RESPIRATORY SYSTEM

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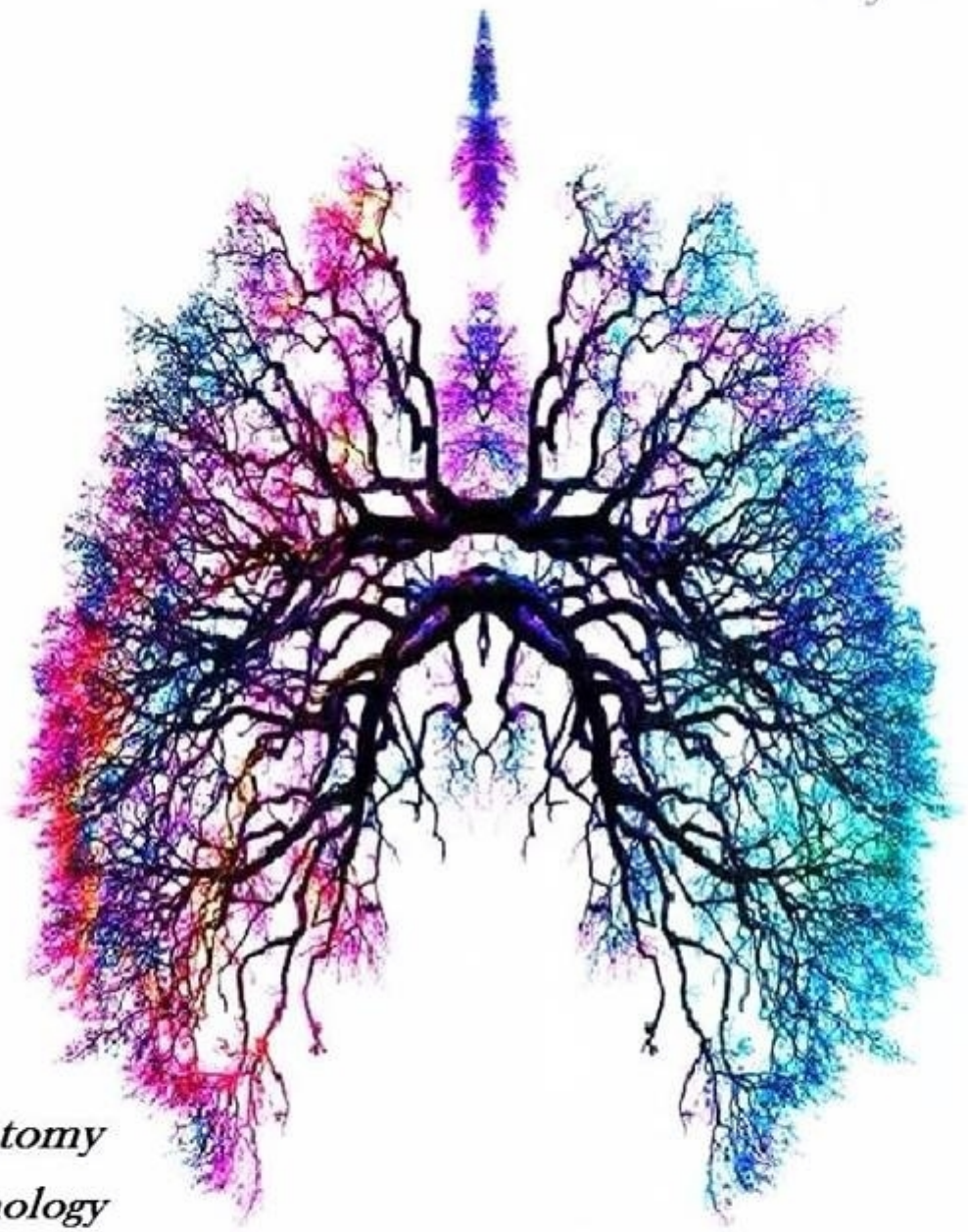

- ○ Anatomy
- ○ Pathology
- ○ Physiology
- ○ Pharmacology
- ● Microbiology
- ○ PBL

