Structure and Function of the Respiratory System

- **Upper respiratory system**
  - Nose, pharynx, middle ear, and eustachian tubes
  - Saliva and tears protect mucosal surfaces

- **Lower respiratory system**
  - Larynx, trachea, bronchial tubes, and alveoli
  - Ciliary escalator moves particles toward the throat via ciliary action
  - Alveolar macrophages destroy microorganisms in the lungs
  - Respiratory mucus protects mucosal surfaces

Figure 24.1 Structures of the upper respiratory system.
Normal Microbiota of the Respiratory System

- Normal microbiota suppress pathogens by competing for nutrients and producing inhibitory substances
- Lower respiratory system is nearly sterile
Microbial Diseases of the Upper Respiratory System

- **Pharyngitis**
  - Sore throat
- **Laryngitis**
- **Tonsillitis**
- **Sinusitis**
  - Usually self-limiting
- **Epiglottitis**
  - Most life-threatening disease of the upper respiratory system

Bacterial Diseases of the Upper Respiratory System

- **Streptococcal pharyngitis (strep throat)**
  - Caused by group A streptococci (GAS)
    - *Streptococcus pyogenes*
    - Resistant to phagocytosis
    - Streptokinases lyse clots
    - Streptolysins are cytotoxic
  - Local inflammation, fever, tonsillitis, enlarged lymph nodes
  - Diagnosis by enzyme immunoassay (EIA) tests
- **Scarlet fever**
  - Erythrogenic toxin produced by lysogenized *S. pyogenes*
Figure 24.3  Streptococcal pharyngitis.

Diphtheria

- Caused by *Corynebacterium diphtheriae*
  - Gram-positive rod; pleomorphic
- Forms a tough grayish membrane in the throat
  - Fibrin and dead tissue
  - Blocks passage of air to the lungs
- Exotoxin produced by lysogenized bacteria
  - Circulates in the blood; damages the heart and kidneys
- **Cutaneous diphtheria**
  - Forms skin ulcer
- Prevented by **DTaP vaccine**
  - Diphtheria toxoid
Figure 24.4 Corynebacterium diphtheriae, the cause of diphtheria.

Otitis Media

- Infection of the middle ear
  - Formation of pus puts pressure on the eardrum
- Causes
  - *Streptococcus pneumoniae* (35%)
  - Nonencapsulated *Haemophilus influenzae* (20–30%)
  - *Moraxella catarrhalis* (10–15%)
  - *S. pyogenes* (8–10%)
  - *Staphylococcus aureus* (1–2%)
- Common in childhood due to smaller auditory tube
- Treated with broad-spectrum penicillins
The Common Cold

• Over 200 different viruses
  • Rhinoviruses (30–50%)
    • Thrive in temperatures lower than body temperature
    • Coronaviruses (10–15%)
  • Sneezing, nasal secretion, congestion
    • Can lead to laryngitis and otitis media
    • Not accompanied by fever
  • Antibiotics are of no use
    • Relief via cough suppressants and antihistamines
Diseases in Focus: Microbial Diseases of the Upper Respiratory System

• A patient presents with fever and a red, sore throat. Later, a grayish membrane appears in the throat. Gram-positive rods are cultured from the membrane.
• Can you identify infections that could cause these symptoms?
Microbial Diseases of the Lower Respiratory System

- Caused by many of the same bacteria and viruses as the upper respiratory system
  - Bronchitis
  - Bronchiolitis
  - Pneumonia
    - Pulmonary alveoli are involved
Pertussis (Whooping Cough)

- Caused by *Bordetella pertussis*
  - Gram-negative coccobacillus
- Produces a capsule
  - Allows attachment to ciliated cells in the trachea
    - Destroys ciliated cells and shuts down the ciliary escalator
- Tracheal cytotoxin of cell wall damages ciliated cells
- Pertussis toxin enters the bloodstream
Pertussis (Whooping Cough)

- Stage 1: catarrhal stage, like the common cold
- Stage 2: paroxysmal stage, violent coughing, gasping for air
- Stage 3: convalescence stage, may last for months
- Prevented by DTaP vaccine
- Treated with erythromycin or other macrolides

Big Picture: Pertussis

- Before vaccines, 6000 people died annually in the United States from pertussis
- Today the acellular pertussis vaccine (DTaP) is given
Big Picture: Pertussis

