CASE 3: FROM INDIA TO CANADA
The body system

PATH 417

FRANK LAM

Q1 SIGNS & SYMPTOMS

What are the signs (objective characteristics usually detected by a healthcare professional) and symptoms (characteristics experienced by the patient, which may be subjective)?

SIGNS VS SYMPTOMS

What is the difference?

The main difference between the two is the **observer:**

SIGNS are objective observations made by a healthcare professional.

Examples: Breathing sounds observed or heard through auscultation, blood pressure, body temperature.

SYMPTOMS are subjective observations made by the patient.

Examples: Pain, chills, fever

WHAT ARE THE SINGS AND SYMPTOMS OBSERVED FOR ROBERT'S INFECTION?

SIGNS

- Fever (38.5°C)
- Chronic productive cough
- Crackles
- Decreased breathing sounds (lower right lung)
- X-ray results
- Deep sputum samples

SYMPTOMS

- Fever
- Productive cough
- Chills
- Night sweats

Q2 BODY SYSTEMS

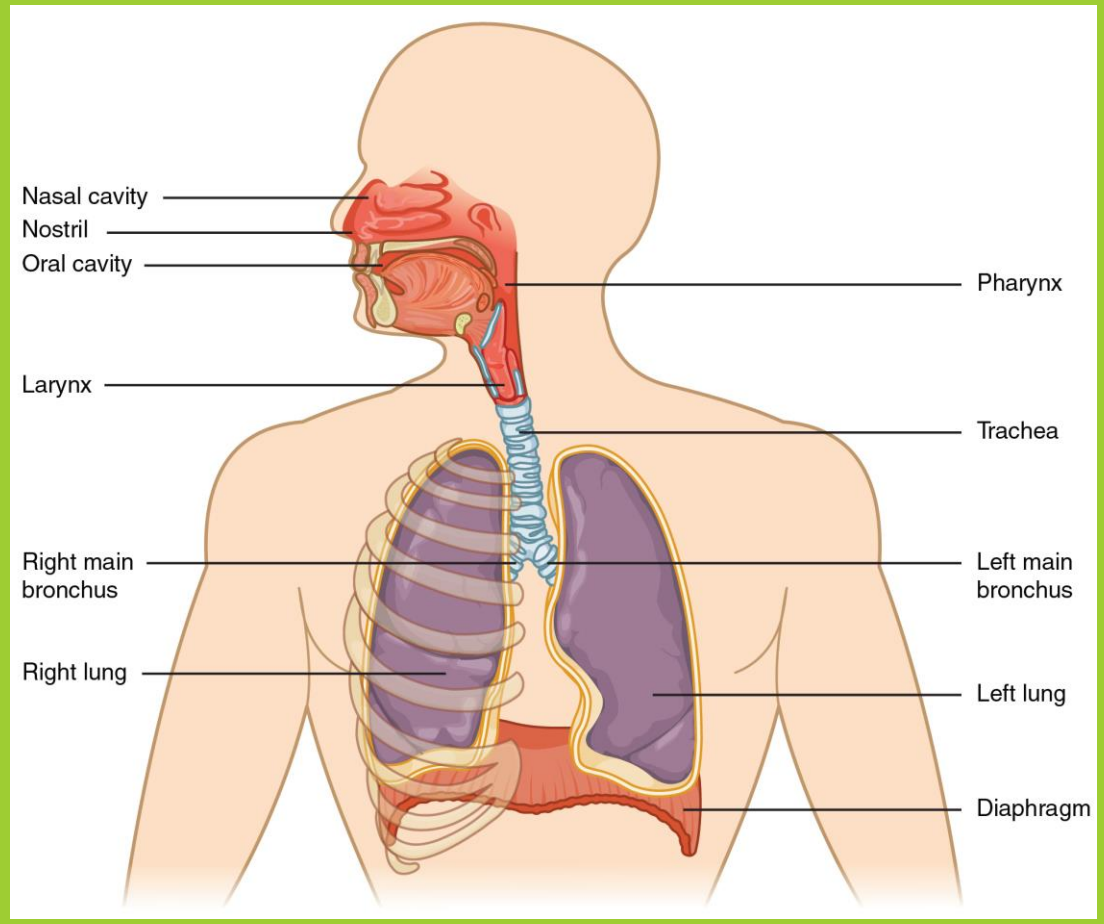
Which body system is affected, in what specific area and what is the normal physiological function of this area of the body?

WHICH BODY SYSTEM IS AFFECTED?

Robert's infection affects his respiratory system, specifically his lung function[1].

- **Upper respiratory tract**
  - Mouth and oral cavity
  - Nose and nasal cavity
  - Pharynx
  - Larynx
- **Lower respiratory tract**
  - Trachea
  - Bronchi
  - Bronchioles
  - Lungs

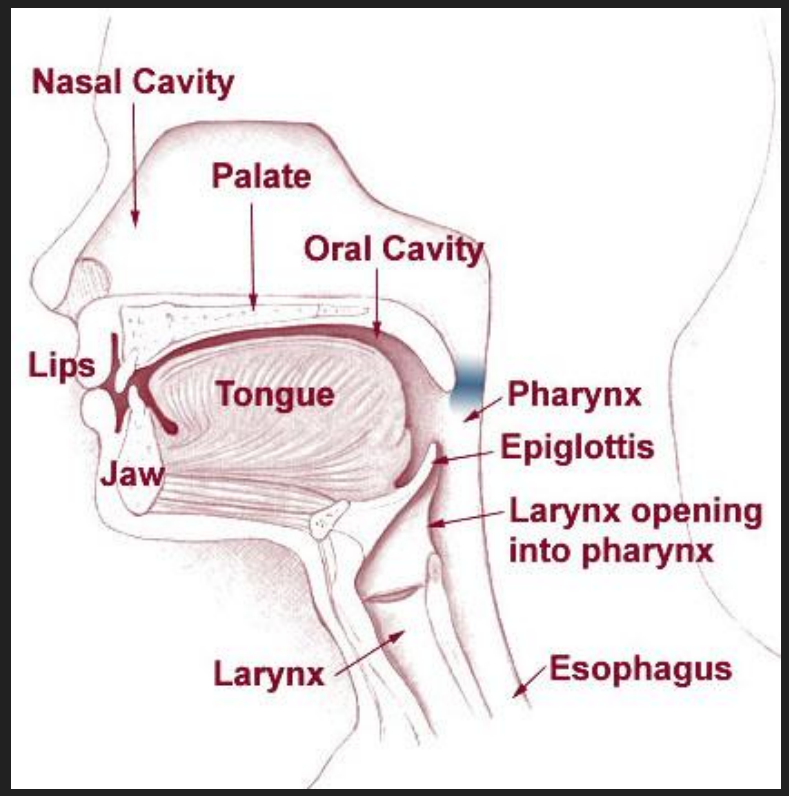
Respiratory system



Major respiratory structures, Anatomy & Physiology, 2017

NOSE & NASAL CAVITY
MOUTH & ORAL CAVITY[2]

