4.2 Respiratory infections in Primates
Chris Colin

Tuberculosis is not included here, as addressed elsewhere in the manual, but tuberculosis is a major cause of respiratory disease.

- Brief overview of case studies of respiratory outbreaks in wild apes
  a. Principles of studies
  An increasing number of studies have now shown a link between respiratory disease outbreaks in groups of wild habituated apes and human pathogens. These studies provide data on the health status of individual apes, faecal sample analysis, and necropsy and tissue analyses. Isolated pathogens were then identified phylogenetically. The results revealed that human pathogens were clearly implicated in both morbidity and mortality of great apes, thus highlighting the high probability that the infected apes were contaminated by researchers studying them, tourists or local people living close by.

  b. Human Pathogens linked to RD outbreaks in wild apes
  The human pathogens found were:
  - Human Respiratory Syncitial Virus
  - Human Metapneumovirus (HMPV)
  - Streptoccus pneumoniae
  Example of results from different groups of wild habituated chimpanzees in the Taï Forest (Côte d’Ivoire) who have experienced respiratory disease outbreaks

<table>
<thead>
<tr>
<th></th>
<th>May 1999</th>
<th>March 2004</th>
<th>February 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>North</td>
<td>South</td>
<td>South</td>
</tr>
<tr>
<td>Pathogens identified</td>
<td>HRSV, S.pneumoniae strain 2308</td>
<td>HMPV, S.pneumoniae strain 2309, P.multocida</td>
<td>HRSV, S.pneumoniae strain 2309</td>
</tr>
<tr>
<td>Morbidity</td>
<td>100%</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>Mortality</td>
<td>6/32 (19%)</td>
<td>8/44 (18%)</td>
<td>1/34 (3%)</td>
</tr>
<tr>
<td>Adult &amp; adolescent (≥15; 10 – 15)</td>
<td>5/15</td>
<td>0/22</td>
<td>0/19</td>
</tr>
<tr>
<td>Juvenile (5 – 10)</td>
<td>1/7</td>
<td>3/10</td>
<td>0/5</td>
</tr>
<tr>
<td>Infant (0 to 5)</td>
<td>0/10</td>
<td>5/12</td>
<td>1/10</td>
</tr>
</tbody>
</table>

Köndgen et al., Pandemic human viruses cause decline of endangered great apes, Current Biology (2008), doi:10.1016/j.cub.2008.01.012
Presentation of these 3 pathogens

- The Human Respiratory Syncitial Virus (RSV) is the most important cause of viral respiratory tract illness in infants and children worldwide, according to the Center for Diseases Control and Prevention (CDC). RSV’s tropism is directed at epithelium in the respiratory tract and can cause rhinitis, otitis media, pneumonia or bronchiolitis. Humans are the only known reservoir for RSV. Spread of the virus from contaminated nasal secretions occurs via respiratory droplets, and close contact with an infected individual or with a contaminated surface. The virus can persist for several hours on objects and surfaces. In developing countries, there are few studies on the incidence of RSV in respiratory diseases but existing data show that RSV accounts for a high proportion of respiratory infections in children. Researchers estimate that RSV around the world is responsible for 64 million cases of respiratory disease and 160,000 deaths every year. Studies showed that naturally acquired immunity to RSV is neither complete nor durable and recurrent infections occur frequently during the first three years of the life. Adults and older children are usually protected against severe RSV infection which suggests that resistance develops after primary infection.

- Human Metapneumovirus (HMPV) was discovered and described only recently in 2001 by researchers in the Netherlands. Since this first study, HMPV has been identified in countries all over the world except Antarctica. There are two major groups (A and B) and four subgroups for this virus.