- Increasing pertussis cases due to:
  - Breakdown in herd immunity
  - Mutation of the organism
  - Better diagnostic test leading to more reporting
  - Acellular vaccine having lower long-term immunity

- New strategies for fighting pertussis
  - New booster for teens, adults, and pregnant women
  - Additional vaccination requirements for students
  - More government health campaigns
Tuberculosis

- Caused by *Mycobacterium tuberculosis*
  - Acid-fast rod; obligate aerobe
  - 20-hour generation time
  - Lipids in the cell wall make it resistant to drying and antimicrobials
- Other causes
  - *Mycobacterium bovis*
    - Bovine tuberculosis; <1% of U.S. cases
  - *Mycobacterium avium-intracellulare* complex
    - Infects people with late-stage HIV infection
Pathogenesis of Tuberculosis

- Inhaled organisms are phagocytized by alveolar macrophages
- Mycolic acids in the cell wall stimulate an inflammatory response
- Organisms are isolated in the walled-off tubercle
- Tubercles heal and become calcified (Ghon's complexes)
- Tubercle breaks down, releasing bacteria into the lungs and cardiovascular and lymphatic systems
  - Miliary tuberculosis: disseminated infection
Tubercle bacilli that reach the alveoli of the lung are ingested by macrophages, but often some survive. Infection is present, but no symptoms of disease.

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.

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.

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.

Liquefaction continues until the tubercle ruptures, allowing bacilli to spill into a bronchiole and thus be disseminated throughout the lung and then to the circulatory and lymphatic systems.
Diagnosis of Tuberculosis

- **Tuberculin skin test**
  - Positive reaction means a current or previous infection
  - T cells react with purified protein derivative from the TB bacterium
    - Delayed hypersensitivity induration
  - Followed by an X-ray or CT exam, acid-fast staining of sputum, and culturing of bacteria
  - New rapid blood test for IFN-γ and PCR test
    - Higher specificity and less cross-reactivity
Treatment of Tuberculosis

- Minimum of 6 months of drug therapy due to slow growth and dormancy
- **First-line drugs**: isoniazid, ethambutol, pyrazinamide, rifampin
- **Second-line drugs**: aminoglycosides, fluoroquinolones, para-aminoslicyclic acid (PAS)
- **Multi-drug-resistant (MDR)** strains: resistant to first-line drugs
- **Extensively drug-resistant (XDR)** strains: resistant to second-line drugs

Tuberculosis

- 9 million develop TB annually; 2 million die
- 1/3 of the world's population infected
- Leading cause of death for those with HIV
- **BCG vaccine**: live culture of avirulent *M. bovis*
  - Not widely used in the United States due to questionable effectiveness
Figure 24.10a: Distribution of tuberculosis.

(a) Estimated tuberculosis incidence worldwide, per 100,000 population

Figure 24.10b: Distribution of tuberculosis.

(b) Reported tuberculosis cases per 100,000 population among American ethnic groups in 2012

Asian
Black
Hispanic
White

Reported cases per 100,000 population
### Bacterial Pneumonias

- **Typical pneumonia**
  - Caused by *S. pneumoniae*

- **Atypical pneumonia**
  - Caused by other microorganisms

- **Lobar pneumonia**
  - Infects the lobes of the lungs

- **Bronchopneumonia**
  - Infects the alveoli adjacent to the lungs

- **Pleurisy**
  - Pleural membranes inflamed

---

### Pneumococcal Pneumonia

- **Caused by *S. pneumoniae***
  - Gram-positive; encapsulated diplococci
  - 90 serotypes

- Infected alveoli of the lung fill with fluids and RBCs; interferes with oxygen uptake

- Diagnosis: optochin-inhibition test, bile solubility test, or antigen in urine

- Treated with macrolides and fluoroquinolones

- Prevented with conjugated pneumococcal vaccine
Figure 24.11  *Streptococcus pneumoniae*, the cause of pneumococcal pneumonia.