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Lecture # 4 (3- virology)

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Other ☐

Medical Virology
Lower Respiratory Tract Infections

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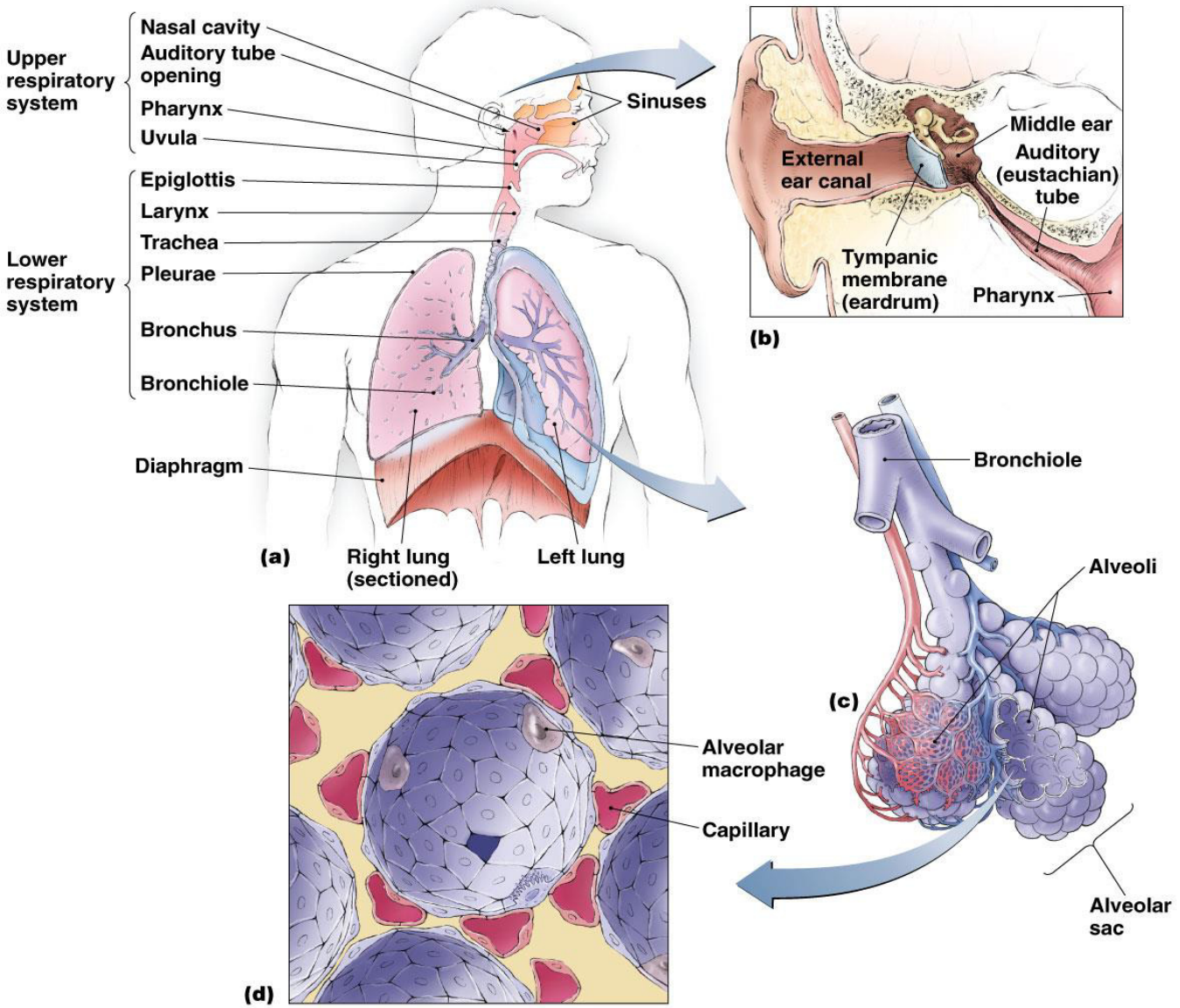
Viral
Lower Respiratory Tract Infections