  The pathophysiology of HMPV infection is thought to be closely related to RSV. Like RSV, HMPV has a tropism for the respiratory epithelium. The patient may be asymptomatic, or symptoms may range from mild upper respiratory tract symptoms to severe bronchiolitis and pneumonia. Some studies had shown that HMPV is the second most commonly identified cause of lower respiratory illness in children, after RSV. It also causes disease in all age groups. Usually HMPV infection occurs early in childhood and the seropositivity rate approaches 100% by 10 years old. Re-infection is however possible as HMPV infections had been seen in adults patients. Elderly and immuno-compromised patients are also at greater risk of contracting HMPV.

  A really interesting point is that multiple animal models have been used to study the pathophysiology of HMPV and chimpanzees have been the only animal to demonstrate symptomatology consistent with human disease.

  There is currently no vaccine for HMPV.

- Streptococcus pneumoniae is a Gram-positive aerobic encapsulated diplococcus. The differences in the composition of the capsule have permitted the identification of 90 serotypes, but only about 11 of the most common serotypes seem to be involved in 75% of the pneumococcal diseases.

  Pneumococci commonly colonize the human respiratory tract (nasopharynx region) and are transmitted exactly in the same way as RSV and HMPV are, by direct contact with respiratory secretions. Young children are common healthy carriers.

  When exposed to Pneumococci, an individual might have a transient nasopharyngeal colonization without expressing the disease, but the bacteria can spread to the sinuses or the middle ear or a bacteriema is possible if the bacteria have penetrated the mucosal layer, when
the individual is susceptible to the particular serotype and when his/her immune system is depressed by other pathogens (e.g. HMPV or RSV). Pneumococci can cause upper respiratory tract infections and can also result in pneumonia, meningitis and septicaemia. In developed countries it affects more the elderly population while it affects the youngest children in developing countries. Nowadays *Streptococcus pneumoniae* is resistant to many antimicrobials (penicillins, cephalosporins and macrolides) and it is a serious health problem worldwide. Treatment therefore requires nowadays stronger doses of antibiotics taken over a longer period of time. It is a major cause of morbidity and mortality among children worldwide, especially in developing countries. Some studies have estimated that more than 10 million children less 5 years old are infected with pneumococcal disease every year.

There is a polysaccharide vaccine against *Streptococcus pneumoniae* but this does not appear to be effective in non human primates.

These 3 pathogens spread from one individual to another through direct physical contact with secretions or droplets and are responsible for serious disease outbreaks of concern worldwide.

c. Consequences

- Many long-term field sites of wild great apes have now put in place strict protocols both for researchers and tourists: compulsory wear of masks, strict minimal observation distances to be maintained between humans and great apes, no sick human is allowed to go and approach the apes, no human wastes are allowed in the forest, etc. An increasing number of sites are also developing health community programs for local people surrounding wild great ape populations.

- As these human pathogens are responsible for many of the respiratory outbreaks witnessed in groups of habituated great apes, it is clear that the risks as extremely elevated in sanctuaries caring for rescued great apes, where contact between the animals and staff is extremely frequent and direct physical contact is common (e.g. during nursing, feedings, veterinarian care, rehabilitation of young orphans etc.). In addition, there is a significant risk that rescued individuals are infected with or carrier of such pathogens, as the probability of them contracting these pathogens whilst in captivity, often in poor conditions, is often extremely high.

- This means that strict hygiene and health protocols and implementation of quarantine procedures must be implemented to prevent the risk of spread of pathogens to both humans and great apes in sanctuaries.
INFECTIONS OF THE UPPER RESPIRATORY TRACT (URT)

a. Definition of URT
The upper respiratory tract is composed of the sinuses, nasal passages, pharynx, and larynx.

b. Pathogens (in humans and apes)
Primary infections of URT are mostly caused by viruses in Humans. These include rhinoviruses, coronaviruses, adenoviruses, paramyxoviruses or coxsackieviruses. Bacterial primary infections are possible, although they are often secondary, especially in young or immuno-compromised individuals. *Streptococcus pneumoniae* is one of the numerous bacteria responsible for such infections.

c. Physiopathology
The pathogens are transmitted through physical contact with secretions or droplets produced when an infected individual sneezes or coughs. The pathogens then invade the mucosa of the URT, causing local inflammation and an immune reaction.
The frequent changes of the antigenicity of the viruses involved pose challenges to the immune system and their resistance to destruction (by production of toxins, proteases, etc.) is particularly challenging when treating weak or young individuals.
The most common symptoms vary from nasal discharge and congestion, cough, sneezing, sore throat; fever is most common in children. In human children, such infections can be serious when it involves the larynx area which is much smaller than in an adult, and this can dangerously compromise the airflow.

