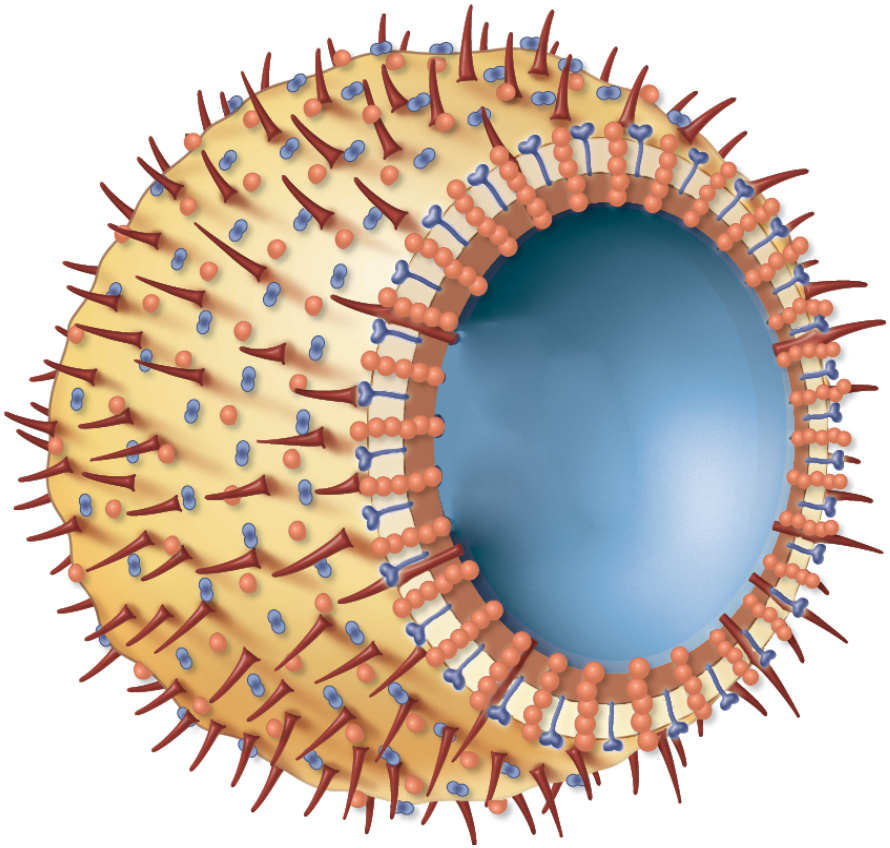
Chapter 24

Microbial Diseases of the Respiratory System

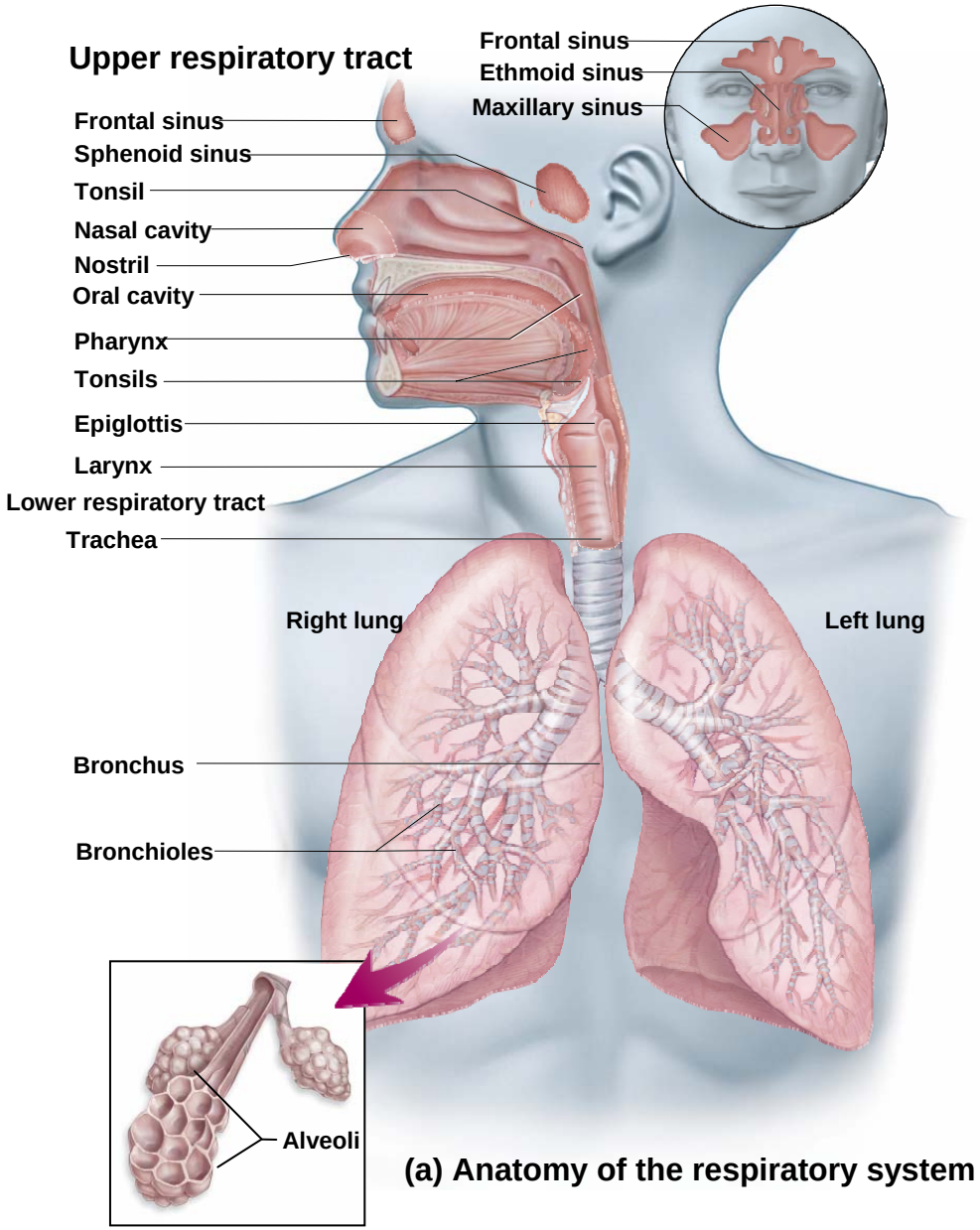


Respiratory System

Divided into **two** parts:

the **upper** tract
- -mouth
- -nose, nasal cavity, sinuses
- -pharynx

the **lower** tract
- -epiglottis
- -larynx
- -trachea
- -bronchi
- -bronchioles
- -alveoli



(a) Anatomy of the respiratory system

Respiratory Defenses

The respiratory tract is the most common **portal of entry**

Protection from infection:

first line defenses

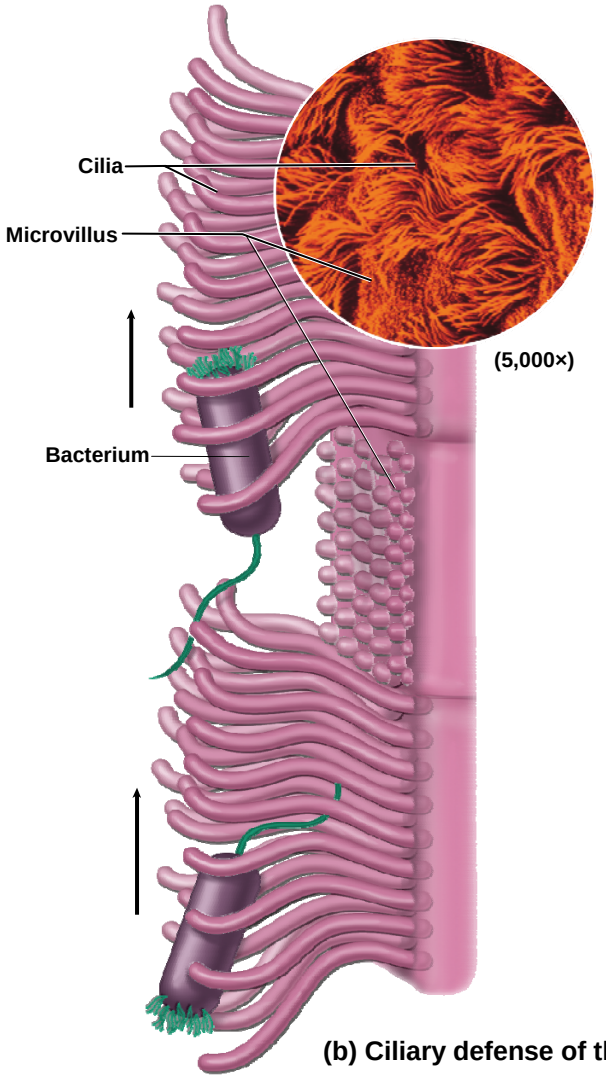
- nasal hairs
- cilia (the ciliary escalator)
- mucus

second line defenses

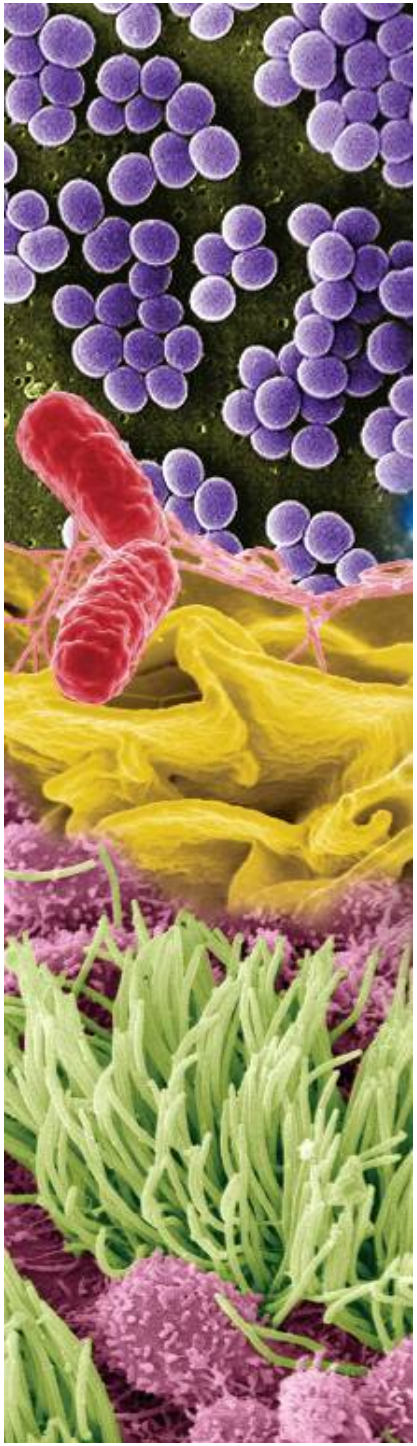
- macrophages

third line defenses

- pathogen-specific
- secretory IgA



(b) Ciliary defense of the tracheal mucosa



Normal Biota of the Respiratory Tract

This system harbors a large number of **commensal** microbes

Normal biota mainly found in the upper respiratory tract // play a role in **microbial antagonism**

Gram-positive bacteria are common in the normal biota // e.g. streptococci, staphylococci

Some “normal” biota” can be **pathogenic**:

Streptococcus pyogenes
Haemophilus influenzae
Streptococcus pneumoniae
Neisseria meningitidis
Staphylococcus aureus

Candida albicans **(yeast)** colonizes the oral mucosa

Normal Microbiota of the Respiratory System

- Suppress pathogens by competitive inhibition in upper respiratory system
- Lower respiratory system is sterile

Bacterial Diseases of the Upper Respiratory System

- **Streptococcus Pharyngitis (Step Throat)**
- **Scarlet Fever**
- **Diphtheria**
- **Otitis Media**
- **Laryngitis**
- **Tonsillitis**
- **Sinusitis**
- **Epiglottitis**: *H. influenzae* type b

Streptococcal Pharyngitis

- Also called **strep throat**
- *Streptococcus pyogenes (group A S. pyogenes / GAS)*
- Resistant to phagocytosis
- Streptokinases lyse clots
- Streptolysins are cytotoxic / lyses RBC and WBC
- Diagnosis by **enzyme immunoassay (EIA)** tests

Pharyngitis

Signs and Symptoms:

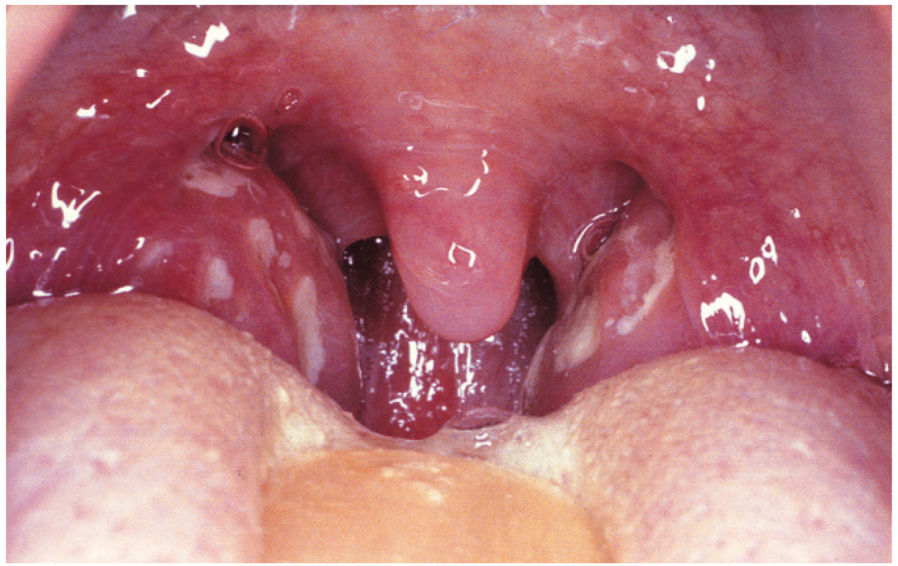
inflammation of the throat

reddened and/or swollen mucosa

swollen tonsils

foul-smelling breath

white packets visible on the walls of the throat (**streptococcal disease**)



Pharyngitis // Causative Agents

Pharyngitis can be caused either by bacteria or virus

Most often caused by common cold **viruses**

More serious infection by common bacterial cause = Streptococcus pyogenes (Group A)

S. Pyogenes undergoing phagocytosis by neutrophil

Pharyngitis // *Streptococcus pyogenes*

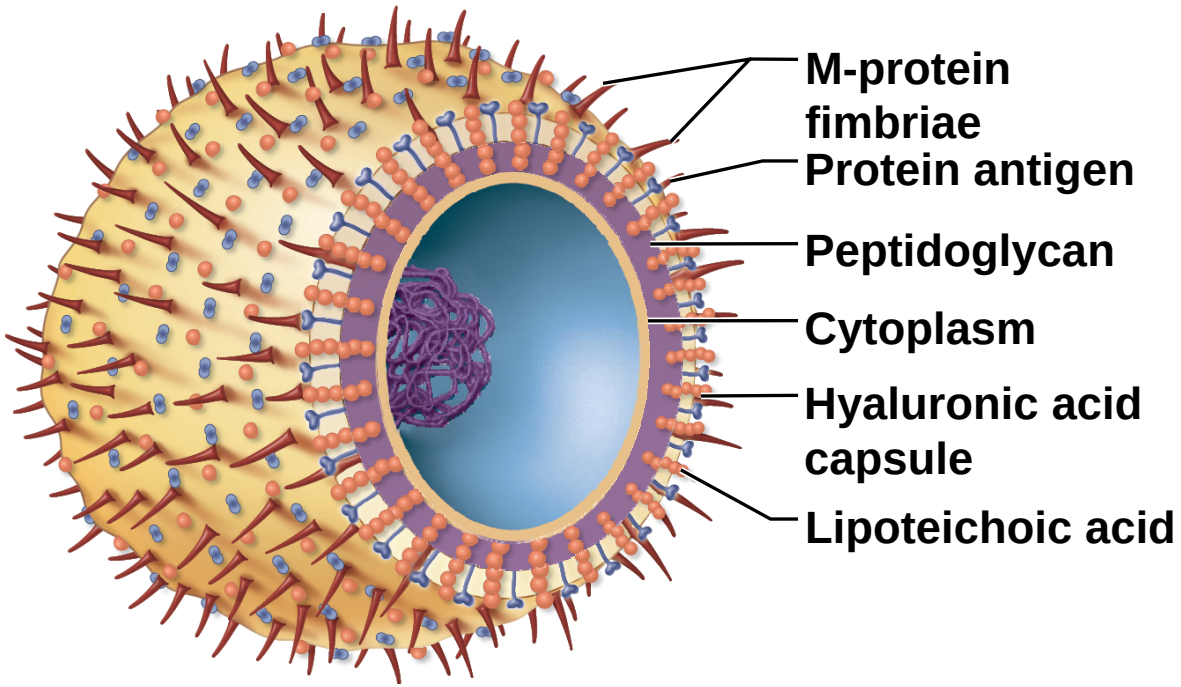
gram-positive coccus that grows in chains

virulence factor = forms capsules (slime layers)

facultative anaerobe // grows in areas of low oxygen

Pharyngitis //

S. pyogenes: More Virulence Factors



Surface Antigens:

lipoteichoic acid (LTA)
M protein
hyaluronic acid (HA)