**capsules**

haemophilus influenzae pneumonia

- Gram-negative coccobacillus
- Predisposing factors: alcoholism, poor nutrition, cancer, or diabetes
- Symptoms resemble those of pneumococcal pneumonia
- Diagnosis: isolation on special media for nutritional requirements (X and V factors)
- Treated with cephalosporins
Mycoplasmal Pneumonia

• Also called primary atypical pneumonia or walking pneumonia
• Caused by *Mycoplasma pneumoniae*
  • No cell wall
• Mild but persistent respiratory symptoms; low fever, cough, headache
  • Common in children and young adults
• "Fried-egg" appearance on media
• Diagnosis: PCR and serological testing
• Treated with tetracyclines
Legionellosis

- Also called Legionnaires' disease
- Caused by Legionella pneumophila
  - Aerobic, gram-negative rod
  - Grows in water and air conditioning, biofilms, and waterborne amebae
- Transmitted by inhaling aerosols; not transmitted person to person
- Symptoms: high fever and cough
  - Similar to symptoms of Pontiac fever
- Treated with erythromycin and macrolides

Psittacosis (Ornithosis)

- Caused by Chlamyphila psittaci
  - Gram-negative intracellular bacterium
- Transmitted to humans by elementary bodies from bird droppings transmitted through air
- Fever, headache, chills, disorientation
- Diagnosis: growth of bacteria in eggs or cell culture
- Treated with tetracyclines
Chlamydial Pneumonia

- Caused by *Chlamydia pneumoniae*
- Transmitted person to person
- Mild respiratory illness common in young people; resembles mycoplasmal pneumonia
- Possible association with artherosclerosis
- Diagnosis: serological tests
- Treated with tetracyclines

Q Fever

- Caused by *Coxiella burnetii*
  - Obligately parasitic, intracellular gamma proteobacteria
- Acute Q fever
  - High fever, muscle aches, headache, coughing
- Chronic Q fever
  - Endocarditis (may occur years after infection)
- Transmitted to farm animals from tick bites
  - Transmitted to humans from the inhalation of aerosols from animals and unpasteurized milk
- Treated with doxycycline; chloroquine for chronic infections
Melioidosis

- Caused by *Burkholderia pseudomallei*
  - Gram-negative rod
- Occurs mostly in southeast Asia and northern Australia (in moist soils)
- Commonly affects those with lowered immune systems
  - Pneumonia or tissue abscesses (necrotizing fasciitis) and severe sepsis
- Transmission by inhalation, puncture wounds, and ingestion
- Treated with ceftazidime
Diseases in Focus: Common Bacterial Pneumonias

- A 27-year-old man with a history of asthma is hospitalized with a 4-day history of progressive cough and 2 days of spiking fevers. Gram-positive cocci in pairs are cultured from a blood sample.
- Can you identify infections that could cause these symptoms?
Viral Pneumonia

- **Viral pneumonia** occurs as a complication of influenza, measles, or chickenpox
- Few labs are equipped to test clinical samples properly for viruses
- **SARS-associated coronavirus (SARS)**
  - Emerged in Asia in 2003
- **Middle East respiratory syndrome (MERS-CoV)**
  - Reported in Saudi Arabia in 2012
Respiratory Syncytial Virus (RSV)

- Most common viral respiratory disease in infants
  - Almost all children are infected by age 2
  - 4500 deaths annually
- Causes cell fusion (syncytium) in cell culture
- Coughing and wheezing for more than a week
- Diagnosis: serological test for viruses and antibodies
- Treated with ribavirin and palivizumab

Influenza (Flu)

- Influenzavirus
  - Contains eight RNA segments and an outer lipid bilayer
- Chills, fever, headache, and muscle aches
  - No intestinal symptoms
  - 30,000 to 50,000 deaths in the United States annually
- Avian, swine, and mammalian strains
  - Swine serve as "mixing vessels" for new strains
**Influenza (Flu)**

- Hemagglutinin (HA) spikes
  - Recognize and attach to host cells
- Neuraminidase (NA) spikes
  - Help the virus separate from the infected cell
- **Antigenic drift**
  - Minor antigenic changes in HA and NA
  - Allow the virus to elude some host immunity
- **Antigenic shifts**
  - Changes great enough to evade most immunity
  - Lead to pandemics
  - Involve the reassortment of the eight RNA segments
Table 24.1  Human Influenza Viruses*