A URI can easily spread and evolve into pneumonia.
We have all experienced in sanctuaries how young primates are extremely sensitive to simple URI and how URI can rapidly result in more serious respiratory infections if gone untreated.

Incubation times before the apparition of symptoms vary from 1 to 14 days depending on the pathogen.

d. Treatment
The treatment is symptomatic when the symptoms are moderate.
- **Analgesics** like acetaminophen can be useful to reduce the pain (do not use Aspirin on young individuals because of the risk of Reye Syndrom – see Rosa Garriga’s case study 2008)
- **Antipyretic if fever** and be sure the individual drinks enough (water, fruit juices for example)
- **Decongestants PO or topical** (pseudoephedrine, phenylephrine), but be careful with side effects on young individuals: these include burning of mucosa, sneezing, increased nasal discharge and when given PO, side effects may include restlessness, anxiety, nervousness, weakness and difficulty breathing
• Corticosteroids in nebulization to decrease edema by suppressing the local inflammation but do not use if there is any suspicion of bacterial or fungal infection!

In more severe cases, and if there is any suspicion of bacterial co-infection:
• Epinephrine (nebulization) can help in cases of severe bronchostriction
• Antibiotherapy: Penicillin G, amoxicillin, amoxicillin + clavulanic acid, cephalosporins of 2nd generation, erythromycin, azithromycin are the most used to treat co-infections in URI

e. Prevention
Prevention measures must be put in place to protect the animals and sanctuary staff and visitors must adhere to some basic prevention rules.
• For the primates:
  ✓ Respect quarantine procedures for all new primates. Babies and juveniles who were in captivity in poor condition are often sick with respiratory diseases. Avoid contact with other primates until the individual has been treated or ensure that the individual does not exhibit respiratory symptoms during the whole quarantine period (do not forget that incubations time can be as long as 2 weeks)
  ✓ Whenever there is a case of URI in a group, try to isolate the sick individuals if possible. If not possible, be really careful to monitor the evolution of the disease, especially in young primates. Do not hesitate to treat, symptomatically first, but also with antibiotics in severe cases or if complications arise.
  ✓ You can supplement primates’ food with multi-vitamins and make sure they receive food of really high quality especially if there is a loss of appetite
  ✓ Maintain good hygiene standards for all the infrastructures and any equipment used for the primates (e.g. buckets)

• For the staff and visitors:
  ✓ Any staff member showing signs of URI should not have contact with the primates or equipment used for the primates.
  ✓ When there is an outbreak of URI in the animals, staff should wear masks (and gloves if possible) to prevent zoonotic transmission
  ✓ If you receive visitors in your sanctuary, make sure you have strict rules concerning the distance to respect between visitors and primates. Visitors must not give food to the primates.
  ✓ Be really careful with children visiting the sanctuary. In general, if a child shows any signs of respiratory disease or childhood disease, he/she should not be allowed to enter in the sanctuary.

➢ INFECTIONS OF THE LOWER RESPIRATORY TRACT
### a. Bronchitis

**Bronchitis is an inflammation of the bronchi** usually following an infection of the upper respiratory tract. Acute bronchitis is often caused by a virus which first caused an URI. It is rarely caused by bacteria. It can also be caused by the inhalation of food or vomit or irritating products (such as smoke in humans). The inflamed bronchi produce mucus.

The symptoms generally appear few days after an URI and include a dry cough at the beginning, but it is usually productive after few days, with production of white, then yellow/green mucus. This kind of cough can last for several weeks. There can be a mild fever (<101°F or <38.3°C), chest pain, tiredness, wheezing noises.