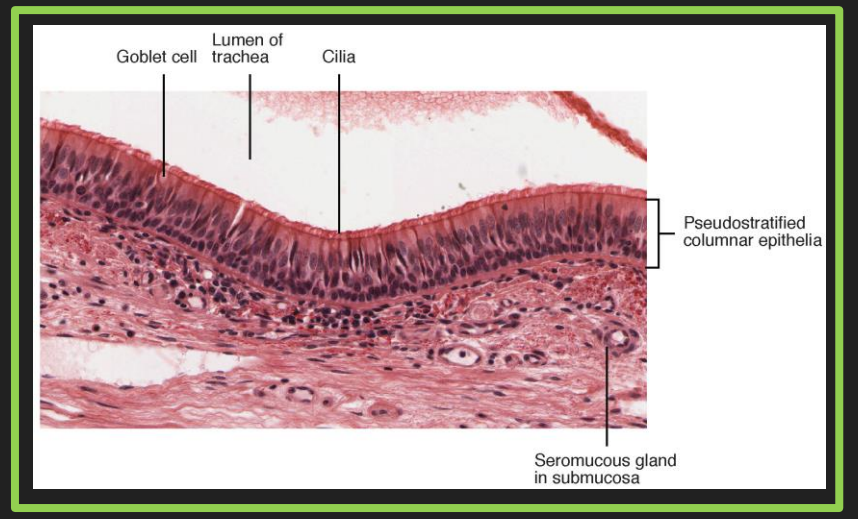
- Provide a route for inhaling and exhaling air
- Filters out debris and pathogens (nasal cavity only)
- Warms and humidifies inhaled air



Head and neck overview, National Cancer Institute

RESPIRATORY EPITHELIUM[2]

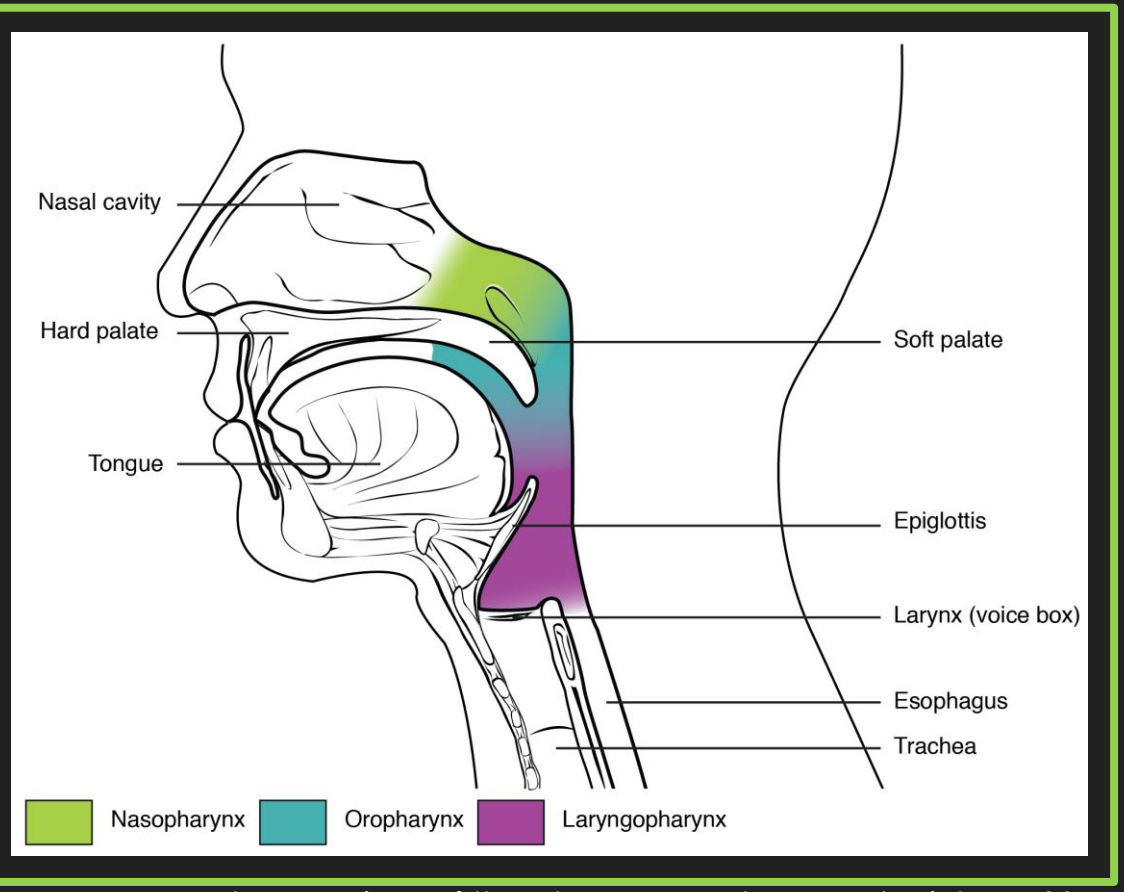
- Epithelium that lines the respiratory tract
- Made of pseudostratified columnar epithelia
- Comprised of:
  - Cilia
    - Uses a beating motion to help sweep mucus and debris from the nasal cavity towards the throat
  - Goblet cells
    - Specialized columnar cell that secretes **mucus** to trap debris and pathogens



Respiratory epithelium is pseudostratified ciliated columnar epithelium.

Anatomy & Physiology, 2017

PHARYNX[2]