- Structures of the Lower Respiratory System
  - Components of the lower respiratory system
    - Larynx
    - Trachea
    - Bronchi
    - Alveoli
    - Diaphragm
    - Various protective components
      - Ciliated mucous membrane, alveolar macrophages, and secretory antibodies

Structures of the respiratory system-overview



Important Viral Causes of Lower Respiratory Infections

- Influenza
- Para-influenza
- Respiratory syncytial virus
- SARS
- MERS
- Human metapneumovirus (2001) common in comprised children and elderly persons
- No etiologic agent found (33%)

Para influenza Viruses

- **Croup (Acute Laryngotracheobronchitis)** and pneumonia in children
- Common cold – like disease in adults.
- 5 subtypes: 1, 2, 3, 4a and 4b
- Surface spikes consist of H, N and fusion proteins. H and N on the same spike while fusion protein is on a different spike.

Epidemiology

- Transmission: respiratory droplets, winter months.
- Croup is the commonest clinical manifestation of parainfluenza virus infection, caused by subtypes 1 and 2.
  - It occurs in children (below 3 years).
- Parainfluenza 3 is prone to produce bronchiolitis and pneumonia.
- The majority of infections with parainfluenza viruses are subclinical.

Clinical Findings

- **Croup**
  - Harsh cough
  - Inspiratory stridor
  - Hoarse voice

- Patients are usually afebrile.
- About 80% of patients exhibit runny nose 1 to 3 days before the onset of the cough. Usually, respiratory symptoms subside within 1 or 2 days.

- In addition to croup, parainfluenza viruses cause
  - common cold,
  - pharyngitis,
  - otitis media,
  - bronchitis
  - pneumonia.

- Other viruses can induce croup, such as influenza viruses, RSV, measles and chickenpox.

- Parainfluenza virus infections in adults are relatively uncommon, and symptoms are usually less severe in adults than children.

Laboratory Diagnosis

- Croup is a well-defined, easily recognized clinical entity.
- Cell culture isolation
- Immunoflurescence
- Antibody rising titre using HAI or ELISA

Treatment

- Hospital admission
- Nursing in plastic tents supplied with cool, moistened oxygen
- Severe respiratory obstruction may require endotracheal intubation followed by a tracheotomy.

Respiratory Syncytial Virus Infection

- RSV causes Pneumonia and bronchiolitis in infants
- Fusion protein causes cells to fuse, forming multinucleated giant cells (syncytia)
- RSV causes outbreaks of respiratory infections ***every winter***.
- RSV is a major ***nosocomial pathogen in pediatric wards***.
- The pathogen may be introduced by infected infants who are admitted from the outside and adults, especially members of staff with mild infections.

Transmission

- Respiratory droplets and direct contact of contaminated hands with the nose or eye
- The incubation period is usually 3 - 6 days
- The virus spreads along the epithelium of the respiratory tract, mostly by cell-to-cell transfer

Pathogenesis

- Virus causes syncytia to form in the lungs
- Immune response to RSV further damages the lungs

CLINICAL FINDINGS

- RSV is the most common cause of severe lower respiratory disease in **young infants**. It is responsible for 50 - 90% of cases of **bronchiolitis**, 5 - 40% of **pneumonias** and bronchitis and less than 10% of croups in young children.
- Young children
  - otitis media
- Older children & adults
  - common cold like – disease

- **Infants**
  - Febrile URTI
  - Lower respiratory tract involvement
  - Worsening cough
  - Tachypnoea and dyspnoea
- In bronchiolitis, the respiratory rate may be elevated, with wheezing and hyperinflation. Cyanosis may be present in severe cases.

