Risk of zoonotic diseases when working in laboratory research

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This lecture on zoonoses will include:

- Definitions
- Brief historic overview
- General description of zoonoses and transmission
- Zoonotic situation in Norway
- Zoonoses in laboratory research
- Zoonoses in field research
- Regulations and guidelines for risk management and risk reduction
Definitions

**ZOONOSIS:** An infectious diseases that are transmissible *between animals and humans*

From Greek: "Zoo" = animals  "nosis" = disease

**Epidemic** – “disease outbreak”

- an infection that appears as new cases in a given *human* population, during a given period, at a rate that substantially exceed what is "expected" based on recent experience
- Can be an “old” well-known disease or a new disease

**Epizootic:**

- the *animal* analogue to human epidemics
Definitions continued

Pandemics:

- an epidemic disease that cause serious illness and is spreading easily and sustainably through human populations across a large region; for instance a continent, or even worldwide.

Panzootic:

- the animal analogue to human pandemics
General description of zoonotic diseases

- Of the >1400 pathogens known to affect humans, >60% are zoonotic
- Zoonotic diseases are caused by infectious agents such as:
  - Virus
  - Bacteria
  - Parasites
  - Fungi
  - Prions ("infectious protein")
- Mammals, birds, reptiles and fish may all carry zoonotic diseases (as well as insect vectors)
History of zoonotic diseases

- Hunter-gatherer culture – close contact between humans and (wild) animals

- Rabies (virus)
- Rabies (lat): “madness”
  - Typically from bites of rabid, aggressive animals

- Black death (bacteria, *Yersinia pestis*), no: “Svartedauden”
- Around 1350
- Killed ~ 45% of Europe population
  - Spread from contact with wild and domestic rodents, as well from humans to humans
Ebola – “haemorrhagic fever”
- one of the highest fatality rates of any known human pathogenic virus (epidemics in 1970ies, 90ies, 2002, 2007 and July 2012 in Uganda)
BERLIN — It’s a nightmare scenario worthy of a sci-fi movie script: A scientist accidentally pricks her finger with a needle used to inject the deadly Ebola virus into lab mice.

But in this case, it really happened — to an unidentified 45-year-old woman in Germany.

Within hours of the accident on March 12, several of the scientist’s colleagues held a trans-Atlantic telephone conference to map out a way to save her life.

Within 24 hours, an experimental vaccine — never before tried on humans — was on its way to Germany from a lab
Severe Acute Respiratory Syndrome (SARS)

2002-2003 – “near” pandemic
• >8000 infected, 900 deaths
Influenza – “flue”

- caused by **viruses** of the family Orthomyxoviridae (*the influenza viruses*)
- affects birds and mammals
- **In humans** influenza spreads around the world in seasonal epidemics, resulting in the deaths of hundreds of thousands annually
- 3 influenza pandemics occurred in the 20th century and killed tens of millions of people, with each of these pandemics being caused by the appearance of a new strain of the virus
- Often, these new strains appear when:
  - an existing flu virus spreads to humans from other animal species
  - when an existing human strain picks up new genes from a virus that usually infects birds or pigs
Influenza pandemics with influenza A in the 20th century

- “Spanish flue” – H1N1 (1918-20)
  - Approx. 1/3 of the world population affected (500 mill) and 50-100 mill died

Wikipedia.org
Influenza pandemics with influenza A in the 20th century

- “Asian flue” – H2N2, “bird flue” (1956-58), about 2 million deaths
- “Hong Kong flue” – H3N2 (1968-69), about 1 million deaths
  - descended from H2N2 through antigenic shift, a genetic process in which genes from multiple subtypes formed a
Avian influenza – “Bird flue” H5N1, first reported in 1997 in Hong Kong, potential pandemic
2009 Pandemic influenza – “Swine flue” (H1N1)

- 2009 pandemic
- > 18 000 deaths (by the end of 2010)
- Now in the “post pandemic period”
- ~80 Norwegian pig farms infected by December 2009

Photos: TV2, Dagbladet,
2009 Pandemic H1N1 influenza – “Swine flue”