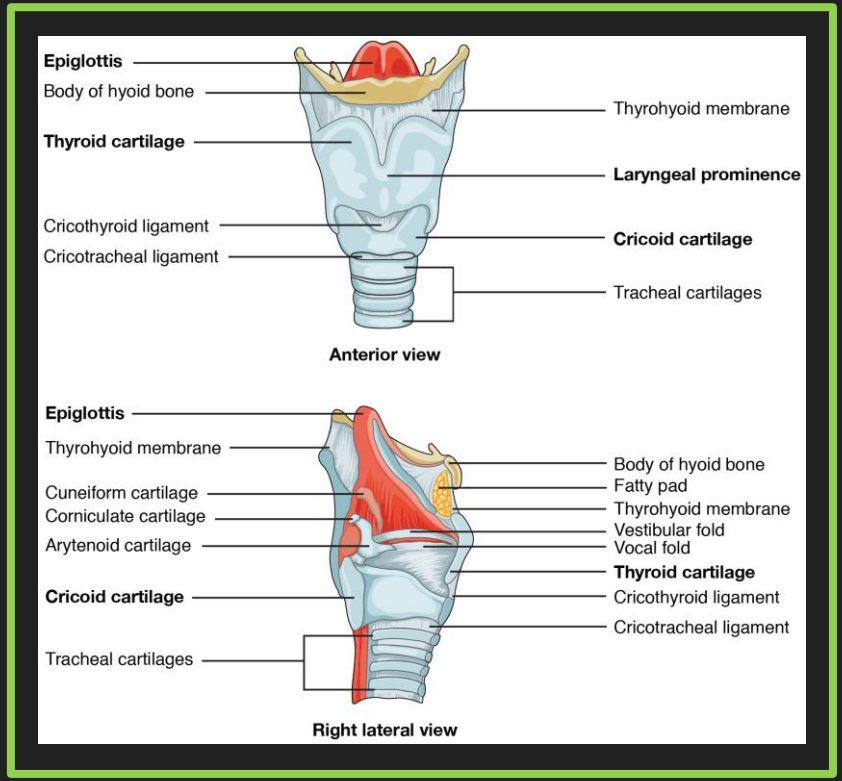


Three regions of the pharynx. Anatomy & Physiology, 2017

- Divided into the nasopharynx, oropharynx and laryngopharynx

- **Nasopharynx**
  - Provides passage for air, functions as an airway
  - Adenoid (pharyngeal tonsil) is at the top of the nasopharynx
    - Lymphatic reticular tissue that contains lymphocytes
- **Oropharynx**
  - Provides passage for air and food
  - Contains palatine and lingual tonsils, which are made of lymphoid tissue
  - Epithelium switches from pseudostratified ciliated columnar epithelium to stratified squameous epithelium
- **Laryngopharynx**
  - Diverging point for food and air
  - The anterior laryngopharynx leads to the larynx

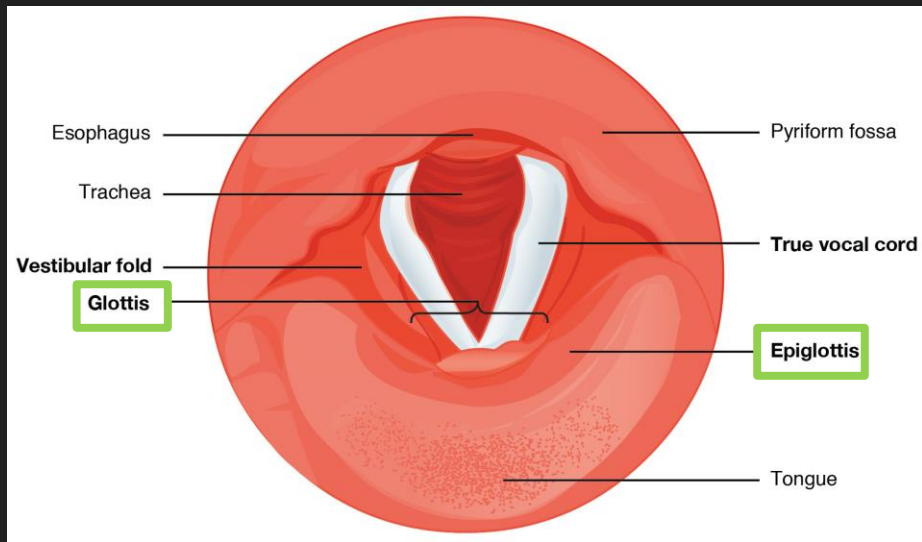
LARYNX2



Larynx. Anatomy & Physiology, 2017

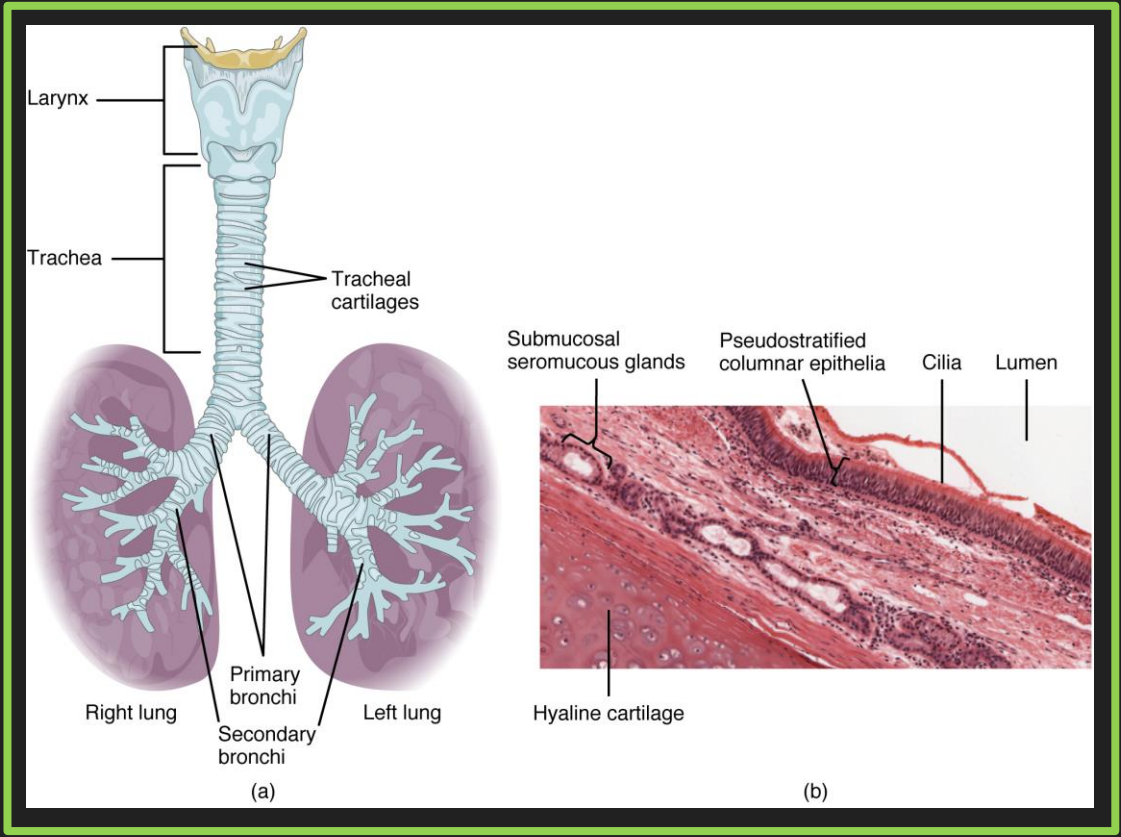
- Also known as the voice box, the larynx is a cartilaginous structure that controls the amount of air entering and leaving the lungs
- Three main cartilage structures:
  - Epiglottis
  - Thyroid cartilage
  - Cricoid cartilage

