What is a virus?

“piece of bad news wrapped up in a protein”
original meaning in Latin: poison

Features:
- Filterable
- Non visible in light microscope
- Obligate intracellular parasite without own metabolism
- Only one species of nucleic acids (DNA or RNA)
Replication:
DNA: nucleus
RNA: cytosol

DNA or RNA (ss or ds)

+/- envelope
NA: genetic information/genome
capsid, envelope: protection and cell targeting

Virus entry
specific host and specific cell
receptor-mediated

Uncoating
release of genome

Replication
of genomes

Protein synthesis

Host cell

Virus exit
via budding or cell lysis

Deaths by infectious diseases

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Deaths per year</th>
</tr>
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<tbody>
<tr>
<td>HIV</td>
<td>1-2 Millions</td>
</tr>
<tr>
<td>Hepatitis B and C</td>
<td>1-2 Millions</td>
</tr>
<tr>
<td>Malaria</td>
<td>~2 Millions</td>
</tr>
<tr>
<td>Tuberculosis/TB</td>
<td>~2 Millions</td>
</tr>
<tr>
<td>Measles</td>
<td>~800,000</td>
</tr>
<tr>
<td>Diarrhea by rotavirus</td>
<td>~1 Million</td>
</tr>
<tr>
<td>etc...</td>
<td></td>
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<tr>
<td>Influenza A 1918/19:</td>
<td>20-50 Millions</td>
</tr>
<tr>
<td>Influenza (each year):</td>
<td>5,000-30,000 D/40,000 US</td>
</tr>
</tbody>
</table>
Pathomechanism
A) Lytic infection (e.g. Ebola, Lassa)
B) Persistent infection (e.g. CMV, HSV, EBV...)
C) Latent infection (e.g. HIV?)
D) Re-infection (LTx HBV)
F) Transformation (e.g. HBV, HCV, HPV, EBV)

How is a virus killing a cell?
I) direct cytopathic (e.g. Ebola)
   - apoptosis
   - necrosis
II) Immune system mediated (e.g. HBV)
   dose... ("dosis makes the venom...")
susceptibility (individual susc.; modulating factors)...
The host immune response to virus infection

Immunity: Protection against (repeated) infection
Genuine infection (e.g. childhood diseases)
Condition after vaccination (industrial nations)
Passive/maternal immunity (IgG!)
Based on: neutralizing antibodies

Spread of infection: age-dependent, hygiene!
HHV-6: 2-5 years; EBV: 15-20 years...
Infection age differs!!!
Complications increase with age (HAV, Measles, Mumps...)

Hygiene: Advantages and disadvantages!!!!
Immune evasion:
=permanent quarrel with host (reaction and counter-reaction…)

Immune evasion:
RNA viruses: Quasi-species polymerases: errors; genome small
DNA viruses: additional genes
- acquired from host genome
- own, engineered by virus

Human tumorviruses
• HPV 16, 18 cervical/anal/oral carcinomas
• HBV liver cell carcinoma (HCC)
• HCV liver cell carcinoma (HCC)
• HTLV-1 adult T-cell leukemia (ATLL)
• EBV Burkitt’s lymphoma, Nasopharynx carcinoma (NPC)
• HHV 8 Kaposi sarcoma (with HIV)

multi-step carcinogenesis!!!
Burkitt lymphoma (EBV)

Malignant B-cell lymphoma, polyclonal tumor
- Primary face and throat/pharynx
- Rarely inner organs, bone marrow and CNS
- Two forms:
  - Endemic (malaria area Africa)
  - Sporadic

Pathogenesis:
- Chromosome translocation between 8.q (c-myel)
- and 14, or 14, 2 and 22 (vicinity immunglobin complex)
- Malaria (chronic infection)...

Human Papillomaviruses

- Cutaneous warts (epidermis)
- Genital warts (mucosa)
- Epidermodysplasia verruciformis
- Genital/oral cancers

Normal course of genital HPV infections

- In most cases cure with elimination of virus after some weeks to months (type specific immunity?)
- If not: virus persistence
  - Without or only very mild cytological alterations
  - With transient cytological alterations which then entirely heal up
  - With persistent cytological changes
  - With cytological changes which progress into carcinoma in situ and further to invasive carcinoma
From hyperplasia to invasive cancer

• Unlimited cell division (immortalisation): hyperplasia/dysplasia
• Limited assembly of cells (benign tumor): dysplasia
• Unlimited assembly of cells (malignant tumor): carcinoma in situ
• Invasion in surrounding tissues: invasive cancer
• Dissemination: metastasis

HPV transformation

• In benign lesions: HPV genome extrachromosomal, but in high-grade intraepithelial neoplasms and cancers, it is generally integrated
• Integration disrupts E2 ORF and leads to upregulation of E6 & E7, whose products interfere with the p53 and retinoblastoma (RB) tumor suppressor proteins (G1 to S transition in cell cycle)
• Other mechanisms: chromosomal instability, activation of oncogenes, methylation of viral & cellular DNA sites, telomerase activation...