Risk groups for fatal RSV infection

- **Infants with congenital heart disease**
- **Infants with underlying pulmonary disease**
  - especially bronchopulmonary dysplasia
- **Immunocompromized infants**
  - children who are immunosuppressed or have a congenital immunodeficiency disease.
- **Nephrotic syndrome and cystic fibrosis**

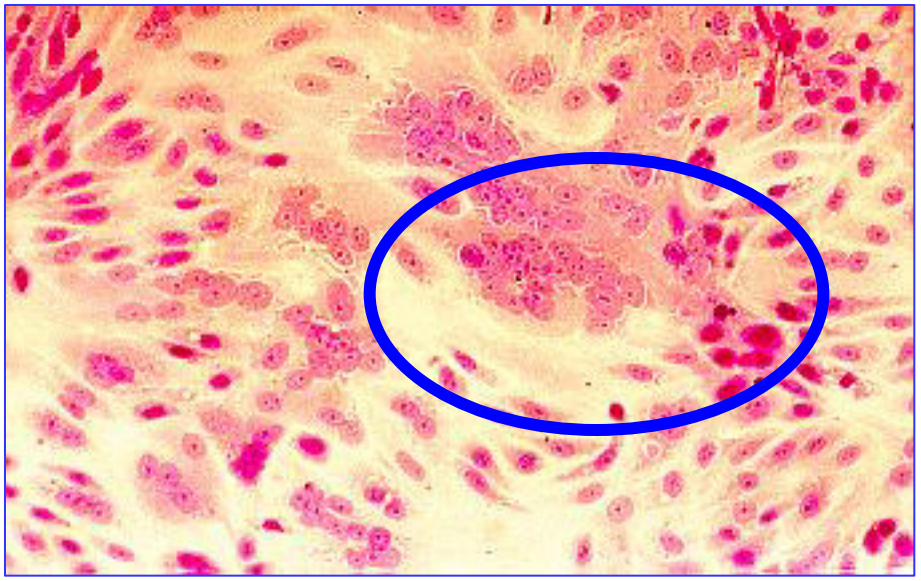