It is really important to differentiate bronchitis from pneumonia, where the symptoms are high fever, shortness of breath, shaking chills, etc.

There is no treatment when a virus is the cause of bronchitis, it disappears generally by itself. Give plenty of fluids to help thinning of the secretions. In cases of suspicion of bacterial infection, try to make a sputum culture and give antibiotics if necessary.

Supportive treatment: antipyretic, expectorants.

Prevention is the same as for URI.

### b. Pneumonia

"Pneumonia is an inflammation of the lung parenchyma characterized by consolidation of the affected part, the alveolar air spaces being filled with exudate, inflammatory cells, and fibrin. Most cases are due to infection by bacteria or viruses, a few to inhalation of chemicals or trauma to the chest wall, and a few to rickettsiae, fungi, and yeasts. Distribution may be lobar,
When pathogens enter the lungs, they reach the space between alveoli (bacteria and fungi) or invade the pulmonary cells (virus). In case of bacteria or fungi, the immune system of the body responds by sending neutrophils which destroy the pathogens, releasing cytokines and leading to an inflammatory response (then you have appearance of general symptoms such as fever, chills, cough, chest pain, shortness of breath, etc.). The alveoli are then filled with a mix of neutrophils, exudates and pathogens and this prevents the oxygen/carbon dioxide exchanges between blood and air normally present in the alveoli, causing respiratory distress and low oxygen pressure in the blood. Bacteria can spread in the body through the bloodstream and cause severe complications including meningitis, septicaemia, etc.

In the case of viruses, they invade the pulmonary parenchyma cells, destroying them. The response of the immune system (with lymphocytes) increases local damage and similarly to infections due to bacteria or fungi, respiratory distress and low oxygen pressure in the blood as a result of the effect on the alveoli. Viral infections of the respiratory tract can cause secondary bacterial infection by depressing the immune system.

- **Pathogens**
  
  **Bacteria:** in humans, the most common is *Streptococcus pneumoniae*, but other bacteria that may cause pneumonia include *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, *Neisseria meningitidis*, or *Klebsiella pneumoniae*.
  
  In Non-human Primates, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Bordetella bronchiseptica*, *Haemophilus influenzae*, and various species of streptococci, staphylococci, and pasteurellae can also lead to pneumonia.

  **Viruses:** RSV, influenza, parainfluenza, adenovirus are the most common

  **Fungi:** many fungi can cause pneumonia in humans, such as histoplasmosis, coccidioidomycosis, pulmonary blastomycosis and pneumocystis (these typically occur in immuno-compromised people (e.g. HIV Positive patients)), sporotrichosis (primarily a lymphocutaneous disease, but can involve the lungs as well), cryptococcosis and aspergillosis. Candidiasis can also in some rare cases result in pulmonary infections in immuno-compromised patients.

  The fungi spores penetrate the lungs after inhalation or through the blood if there is fungal infection in another part of the body.

  **Parasites:** in humans, these can yield ascariasis, schisostomiasis, toxoplasmosiasis (caused by *Toxoplasma gondii*). The parasites enter the body through the skin or orally. They travel to the lungs usually through the blood. Parasitic pneumonia is rare in humans

- **Symptoms**

http://dictionary.webmd.com/terms/pneumonia
In Non Human Primates, symptoms include high fever, productive cough, sneezing, mucoid or mucopurulent nasal discharge, lethargy, anorexia, loss of weigh. The symptoms are more serious in bacterial pneumonia. Especially in young individuals breathing difficulties can be serious and the general condition can deteriorate rapidly.

