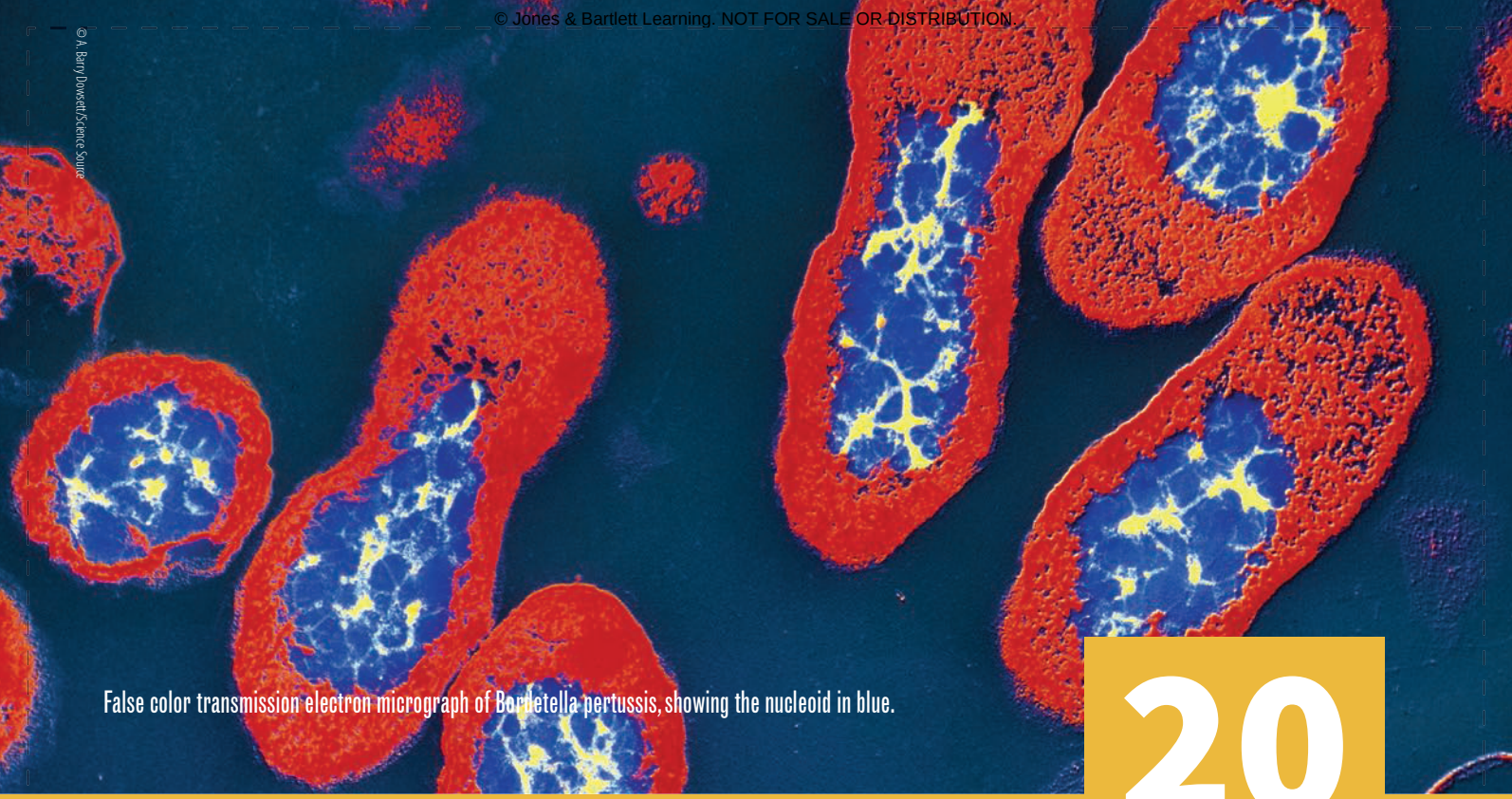


False color transmission electron micrograph of Bordetella pertussis, showing the nucleoid in blue.

20

Infectious Diseases Affecting the Respiratory System

In March 2010, the California Department of Public Health (CDPH) began receiving an abnormally large number of reports detailing patients with symptoms of runny nose, low-grade fever, and a mild, occasional cough that persisted for 7 to 14 days. For many, the symptoms lead to a series of rapid coughs followed by a high-pitched "whoop." It appeared that an outbreak of pertussis, commonly called whooping cough, was occurring in California. Caused by *Bordetella pertussis*, this highly communicable bacterial disease was spreading throughout the state.