Complications

- ***Apnea***
  - occurs in approximately 20% of cases (premature infants). The apnea is non-obstructive and develops at the onset or within the first few days of illness.

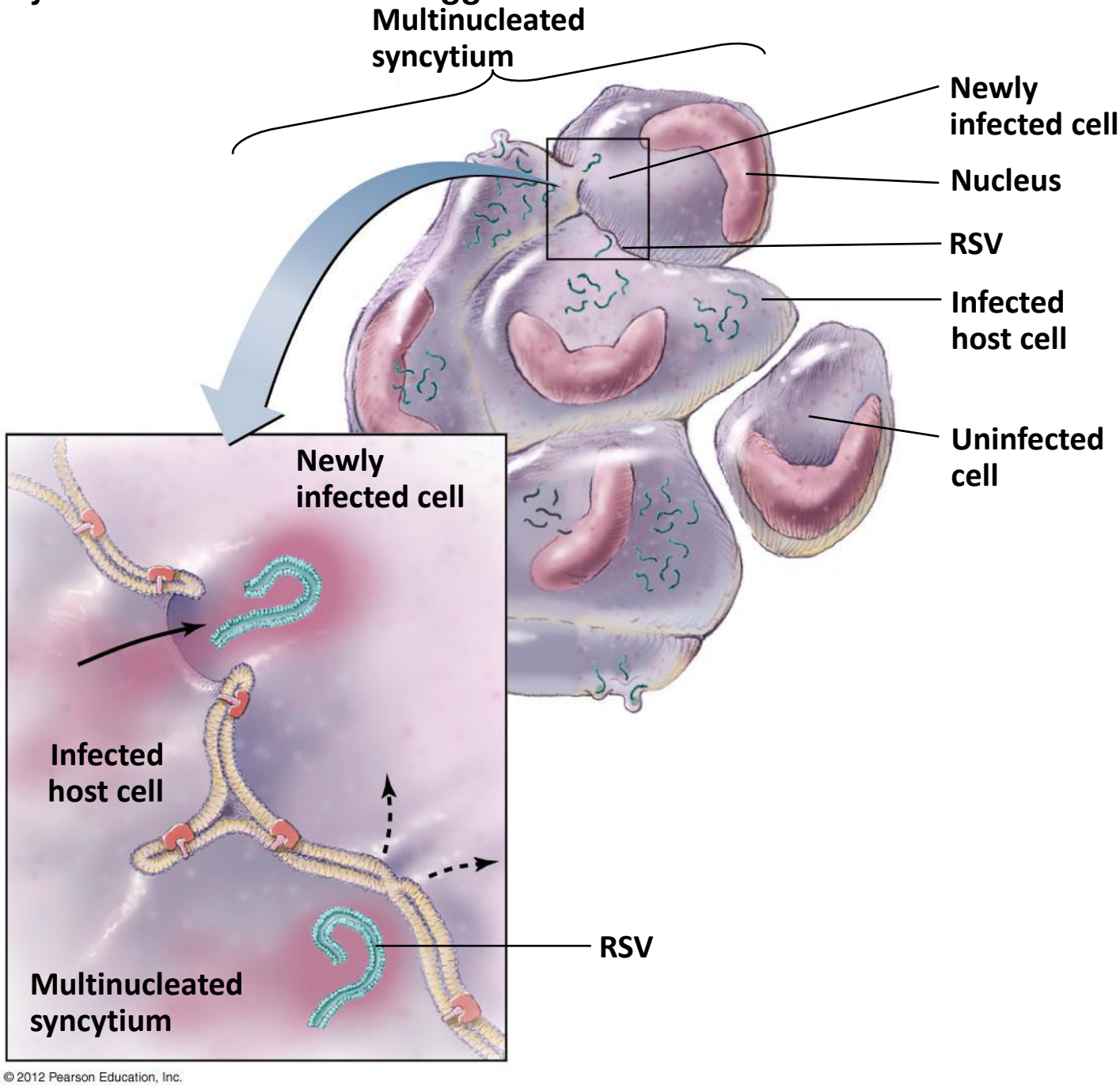
- The most common complication is prolonged ***alterations in pulmonary function***, which may lead to chronic lung disease in later life.