• 17 April 2009: First reported cases (diagnosed in California, US)
• Shortly after, confirmation of a relatively serious influenza epidemic among Mexican citizens with the same virus
• The virus was identified as a novel influenza virus with a combination of gene segments not previously seen in humans or pigs
• 29 April: WHO declares “phase 5 of pandemic alert” (continuous spread in several countries on the same continent)
• 11 June 2009: phase 6 of pandemic alert, i.e. global pandemic
• By July 2010 (source WHO):
   totally 18449 reported deaths, of these about 13000 in 2009
   > 200 countries
   > 500 000 laboratory confirmed cases
• 10 September 2010, WHO declares that the H1N1 influenza event has moved into the post-pandemic period

www.wikipedia.org
2009 Pandemic and pigs

• 2 May 2009 the first report about the disease transmission from pigs to humans (Canada)

• April-July 2009 several reports of transmission of the disease from humans to pigs
   About 30% of infected pigs showed disease symptoms (fever, respiratory disease), but low mortality

• Before 2009 a very “fortunate” situation in Norwegian pigs
   One of the few countries free of any influenza virus in pigs
   Intensive monitoring programs to control the situation

• Norwegian pigs “naive” to influenza
   Susceptible for disease
   By the end of 2009 about 80 Norwegian farms infected

• Any consequence for laboratory work?

STOP!
PROTECT THE PIGS AGAINST INFLUENZA

• You can not enter the large animal facility if you have had influenza symptoms the last 7 days

• If you have been in contact with people with influenza you have to wait 72 hours before entering this facility

• If you have been travelling abroad you have to wait 48 hours before entering this facility
“One world – One health”

- Human health and animal health closely related
- In many societies humans live in very close contact with animals
- More travel activity and transport of animals and animal products across national borders increases the risk
- Wild animals an important source of new infections ("invasive species", global warming)
- **Emerging infectious diseases (EIDs):** diseases that have increased in incidence, moved to new host populations or are caused by new pathogens
- Between 1940 and 2004 more than 330 EID events in humans:

Emerging infectious diseases – where do they come from?

- About 60% of EIDs events in humans between 1940-2004 were zoonoses
- A majority of these (>70%) originated from wildlife (white column)

For more info on pandemic influenza

Human health, protection and vaccination:
• www.pandemi.no
• www.fhi.no

Animal health:
• www.mattilsynet.no
• www.vetinst.no
Modes of transmission of zoonotic infections

1. Direct transmission

• Direct contact (including faeces, saliva etc)
  ▪ Tularemia (no: “harepest”)
  ▪ Influenza
  ▪ Salmonella

• Aerosoles
  ▪ Influenza virus
  ▪ Hantavirus (no: musepest)
  ▪ Tularemia

• Bites
  ▪ Rabies
  ▪ Tetanus (no: stivkrampe)
  ▪ Streptococcus
Modes of transmission continued

2. Indirect transmission
   • **Food- and waterborne**, e.g.
     ▪ Salmonella
     ▪ Camphylobacteria
     ▪ Tularaemia
   • **Vector borne**
     ▪ Mechanical vectors
       • Many
     ▪ Biological vectors (like ticks, flies, mosquitoes)
       • Borreliose (Lyme disease)
       • Tularaemia
Monitoring and surveillance of zoonotic agents in Norway

- The Norwegian Zoonosis Centre

Zoonoserapporten 2010

Om sykdommer som kan smitte mellom dyr og mennesker

Norges situasjon
Zoonosis in Norway continued

- Overall a fortunate zoonotic situation in Norway - minus Svalbard
- Most of the zoonoses are notifiable and has to be reported to:
  - The Norwegian Food Safety Authority (www.mattilsynet.no)
  - The Norwegian Institute of Public Health (www.folkehelsa.no)
  - The Norwegian Surveillance System for Communicable Diseases, the **MSIS weekly report**
Zoonosis in Norway

- > 4000 human cases reported in Norway annually
- Salmonellosis and Campylobacteriosis accounts for >90%
- Most dangerous activities:
  - ~75% of Salmonella cases acquired abroad; ~50% of Campylobacter
  - Domestic cases
Risk of zoonotic infections in research

Laboratory work
1. Handling of laboratory animals
2. Working with animal tissue/secrections/excretions
3. Cell culture and microbiology (animal tissue, cell cultures, microbiological cultures etc)

Field work
- Handling of wild animals and wild animal samples (tissue samples, organs, blood, body fluids/excretion, faeces, etc.).
Microbiological status of laboratory animals