In the early parts of the twentieth century, one of the most common childhood diseases and causes of death in the United States was pertussis. Before the introduction of a pertussis vaccine in 1940, *B. pertussis* was responsible for infection and disease in 150 out of every 100,000 people. By 1980, there was but one case in every 100,000 individuals. The vaccine had almost eliminated the pathogen.

In June of 2010, the CDPH said there had been a 418% increase in cases reported from the same period in 2009. Five infants had died and a major epidemic of pertussis was in full swing in California. In fact, by the end of 2010, the CDPH had reported 9,273 cases of pertussis (including

CHAPTER PREVIEW

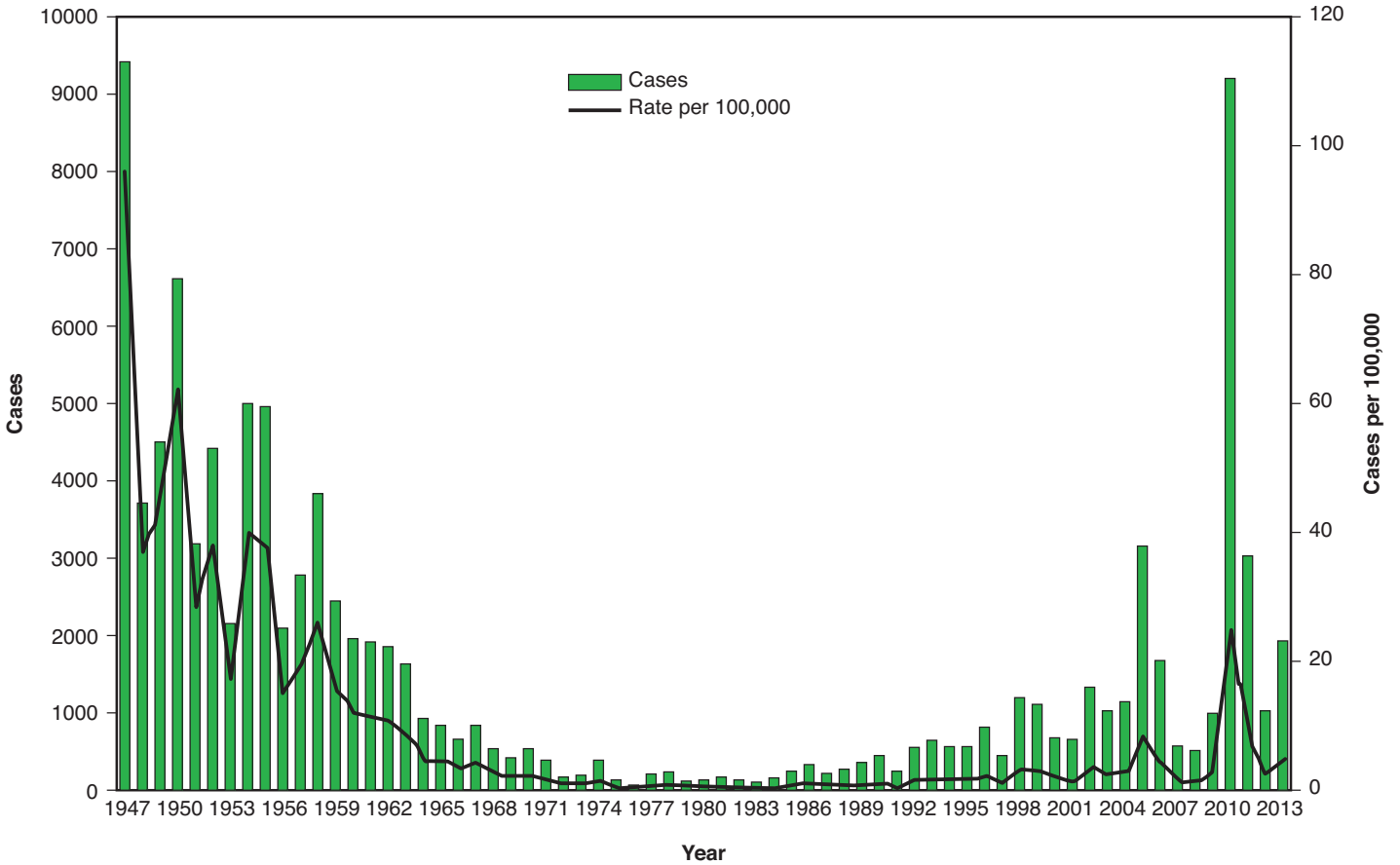


FIGURE 20.1 Reported Cases of Pertussis—California, 1947–2013. In 2010, the California Department of Public Health reported the largest number of pertussis cases since 1947. **What was responsible for the reduction in cases during the 1950s and 1960s?**

Reproduced from Pertussis Report-December 18, 2013/California Department of Public Health.

ten infant deaths), making this the most cases reported in 65 years (FIGURE 20.1).