- **Diagnostic**
  - General examination
  - Pulmonary inspection: rales, sound variation upon percussion indicating consolidation of the lungs (they lose their “elasticity” because of the inflammation)
  - Blood count to see if there any signs of infection and to evaluate the state of the kidneys (important for the choice of medicine to be used for treatment of pneumonia)
  - Sputum examination and culture (if possible) to determine the pathogen and its sensitivity
  - X-Ray if available can be useful to confirm pneumonia (but not always) and see possible complications

- **Treatment**
  - **Antipyretic** and **analgesic** to reduce fever and pain (Acetaminophen, ibuprofen) (do not use Aspirin on young individuals because of the risk of Reye Syndrom – see Rosa Garriga’s case study 2008)
  - **Expectorants** (carbocistein), **mucolytics** (Acetylcysteine) to help thinning and evacuation of mucus
  - Give enough fluids to drink to prevent dehydration
  - If bacterial pneumonia confirmed or suspected, give **antibiotics**: trimethoprim/sulfamethoxazole, amoxicillin, amox/clavulanic acid, cephalosporins (ceftriaxone IV if really severe case), fluoroquinolones (enrofloxacin)
  - **Supportive care in really bad cases**: fluid therapy, oxygen therapy. You need to sedate the individual but do not use respiratory depressant anaesthetics!

- **Prevention**
  The same rules as prevention of URI are applicable. But as pneumonia has a high morbidity and mortality rate, isolation of sick individuals is an important measure to prevent pneumonia from spreading in your sanctuary.

Remark: aspiration pneumonia is defined as the inhalation of either oropharyngeal or gastric contents into the lower airways. This leads to chemical damages of the lungs. It can cause severe respiratory distress and septic shock. Secondary bacterial infection is possible.

For treatment: intubation, aspiration of contents if possible, oxygen therapy, IV fluids, antibiotics (azythromycin, Augmentin©, ceftriaxone)
References:

- Kaur et al., (2008). Descriptive Epidemiology of Fatal Respiratory Outbreaks and Detection of a Human-Related Metapneumovirus in Wild Chimpanzees (Pan troglodytes) at Mahale Mountains National Park, Western Tanzania. American Journal of Primatology

- Skiadopoulos et Al. The two major human metapneumovirus genetic lineages are highly related antigenically, and the fusion (F) protein is a major contributor to this antigenic relatedness. J Virol. Jul 2004;78(13):6927-37. [Medline]
- www.emedicine.medscape.com
- www.merck.com
- www.merckvetmanual.com
- www.cdc.gov
- http://www.who.int/
- http://www.uac.arizona.edu/VSC443/primatediseases/primatediseases.htm
Simple infection of URT:
sneezing, coughing, slight fever

Ind > 5 years old

1 individual:
symptomatic/supportive treatment = AINS*, plenty of fluids PO, multivitamins, decongestants.
Close supervision of other primates

Several individuals:
symptomatic/supportive treatment, isolation if possible from others. Strict hygiene protocols to prevent disease spreading

Ind < 5 years old

1 individual:
symptomatic/supportive treatment, isolation if possible from others. Give plenty of fluids PO to prevent dehydration. Give AB if any sign of bacterial infection (higher fever, intense coughing and loss of appetite)

Several individuals:
symptomatic/supportive treatment, isolation of this group, strict hygiene protocols. Give AB if any sign of bacterial infection

Ind < 5 years old:

Getting worse, secondary bacterial infection or directly PNEUMONIA

Ind > 5 years old

Antipyretic, analgesic, decongestants
Antibiotics (Augmentin®, Bactrim®, cephalosporins 2nd and 3rd generation).
Supportive treatment under anesthesia (IV fluids, oxygen therapy)
Isolation of sick individual(s), preventive measures for care-givers (mask and gloves), keep primates holding facilities and equipment clean and disinfected

Ind < 5 years old

Antipyretic, analgesic, decongestants
Antibiotics (Augmentin®, Bactrim®, cephalosporins 2nd and 3rd generation).
Supportive treatment without anesthesia if possible (IV fluids, oxygen therapy)
Isolation of sick individual(s), preventive measures for care-givers (mask and gloves)
Intense nursing (24/24h if necessary) really important for young primates

*AINS: acetaminophen, ibuprofen