- Epiglottis
  - Flexible, elastic cartilage that covers the trachea
  - Closes over trachea when swallowing food to prevent choking and opens up when breathing air
- The epiglottis rests on top of the **glottis**
- The glottis contains membranous folds such as the true vocal cord that oscillate when air passes through, creating sound



The true vocal cords and vestibular folds of the larynx . Anatomy & Physiology, 2017

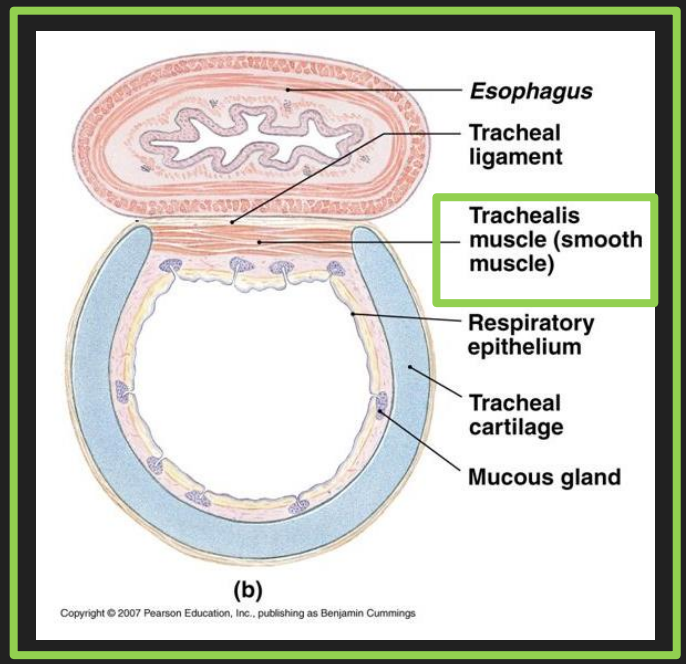
TRACHEA[2]



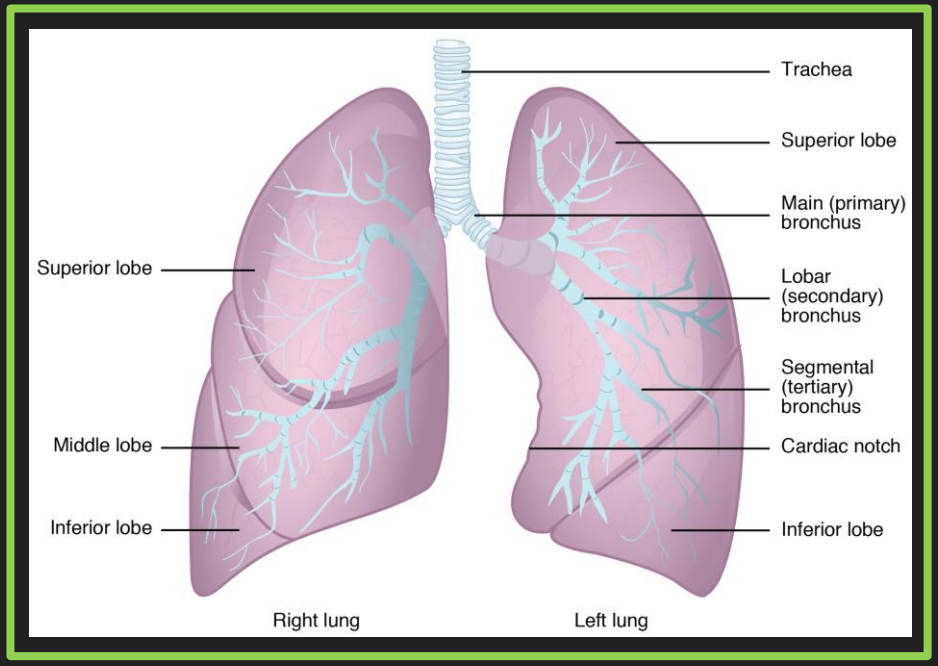
Tracheal tube. Anatomy & Physiology, 2017

- Also known as the windpipe
- Allows the passage of air from larynx into the bronchioles

- Lined with pseudostratified columnar epithelial cells
- 16-20 stacks of hyaline cartilage form the primary structure
- Fibroelastic membrane is formed with the trachealis muscle and elastic connective tissue, allowing the trachea to stretch and expand during breathing
- The trachealis muscle also contracts during exhalation to force air through the trachea

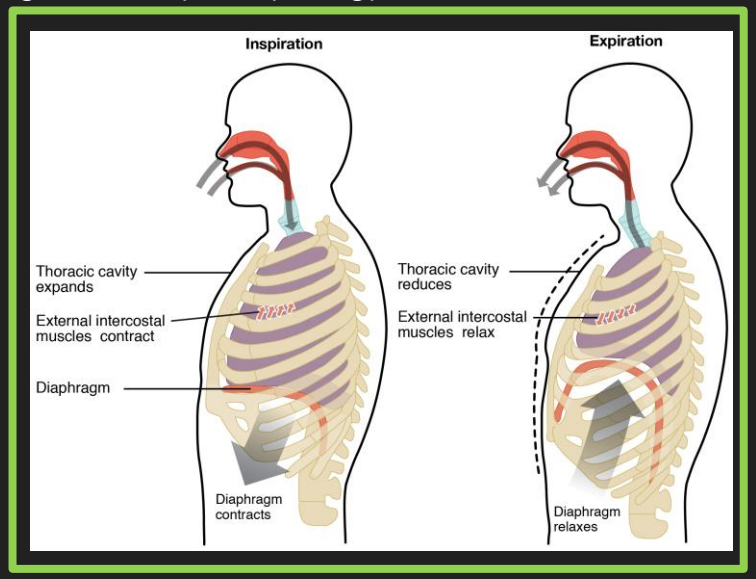


THE LUNGS[2]



The lungs. Anatomy & Physiology, 2017

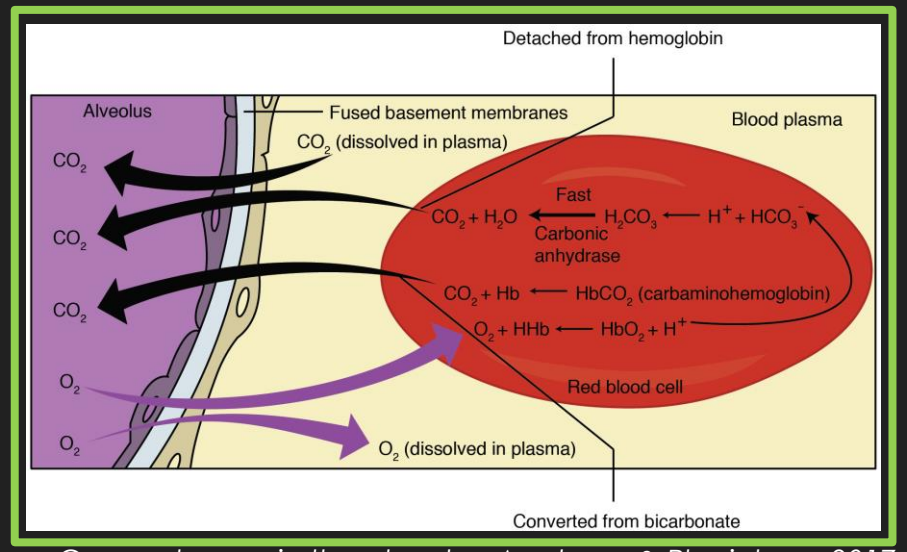
- Pyramid-shaped organ consisting of lobes:
  - Three on the right (superior, middle and inferior)
  - Two on the left (superior and inferior)