In 2013, nationally there were more than 24,000 cases reported to the Centers for Disease Control and Prevention (CDC), up from 7,500 cases in 2000. Moreover, other countries around the world, from Australia to the Netherlands, are experiencing similar pertussis epidemics, forcing medical experts to quickly devise new prevention strategies.

Pertussis is but one of a group of infectious diseases affecting the respiratory system. We divide these diseases into three general categories. The first category includes diseases of the upper respiratory tract, such as strep throat and the common cold. The second category comprises diseases affecting both the upper and lower respiratory tract, such as pertussis and influenza, while the third category includes those diseases affecting the lower respiratory tract, such as tuberculosis and pneumonia.

CHAPTER CHALLENGE

In this chapter we consider many examples of infectious diseases affecting the respiratory system. Therefore, each section will provide a mini-challenge to identify a disease or pathogen based on the provided clinical case signs and symptoms. This helps link the diagnosis to real patients one may encounter in their health profession—and may be helpful when preparing for board examinations.

The Respiratory System and Resident Microbiota Normally Block Microbial Colonization

Because air typically contains microbes and viruses carried on dust and droplet nuclei, the

respiratory system is a common portal of entry for many infectious agents.

Upper Respiratory Tract Defenses Hinder Microbe Colonization of the Lower Respiratory Tract

The **respiratory system** is divided into the upper and lower respiratory tracts (FIGURE 20.2). The **upper respiratory tract** (**URT**) is composed of the nose, sinus cavities, pharynx (throat), and larynx, while the **lower respiratory tract** (**LRT**) is composed of the trachea, and the bronchi and bronchioles within the lungs. Attached to the bronchioles are the alveoli where gas exchange occurs.

The URT can contain a variety of resident microbes and potential pathogens, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus*. Therefore, the URT plays a critical role in defending against and filtering out foreign material, such as bacterial cells, viruses, dust particles carrying these microbes, and other foreign particles. In particular, the airway epithelium lining the URT surfaces is involved in a defensive process called **mucociliary clearance** (FIGURE 20.3A). Mucus, consisting of glycoproteins secreted from the goblet cells in the airway epithelium, traps microbes and particulate matter, which are then moved by ciliated epithelial cells toward the pharynx, where they are cleared through swallowing or expectorating (FIGURE 20.3B). In addition, antimicrobial substances, including interferon, and several human defensins, along with immune defensive cells (macrophages), help protect the URT from infection.

In the LRT, the epithelial cells lining the alveolar and respiratory bronchioles are not ciliated. However, the region is covered by alveolar fluid, which contains a number of antimicrobial