Extracellular Toxins:

streptolysins:
streptolysin **O** (SLO) and streptolysin **S** (SLS) for hemolysis

erythrogenic toxin:
responsible for the rash, fever typical of **scarlet fever**

Superantigens: induce **tumor necrosis factor** (TNF)-mediated damage

Pharyngitis

Complications of *S. pyogenes* Infection
Scarlet Fever

Scarlet fever caused when *bacteriophage infects S. pyogenes*

Bacteriophage *delivers plasmid* // genetic code to make Erythrogenic Toxin

Lysogenized *S. pyogenes*

Also called “scarlatina”

Sandpaper-like rash with high fever

Common in school-age children

Pharyngitis

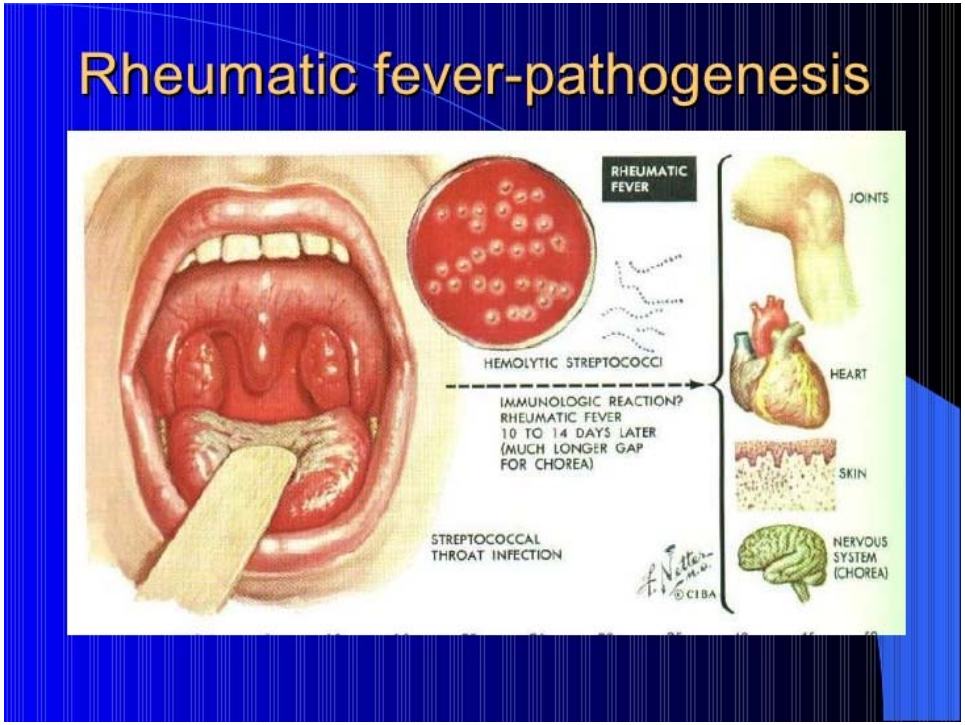
Complications of *S. pyogenes* Infection
Rheumatic Fever

Reaction between streptococcal M protein and heart muscle // may also involve other tissues

Occurs ~3 weeks after pharyngitis has subsided

Damage to heart valves

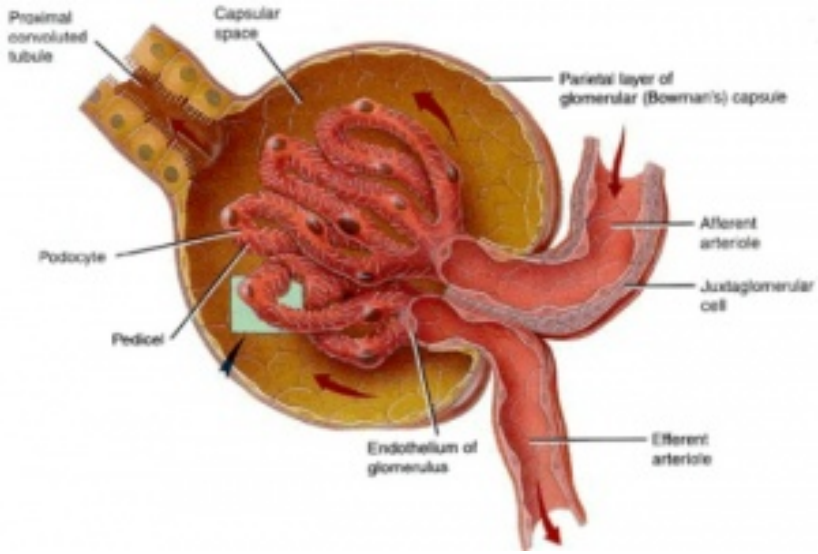
Arthritis in multiple joints

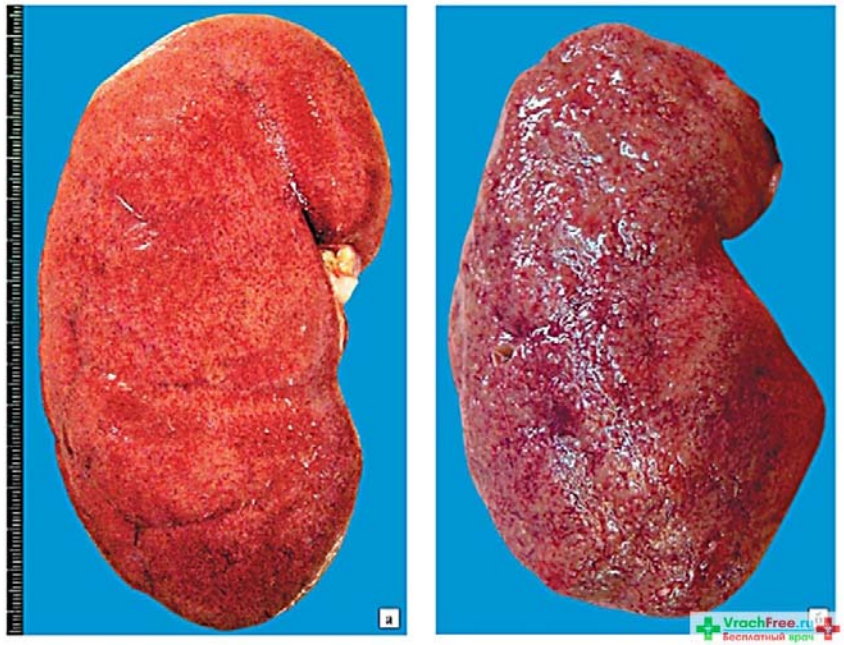


Pharyngitis

Complications of *S. pyogenes* Infection
Glomerulonephritis

formation of antigen-antibody complexes in the **glomeruli** characterized by **nephritis**





Complications of *S. pyogenes* Infection

Toxic Shock Syndrome

- Caused by prolonged use of a single tampon which creates a buildup and subsequent infection of bacteria
- Symptoms: fever, diarrhea, vomiting, sore throat, muscle ache, rash,
- May cause: dizziness, respiratory distress, kidney failure, heart failure, death
- Avoid by changing tampons regularly, using less absorbent tampons, using sanitary pads

Pharyngitis

Complications of *S. pyogenes* Infection

Necrotizing fasciitis also possible outcomes associated with S. pyogenes

Pharyngitis

S. Pyogenes Transmission and Epidemiology

30% of sore throats may be caused by *S. pyogenes*

More than 80 serotypes of *S. pyogenes* exist

15% of the population carries *S. pyogenes* as “normal” biota

Humans are the only significant reservoir of S. pyogenes

Transmission via

respiratory droplets // direct contact with mucus secretions // fomites

Pharyngitis
S. pyogenes: Treatment

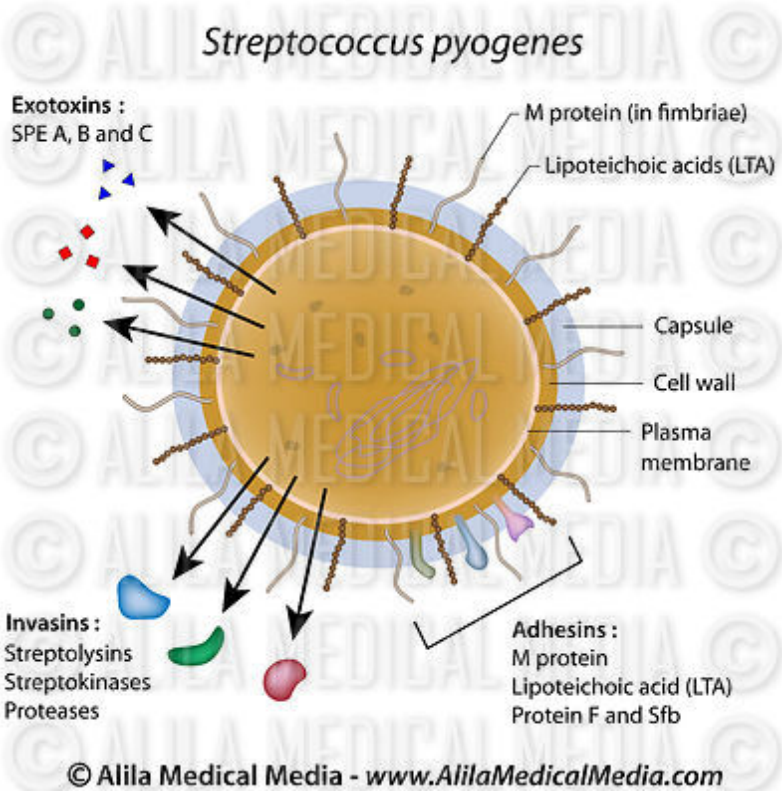
Penicillin first choice

Many group A streptococci are resistant to **erythromycin**

Use first-generation cephalosporin (**cephalexin**) for patients with penicillin allergies

No vaccine

Prevention = good hygiene + **hand washing**



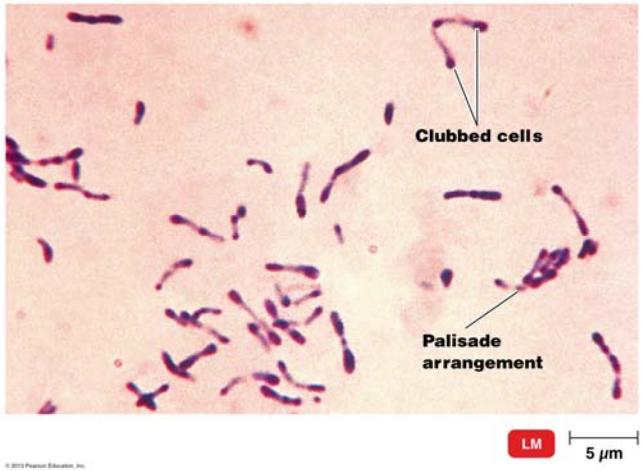
Pharyngitis

Disease Table 19.1

Causative Organism(s)	Fusobacterium necrophorum	Streptococcus pyogenes	Viruses
Most Common Modes Of Transmission	Opportunistic	Droplet or direct contact	Allforms of contact
Virulence Factors	Endotoxin, leukotoxin	LTA, M protein, hyaluronic acid capsule, SLS and SLO, superantigens	—
Culture/Diagnosis	Growth on anaerobic agar	Beta-hemolytic on bloodagar, sensitive to bacitracin, rapid antigen tests	Goal is to rule out S. pyogenes, further diagnosis usually not performed
Prevention	Hygiene practices	Hygiene practices	Hygiene practices
Treatment	Penicillin, cefuroxime	Penicillin, cephalexin in penicillin-allergic	Symptom relief only
Distinctive Features	Common in adolescents and young adults, Infections spread to cardio-vascular system or deeper tissues	Generally more severe than viral pharyngitis	Hoarseness frequently accompanies Viral pharyngitis

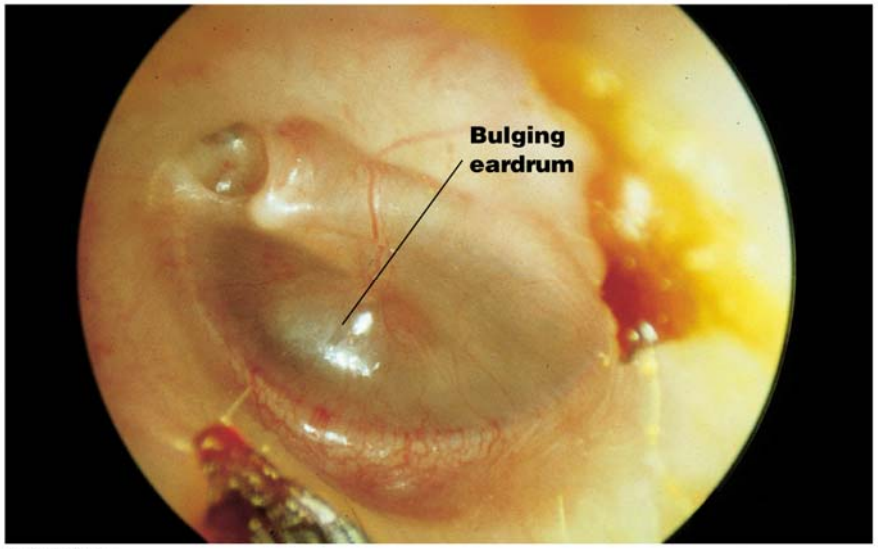
Diphtheria

- Until 1935 leading killer of children in United States
- Corynebacterium diphtheriae // gram positive, non-endospore forming rod
- Immunization program = DTaP vaccine
- Begins with sore throat // bacteria does not invade tissue
- If bacteria lysogenized by phage then produces powerful toxin // toxin interferes with protein synthesis – 0.01 mg can be fatal
- Toxin can destroy heart and kidney tissue
- Penicilin and erythromycin may control bacterial growth but does not neutralize toxin



Otitis Media

- Complication of common cold or other upper respiratory infection
- Affects 85% of children before age 3
- Pus builds up pressure on eardrum // tympanic membrane becomes inflamed and painful
- Maybe caused by S. pyogenes, S. aureus, or viral infections
- Concern with meningitis or encephalitis



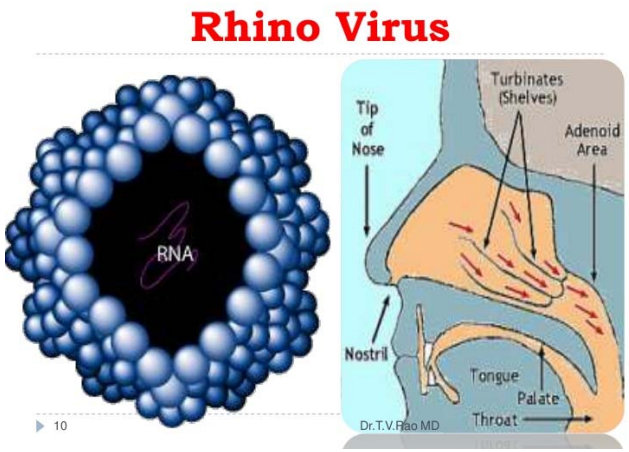
Viral Diseases of the Upper Respiratory System

- **Common Cold**

Rhinitis: The Common Cold

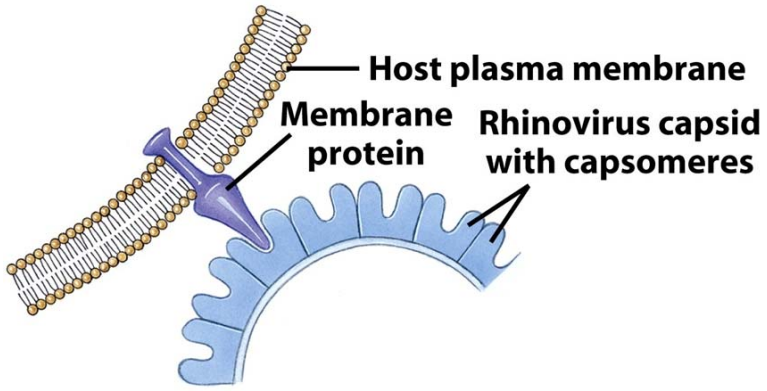
Causative agent: over 200 different **viruses**

Rhinoviruses (99 **serotypes**)
Coronaviruses
Adenoviruses
Respiratory syncytial virus (RSV)



Transmission:

indirect contact // droplet contact

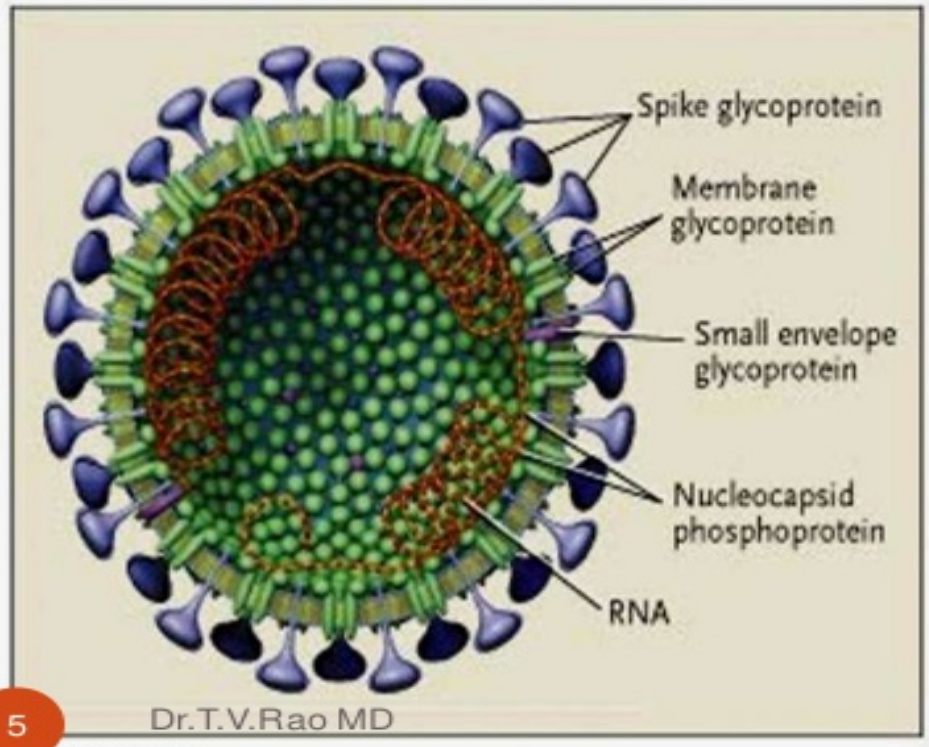


Symptoms:

sneezing and runny nose
scratchy throat
low fever in kids

SARS - Coronavirus

Schematic drawing of SARS coronavirus



Source: Drazen JM[14]