Cervical dysplasia and cancer
### HPV and cervical cancer

- >>>90% of cervical cancer is HPV DNA+
- 50% HPV-16
- 30% HPV-18
- 20% others
- Median latent period: 15 years *(probably much shorter!!!)*
- Rate: about 1 in 80 infected get cervical cancer if left untreated over years/decades...

### Cervical cancer 2010 USA

New cases: 12,200  
Deaths: 4,210  
*Compared to D: under-diagnosing in USA*  
>>70% HPV 16/18-related!!!
Influenza virus (ortho-myxovirus)

“real influenza” (orthos: real, myxo: slime)

Hosts: humans, pigs, horses, seals, turkeys, ducks, seagulls, and other birds/poultry

- Influenza A
  - human
  - bird
  - pig etc.
- Influenza B
  - only human
- Influenza C
  - only human

Genome (genetic information): segmented!

ss (−) RNA, 8 segments

Virus reservoir

receptors!
Problems of Influenza A viruses

- segmented RNA genome (8 segments)
- re-assorting (genetic shift)
- infections of birds, pigs and human...
  - “mixing vessel”
- RNA-dependant RNA-polymerase error rate $10^{-5}$
- genetic drift

Pandemic vs. epidemic

Epidemic:
1. frequent –almost yearly [Lethality D 5,000-10,000/a, USA >40,000/a]
2. antigenic drift in HA and NA
3. RNA-dependent RNA-polymerase

Pandemic:
1. very rare (3-4 per century)
2. antigenic shift
3. re-assortants via segmented genomes, animal reservoir
4. often further adaption to humans via antigenic drift
5. hits immunologically (almost) naive population

Influenza-Epidemien 11/98 AZ
Original AH
New Influenza H1N1: Reassortant (Quadrupel)

Porcine origin
2 segments prior in man and/or bird

June 2009

February 2011
**Avian Influenza A virus**

**Worldwide**
- All birds (with differences...)
- Infects mainly GI tract of birds
- Mostly subclinical or mild course in wild-living birds
- Reassortants frequent (H1-15; N1-9)
- Usually high mortality in domestic poultry

**Desinfection difficult:**
- Survive at low temp./high humidity days to weeks
- Survive in water
- Survive at surfaces (items, hankerchief...)
- Desinfection of surrounding necessary

**Comparison human Influenza A/ avian Influenza A**

<table>
<thead>
<tr>
<th></th>
<th>Human Influenza A</th>
<th>Avian Influenza</th>
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</thead>
<tbody>
<tr>
<td><strong>Infection</strong></td>
<td>Droplet infection</td>
<td>Fecal-oral (cleavage HA)</td>
</tr>
<tr>
<td><strong>Propagation</strong></td>
<td>Respiratory tract</td>
<td>GI tract</td>
</tr>
<tr>
<td><strong>Subtypes</strong></td>
<td>H1-H3, N1-N2 (exceptions)</td>
<td>H1-15, N1-9</td>
</tr>
</tbody>
</table>
| **Virulence factors**| HA and viral genes | Main determinant HA
                                      Polybasic HA cleavage site
                                      Non-polybasic HA cleavage site

**Avian flu: Features 2004...**

- Highly pathogenic (H5N1)
  since 1959: only 21 outbreaks/local
  5 with strong spread
  now: 8 countries in Asia massively affected
  more aggressive
  >>100 Mill. poultry culled

- Asia: not big farms, more garden plots...
- close contact: human/poultry/wild birds
  Only solution: Culling (not wild birds!)
Danger of pandemic

- Vaccination
- Antigenic drift
- Antigenic shift
- Pandemic

No immunity
Better adapted to man
Antigenic shift
H5N1
Vaccination
No disease, feces, bird migration
Silent reservoir wild birds
Poultry reservoir grows
Pandemic

534 lab. confirmed cases, with 316 casualties (WHO: 03/2011)

No (or only very rare) transmission from man-man!!!
in Vietnam, Cambodia, Thailand, Egypt, Indonesia...