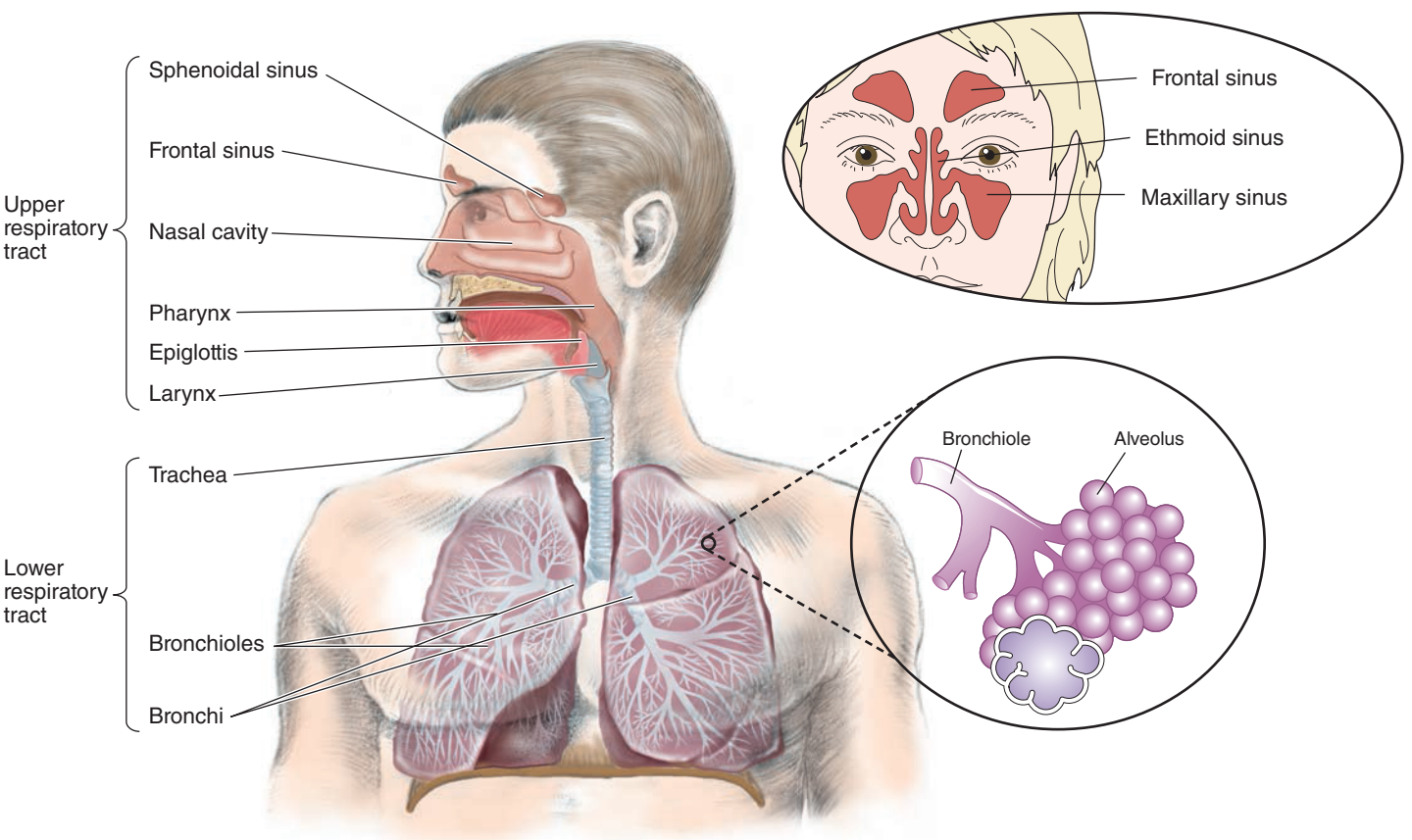


FIGURE 20.2 **Respiratory System Anatomy.** The major parts of the respiratory system are organized into the upper and lower respiratory tracts. **Which part of the respiratory system would be the most susceptible to colonization and infection?**

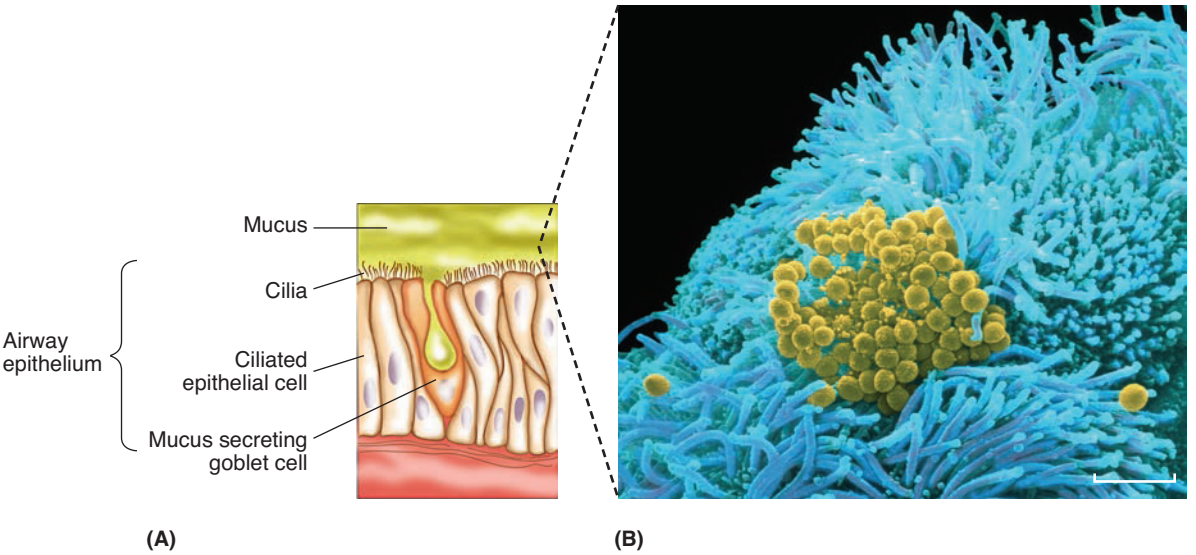


FIGURE 20.3 Defenses of the Airway Epithelium. **(A)** Epithelial cells provide a physical, chemical, and cellular barrier against potential pathogens. **(B)** False-color scanning electron micrograph of a *Staphylococcus* colony (yellow) on the epithelial cells of the trachea. The cilia (blue hair-like projections) keep the trachea free of dust and other irritants. (Bar = 4 μm.) **How does the ciliated epithelium work to eliminate these bacterial cells?**

components, including immunoglobulins. If excessive numbers of microbes enter the alveoli, the alveolar macrophages recruit neutrophils from the pulmonary capillaries to help clear the invaders.