<table>
<thead>
<tr>
<th>Type</th>
<th>Antigenic Subtype</th>
<th>Year</th>
<th>Disease Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>H3N2 (the first “modern” pandemic; originated in southern China)</td>
<td>1889</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>H1N1 (Spanish)</td>
<td>1918</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>H2N2 (Asian)</td>
<td>1957</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>H3N2 (Hong Kong)</td>
<td>1968</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>H1N1 (Russian)</td>
<td>1977</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>H1N1 (Mexico)</td>
<td>2009</td>
<td>Low</td>
</tr>
<tr>
<td>B</td>
<td>None</td>
<td>1940</td>
<td>Moderate</td>
</tr>
<tr>
<td>C</td>
<td>None</td>
<td>1947</td>
<td>Very mild</td>
</tr>
</tbody>
</table>

*The conventional wisdom is that H1, H2, and H3 are human-infecting strains; H4, H5, H6, and H7 primarily infect animals, especially swine and poultry. (Avian influenza strains H5N1 and H7N7 have caused human fatalities.)

†Probably escaped from a laboratory. At this time persons over age 20 were mostly immune from similar viruses circulating in the 1950s and earlier in the century.

††The H1N1 virus causing this recent pandemic, the first in more than 40 years, differs significantly from the regular H1N1 virus that had been circulating. There has been confusion concerning a differentiating name for this virus. It has popularly been called the swine flu, and the CDC has referred to it as 2009H1N1, but in 2014 the WHO designed it as A(H1N1) pdm09.


Influenza (Flu)

- 1% mortality; usually the very young and very old
- Multivalent vaccine for the most important strains
  - Composition of the vaccine determined annually by the identification of circulating viruses
    - Labor-intensive to produce
    - Does not provide long-term immunity
- Difficult to diagnose from clinical symptoms
- Treated with zanamivir (Relenza) and oseltamivir (Tamiflu)
  - Inhibits neuraminidase
Histoplasmosis

- Caused by *Histoplasma capsulatum*
  - Dimorphic fungus
  - Yeast-form grows intracellularly in macrophages
- Forms lung lesions; 0.1% of cases become a severe, generalized disease
- Acquired from airborne conidia in areas with bird or bat droppings
  - Limited geographical range in the United States
- Treated with amphotericin B or itraconazole

---

Figure 24.15 *Histoplasma capsulatum*, a dimorphic fungus that causes histoplasmosis.

The macroconidia of *Histoplasma capsulatum* are especially useful for diagnostic purposes. Microconidia bud off from hyphae and are the infectious form. At 37°C in tissues, the organism converts to a yeast phase composed of oval, budding yeasts.
Coccidioidomycosis

- Also known as Valley fever or San Joaquin fever
- Caused by *Coccidioides immitis*
  - Dimorphic fungus
- Arthroconidia found in alkaline desert soils of the American Southwest
- Form a spherule filled with endospores in tissues
- Most infections are not apparent; fever, coughing, weight loss
  - <1% of cases resemble tuberculosis
- Treated with amphotericin B or imidazole drugs
Figure 24.17  The life cycle of Coccidioides immitis, the cause of coccidioidomycosis.

1. Endospores develop within spherule.
2. Spherule in tissue (about 30 μm in diameter)
3. Inhaled arthroconidium enlarges and begins to develop into a spherule.
4. Human
5. Soil

- Arthroconidium (about 5 μm long) germinates into tubular hypha.
- Hypha begins to segment into arthroconidia.
- Some arthroconidia separate from hypha.
- Some arthroconidia become airborne.
- Arthroconidia
- Released endospores spread in tissue—each developing into new spherule.
- Some arthroconidia return to soil.
- Airborne arthroconidium is inhaled.
- Tubular hypha
- Human
- Soil

Figure 24.18  The U.S. endemic area for coccidioidomycosis.