Inspiration & Expiration. Anatomy & Physiology, 2017

- The lobes house **bronchi**, **bronchioles** and **alveoli** which function to conduct air passage and participate in gas exchange.
- External muscles such as the **intercostal muscles** and the **diaphragm** help the lung expand and contract which changes the air pressure in the lungs and ventilates the lungs

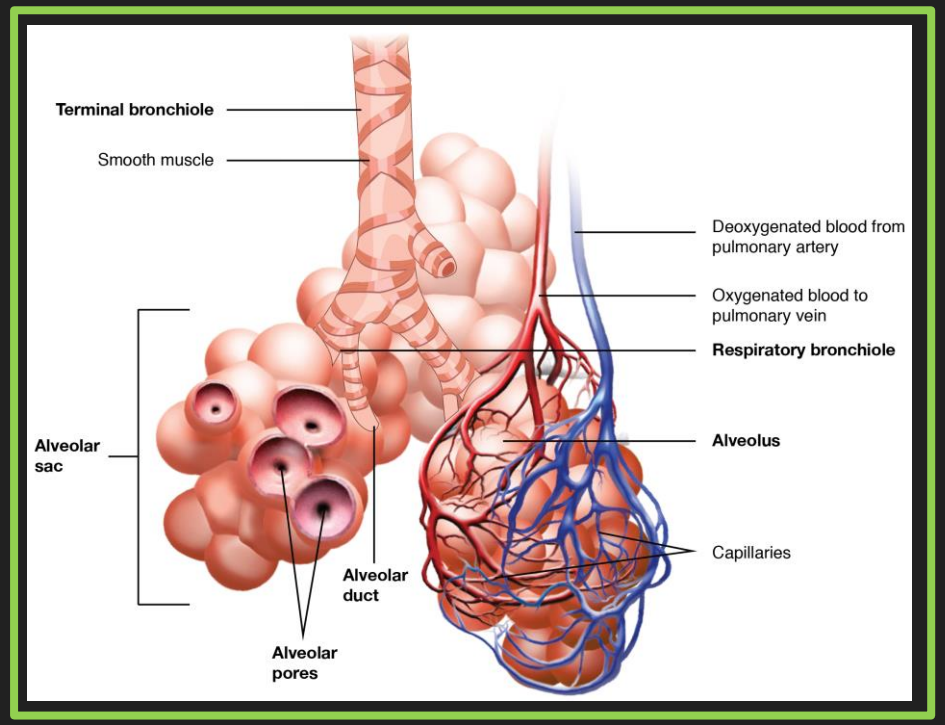
GAS EXCHANGE[2]



Gas exchange in the alveolus. Anatomy & Physiology, 2017

- Alveolar and capillary walls meet at the respiratory membrane
- CO_2 diffuses into the alveolus and O_2 diffuses into the pulmonary capillary via a pressure gradient

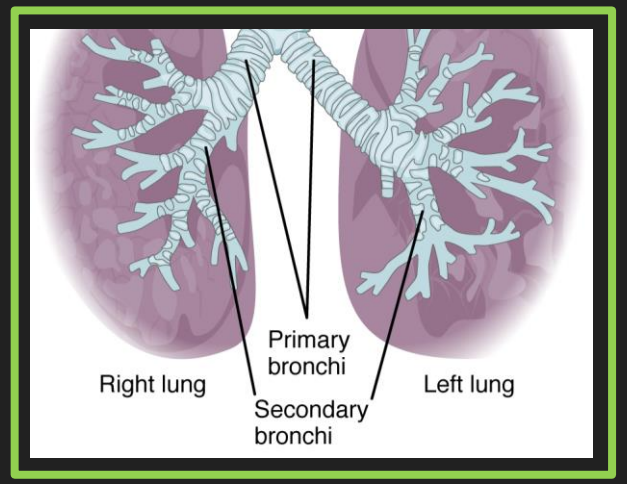
BRONCHIOL TREE2



The bronchioles. Anatomy & Physiology, 2017

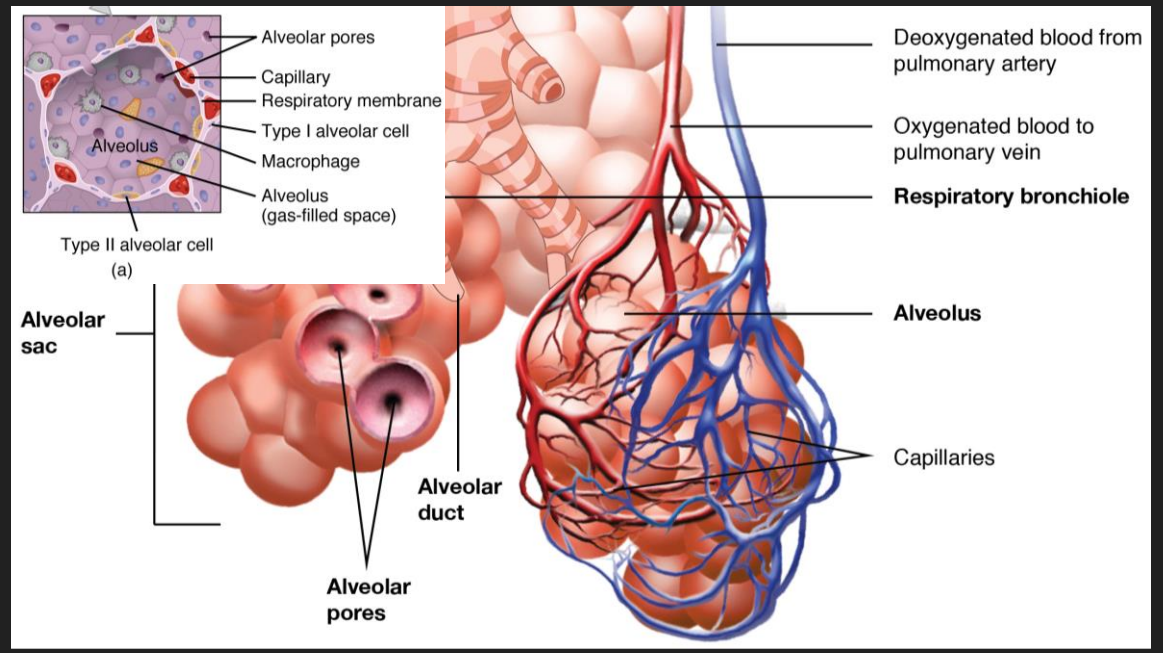
- Trachea branches (tracheal bifurcation) at a dividing point called the carina into the right and left primary bronchus
- The carina is mostly cartilage, and has specialized nervous tissue that induces a coughing reflex if a foreign object such as food comes into contact with it.
- Primary function of bronchiole tree is air passage