The Upper Respiratory Tract Harbors a Large and Diverse Resident Microbiota

Many different microorganisms form part of the resident microbiota of the URT. As in other body systems having a resident microbiota, its role is one of **microbial antagonism** where the resident microbiota outcompetes any invading pathogens for space and nutrients.

The microbial community will vary in different parts of the tract because of its anatomical and physiological variations (see Figure 20.2). For example, colonization of the nostrils primarily involves gram-positive members (phylum Actinobacteria and Firmicutes). In the nasopharynx (the upper portion of the pharynx), the mucosal surface is mainly colonized by species of *Streptococcus*, *Neisseria*, and *Haemophilus*. In the oropharynx (the middle portion of the pharynx), members of the phyla Firmicutes, Proteobacteria, and Bacteroidetes prevail.

Until recently it was thought that the LRT and the lungs of healthy individuals were sterile. However, it now appears that the LRT does contain a resident microbiota similar to, but in reduced numbers from, the URT. For example, microbial genomic studies have been carried out on the lungs of healthy individuals and those of patients with genetic conditions like **cystic fibrosis** (CF), and **chronic obstructive pulmonary disorder** (**COPD**). These studies report that the lung microbiome in healthy nonsmokers and smokers has a significant core community of resident microbes dominated by three bacterial phyla (and a few dominant genera): Proteobacteria (*Pseudomonas, Haemophilus*), Firmicutes (*Streptococcus, Veillonella*), and Bacteroidetes (*Prevotella, Porphyromonas*) (FIGURE 20.4).

So, the human respiratory microbiome is slowly becoming better understood and the major players identified. Breakdown in respiratory system defenses or imbalances in the respiratory microbiota can lead to disease in the URT and LRT (FIGURE 20.5).

Cystic fibrosis: A life-threatening disorder caused by a defective gene that leads to difficulty breathing and to lung infections.

COPD: A progressive and potentially fatal lung disease caused predominantly by smoking.