- Areas where disease is known to be endemic
- 2001 outbreak
- San Joaquin Valley

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Pneumocystis Pneumonia

- Caused by *Pneumocystis jirovecii*
  - No universal agreement if it is a protozoan or fungus
- Asymptomatic in the immunocompetent; causes pneumonia in the immunocompromised
  - Primary indicator of AIDS
- Found in the lining of the alveoli
  - Forms a cyst
  - Cysts rupture, releasing eight trophozoites
- Treated with trimethoprim-sulfamethoxazole

**Figure 24.19** The life cycle of *Pneumocystis jirovecii*, the cause of Pneumocystis pneumonia.

1. Mature cyst
2. The mature cyst contains 8 intracystic bodies.
3. The cyst ruptures, releasing the bodies.
4. The bodies develop into trophozoites.
5. Each trophozoite develops into a mature cyst.
6. The trophozoites divide.
### Blastomycosis (North American Blastomycosis)

- Caused by *Blastomyces dermatitidis*
  - Dimorphic fungus
  - Grows in soil
- Symptoms resemble bacterial pneumonia; cutaneous abscesses; extensive tissue damage
- 30 to 60 deaths annually
- Treated with amphotericin B

### Other Fungi Involved in Respiratory Disease

- *Aspergillus fumigatus*
  - Causes **aspergillosis**
  - Airborne conidia; grows in compost piles
- *Rhizopus* and *Mucor*
  - Mold spores
- Predisposing factors:
  - Immunocompromised state
  - Cancer
  - Diabetes
Diseases in Focus: Microbial Diseases of the Lower Respiratory System

• Three weeks after working on the demolition of an abandoned building in Kentucky, a worker is hospitalized for acute respiratory illness. At the time of demolition, a colony of bats inhabited the building. An X-ray examination reveals a lung mass. A purified protein derivative test is negative; a cytological examination of the mass reveals ovoid yeast cells.

• Can you identify infections that could cause these symptoms?
<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Symptoms</th>
<th>Reservoir</th>
<th>Diagnosis</th>
<th>Treatment</th>
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<td><strong>BACTERIAL DISEASES</strong></td>
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<tr>
<td>Bacterial Pneumonia</td>
<td><em>Bacillus anthracis</em></td>
<td>Fever, coughing, abscesses</td>
<td>Humans</td>
<td>Culture</td>
<td>Antitoxin or Rifampin</td>
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<tr>
<td>Pertussis (whooping</td>
<td><em>Bordetella pertussis</em></td>
<td>Spasms of intense coughing to tear mucus</td>
<td>Cough</td>
<td></td>
<td></td>
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<tr>
<td>Tuberculosis</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Cough, blood in mucus</td>
<td>Humans</td>
<td>X-ray imaging</td>
<td>Multidrug-resistant antibiotics</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>culture</td>
<td></td>
</tr>
<tr>
<td>Melioidosis</td>
<td><em>Brucella melitensis</em></td>
<td>Pneumonia, or as tissue abscesses and severe sepsis</td>
<td>Soil</td>
<td>Culture</td>
<td>Ceftriaxone</td>
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<td><strong>VIRAL DISEASES</strong></td>
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<td>Respiratory Syncytial</td>
<td><em>Respiratory syncytial virus</em></td>
<td>Pneumonia in infants</td>
<td>Humans</td>
<td>Serological tests</td>
<td>Palivizumab (if life-threatening)</td>
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<td>Virus (RSV) Disease</td>
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<td>Influenza</td>
<td><em>Paramyxoviridae</em></td>
<td>Chills, fever, headache, and muscular aches</td>
<td>Humans, pigs, birds</td>
<td>Serological tests</td>
<td>Amantadine, oseltamivir (phosphates, rimantadine)</td>
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<td><strong>FUNGAL DISEASES</strong></td>
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<td>Histoplasmosis</td>
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<td>Resembles tuberculosis</td>
<td>Soil, widespread in Ohio and Mississippi river valleys</td>
<td>Serological tests</td>
<td>Amphotericin B</td>
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<td>Coccioidomyces</td>
<td><em>Coccioides immitis</em></td>
<td>Fever, coughing, weight loss</td>
<td>Desert soils of U.S. Southwest</td>
<td>Serological tests</td>
<td>Amphotericin B</td>
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<td>Pneumocystis Pneumonia</td>
<td><em>Pneumocystis jiroveci</em></td>
<td>Pneumonia</td>
<td>Unknown possibility</td>
<td>Microscopy</td>
<td>Trimethoprim-sulfamethoxazole, pentamidine</td>
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<td>Blastomycesis</td>
<td><em>Blastomyces dermatitidis</em></td>
<td>Abscesses, extensive tissue damage</td>
<td>Soil in Mississippi Valley area</td>
<td>Isolation of pathogens</td>
<td>Amphotericin B</td>
</tr>
</tbody>
</table>