- **SARS coronavirus is a positive and single stranded RNA virus belonging to a family of enveloped coronaviruses. Its genome is about 29.7kb, which is one of the largest among RNA viruses. SARS is similar to other coronaviruses in that its genome expression starts with translation of two large ORFs 1a and 1b, which are two polyproteins.**

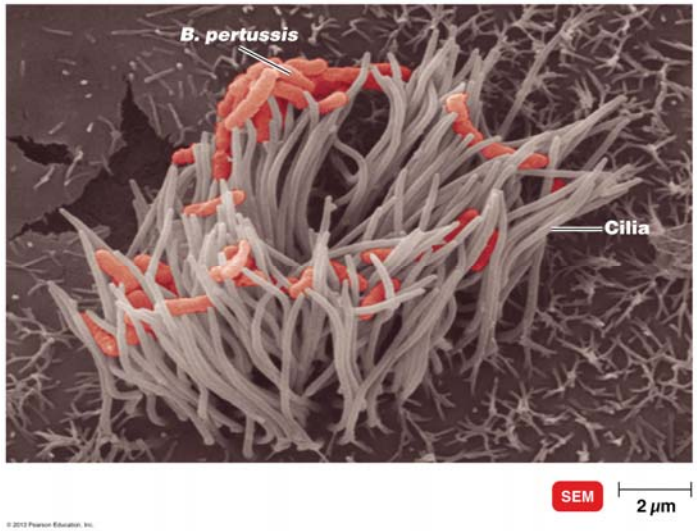
SARS – severe acute respiratory syndrome

Bacterial Diseases of the Lower Respiratory System

- Pertussis (Whooping Cough)
- Tuberculosis
- Bacterial Pneumonias
- Meliodosis

Pertussis

- Bordetella pertussis // obligately aerobic gram negative coccobacillus
- Bacteria specifically attach to ciliated cells in the trachea
- Slow down action of cilia then destroy cilia
- Produce toxin which enters blood to cause systemic affects
- Severe coughing can break ribs // grasping for air between coughing episodes
- Major disease in 1940 /// DTP vaccine caused rapid decline // since 1980 increase – immunity of DTP declines over time



Tuberculosis: the “White Plague”

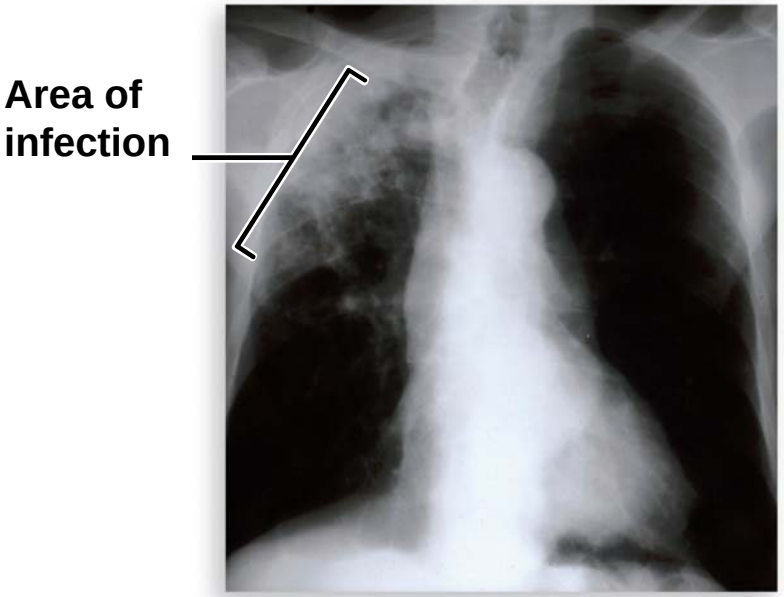
<u>Signs and Symptoms</u>:

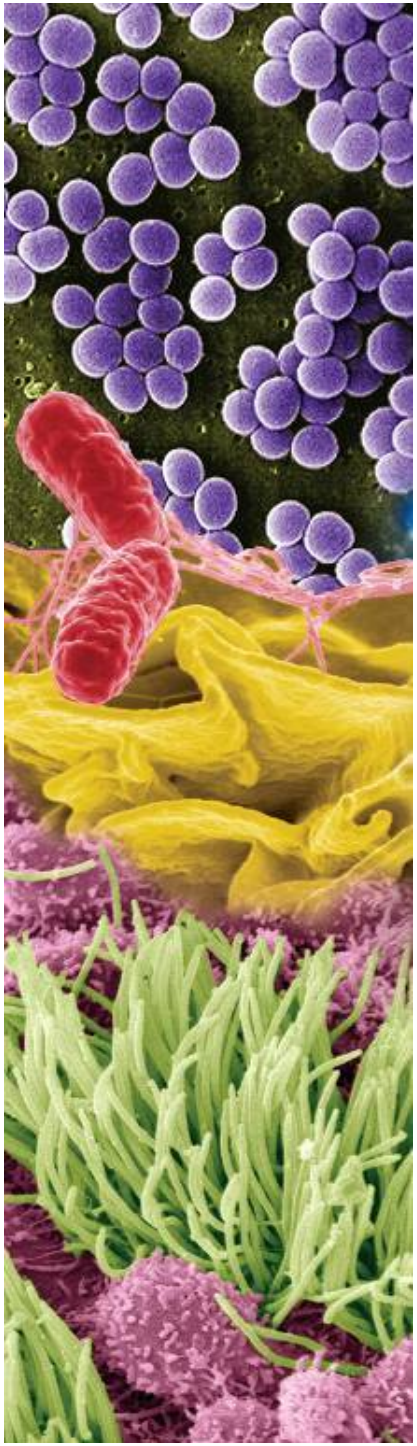
humans easily infected but quite resistant to **disease** development

85% TB cases contained in the **lungs**

clinical tuberculosis forms:

- **primary**
- **secondary**
- **disseminated / extrapulmonary**





Tuberculosis // Causative agent

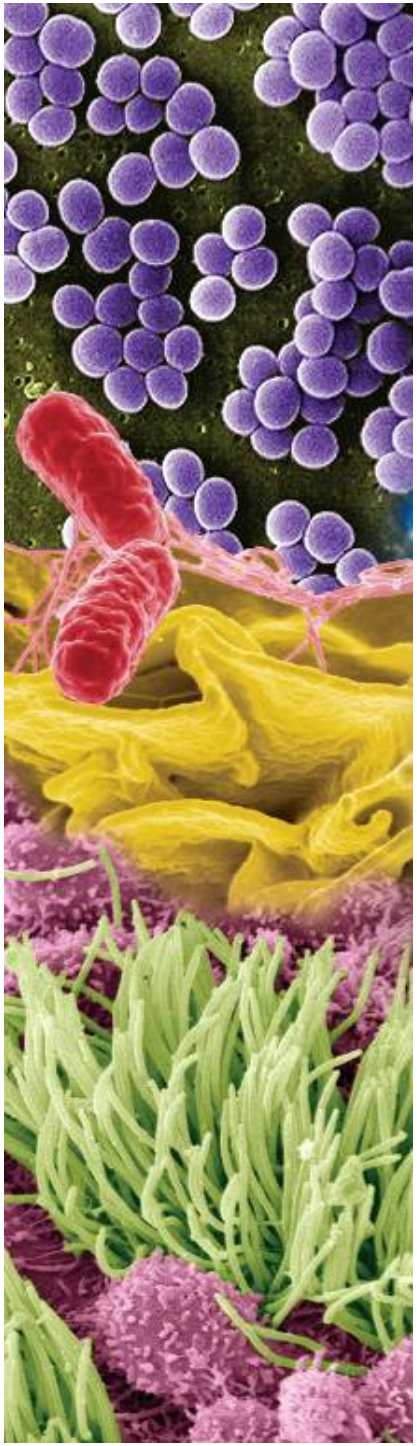
Mycobacterium tuberculosis

acid-fast bacillus, strict aerobe, slow-growing

mycolic acids, waxes in cell wall

resistant to drying and disinfectants

cord factor linked to virulence



Tuberculosis // Primary Tuberculosis

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minimum infectious dose is ~10 bacterial cells

bacteria multiply inside **macrophages**

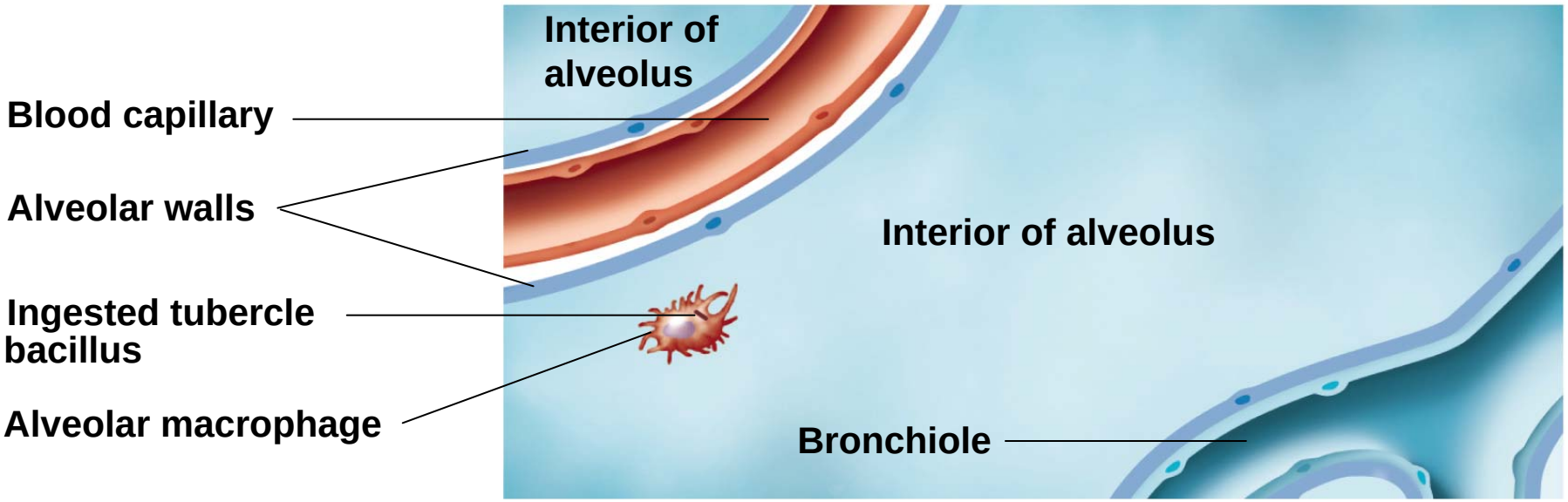
escape leads to cell-mediated attack on bacteria

tubercle formation in lungs // macrophage surrounded by fibroblast and WBC

neutrophils release enzymes causing necrotic **caseous lesions** that heal by calcification // consumption

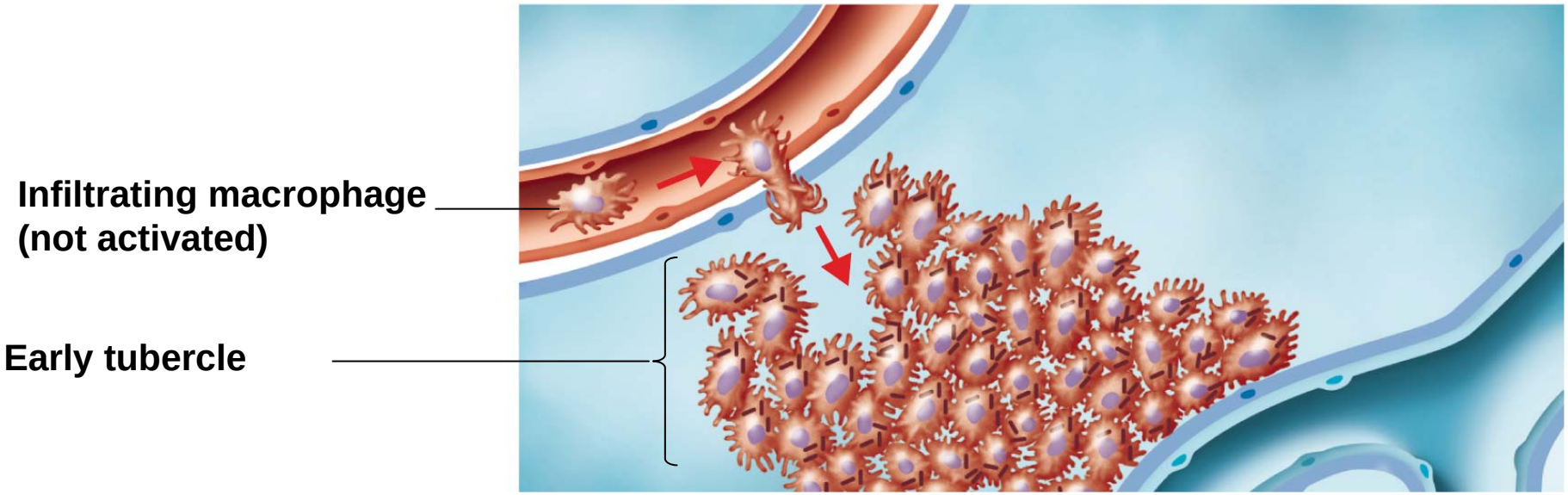
T cell action seen in **tuberculin reaction**

The pathogenesis of tuberculosis.



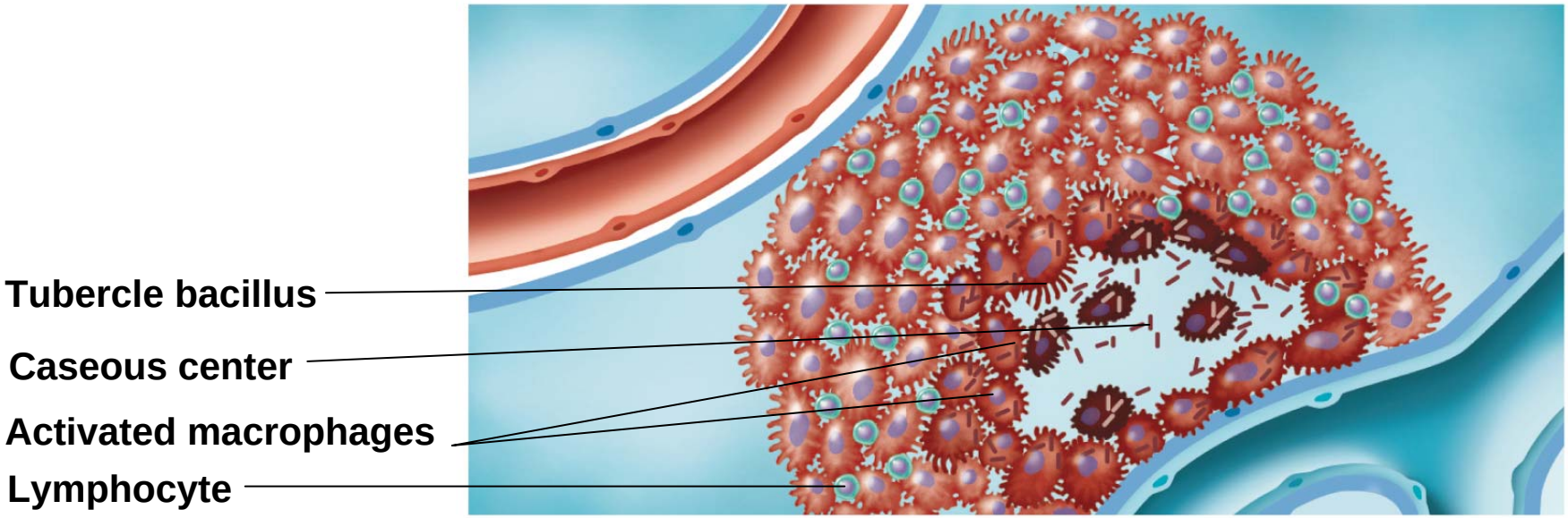
1 Tubercle bacilli that reach the alveoli of the lung (see Figure 24.2) are ingested by macrophages, but often some survive. Infection is present, but no symptoms of disease.

The pathogenesis of tuberculosis.