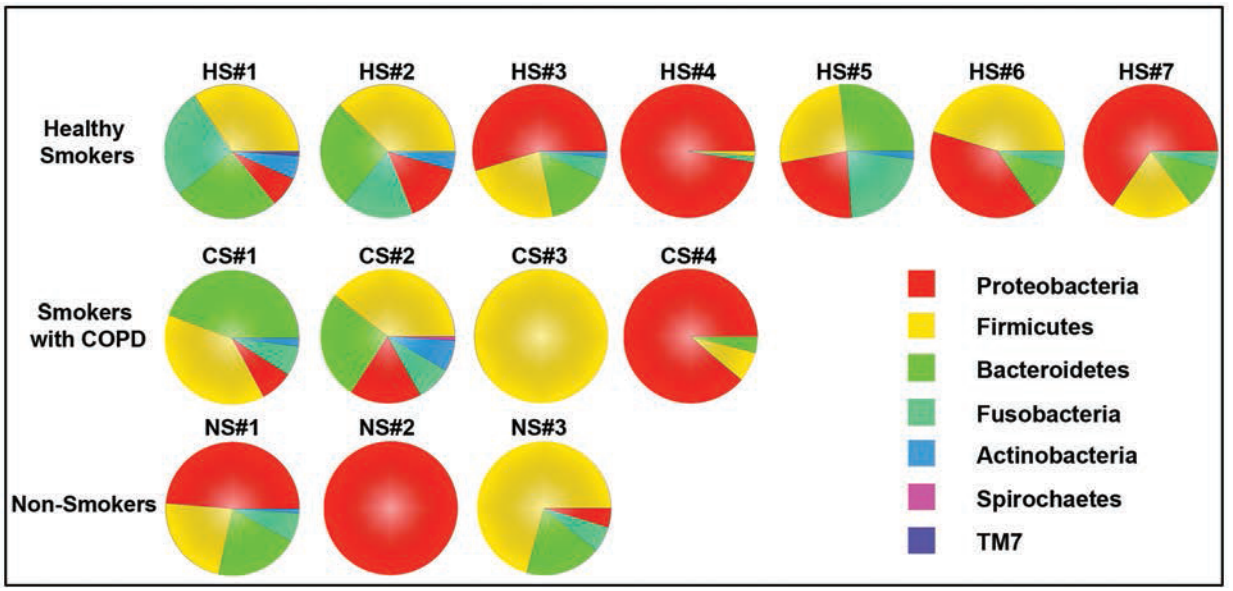


FIGURE 20.4 **Bacterial Phyla Present in the Lungs of Volunteers.** The Proteobacteria, Firmicutes, and Bacteroidetes phyla dominate but show a varied distribution between individual volunteers. TM7 is a major lineage of Bacteria that has not been cultured in the lab. **From these phylum-level microbiome analyses, does it appear that COPD patients have a unique bacterial community profile? Explain.**

Reproduced from: Erb-Downward, et al. (2011) Analysis of the Lung Microbiome in the "Healthy" Smoker and in COPD. *PLoS ONE* 6(2): e16384.

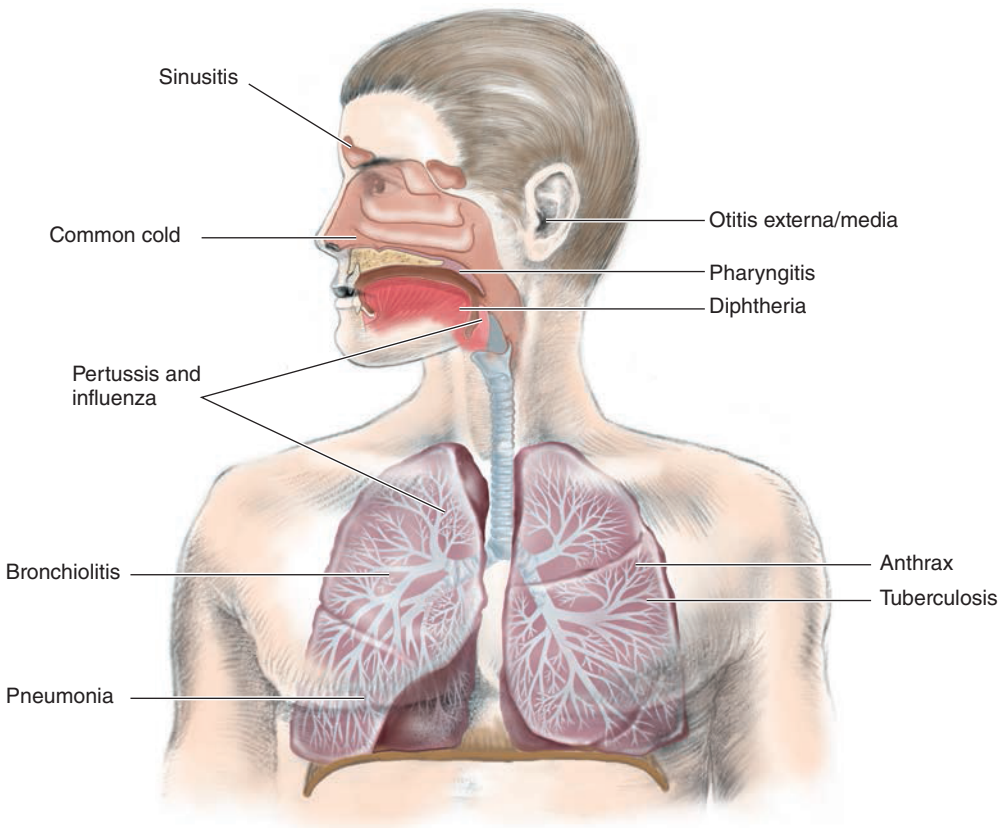


FIGURE 20.5 **Major Diseases of the Respiratory System.** Some pathogens target the URT or LRT, while others can progress from the URT to the LRT. **Why is the respiratory system such an accommodating environment for some pathogens?**

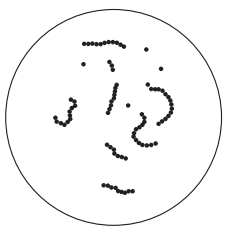
CONCEPT AND REASONING CHECKS 1 Bacteria: © NIAID

a. **Identify the anatomical features of the upper and lower respiratory tracts.**
b. **Why is a resident microbiota primarily found in the URT?**

KEY CONCEPT 20.2 Bacteria: © NIAID

Several Bacterial and Viral Diseases Affect the Upper Respiratory Tract

The bacterial diseases of the URT are usually mild but can be more serious if a pathogen in the respiratory tract spreads to the blood, and from there to other sensitive internal tissues and organs.