- Rodents and rabbits are provided by commercial vendors that have successfully eliminated all or most zoonotic agents from their colonies.
- Regularly health monitored in the animal facility using sentinel animals ("vokterdyr").
  - Sentinel animals: animals that are housed in the same room as the research animals to monitor the microbiological status of the room.
  - The sentinel animals are tested for all relevant pathogens (using gross examination, necropsy, histology, PCR, ELISA) with regular frequency (every 3 months), including some important zoonosis.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Test Frequency</th>
<th>Latest Test Date</th>
<th>Latest Results</th>
<th>Test Method</th>
<th>Historical Results (18 months)</th>
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</thead>
<tbody>
<tr>
<td>Minute virus of mice</td>
<td>3 months</td>
<td>06/06/11</td>
<td>0/4</td>
<td>ELISA</td>
<td>0/4</td>
</tr>
<tr>
<td>Mouse hepatitis virus</td>
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<td>0/4</td>
<td>ELISA</td>
<td>0/4</td>
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<td>ELISA</td>
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<td>Pneumonia virus of mice</td>
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<td>0/4</td>
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<td>Reovirus type 3</td>
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<td>Theiler's murine oncosphalomyelitis virus (TMV)</td>
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<td>Hantaviruses</td>
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<td>IFA</td>
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<td>Lymphocytic choriomeningitis virus (LCM)</td>
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<td>Ectromelia virus</td>
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<td>Mouse cytomegalovirus</td>
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<td>Mouse adenovirus type 2 (K57)</td>
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<td>ELISA</td>
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<tr>
<td>Lactate dehydrogenase virus (LDV)</td>
<td>annual</td>
<td></td>
<td></td>
<td>Biochemical</td>
<td></td>
</tr>
</tbody>
</table>

**Additional tests:**
- Parvovirus (NS antigen) | 3 months | 06/06/11 | 0/4 | ELISA | 0/4 |
- Mouse K virus | as required |                  |                | ELISA       | |
- Mouse thymic virus (MTV) | as required |                  |                | IFA         | |
- Mouse polyoma virus | as required |                  |                | ELISA       | |
- Mouse norovirus | MNV | 3 months | 06/06/11 | 0/4 | ELISA | 0/4 |

**Bacteria**
- *Citrobacter rodentium* | 3 months | 06/06/11 | 0/4 | Culture | 0/4 |
- *Clostridium difficile* | 3 months | 06/06/11 | 0/4 | ELISA | 0/4 |
- *Corynebacterium kutscheri* | 3 months | 06/06/11 | 0/4 | Culture | 0/4 |
- Helicobacter spp. | annual |                  |                | PCR         | |
- Lactospira spp. | annual |                  |                | MAT         | |
- Pasteurella spp. | 3 months | 06/06/11 | 0/4 | Culture | 0/4 |
- Salmonella spp. | 3 months | 06/06/11 | 0/4 | Culture | 0/4 |
- *Streptococcus B haemolytic (not group D)* | 3 months | 06/06/11 | 0/4 | Culture | 0/4 |
- *Streptococcus moniliformis* | 3 months | 08/06/11 | 0/4 | Culture | 0/4 |
- *Streptococcus pneumoniae* | 3 months | 08/06/11 | 0/4 | Culture | 0/4 |
- Additional organisms tested:
  - *Cilia associated respiratory bacillus* | annual |                  |                | ELISA       | |

**Mycoplasma**
- *Mycoplasma pulmonis* | 3 months | 06/06/11 | 0/4 | ELISA | 0/4 |

**Parasites**
- *Ectoparasite arthropods* | 3 months | 08/06/11 | 0/4 | Microscopy | 0/4 |
- *Endoparasites* | *Heimraths* | 3 months | 08/06/11 | 0/4 | Microscopy | 0/4 |
- Protozoa | 3 months | 08/06/11 | 0/4 | Microscopy | 0/4 |

Abbreviations used in this report:
- ELISA = Enzyme Linked Immunosorbent Assay
- PCR = Polymerase Chain Reaction
- IFA = Immunofluorescence Assay
- MAT = Microscopic Agglutination Test
- NT = Not Tested

**COMMENTS**

The animal presented in good condition. The mouse had good coverage of body hair. There was no evidence of fecal soiling around the anus. At necropsy all organs were normal. There were very large amounts of body fat in the animal.
Zoonosis risk when working with live animals in the laboratory continued

- Some animals used do not have documented health status and may carry zoonotic pathogens.