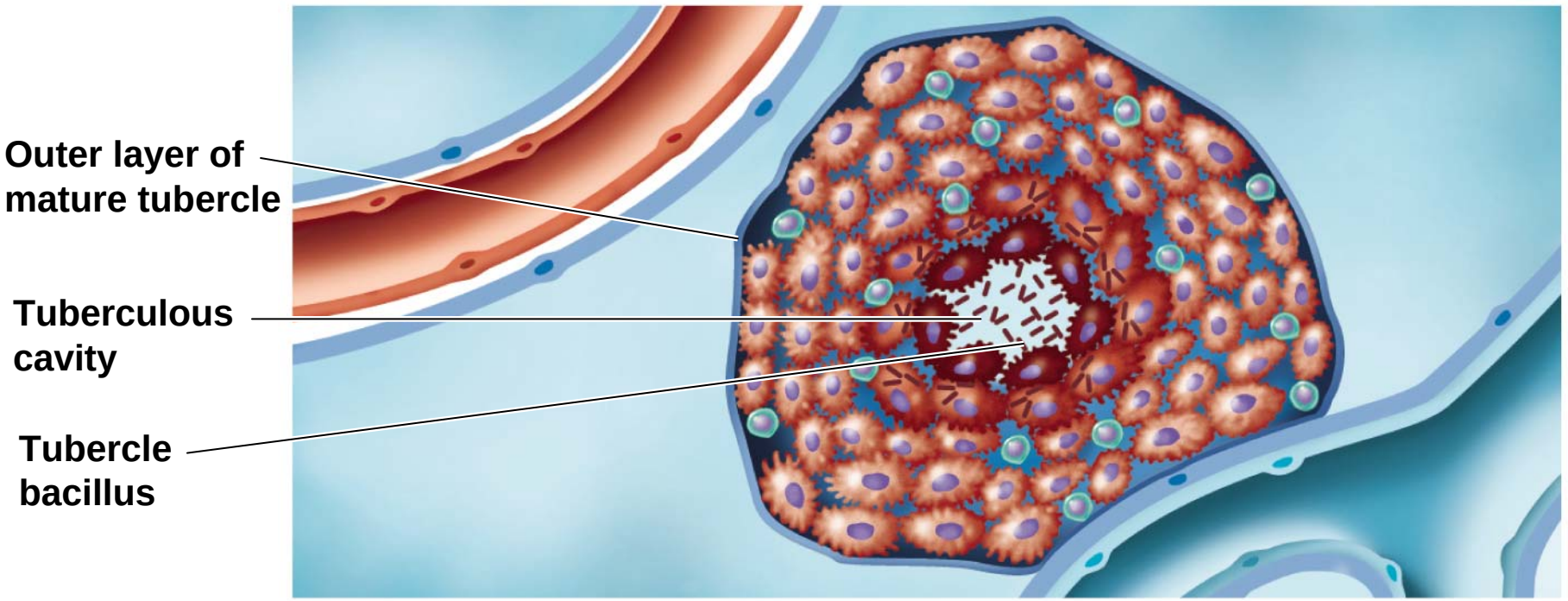
2 **Tubercle bacilli multiplying in macrophages cause a chemotactic response that brings additional macrophages and other defensive cells to the area. These form a surrounding layer and, in turn, an early tubercle. Most of the surrounding macrophages are not successful in destroying bacteria but release enzymes and cytokines that cause a lung-damaging inflammation.**

The pathogenesis of tuberculosis.



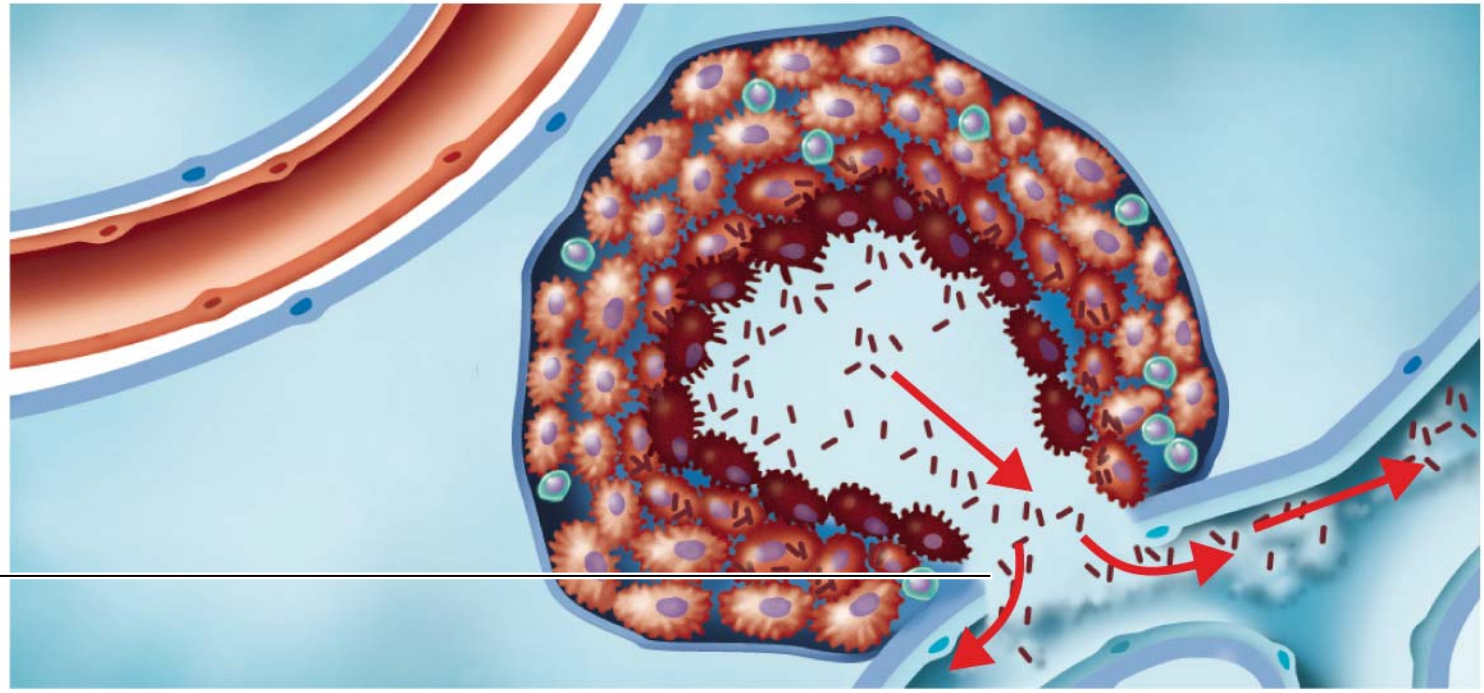
3 **After a few weeks, disease symptoms appear as many of the macrophages die, releasing tubercle bacilli and forming a *caseous center* in the tubercle. The aerobic tubercle bacilli do not grow well in this location. However, many remain dormant (latent TB) and serve as a basis for later reactivation of the disease. The disease may be arrested at this stage, and the lesions become calcified.**

The pathogenesis of tuberculosis.

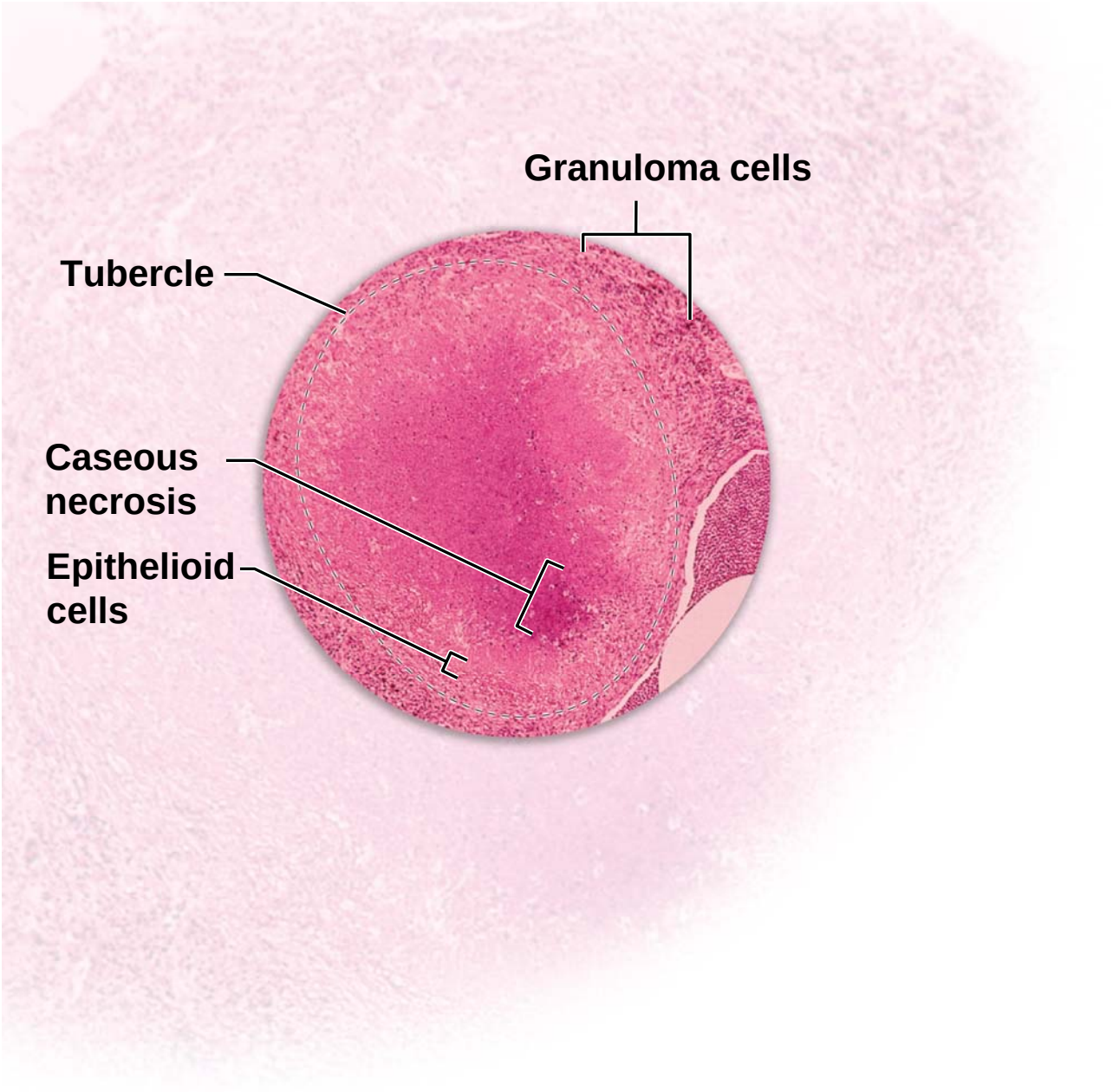


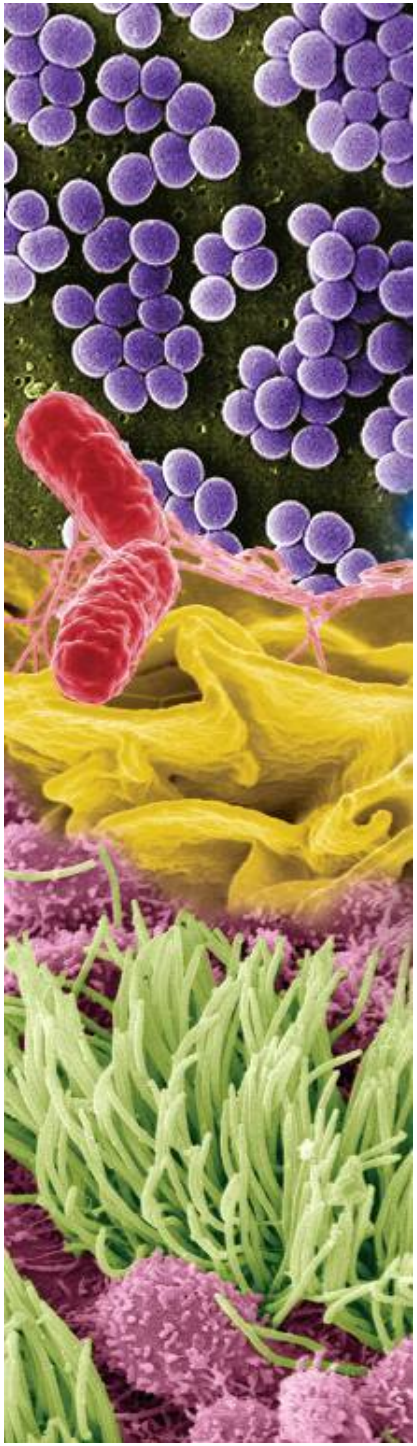
4 **In some individuals, disease symptoms appear as a mature tubercle is formed. The disease progresses as the caseous center enlarges in the process called *liquefaction*. The caseous center now enlarges and forms an air-filled *tuberculous cavity* in which the aerobic bacilli multiply outside the macrophages.**

The pathogenesis of tuberculosis.



5 **Liquefaction continues until the tubercle ruptures, allowing bacilli to spill into a bronchiole (see Figure 24.2) and thus be disseminated throughout the lungs and then to the circulatory and lymphatic systems.**





Tuberculosis // Secondary Tuberculosis:

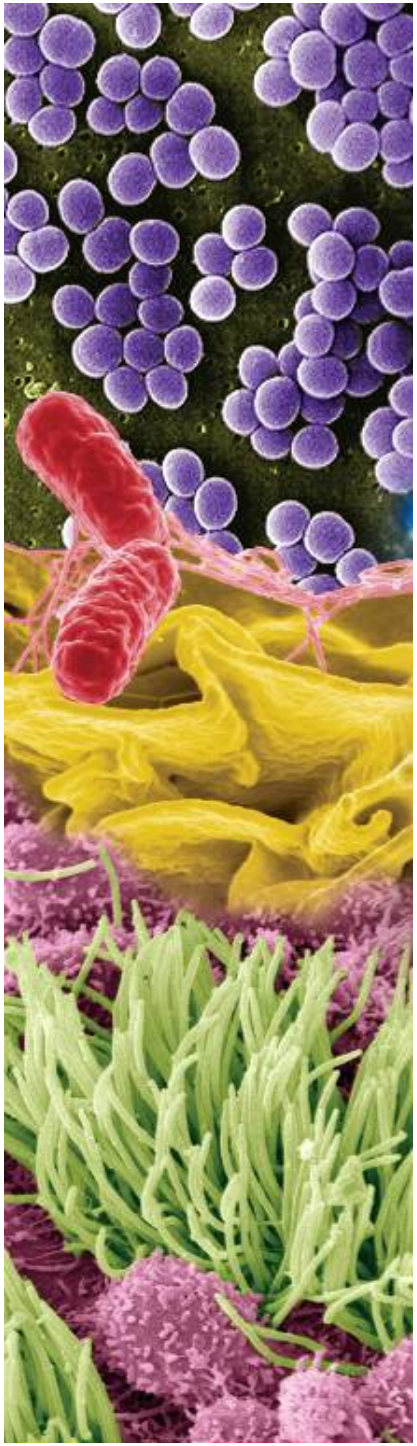
live bacteria can remain **dormant //** then **reactivate**

chronic tuberculosis: tubercles expand

severe symptoms develop = **consumption**

- -violent coughing
- -greenish or bloody sputum
- -low-grade fever
- -anorexia, weight loss
- -extreme fatigue
- -night sweats
- -chest pain

Many countries complicated by AIDS

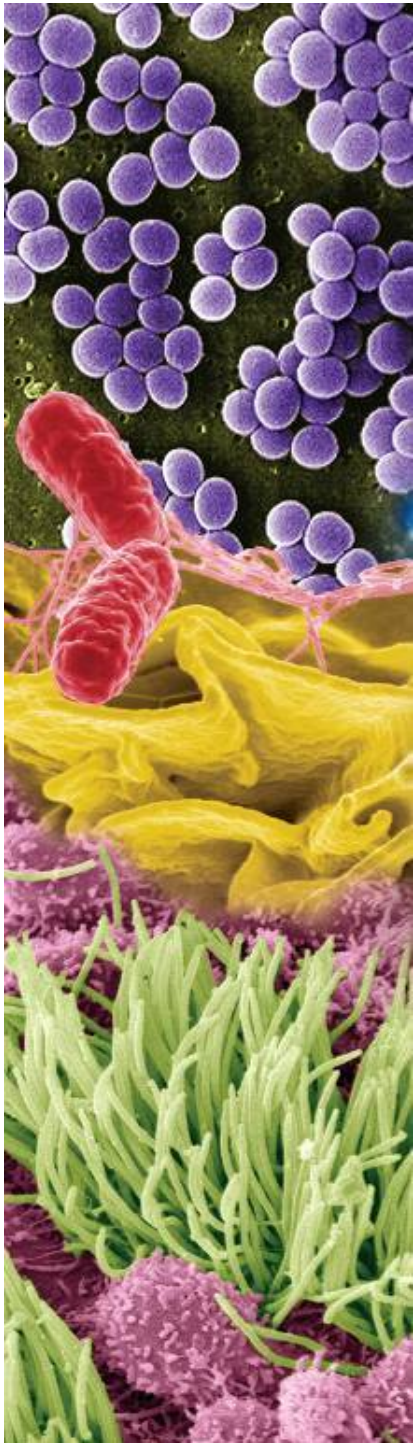


Tuberculosis // Extrapulmonary Tuberculosis

infection **outside** of the lungs:

- regional lymph nodes
- kidneys (**renal tuberculosis**)
- long bones
- genital tract (**genital tuberculosis**)
- brain and meninges (**tubercular meningitis**)

immunosuppressed patients, young **children**



Tuberculosis // Pathogenesis and Virulence Factors

waxy cell wall enhances survival in environment and within macrophages

stimulates strong cell-mediated immune response enhancing disease pathology

the host's own immune system causes the tissue necrosis // e.g. respiratory burst of neutrophils

Tuberculosis // Transmission/Epidemiology

"infection of poverty"