- The bronchi structure is supported by C-shaped cartilage rings
- The primary bronchi branch out into progressively smaller branches of bronchi
- Primary bronchus ► Secondary bronchus ► Tertiary bronchus ► Terminal bronchioles ► Respiratory bronchioles
- ~1000 terminal bronchioles in each lung
  - Bronchioles have smooth muscles and elastin but **no cartilage**
  - Muscular wall allows tube diameter to change and control airflow
  - Produce little mucus to keep airway clear



Primary and secondary bronchi. Anatomy & Physiology, 2017

ALVEOLI



The alveolus cells. Anatomy & Physiology, 2017

- Respiratory bronchioles ► Alveolar duct ► Alveolus (plural Alveoli)
- Alveolus
  - 200um diameter
  - Alveolar pores connect alveoli to neighbour cells

- Alveolus
  - 200um diameter
  - Primary unit for gas exchange
  - Alveolar pores connect alveoli to neighbour cells and help to maintain equal air pressure
- Alveolar cell wall
  - 1. **Type I alveolar cell**
    - Squamous epithelial cell
    - 97% surface area of alveolus
    - Permeable to gas
    - Forms the **blood-air barrier**
  - 2. **Type II alveolar cell**
    - Produces pulmonary surfactant
      - Composed of phospholipids and proteins designed to reduce surface tension
  - 3. **Macrophage**
    - Phagocytic cell that removes debris and pathogens

Q3 PHYSIOLOGICAL FUNCTIONING

In what way has the normal physiological functioning of this area of the body been disturbed by the infection?.

WHERE DO THE PROBLEMS START?

S. pneumoniae is part of the normal respiratory flora in the nasopharynx[1,3]. Infection occurs when S. pneumoniae makes its way to the upper or lower respiratory tract without being cleared, where it can colonize and cause pneumonia[1,3].

SP

Infection occurs when respiratory aerosol droplets containing M. tuberculosis are inhaled through the upper respiratory tract and colonizes the alveoli[1,3].

MT

SP Streptococcus pneumoniae

MT Mycobacterium tuberculosis

CILIA

Pneumococcal pneumolysin arrests cilia sweeping activity. Mucus can build up in the lungs and trigger **coughing** in Robert[4].

SP

IMMUNE SYTEM

Most of the physiological disruption is due to the innate and adaptive immune system being put into action. Proinflammatory cytokines and recruitment of immune cells such as neutrophils and macrophages are catalysts for these changes[1,3].

SP

MT

TEMPERATURE REGULATION

Proinflammatory cytokines raises the set-point hypothalamic temperature of the body[5]. With this new set point, the body thinks the temperature is too low and tries to produce heat through shivering[5]. Robert feels **chills** when this happens[5]. It is not uncommon that the new set point can reach up to **38.5°C.**

SP

MT

When the fever breaks, the set point can reset and the hypothalamus attempts to cool the body through **nocturnal hyperhidrosis (night sweats)** and cutaneous vasodilation[5].

MT

GAS EXCHANGE

Neutrophils and macrophages release bactericidal elements to kill pathogens[1,3]. Healthy host tissue in the vicinity such as the alveoli can also be damaged by these products[1,3]. Damaging the blood-air barrier reduces its effectiveness in its ability to **exchange gas**.

SP

MT

Caseous necrosis can occur when necrosis occurs in the center of the granuloma[6]. This can lead to tubercle formation, and the process of healing tubercles causes fibrosis which reduces the **diffusion capacity** of the lungs[3].

MT

AIR CONDUCTION

The lysing of pathogens, immune cells and host tissue at the site cause fluids to leak into the alveolar space (pulmonary edema)[1,3]. Damage to type II alveolar cells reduces pulmonary surfactant production, increasing surface tension[2]. Both impair the **passage of air** through airways like the bronchioles.

SP

MT

Liquid plugs form from the fluids, and when air attempts to pass in/out of the lungs, the plugs can rupture causing the air passage to open and produce transient pressure waves[7]. These are the **respiratory crackles** that can be heard[7].

SP

MT

SUMMARY

The immune system responds to the presence of pathogens, inducing inflammation and **fever** that the body needs to compensate for.

Lung function is impaired.

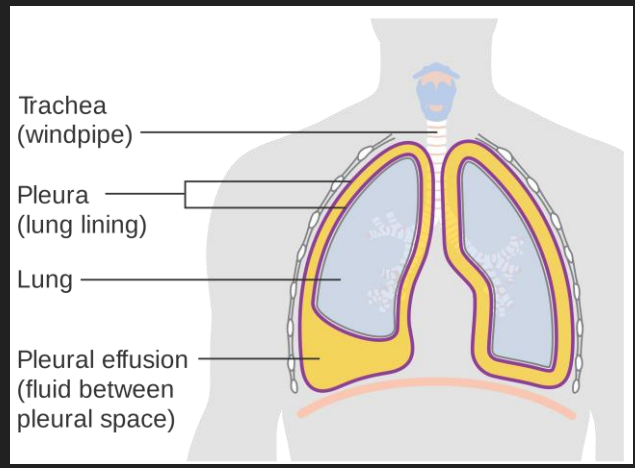
Fluid accumulation and retention in the respiratory tract reduce the amount of air that can flow into the alveoli for gas exchange.

Toxic products damage the alveoli and reduce lung diffusion capacity.

Resulting fibrosis from damage also reduces diffusion capacity.

The infection may have spread beyond the initial colonization site to other areas such as the pleural space.

Infection at the pleural cavity causes pleural effusion, where fluid builds up in the pleural space[8]. Excess fluid in the pleural space limits expansion of the lung and reduces **breathing sounds**[8].



Pleural effusion.

Cancer Research UK, distributed under a CC-ASA 4.0 license.

The changes in Robert's normal lung function likely stems from an infection to the lower lobe of his right lung.

Q4 SECONDARY SITES OF INFECTION

Are there any secondary sites of infection and, if so, what enables the bacteria to (a) travel to; and (b) affect these areas of the body?

Streptococcus Pneumoniae

HOW DOES IT SPREAD TO OTHER SITES?