- Even animals with documented health status may carry or acquire zoonoses, and/or have an microbiologic flora that contains potential zoonotic agents.
In this cross-sectional survey of laboratory animal workers in the United States, 23 of 1367 persons reported 28 cases of infection with zoonotic agents from research animals at their workplace during the past 5 years, with six persons indicating that their infections were medically confirmed. Based on these data, the annualized incidence rate for work-related transmission of zoonotic agents from laboratory animals was 45 cases per 10,000 worker-years at risk (95% confidence interval, 30 to 65 cases), approximating the rate for nonfatal occupational illnesses in the agricultural production-livestock industry and for those employed in the health services during 2002. Logistic regression analysis found various characteristics of persons and their employers that were significantly associated with the likelihood of having been medically evaluated for exposure to a zoonotic agent from laboratory animals. Most (95.5% ± 1.1%) persons working with laboratory animals or their tissues indicated that they knew whom to talk to at their institution for medical evaluation and care should they be concerned about the possibility of an occupationally acquired zoonotic disease in future. However, occupational illnesses and exposures among laboratory animal workers was underreported, as 10 of the 28 (36%) alleged zoonotic disease cases were not communicated to the employee’s supervisor. Lack of concern about the potential significance to their health and the perception of punitive consequences to the employee were some of the reasons cited for underreporting, an issue which must be vigorously addressed in the interests of continuing progress toward zoonotic disease prevention in this field.
Zoonosis in the laboratory continued

2. Infectious experiments - dedicated research on zoonotic agents (in animals or cell culture)
   - Infectious disease research - Biosafety level 2, 3, 4

3. “Regularly” biology (animals, organs, tissues, etc.) and general cell biology work risk of zoonotic contaminated material
Tetanus

- Acute disease caused by a toxin produced by the bacteria *Clostridium tetani*
- Potentially in the intestines of most warm-blooded animals, in particular horses, sheep, cattle, dogs, cats, rodents, guinea pigs, and chickens
- Typical infection occurs after wounds are contaminated with faeces, soil, dirty needles/scalpels, or after bites
  - often involves a cut or deep puncture wound
- All animals, including humans, may become sick and tetanus affects the skeletal muscles causing spasms and stiffness. May be lethal.
Tetanus prevention

- **Vaccination:** *every 10 years*, and additional immunisation (“boosting”) after accidents depending on degree of damage and vaccination status, see [www.folkehelsa](http://www.folkehelsa) for details

- Careful handling of live animals and excretions, biological samples, etc.

- Good hygiene, including the use of gloves and hand wash

- *Thorough and immediate cleaning* and disinfection of wounds

- Report any accident and seek medical aid for evaluation
General preventive measures of zoonoses in the laboratory

- Risk assessment (now what you work with!)
- Training of personnel that will work with animals, material originating from animals, waste etc. (remember the refuse collectors!)
- Good routines, standard operation procedures of potential infectious material
- High hygienic standard (personnel, facilities, equipment, waste)
- Vaccination of staff (tetanus)
- Strict personnel hygiene
  - Protective clothes, gloves, facemask, hood
  - Hand wash, disinfection
  - No eating, drinking!
- Safe handling of animals, samples and waste
- Regularly health monitoring of animals and staff
- Health monitoring of animals and cell culture
- Procedures for dealing with accidents and contingencies
Aquatic zoonosis – risks when working with fish in research

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>ing. of fish tissue (under cooked or feces cont.)</th>
<th>ingestion of infected aquaria water</th>
<th>dermal contact infected fish</th>
<th>dermal contact infected Aquarium/Sea water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus</td>
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<tr>
<td>Staphylococcus</td>
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<tr>
<td>Clostridium</td>
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<tr>
<td>Erysipelothrix</td>
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<tr>
<td>Mycobacterium</td>
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<tr>
<td>Nocardia</td>
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<tr>
<td>Vibrio</td>
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<td>Plesiomonas shigelloides</td>
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<td>Klebsiella</td>
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<td>Leptospirosis</td>
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<tr>
<td>Candida</td>
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</tbody>
</table>