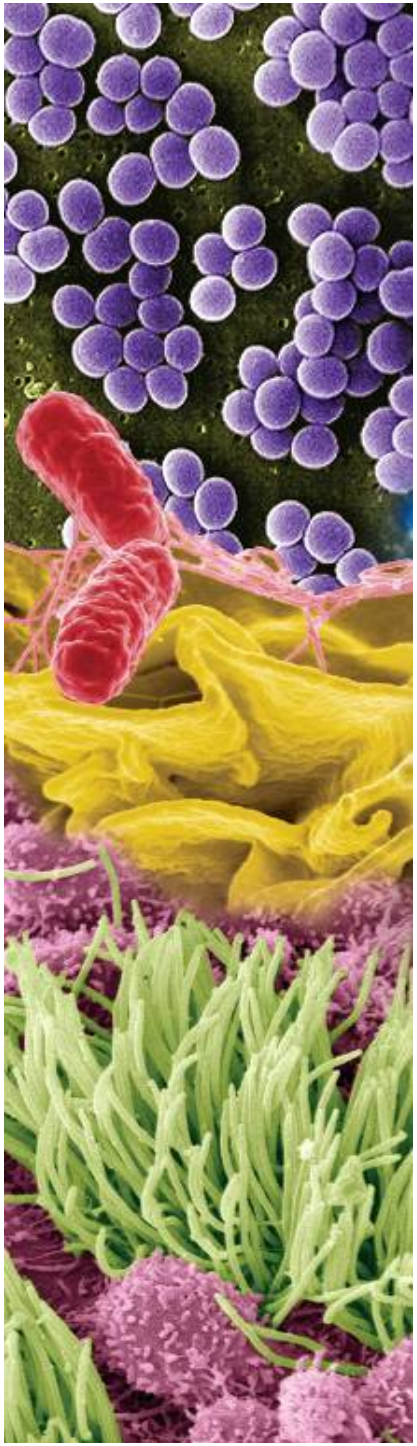
transmitted via droplets of respiratory mucus suspended in air // can survive for 8 months in fine aerosol particles

susceptibility influenced by:

- -inadequate nutrition
- -debilitation of the immune system
- -poor access to medical care
- -lung damage
- -genetics

2 billion currently infected with TB, ~2 million died in 2008

60% of US cases are among foreign-born persons: // Mexico, Philippines, Vietnam, India, and China



Tuberculosis // Culture/Diagnosis

Clinical diagnosis of disease relies on 4 techniques:

tuberculin testing

chest X rays

direct identification of acid-fast bacilli (AFB)

cultural isolation, antimicrobial susceptibility testing

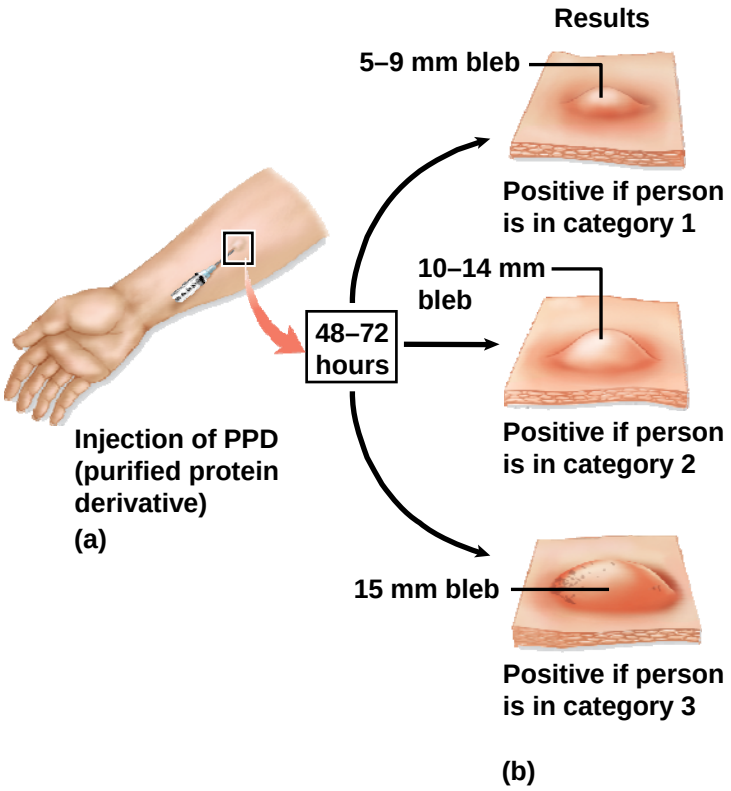
Tuberculosis // Tuberculin testing

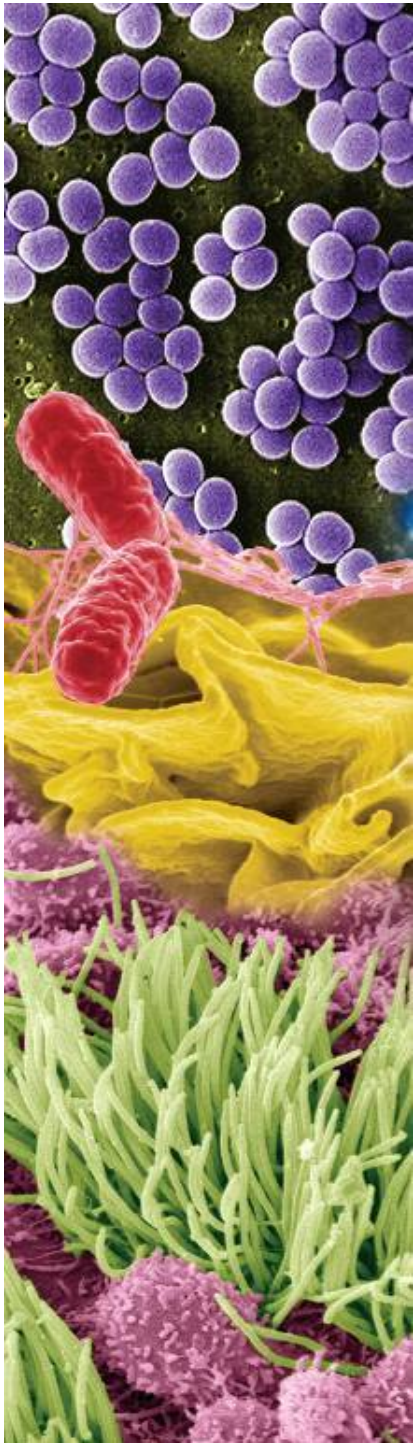
Mantoux test

injection of **PPD** is given **intradermally** into the forearm

after **48 and 72 hours**, site is observed for **induration**

the red wheal is **measured, interpreted as positive or negative** by size





Tuberculosis

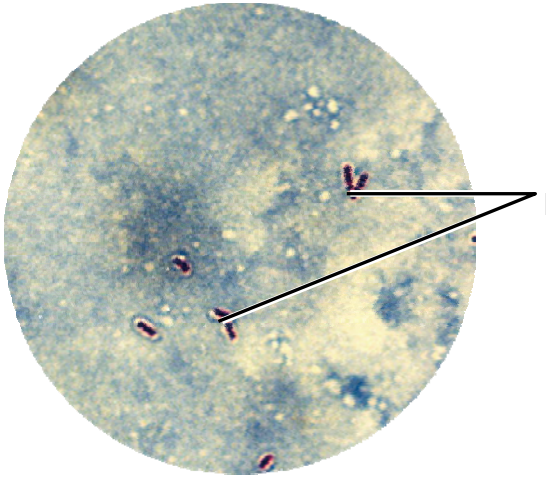
testing limited to groups with **higher risk** for TB

a **positive reaction** is indicative of recent **infection** or **reactivation** of a prior latent infection

false-positive reactions can occur due to vaccination, infection with related species

false-negative reactions can occur in patients with compromised immune systems

Tuberculosis

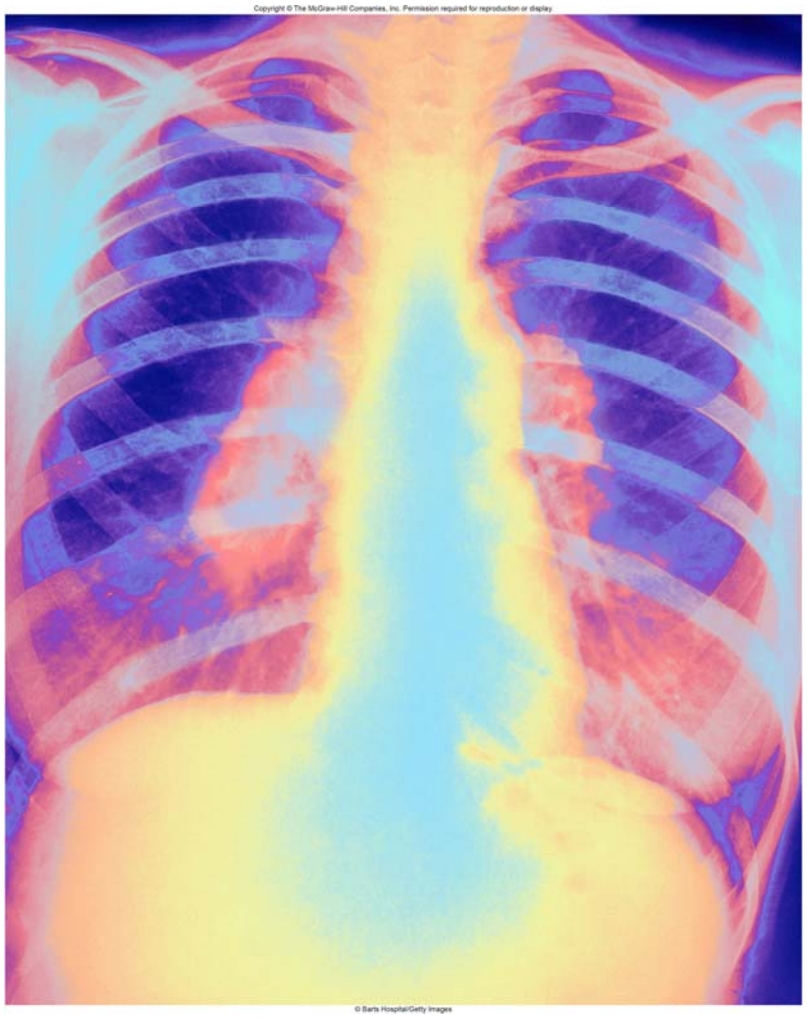


Chest X rays:

verification of a positive tuberculin test

secondary tuberculosis reveals extensive infiltration in the upper lungs/bronchi and marked **tubercles**

scarring from older infections appears on X rays



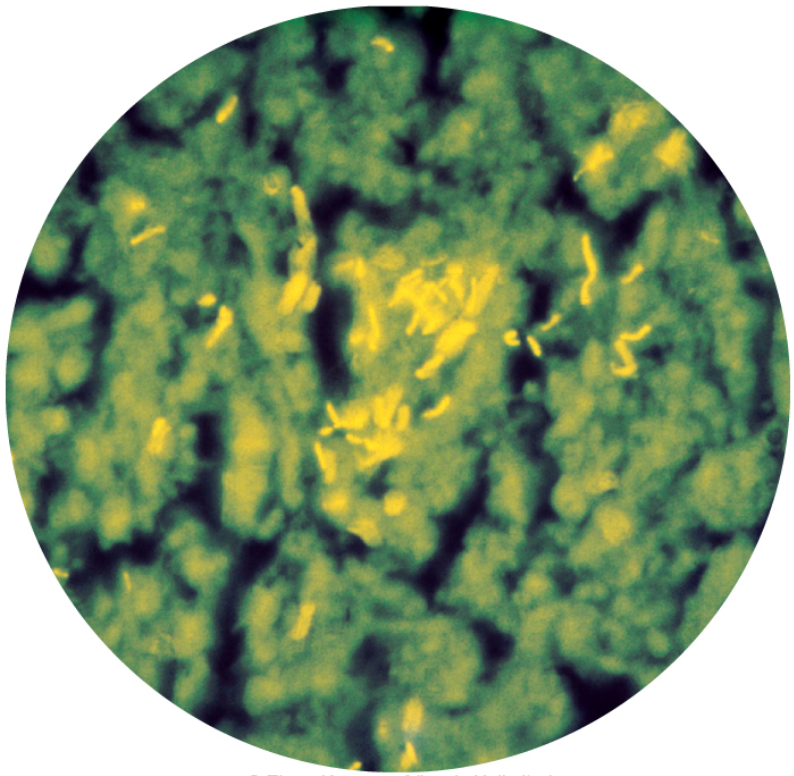
Tuberculosis

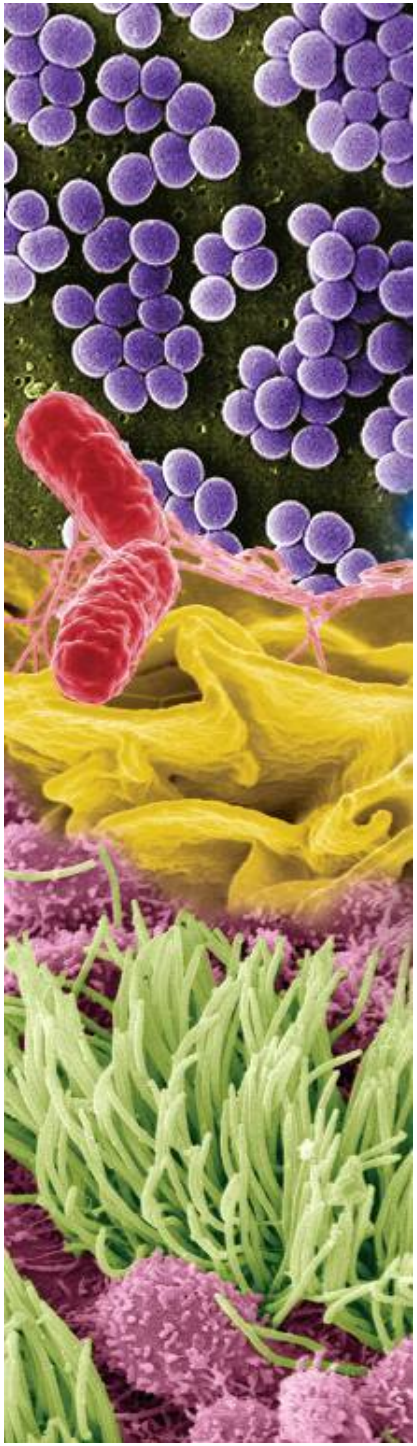
Acid-fast Staining:

sputum or other specimens

Ziehl-Neelsen stain

bright red acid-fast bacilli (AFB)





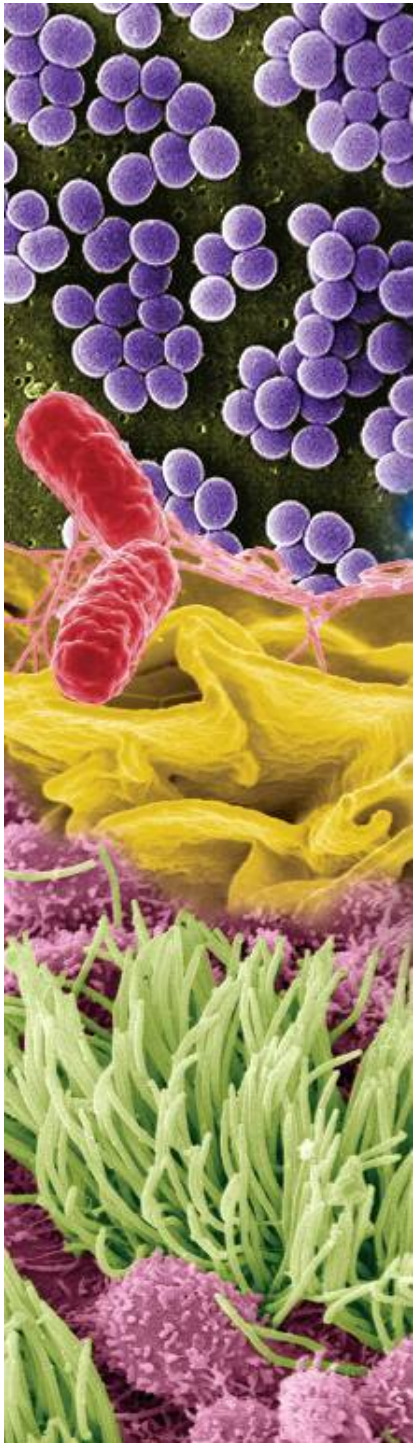
Tuberculosis // Prevention

limiting exposure to infectious **airborne** particles

- patient isolation in **negative-pressure rooms**
- other extensive precautions

live attenuated vaccine (BCG), **not used** in US

- bovine tuberculosis bacterium
- studies show **ineffective**
- vaccinated individuals will respond **positively** to tuberculin test



Tuberculosis // Treatment

Treatment of **latent** TB infection: two approaches

isoniazid for 9 months or // **rifampin** plus **pyrazinamide** for 2 months

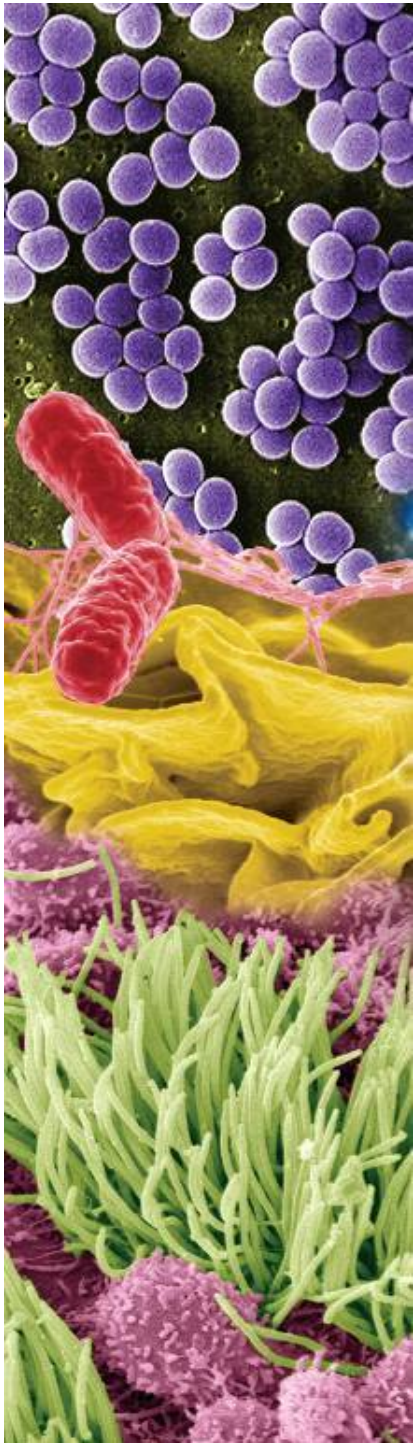
Treatment of **active** TB infection:

9 months **isoniazid** plus **rifampin** (**12** months for extrapulmonary TB infection) // **pyrazinamide** taken for the first 2 months

Treatment of **antibiotic resistant** TB infection:

3 additional antibiotics must be added to regimen, **duration** of treatment extended

Note: isoniazid older drug that targets cell wall



Tuberculosis
Issues of Antibiotic Resistance

high levels of patient **noncompliance** are common

directly observed therapy (DOT), incarceration

MDR-TB (multidrug-resistant TB)

XDR-TB (extensively drug-resistant TB)

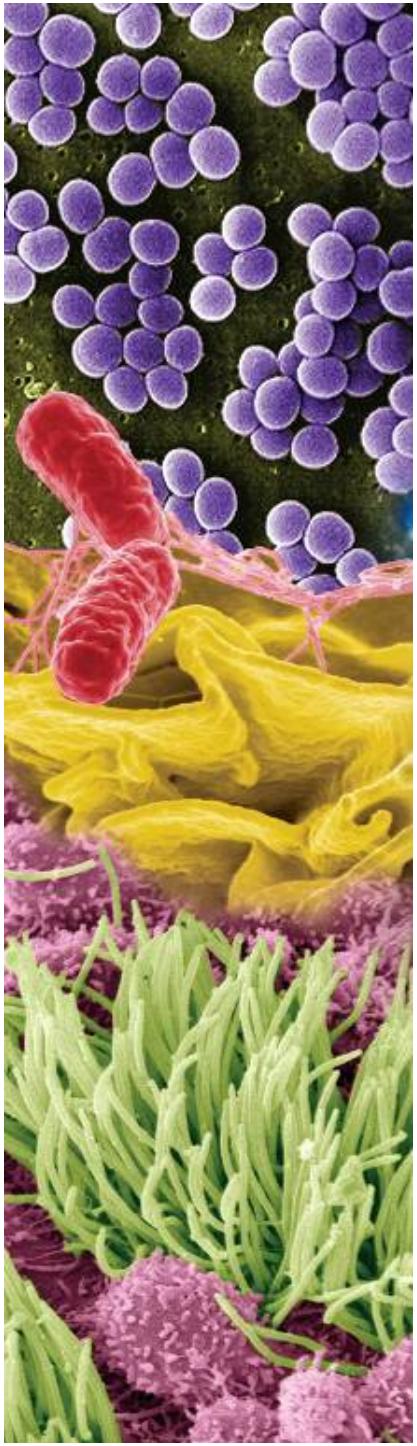
identified in Africa 2006

resistance to isoniazid and rifampin plus to any fluoroquinolone and at least one of 3 injectable secondline anti-TB drugs

infections worldwide today, even in US

Tuberculosis (cont.)

Disease Table 19.9	Tuberculosis	
Causative Organism(s)	Mycobacterium tuberculosis	Mycobacterium avium complex
Most Common Modes of Transmission	Vehicle (airborne)	Vehicle (airborne)
Virulence Factors	Lipids in wall, ability to stimulate strong cell-mediated immunity (CMI)	—
Culture/Diagnosis	Rapid methods plus culture; initial tests are skin testing	Positive blood culture and chest X ray
Prevention	Avoiding airborne M. tuberculosis, BCG vaccine in other countries	Rifabutin or azithromycin given to AIDS patients at risk
Treatment	Isoniazid, rifampin, and pyrazinamide + ethambutol or streptomycin for varying lengths of time (always lengthy); if resistant, additional drugs added to regimen	Azithromycin or clarithromycin plus one additional antibiotic
Distinctive Features	Responsible for nearly all TB except for some HIV-positive patients	Suspect this in HIV-positive patients



Pneumonia

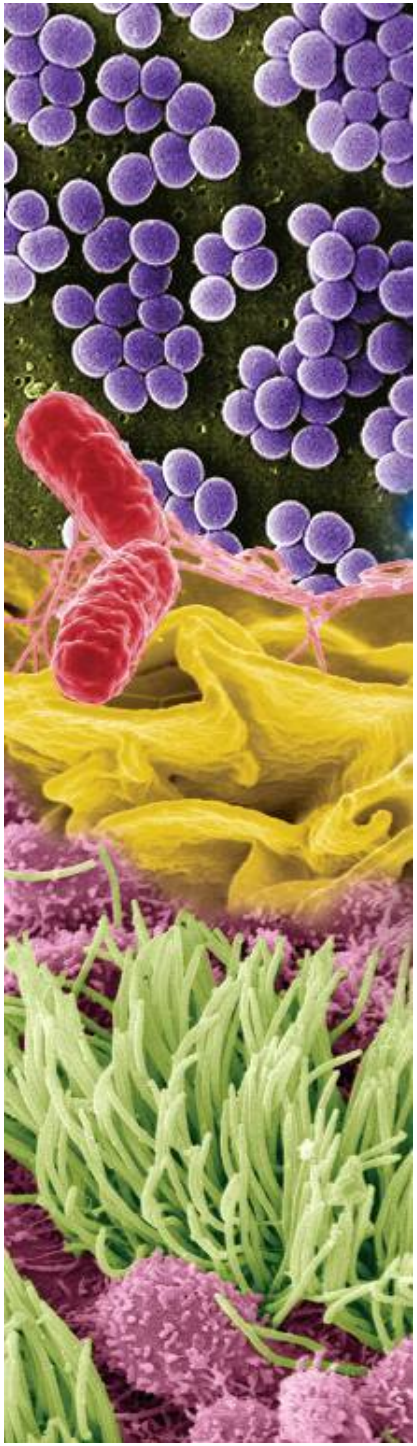
Inflammation leads to fluid-filled **alveoli**

Caused by ***viruses***, ***bacteria*** *and* ***fungi***

Pathogens must avoid being phagocytosed or killed by alveolar **macrophages**

Community-acquired: experienced by persons in general population

Nosocomial: acquired by patients in hospitals, health care facilities



Pneumonia //
Community-Acquired Pneumonia

Causative Agents**:**

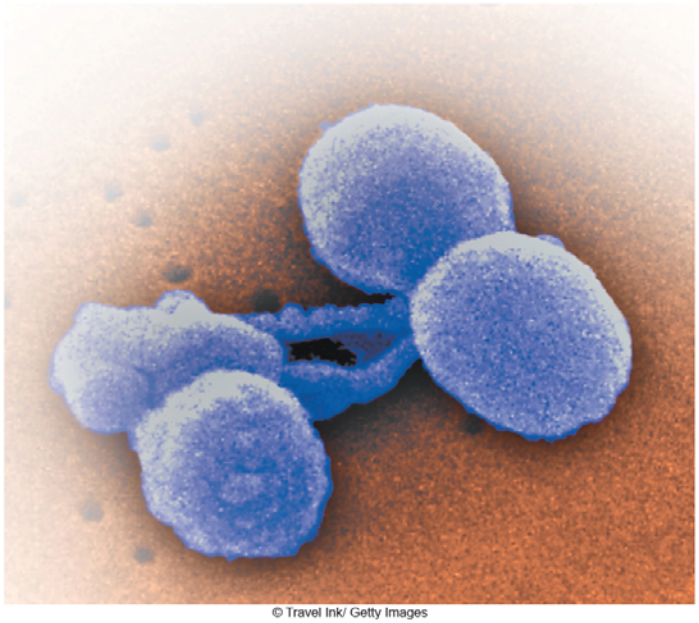
Bacteria-
Streptococcus pneumoniae
Mycoplasma pneumoniae
Legionella sp.

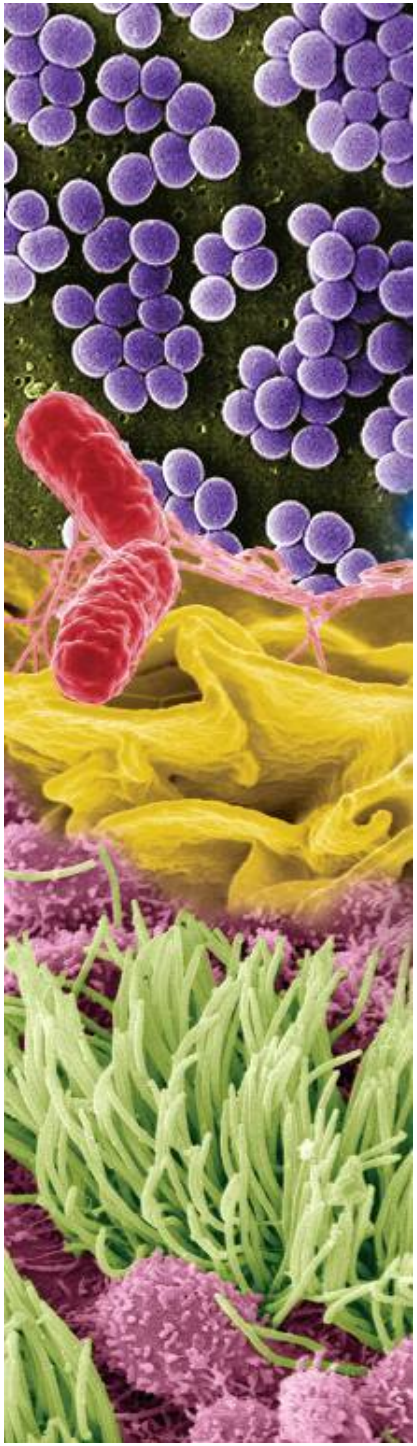
Viruses-
Hantavirus
Emerging viruses (SARS, adenoviruses)

Fungi-
Histoplasma capsulatum
Pneumocystis jiroveci

Pneumococcal Pneumonia

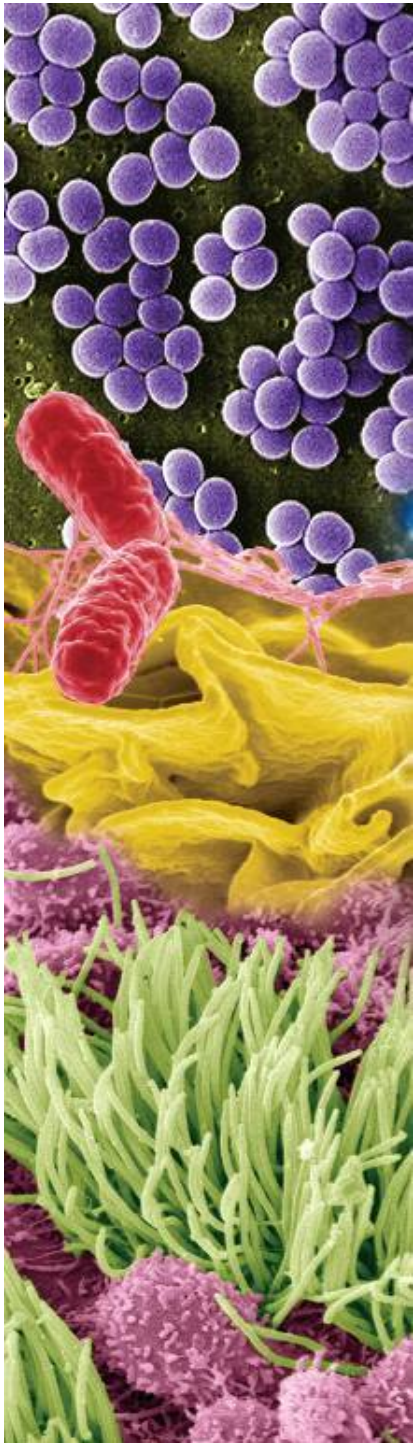
- *Streptococcus pneumoniae* = "**Pneumococcus**"
- **Alpha-hemolytic** on blood agar
- Most common cause of bacterial pneumonia
- **Capsule** is main virulence factor
- 23-valent vaccine available (**Pneumovax**) for older adults





Atypical Pneumonia

- *Mycoplasma pneumoniae*
- Transmitted by aerosol droplets in close living quarters
- Lack of acute illness gives rise to the name “walking pneumonia”



Nosocomial Pneumonia

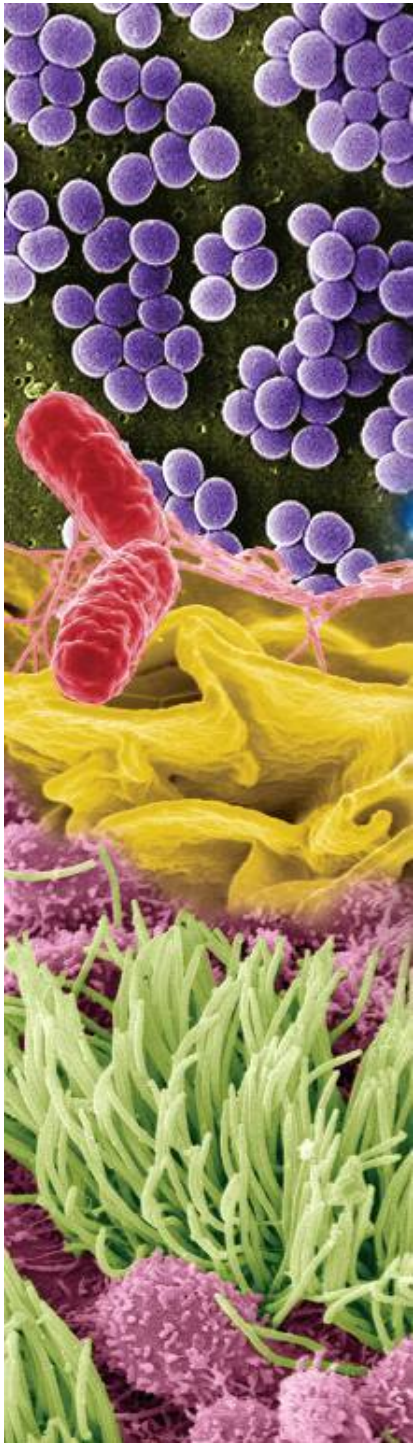
Occurs in 1% of hospitalized people

Second most common nosocomial infection

Causative Agents**:**

Polymicrobial infection

Streptococcus pneumoniae
Klebsiella pneumoniae
Anaerobic bacteria
Coliform bacteria



Nosocomial Pneumonia // Transmission

immunocompromised patients

normal biota enter lower respiratory tract via abnormal breathing, **aspiration,** ventilation

Culturing:

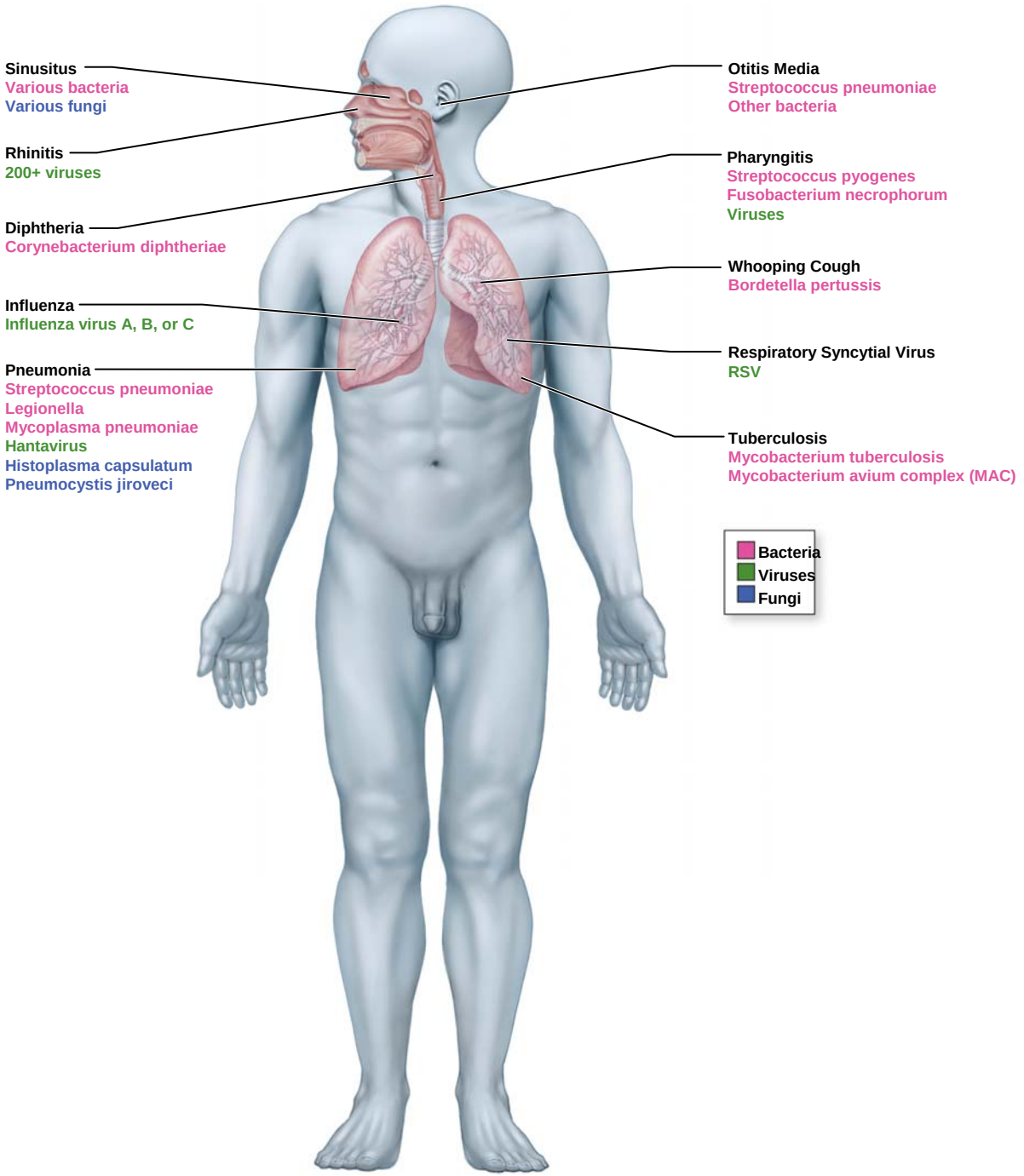
typically reveals only **normal biota**

Prevention:

reduce transfer of upper respiratory biota into lungs

Treatment:

empiric therapy with **broad-spectrum** antibiotics reduces mortality


Sinusitus
Various bacteria
Various fungi
Rhinitis
200+ viruses
Diphtheria
Corynebacterium diphtheriae
Influenza
Influenza virus A, B, or C
Pneumonia
Streptococcus pneumoniae
Legionella
Mycoplasma pneumoniae
Hantavirus
Histoplasma capsulatum
Pneumocystis jiroveci
Otitis Media
Streptococcus pneumoniae
Other bacteria
Pharyngitis
Streptococcus pyogenes
Fusobacterium necrophorum
Viruses
Whooping Cough
Bordetella pertussis
Respiratory Syncytial Virus
RSV
Tuberculosis
Mycobacterium tuberculosis
Mycobacterium avium complex (MAC)
Bacteria
Viruses
Fungi