LABORATORY DIAGNOSIS

- Immunoflurescence on smears of respiratory secretions
- ELISA for detection of RSV antigens
- Isolation in cell culture (**multinucleated giant cells or syncytia**)
- Rise of antibody titer.



A syncytium forms when RSV triggers infected cells to fuse with uninfected cells



Treatment

- All infants with RSV lower respiratory tract disease are hypoxemic and *oxygen* should be given to hospitalized infants

- Aerosolized *ribavirin* in severely ill infants

- *RespiGam* contains ***a high concentration of protective antibodies against RSV***. It is given for the prevention in children under 24 months with bronchopulmonary dysplasia or a history of premature birth.

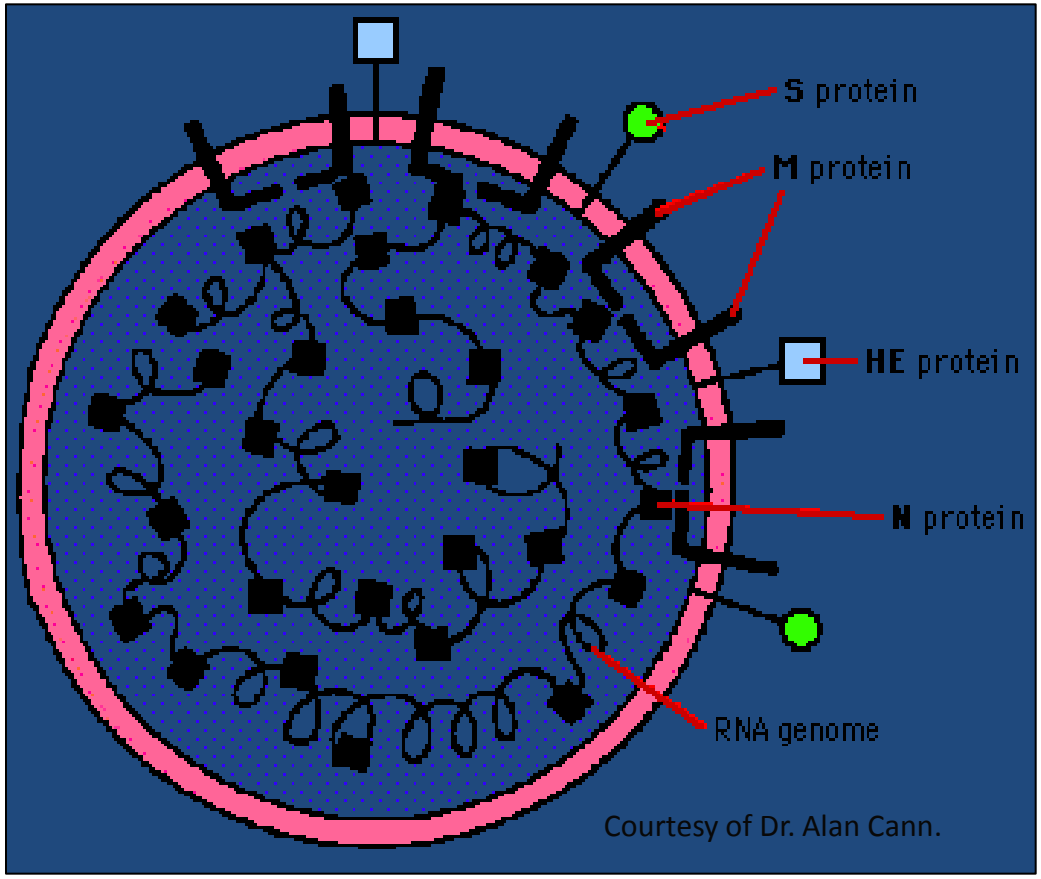
Severe Acute Respiratory Syndrome (SARS)

- Enveloped virus, Replicates in cytoplasm of animal cells
- Single-strand 30 kb RNA genome
- First identified in Guangdong Province, China
- Mortality 3-6% (45-63% in persons over-60)
- Associated Coronavirus SARS-HCoV

SARS History:

- **November 2002**: An outbreak of a mysterious respiratory illness occurs in Guangdong Province, China, making hundreds seriously ill and killing dozens.
- **Mid-February 2003**: Virus spreads to Vietnam and Hong Kong; international travel blamed.
- **Mid-March**: Virus spreads to Singapore and Canada.
- **March 15**: A Singaporean doctor travels through New York on his way to Germany, becoming ill en route; he is diagnosed with SARS in Frankfurt. The World Health Organization issued an unprecedented "Worldwide Disease Alert"
- **March 17**: World Health Organization facilitates the collaboration of 11 laboratories in 10 countries to identify the cause of SARS.
- **March 24**: Centers for Disease Control and Prevention announces that a coronavirus strain causes SARS.
- **March 29**: Dr. Carlo Urbani, a WHO officer who treated the earliest cases in Hanoi, dies of SARS.
- **May 1**: CDC and the British Columbia Cancer Agency in Canada publish near-identical sequences of the SARS virus in *Science*.

Coronavirus Pathogenesis



"The envelope carries three glycoproteins:

- S - Spike protein: receptor binding, cell fusion, major antigen
- E - Envelope protein: small, envelope-associated protein
- M - Membrane protein: transmembrane - budding & envelope formation In a few types, there is a third glycoprotein:
- HE - Haemagglutinin-esterase

The genome is associated with a basic phosphoprotein, N."

- enters via endocytosis & membrane fusion
- + sense genome is translated to produce viral polymerase
- Viral polymerase produces full length – sense strand (poorly understood step)
- - sense strand used as a template to produce mRNA (monocistronic), “nested set” of transcripts
- assembled in the golgi apparatus and transport using secretory nature and released.
- REPLICATION OCCURS IN CYTOPLASM

Symptoms and Diagnostic Tests

- **Initial Symptoms:**
  High fever of 38^{o} C or higher, headaces, body aches, and malaise.
- **Week Later**:
  dry cough, difficulty breathing and severe diarrhea.
- **Recovery**: starts after 5 to 6 days

Early Diagnosis:

- patient is given antibiotics, antiviral, and steroids used for atypical pneumonia.
- Patient is are quarantined in specially ventilated rooms.