- * reported cases in humans
- * no known cases in humans but the potential risk exists
- * exposure route of reported human disease unknown

[iacuc.al.umces.edu/zoonotic-diseases.html](iacuc.al.umces.edu/zoonotic-diseases.html)
Bacterial zoonosis from fish – some examples

- **Aeromonas** bacteria
  - frequently cause disease in cultured and pet fish (often causes wounds in the fishes)
  - primary route for transmission to a person handling fish is *contact* with mucus and tissues from infected or carrier fish
  - In healthy persons, symptoms include localized wound swelling and diarrhoea (more serious disease in immunocompromised individuals)

- **Streptococcus** infections (*S. iniae*)
  - Zebrafish, rainbow trout, etc.
  - In humans: skin infections, systemic infections, meningitis
  - Most humans are infected via an existing wound or a fresh puncture wound during handling of live or dead fish

Fish tuberculosis – “fish handlers’ disease”

- *Mycobacterium* bacteria
- All types of fish
- Most common in tropical aquariums
- Fish: either without symptoms (“carriers”) or chronic disease with scale loss, pigment changes, poor body condition, skin ulcers, etc.
- Humans: Chronic skin infections in the extremities (usually the hands/arms)
- “Fish handlers’ disease” or “fish tank granuloma”
Prevention of fish zoonoses in research

- **GLOVES** should always be worn when working with alive fish, dead fish, materials/tissues from fish AND when handling aquarium water
- Basic hygiene and thorough hand wash/disinfection after contact with fish or water that contains fish
Risk of zoonotic disease in field work

Overview and some examples of zoonotic diseases in wildlife in Norway, including Svalbard
Lab versus field – remarkable differences

LABORATORY

- Approved and authorized, well-equipped facilities with trained personnel
- Protective gear and equipment readily available
- High hygienic standard and controlled environment
- Assessment and control of risk factors
- Medical assistance available
**FIELD FACILITIES**

• **Variable availability of infrastructure** from large, well-equipped research ships/stations with laboratories to simple facilities like tents, trucks, ice flows, open field, etc.

• **Demanding to keep a high hygienic standard** (e.g. availability of clean water)

• **Limitations on equipment** that works incl. protective gear

• **Participating personnel** might lack or have limited training in handling of biological material

• **Limited or no possibility for immediate medical attention** if any accidents, disease, etc.

**PLAN WELL AND IN ADVANCE! – “Worst case scenarios”**

• Protective gear, first-aid equipment, back-up plans, vaccination, communication equipment, etc.
Lab versus field, continued

• Typical laboratory animals:

• Usually of small or medium size

• Domesticated and adjusted to human contact

• Commercial suppliers (particular of rodents) that provide health certificates
  • Known health status
  • Usually specific pathogen free, including most zoonoses
  • Regularly health monitored at the facility
Examples of field research animals:

- Animals size varies from small to very large
- Usually not adapted to humans or to manipulation, might be aggressive/dangerous
- Health status unknown
- NB! Even animals appearing as clinical healthy may carry zoonotic diseases
Tularemia («hare plague»)

- Caused by the intracellular bacteria *Francisella tularensis*
- Hares are in particular sensitive and in this species the disease is usually lethal, but healthy carriers exist (during incubation period)
- Other species may also carry the infection: lemmings, wild mice (voles), beaver, etc.

- Transmission:
  - direct contact with infected, sick or diseased animals
  - aerosols (e.g. old nests, dust, etc)
  - contaminated food or water ("rodent years")

Photos: National Veterinary Institute/Høgskolen i Hedmark
Tularemia in humans in Norway

- Very few bacteria needed to give infection
- The bacteria can penetrate intact skin
- Many cases (>50) in Norway autumn/winter 2011/2012 ("lemming year")
- Direct contact transmission gives skin infection, with accompanying swollen lymph nodes, fever, headache and nausea
- Aerosols may give pneumonia
- Water- and food borne usually as diarrhoea and nausea

Human cases in Norway 1976-2009
Source: Norwegian Public Health Institute

Foto: www.med.sc.edu:85
Tularemia infection prevention

- Caution when handling sick or dead hares and rodents, or biological samples from such
- Use protective gloves and face mask
- Hand wash and disinfection (NB Contaminated water particular during “rodent years”)
- Protection against insect vectors
- Seek medical assistance if symptoms (antibiotics are effective)
Salmonellosis