Viral Diseases of the Lower Respiratory System

- **Viral Pneumonia**
- **Respiratory Syncytial Virus**
- **Influenza (Flu)**

Influenza

<u>Signs and Symptoms</u>:

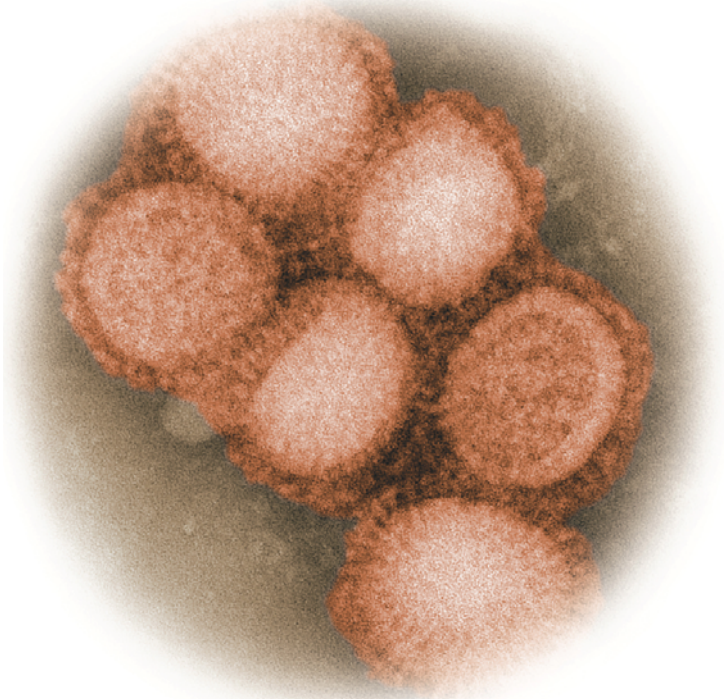
begin in **upper** respiratory tract

can progress to lower tract

headache, chills, dry cough, body aches, fever, stuffy nose, sore throat

extreme fatigue

secondary infections concern



CDC/C. S. Goldsmith and A. Balish

Influenza

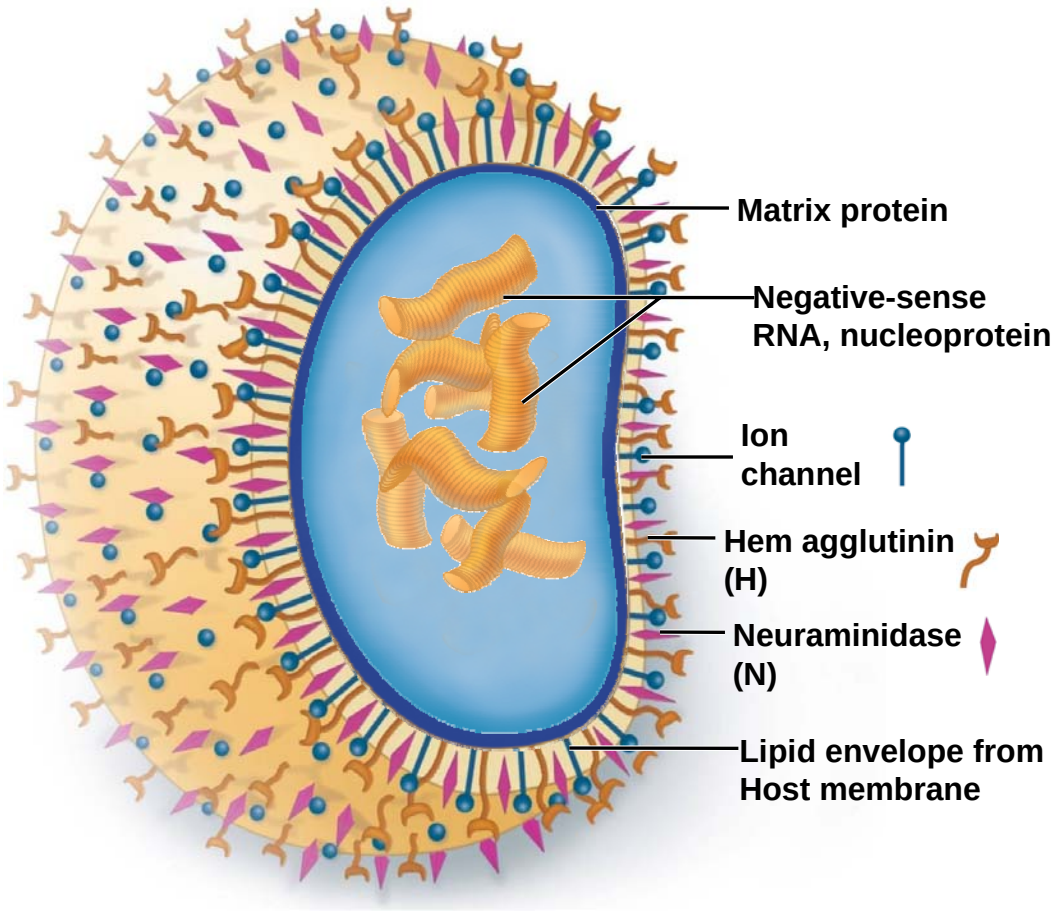
Causative Agents:

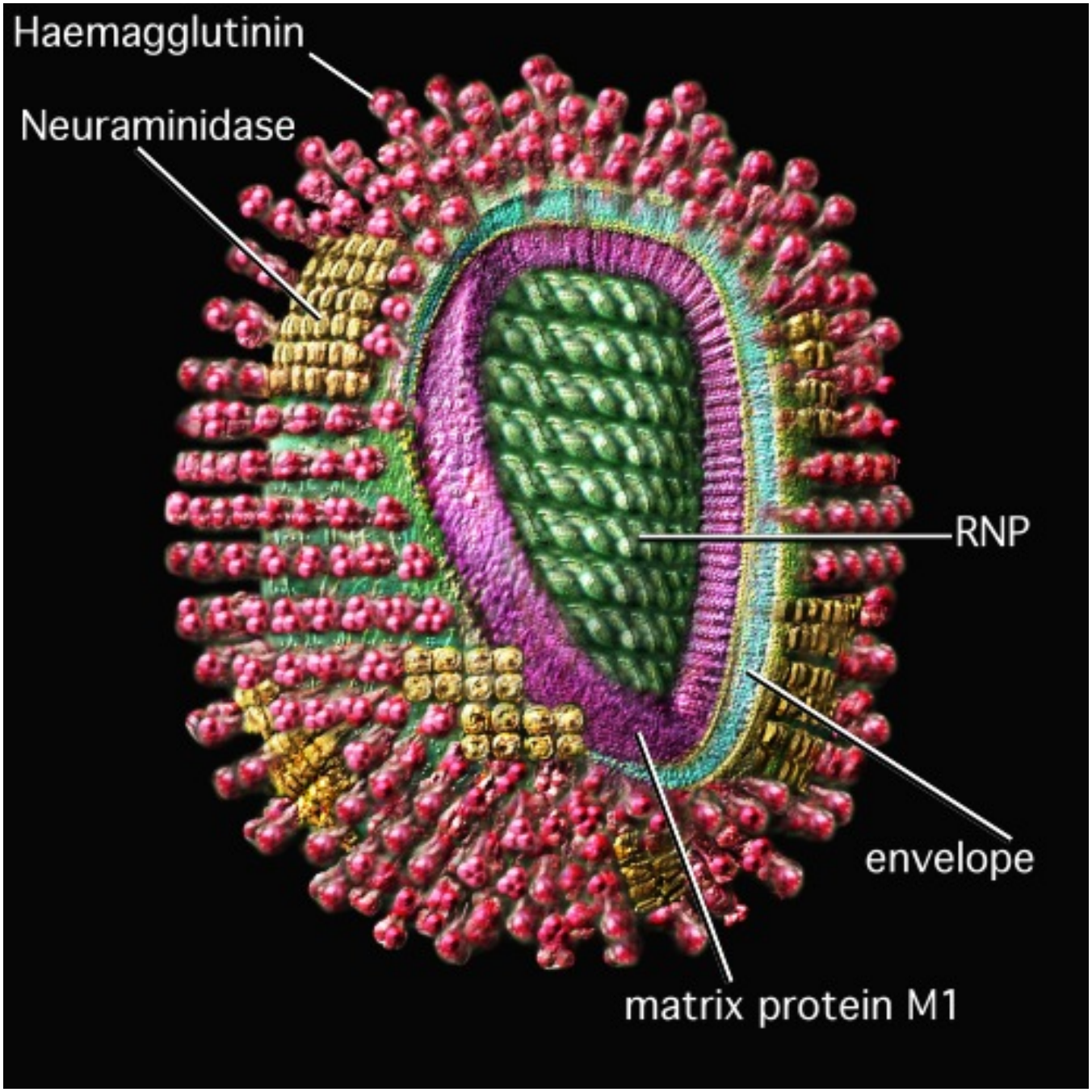
Influenza A, B and C viruses

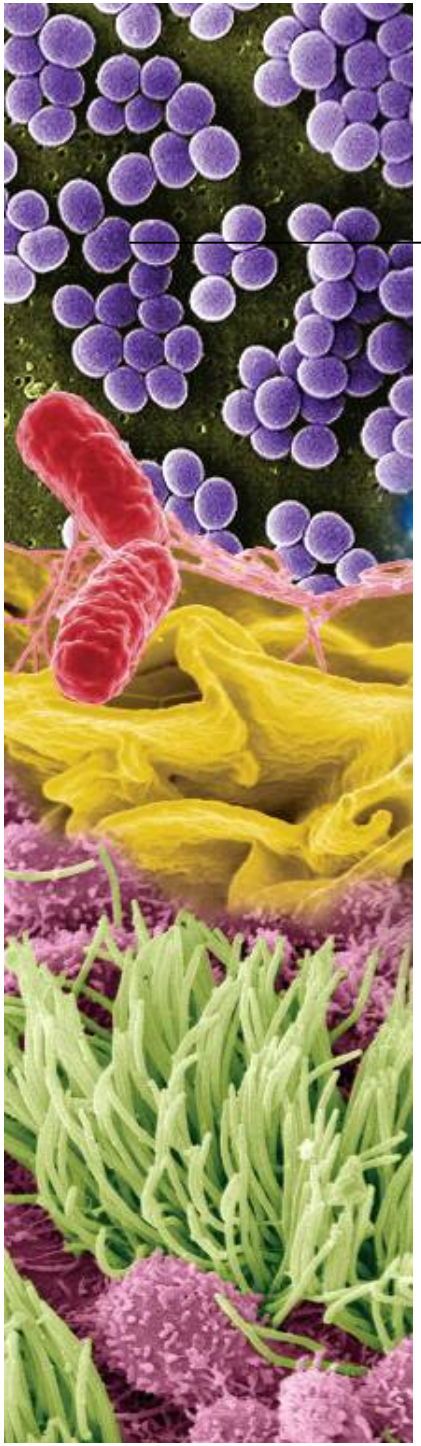
- *Orthomyxoviridae*
- lipoprotein envelope
- glycoprotein spikes

  -**hemagglutinin** (H)
  -**neuraminidase** (N)

- ion channels
- **ssRNA** genome
- 10 genes on 8 RNA strands




Haemagglutinin
Neuraminidase
RNP
envelope
matrix protein M1



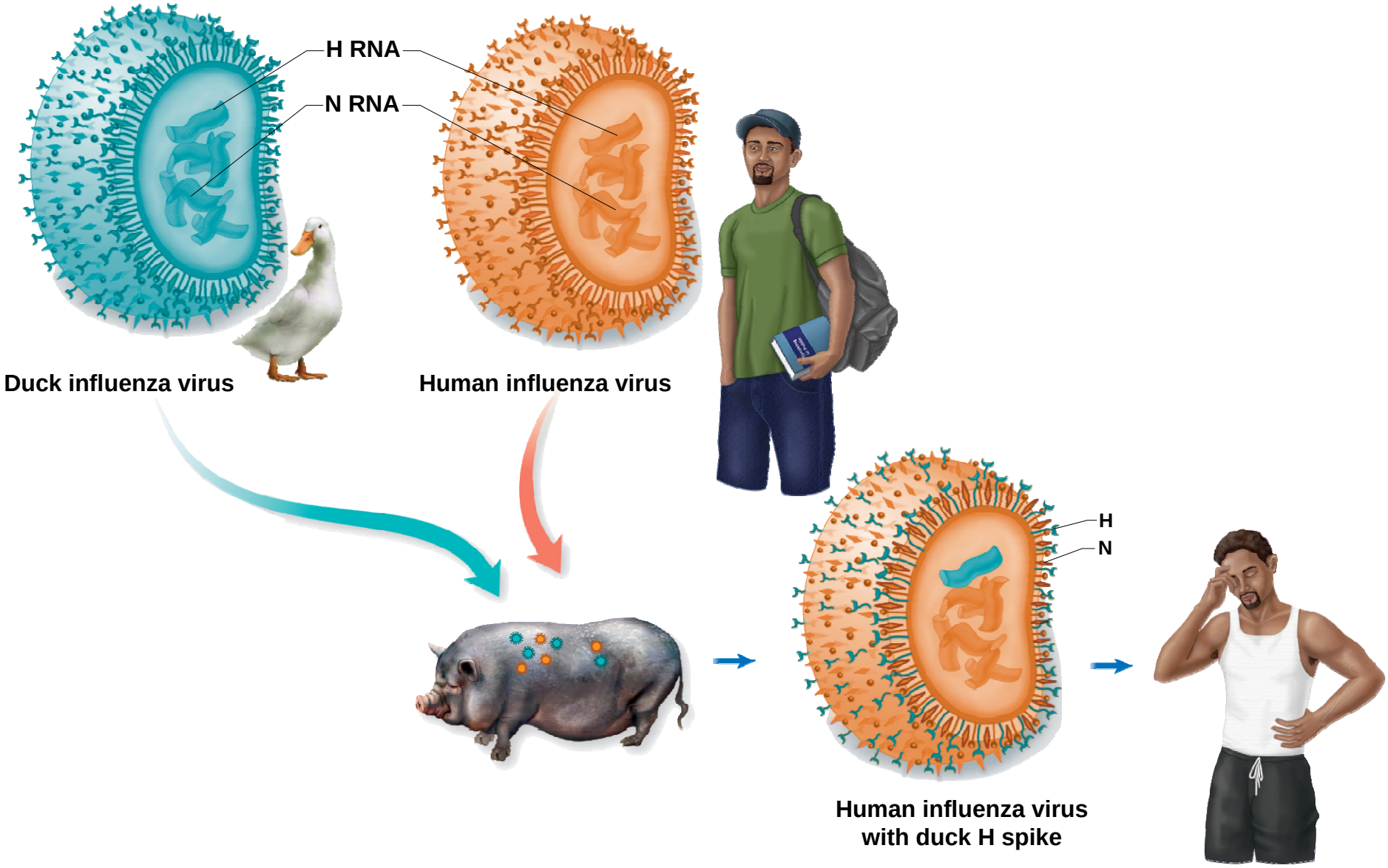
Influenza

Antigenic drift:

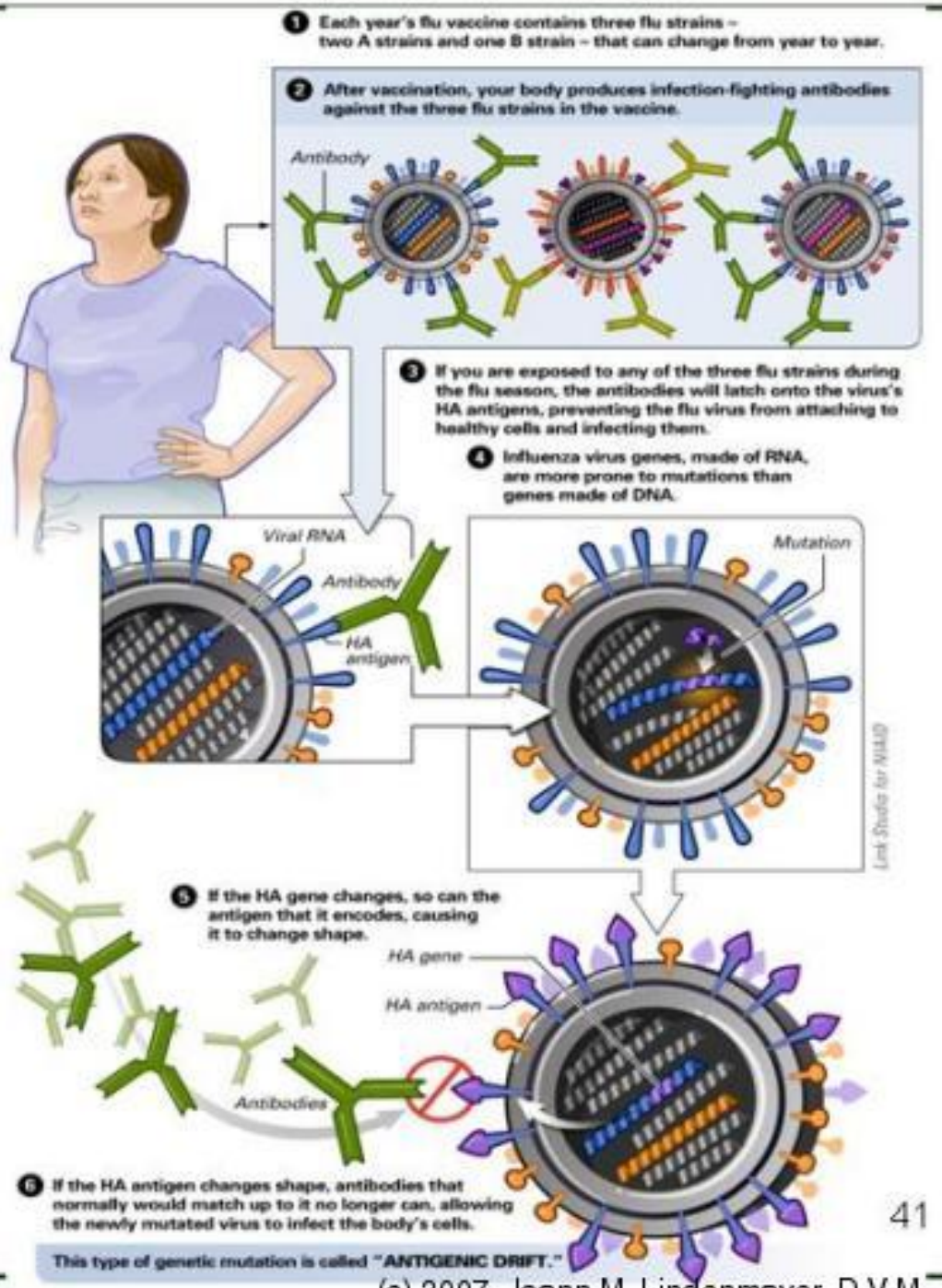
- mutation of glycoprotein (H, N) genes
- reduced host immune response to virus
- produces most seasonal influenza strains

Antigenic shift:

- RNA exchange between different viruses
- occurs during coinfection of a host cell
- more likely to produce pandemic strains

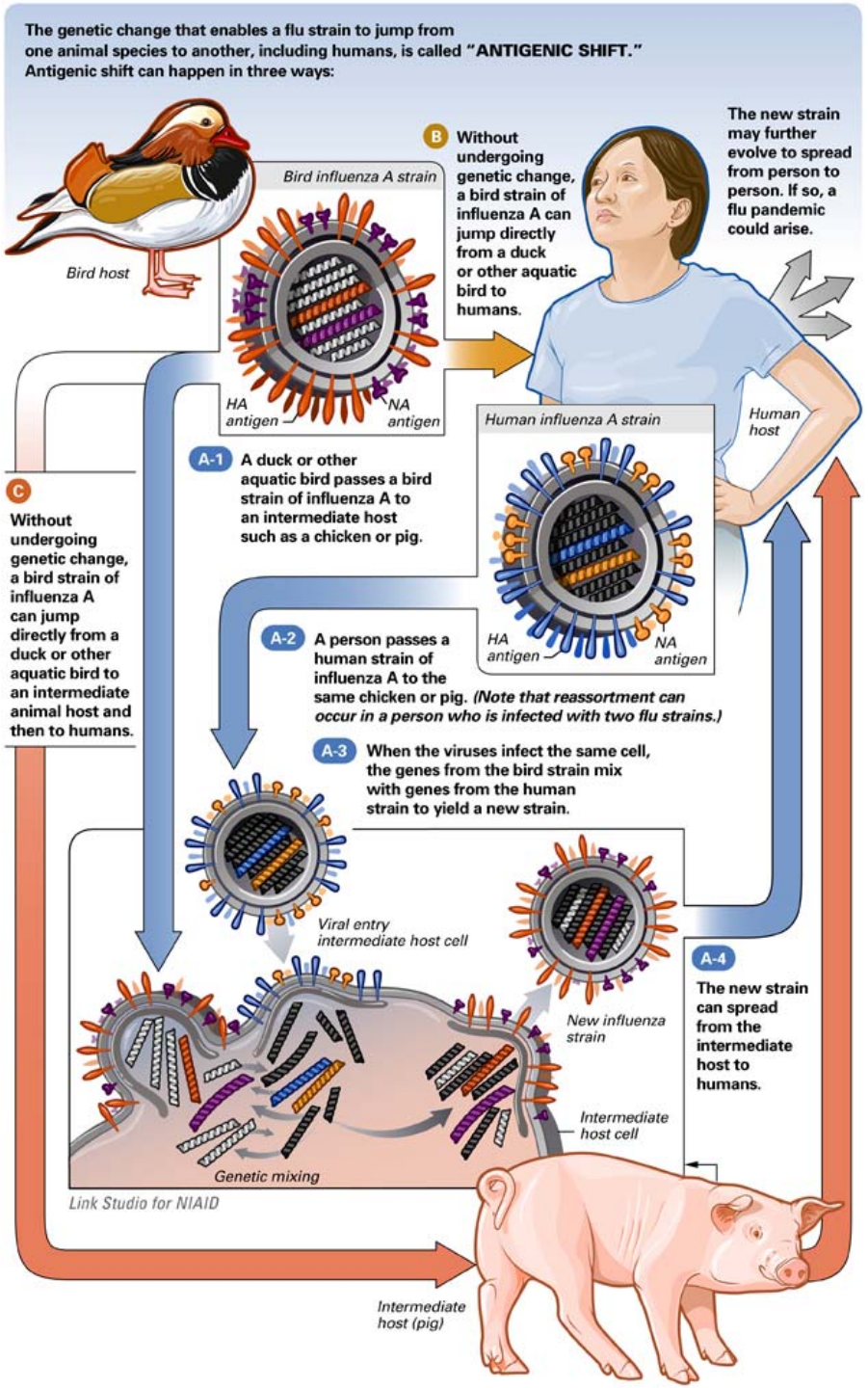

H RNA
N RNA
Duck influenza virus
Human influenza virus
H
N
Human influenza virus
with duck H spike

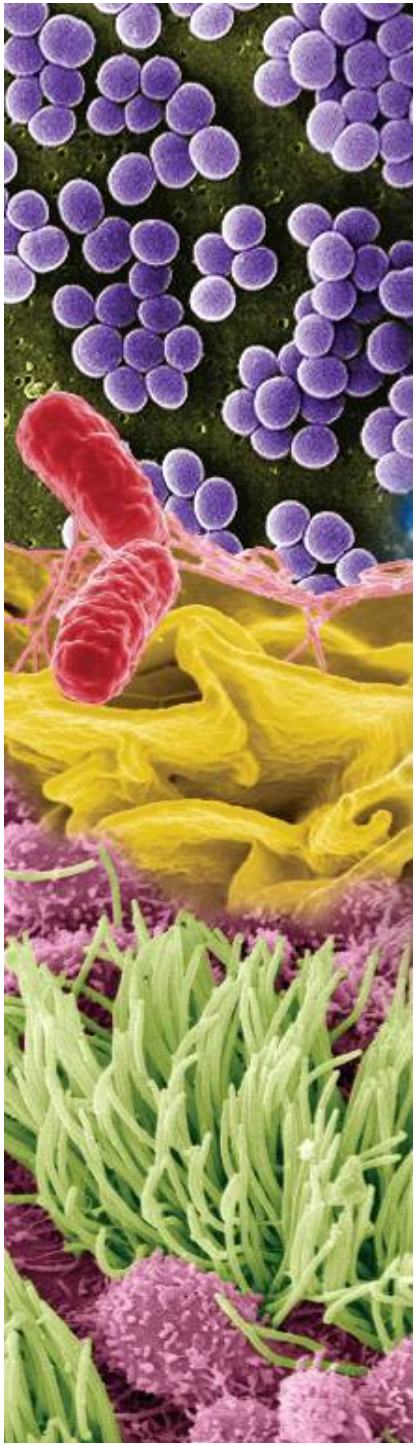
Influenza A: Antigenic Drift



Source: http://orise.orau.gov/

Antigenic Shift





Influenza
Pathogenesis and Virulence Factors

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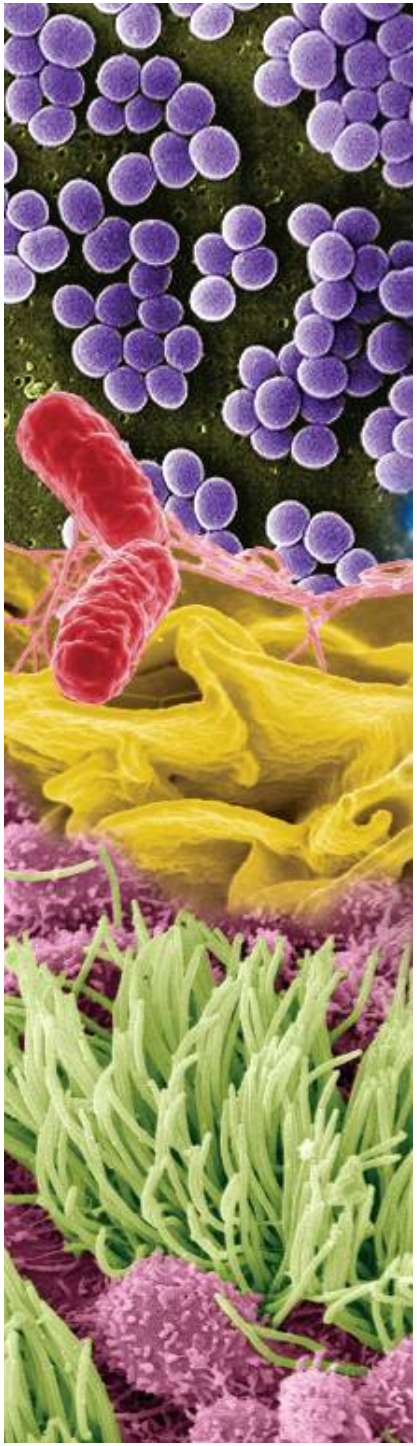
virus binds **ciliated** cells of the respiratory mucosa

severe inflammation // irritation in lungs due to "**cytokine storm**"

hemagglutinin (H) // binding to host cell receptors

neuraminidase (N) // breaks down mucous of the respiratory tract, assists in viral budding and release

2009 H1N1 variants bound lower in respiratory tract // bound more efficiently in respiratory tract // resulting in a more massive cytokine storm



Influenza
Transmission and Epidemiology

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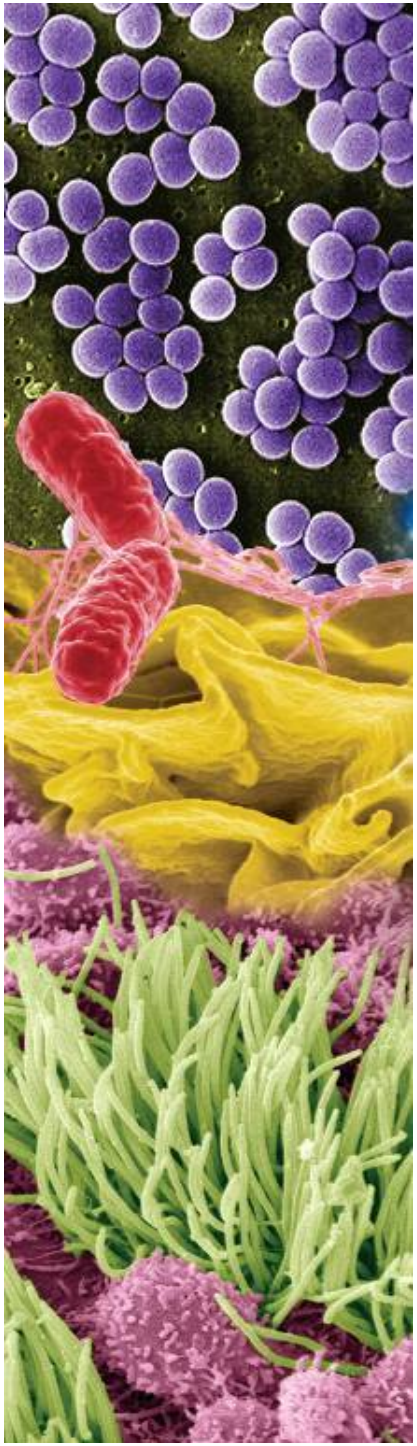
inhalation of virus-laden aerosols and droplets, indirect contact with fomites

transmission aided by crowding // poor ventilation

drier air of **winter** facilitates spread of the virus

~36,000 U.S. influenza deaths annually

mainly affects the very young and the very old



Influenza
Culture and Diagnosis

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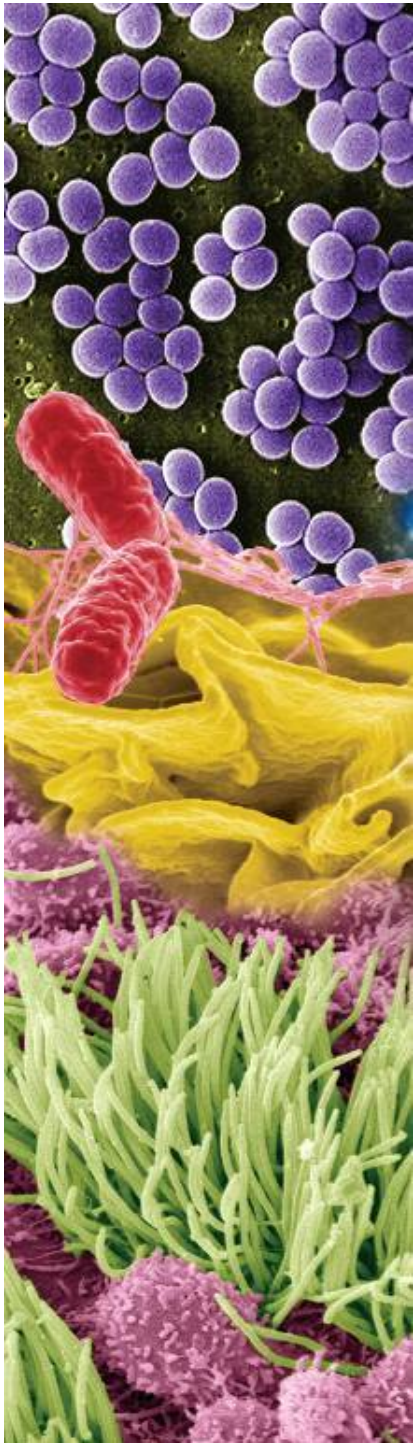
often diagnosed based on **symptoms** alone

culture and non-culture based tests to identify virus **subtype** causing infections

rapid influenza tests (**immunofluorescence, PCR, ELISA**) provide results in 24 hrs

viral culture provides results in 3 to 10 days



Influenza Prevention

Vaccinations // **inactivated** seasonal vaccine:

-70-90% effective

-three different viruses resembling variants predicted in the coming flu season

-for anyone over the age of 6 months

Live attenuated seasonal vaccine: **FluMist**

-stimulates secretory immunity
-for persons between the ages of 5 and 49

2009 H1N1 outbreak prompted production of a new vaccine // target **ion-channel** proteins to eliminate all strains?

Influenza (cont.)	
Causative Organism(s)	Influenza A, B, and C viruses
Most Common Modes of Transmission	Droplet contact, direct contact, indirect contact
Virulence Factors	Glycoprotein spikes, overall ability to change genetically
Culture/ Diagnosis	Viral culture (3–10 days) or Rapid antigen-based or PCR tests
Prevention	Killed injected vaccine or inhaled live attenuated vaccine taken annually
Treatment	Amantadine, rimantadine, zanamivir, or oseltamivir

Fungal Diseases of the Lower Respiratory System

- **Histoplasmosis**
- **Coccidiodomycosis**
- **Pneumocystis Pneumonia**
- **Blastomycosis**
- **Aspergillosis**