Streptococcus pyogenes

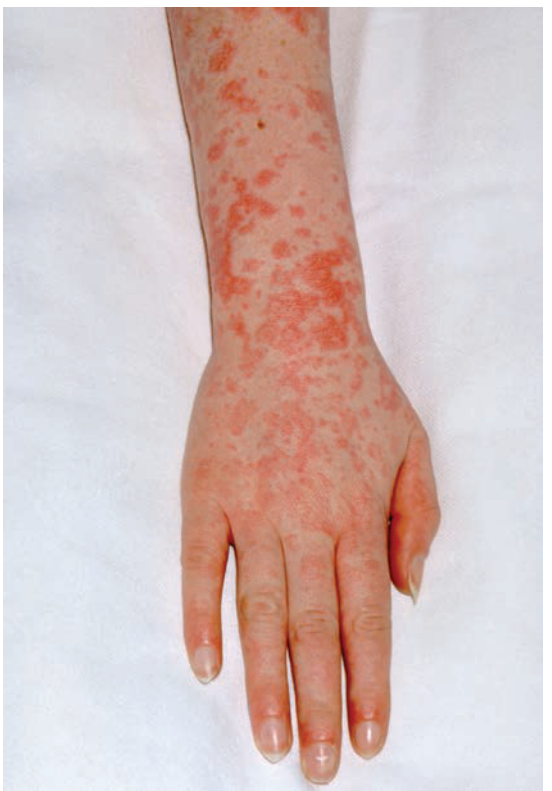
Pharyngitis Is One of the Most Common Infectious Diseases

A sore throat, known medically as **pharyngitis**, is an inflammation of the pharynx and sometimes the tonsils (tonsillitis). The inflammation is most commonly the result of a viral infection, such as the common cold. However, *Streptococcus pyogenes*, a facultative, gram-positive coccus, is responsible for a potentially more dangerous form of pharyngitis in children called **streptococcal pharyngitis**, commonly known as **strep throat**.

Respiratory droplet: A relatively large mucus particle that travels less than one meter.

The *S. pyogenes* cells are highly transmissible and reach the URT within respiratory droplets expelled by infected individuals during coughing and sneezing. If the cells grow and secrete toxins, inflammation of the oropharynx and tonsils can occur. Besides a sore throat, patients may develop a fever, headache, swollen lymph nodes and tonsils, and a beefy red appearance to pharyngeal tissues owing to tissue damage. An oral antibiotic, such as penicillin, is often prescribed to lessen the duration and severity of the inflammation and to prevent possible complications. Hand hygiene is the best prevention.

Scarlet fever is a disease arising in about 10% of children with streptococcal pharyngitis or a streptococcal skin infection. Some strains of *S. pyogenes* secrete **erythrogenic** (*erythro* = "red") exotoxins that cause a pink-red skin rash on the neck, chest, and soft-skin areas of the arms (FIGURE 20.6A). Other symptoms include a sore throat, fever, and a "strawberry-like" inflamed tongue (FIGURE 20.6B). Normally, an individual experiences only one case of scarlet fever in a lifetime because recovery generates



(A)

(B)

FIGURE 20.6 Scarlet Fever. Among the early symptoms of scarlet fever are **(A)** a pink-red skin rash and **(B)** a bright red tongue with a "strawberry" appearance.
What causes the skin rash seen with scarlet fever? What other symptoms are typical of scarlet fever?

immunity. Treatment with antibiotics, such as penicillin or clarithromycin, can shorten the duration of symptoms.

A serious complication resulting from a lack of treatment is **rheumatic fever**. This post-infectious sequela involves the body's antibodies to *S. pyogenes* mistakenly cross-reacting with similar proteins on heart muscle. This can lead to permanent scarring and distortion of the heart valves, a condition called **rheumatic heart disease**.

Streptococcal infections of the LRT are described later in this chapter.

Diphtheria Is a Life-Threatening Bacterial Illness

Through widespread vaccination programs, diphtheria is extremely rare in the United States and other developed countries. However, it continues to occur in developing nations, where almost 4,500 cases were reported to the World Health Organization (WHO) in 2012. Many more cases likely go unreported.

Causative Agent. **Diphtheria** is an infection of the URT caused by *Corynebacterium diphtheriae,* an aerobic, club-shaped, gram-positive rod (*coryne* = "club").

