)</td>
</tr>
<tr>
<td></td>
<td>placebo n=495</td>
<td>n=368</td>
</tr>
<tr>
<td>bronchitis</td>
<td>62 (16%)</td>
<td>38 (10%)</td>
</tr>
<tr>
<td>pneumonia</td>
<td>10 (3%)</td>
<td>7 (2%)</td>
</tr>
</tbody>
</table>

Kaiser L et al., Arch Int Med 2003
Influenza - clinical cohort data

• population based study 2004/5 in Ontario
  - 400 hospitalized patients with laboratory confirmed Influenza
  - 102 children, 73 adults 16-64 y, 228 adults >65 Jahre
  - risk of complications/ comorbidities in 12% of children, 50% of adults and 88% older adults
  - vaccination rates were 4% in children, 25% adults, 55% older adults
  - overall mortality 9.3%. 114 treated with antiviral, 302 with antibiotic
  - RR for death: age >65 (RR 4.1), chronic care institution (RR 4.9), use of oseltamivir (RR 0.31, protective) - still significant if initiated after more than 48h

McGreer et al. ICAAC 2005, # V-630
NA-Inhibitors - who and when?

• Who: patients at risk of complications without vaccine protection
  – transplantation, under antineoplastic chemotherapy
  – medical immunsuppression
  – all patients with indication for vaccine

• When:
  – after contact with influenza patient
  – with signs of clinical disease
  – within 72h ? with ongoing replication?
Resistance against NA-inhibitors

• until 2007
  - low prevalence of resistance to NA-inhibitors (< 1%)
  - resistant virus can be selected in children
  - transmission does not seem to play a role - loss of fitness?

• 2007
  - H1N1 strains with Oseltamivir resistance, highest prevalence in Norway (>60%) and France (50%)
  - single amino acid change in position 274 of viral neuraminidase, confers resistance to oseltamivir but not zanamivir
  - USA rates 10%
  - reason for evolution and geographic distribution
What can we do about a pandemic H5N1?

• Vaccine
  - upscaling of vaccine production
  - several candidate vaccines licensed or under evaluation
  - if new strain antigenically different, vaccine production may still take 2-3 months

• Drug therapy
  - Stockpiles of NA-Inhibitors

• Rapid response is dependent on good surveillance!!
"You know, Burkhart, if you're so damn afraid of the flu maybe you should just stay home."