By penetrating the mucosal epithelium in the respiratory tract, S. pneumonia gains access to the underlying capillary network, where it uses the bloodstream to travel to secondary sites of infection[4].

Capsular polysaccharide helps S. pneumonia survive in the bloodstream as it can makes it difficult for complement C3b to deposit on pneumococcal surface, limiting opsonization[6,9].

S. pneumoniae can adhere to and colonize epithelial and endothelial cells at other sites[4].

Zinc metalloproteases can cleave IgA1, making it easier to adhere to cells[4].

HOW DO INFECTIONS GET ESTABLISHED AT THE NEW SITE?

The same structures and mechanisms are used for adhesion and invasion at the new site: Pili, choline binding protein (CbpA), pneumococcal surface adhesion A and phosphocholine[6,9].

Functioning in secondary site is affected when local inflammatory factors such as IL-1 and TNF-a are generated, usually in response to pneumococcal endotoxins such as pneumolysin and peptidoglycan fragments[10].

This stimulates an inflammatory response, which damages the host tissues at the secondary site and impairs physiological function[10].

SP

WHAT ARE THE SECONDARY SITES OF INFECTION?

The blood, pleura, pericardium, peritoneum, joints and meninges are areas where secondary infections can occur[10].

The middle-ear and sinuses can be infected through non-hematogenous means such as local spread from the nasopharynx[10].

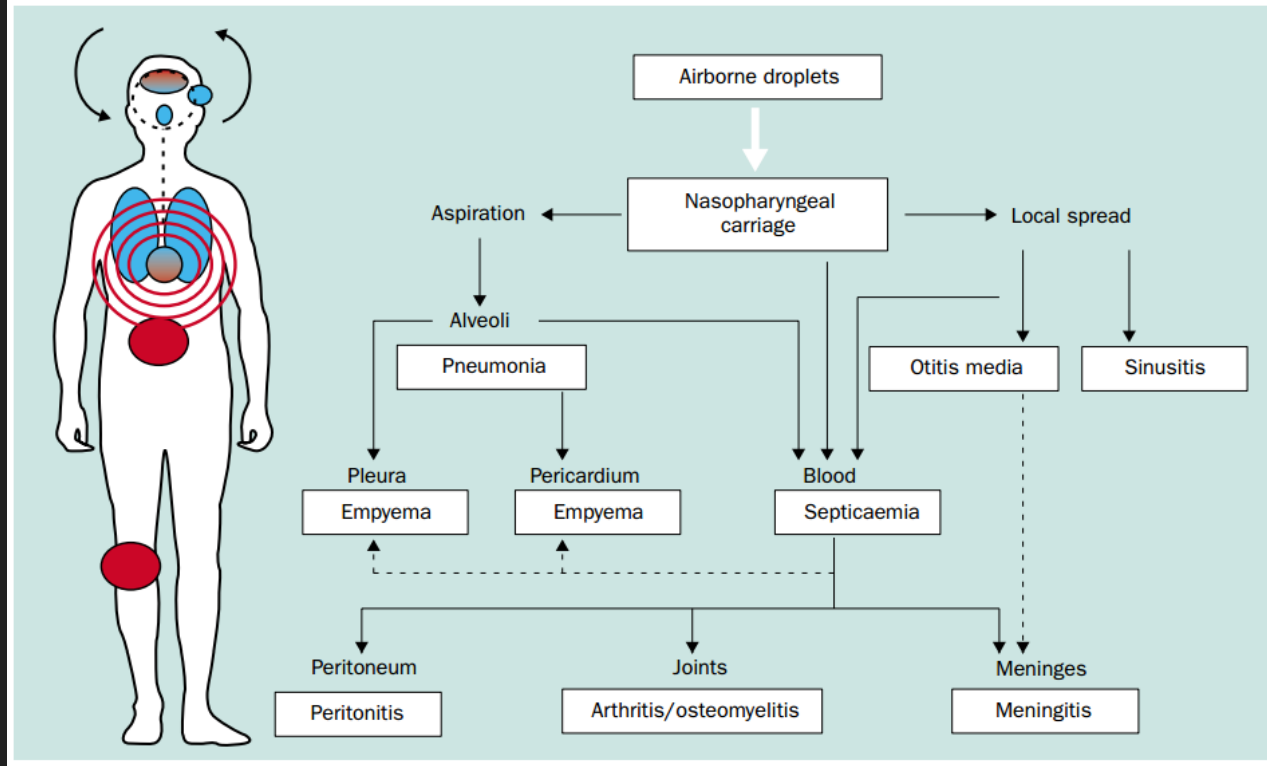


Figure 1. Pathogenic route for S pneumoniae infection. Redrawn from reference 2. Organs infected through the airborne and haematogenic routes are depicted in blue and red, respectively.

Pathogenic route for S pneumoniae infection. Redrawn from reference 2. Organs infected through the airborne and haematogenic routes are depicted in blue and red, respectively.

Bogaert et al., "Streptococcus Pneumoniae Colonisation: The Key to Pneumococcal Disease.", 2004.

SECONDARY SITES OF INFECTION

SITES	INFECTIONS & KEY FEATURES
Meninges	Meningitis (inflammation of the meninges) causes serious lasting deficiencies for survivors[11]. IQ deficits, seizures, blindness and neuropsychological functioning are all impacted negatively[11].
Blood	Bacteremia has a mortality rate of approximately 13%[12]. Septic shock, leukopenia or leukocytosis and anaemia are risk factors associated with pneumococcal bacteremia death[12].

SITES	INFECTIONS
Ear	Otitis media (inflammation of middle ear)
Sinus	Sinusitis (inflammation of sinus)
Heart	Endocarditis
Peritonium	Peritonitis (inflammation of peritoneum)
Joints & bones	Arthritis and osteomyelitis (inflammation of bone and joints)
Eye	Conjunctivitis (pink-eye, inflammation of conjunctiva)

**This list is not exhaustive*

SP

Mycobacterium tuberculosis

HOW DOES IT SPREAD TO OTHER SITES?

When caseating granulomas fail to eliminate Mtb, it continues to grow in size as Mtb kills macrophages and proliferates[13]. Eventually the granuloma erodes into air passages such as the bronchus and a cavity forms into the blood vessels[14].

Infectious material from the granuloma can enter the bloodstream where it can disseminate to other parts of the body[14].

Mtb can spread hematogenously or through the lymphatic system[14].

The same tactics (degrading reactive intermediates, disrupting phagosome-lysosome fusion, etc) that Mtb used to evade the immune system in the initial infection are used to survive at the secondary site.

HOW DO INFECTIONS GET ESTABLISHED AT THE NEW SITE?

Mtb is able to adhere to and invade epithelial and endothelial cells at other sites[14].

Ex. TB meningitis: Herparin binding haemagglutinin adhesin, fibronecting binding proteins and pili aid Mtb in binding to secondary site surfaces. Through a not-well understood mechanism, they are to translocate across the membrane[15].