- Caused by different variants of *Salmonella spp* bacteria
- *S. Typhimurium* one of the most prevalent in Norway
- Food and water borne transmission most common, but the disease can also be transmitted through contact with infected animals (incl. humans), biological samples, faeces, etc. (faecal-oral infection route)
- Carriers in the Norwegian fauna in particular includes wild birds (gulls, passerines), hedgehogs and also prevalent in reptiles
- Human symptoms include diarrhoea, nausea, headache and fever
Bacterial zoonoses in marine mammals

«SEAL FINGER»
- From bacteria found on the skin/blubber in marine mammals
- *Mycoplasma* spp and/or *Erysipelothrix rhusiopathiae*
- Transmission through wounds or cuts
- Painful infection in the skin which untreated can spread to nails, joint and bone
- Treatment: broad-spectrum antibiotics
- Prevention: USE GLOVES! Thorough handwash and desinfection

Marine strains of *BRUCELLA* bacteria—potentially zoonotic
VIRUS: RABIES

- Rabies virus (genus *Lyssavirus*)
- Worldwide distribution, various warmblooded animals, especially canids (dog family), cats and bats
- About 55,000 people die of rabies each year. (95% of the cases in Asia and Africa).
- Transmitted by bites, scratches, licks (virus in saliva)
- Epizootic in red foxes/wolfs in central/eastern Europe
- In polar foxes (and unvaccinated dogs) throughout the Arctic
- **Norwegian mainland free of rabies**
- **At Svalbard and adjacent islands (Hopen), particularly in polar fox (recent epizootic in polar fox and reindeer autumn 2011)**
- Concerns regarding the invasive species raccoon dogs to Norwegian mainland
- Prevention: VACCINATION
Hantavirus – Nephropathia epidemica
“Mouse plague”

- Reservoir: **Wild Rodents**, particularly bank vole (Southern Norway) and likely redbacked vole (Northern Norway)
- Disease transmission
  - Aerosols (particularly urine and faeces).
  - Contaminated drinking water (“rodent years”)  
- Prevalence in Norway
  - 30-60 cases annually
  - Autumn/early winter
  - People at risk: Wildlife biologists, cabin owners
- Symptoms in humans
  - Scandinavia: Influenza-like symptoms followed by acute kidney disease
  - Other parts of the world: pulmonary syndrome
Contagious Echtyma (Orf)

- Orf virus, family Poxviridae ("koppevirus")
- Prevalent in sheep and goats, and also reindeer in Norway
- Causes painful skin wounds in humans (and often secondary bacterial infections)
- USE GLOVES!
Parasites:  

*Echinococcus multilocularis* – fox tapeworm

- Zoonotic, small tapeworm with foxes (red foxes and polar foxes) as main host and small rodents as intermediate hosts
- Other carnivores like dogs, cats, wolfs and raccoon dogs can act as main hosts
- Inhabits the intestine of the main host and produce eggs that are dispersed through the faeces
- Wild rodents such as mice serve as the intermediate host
Echinococcus multilocularis continued

• Humans can become an intermediate host by handling infected animals or ingesting contaminated food (typically berries, mushrooms) and contwater
• Causes severe disease in humans (parasitic cysts in organs like the liver and brain)
• Long incubation period (1- >10 years)
• Endemic in red foxes in central Europe. Recently (2011) found in red foxes in Sweden (new demands for travelling with dogs and cats to/from Finland, Norway and Sweden!, se www.mattilsynet.no )
• Not in the Norwegian mainland, but at SVALBARD (polar fox and Sibling vole)
Egg in faeces

Fecal-oral transmission to rodents (and humans)
Parasitic cysts in internal organs in intermediate hosts (mice and humans).
Echinococcus prevention (fieldwork at Svalbard)

- Use **GLOVES** when handling animals/biological material from affected species
- Handwash/desinfection
- **Boil drinking water**
- **NB! Heat treat** mushrooms and berries picked at Svalbard

- If infection is suspected: seek medical assistance
  - Serological tests available
- Treatment of humans include surgical removal of cysts combined with anti-parasitic treatment (mebendazol)

- For more info: National Veterinary Institute ([www.vetinst.no](http://www.vetinst.no)) and Institute of Public Health ([www.fhi.no](http://www.fhi.no))