Laboratory tests:

- RT-PCR (reverse transcription-polymerase chain reaction) assay
  Detection of SARS-CoV RNA
- EIA (enzyme immunoassay)
  Detection of serum antibody to SARS-CoV RNA
- Enzyme-linked immunosorbent assays (ELISA)
  Detects antibodies against the virus produced in infection

Treatment and Prevention

- No standard treatment yet
- Patients receive combination therapy
  - effective antiviral and steroid (Lopinavir/ritonavir plus ribavirin)
- Prevention
  - Isolation
  - Sterilization of area occupied by SARS patients
  - Caution and extra precautionary measure taken by medical workers and doctors.
  - Vaccines

    According to the SAVI researchers 3 vaccines are possible to be used in the future: Whole killed vaccine, adenovirus vector, and recombination spike protein.

Epidemiology of SARS

- Animal and environmental reservoirs
  - Farms: raising and slaughtering of infected animals like unlucky palm civets
  - Might SARS-CoV recombine with other strains of the coronavirus?
- Onset of illness
  - Incubation period: 4 to 6 days
  - Infectious period is very dangerous if not treated right away leads to death of infected person/animal
- Transmission
  - Close contact – droplet, fomites, direct contact
  - Airborne
  - Fecal-oral

Middle East respiratory syndrome coronavirus (MERS)

- MERS is a newly described disease in human beings, first reported from Saudi Arabia in September, 2012
- It is a novel positive-sense, single-stranded RNA virus of the genus Betacoronavirus.
- As of July 2015, MERS-CoV cases have been reported in over 21 countries, including Saudi Arabia, Jordan, Qatar, Egypt, the United Arab Emirates, Kuwait, Turkey, Oman, Algeria, Bangladesh, Indonesia, Austria,[1] the United Kingdom, South Korea, the United States, Mainland China, Thailand, and the Philippines. About 3-4 out of every 10 patients reported with MERS have died.
- MERS-CoV is distinct from SARS coronavirus and distinct from the common-cold coronavirus and known endemic human betacoronaviruses HCoV-OC43 and HCoV-HKU1.

- In humans, the transmission of coronaviruses between an infected individual and others can occur via respiratory secretions. This can happen either directly through droplets from coughing or sneezing, or indirectly through touching contaminated objects or surfaces as well as close contact, such as touching or shaking hands. Camels are suspected to be the primary source of infection for humans

- There are currently no vaccines or specific treatments for the coronaviruses. Hence, in order to reduce the risk and prevent the spread of infections, simple preventative measure are: good respiratory hygiene, including washing hands; avoiding touching one's eyes, mouth and nose; sanitary disposal of oral and nasal discharges as well as avoiding contact with sick people.

Metapneumovirus

- First described in 2001 by van den Hoogen
  - Nasophargyngeal aspirates from 28 children over a 20 year period
  - Children had similar symptoms to RSV
  - World wide distribution: Has been isolated in US, Brazil, Japan, Australia and UK

Virology

RNA Virus, Paramyxoviridae family

- Antibodies have been isolated in samples from as far back as 1958

Epidemiology

- Most of the early literature is in pediatric population
- In adult population, immune compromised at highest risk - human metapneumovirus infection could be severe in the elderly and that, during some years, metapneumovirus may account for a significant portion of the older people hospitalized with respiratory tract infections

Symptoms

- Cough, fever, dyspnea
- Can range from URTI→Respiratory failure
- Significant pulmonary inflammatory changes in BAL
  - Increased IL-8, foamy macrophages
- In temperate countries, hMPV has a seasonal distribution, overlapping with RSV with most cases reported during the winter/spring.

Treatment

- Primarily supportive measures
- Raza et al (2007) presented a case describing successful use of ribavarin in a patient with a history of double lung transplant and respiratory failure.
- Ribavarin has been shown to have in vitro activity against metapneumovirus (Wyde et al 2007)