The seeding of Mtb at the new site, and formulation of a caseous granuloma is what is responsible for affecting the organ. The toxic effects of the granuloma damages the organ tissue and impairs their function[14,15].

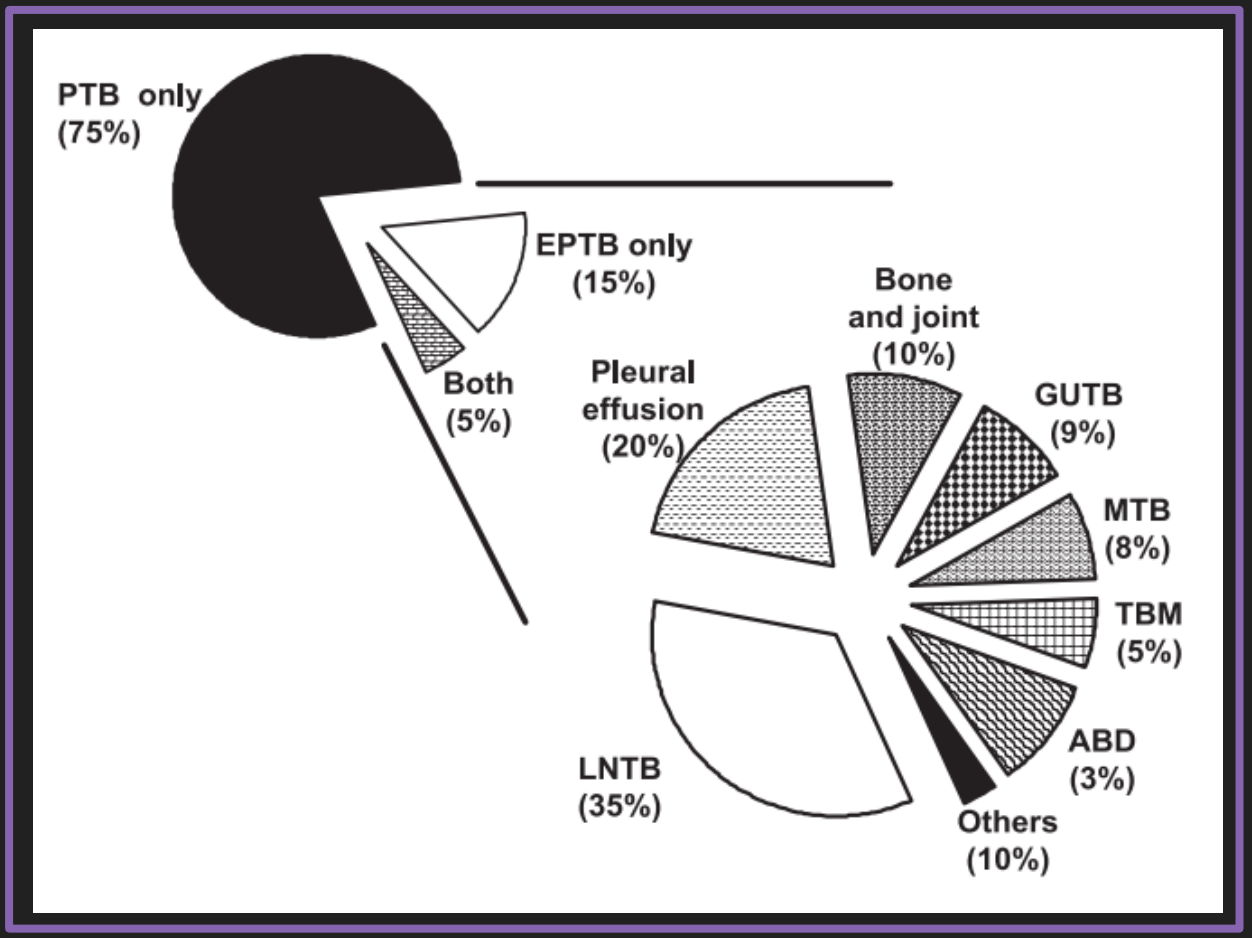
MT

WHAT ARE THE SECONDARY SITES OF INFECTION?

Mtb can spread to all sites in the body. Roughly 20% of Mtb infections are extrapulmonary (outside of the pulmonary system)[14].

The most common sites is the lymph nodes, the pleural space, the bone and joints, the genitourinary area, the meninges and the abdomen[14].

Less common areas include the skin, nose, ear, breast, heart and eyes[14].



Distribution of tuberculosis cases by anatomical site in HIV-negative patients. Sharma and Mohan, "Extrapulmonary Tuberculosis", 2004

LNTB – Lymph node tuberculosis
PTB – Pulmonary tuberculosis
EBTB – Extrapulmonary tuberculosis
GUTB – Genitourinary tuberculosis
MTB – Miliary tuberculosis
TBM – Tuberculosis mengingitis
ABD – Abdominal tuberculosis

MT

SECONDARY SITES OF INFECTION

SITES	INFECTIONS & KEY FEATURES
Lymph nodes[14]	Macrophages harbouring intracellular Mtb can travel to the lymph nodes where Mtb can establish an infection. The lymph node is often a starting point for Mtb dissemination to other parts of the body.
Pleural space[14]	Edema can build up in the pleural space, resulting in pleural effusion which impair lung expansion. Common symptoms include pleuritic chest pain, dyspnea, non-productive cough and fever. Empyema thoracis (accumulation of pus in the pleural space) can occur if a caseous cavity ruptures into the pleural space.
Bone & Joints[14]	Spinal tuberculosis is the most common. Paraplegia (Pott's paraplegia) can occur in 30% of spinal TB patients. Weakness, fever and night sweats are typical symptoms.
Genital & Urinary organs[14]	Active GUTB can take a long to develop, up to 5-25yrs after the initial pulmonary TB infection. Symptoms include dysuria, blood in the urine, and recurrent urinary tract infection.
Blood[14]	Known as dessiminated or miliary tuberculosis (widespread infection in the body). Can occur during primary infection or after reactivation. Causes small lesions throughout and typically seen as millet seeds (hence miliary) on X-ray. Symptoms are non-specific and include fever, chills, cough and dyspnea.
Meninges[14]	Tuberculosis meningitis is the most common neurological tuberculosis (70-80%). More common in developing worlds. Death can occur within 5-8 weeks without treatment. Symptoms include behavioral changes, irritability, seizures and complete or partial loss of vision.
Abdominal area[14]	Includes the GI tract, liver, spleen, and peritoneum. Symptoms are non-specific and the host can present with anorexia, fever, night sweats or jaundice.

**Extrapulmonary tuberculosis can occur at every site in the body. This table lists the common secondary infection sites from top to bottom and is not exhaustive.*

MT

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