Clinical Presentation. Diphtheria is acquired by inhaling respiratory droplets or by direct contact with the skin from an infected person. Initial symptoms include a sore throat and low-grade fever. On the surface of the mucus membrane of the throat or mouth, the bacterial cells secrete a potent exotoxin capable of inhibiting protein synthesis in surrounding host cells and resulting in cell death. A prominent feature is the accumulation of dead tissue, mucous, white blood cells, and fibrous material, called a **pseudomembrane** ("pseudo" because it does not fit the definition of a true membrane) on the tonsils or pharynx (FIGURE 20.7). Mild cases fade after a week, while more severe cases can persist for 2 to 6 weeks. Complications can arise if the thickened pseudomembrane results in respiratory blockage, making breathing extremely difficult. Left untreated, 5% to 10% of respiratory cases result in death. If the exotoxin spreads to the bloodstream, heart and peripheral nerve destruction can lead to cardiac arrhythmia and coma.

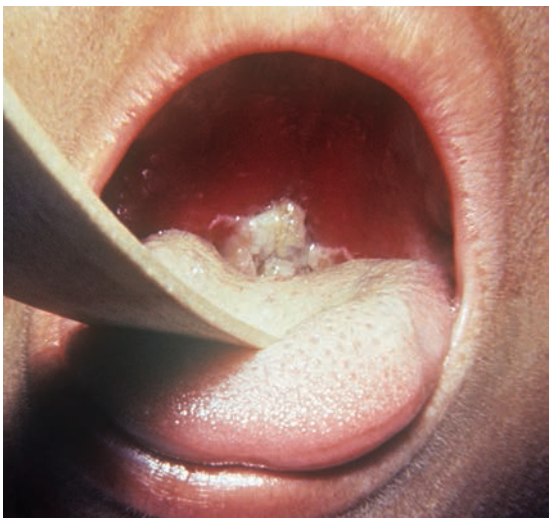
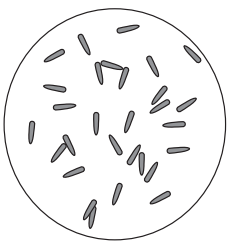


FIGURE 20.7 Diphtheria Pseudomembrane. Diphtheria is an upper respiratory infection of mucous membranes caused by a toxigenic strain of *Corynebacterium diphtheriae.* The infection is characterized by the formation of a pseudomembrane on the tonsils or pharynx. **What is the pseudomembrane composed of?**

Sequela: A pathological condition resulting from a disease.



Corynebacterium diphtheriae

Treatment and Prevention. Treatment requires antibiotics to eradicate the pathogen and antitoxins to neutralize the exotoxins. Protection can be rendered with one of the combination vaccines, such as diphtheria-tetanus-acellular pertussis (DTaP).

Sinusitis Is a Common Infection in the Upper Respiratory Tract

Because of its prominent position in the URT, the nose is a major portal of entry for infectious organisms and viruses. In fact, the microbiota in the nose can be a sign of potential illness. For example, healthy individuals contain primarily bacterial species belonging to the Actinobacteria (68%) and Firmicutes (27%) while hospitalized patients exhibit a disturbance to this equilibrium—Firmicutes (71%) and Actinobacteria (27%).

Sinusitis is inflammation in any of the four pairs of sinuses, the air-filled hollow cavities around the nose and nasal passages (see Figure 20.2 inset). The condition is most

Arrhythmia: An irregular heartbeat.

commonly caused by an allergy or infection, and nearly always occurs in connection with **rhinitis**, an inflammation and swelling of the nasal passages. About 10 to 15 million people each year develop a so-called "sinus infection." Sneezing and other artificial ways, as identified in MicroFocus 20.1, attempt to rid the nose of such nasal irritants.

Acute sinusitis may be caused by a variety of indigenous microbiota of the URT. Trapped fluid increases the pressure in the sinuses, and causes pain, tenderness, and swelling. Yellow or green mucus may be discharged from the nose. Nasal sprays can be used for a short time and antibiotics may be prescribed for a bacterial infection.

If untreated, acute sinusitis may develop into **chronic sinusitis** that can last for 8 to 12 weeks. The symptoms of chronic sinusitis are more subtle and pain occurs less often. The most common symptoms are nasal obstruction, nasal congestion, and postnasal drip. The treatment is the same as with acute sinusitis.

Ear Infections Are Common Illnesses in Early Childhood

The ear consists of the outer, middle, and inner ear. The Eustachian tube vents the middle ear to the nasopharynx, which explains why URT infections (such as the common cold)

MICROFOCUS 20.1: Public Health

Achoo!

Sneezing is a natural response to some irritating trigger in the nose. It might be dust, pollen, or some other atmospheric contaminant. Thus, sneezing is the body's way to eliminate these contaminants, or if we have a cold, to try to eliminate the infecting viruses. Essentially, scientists say the nose needs to "reboot" when overwhelmed with contaminants or microbes, and sneezing is a natural response to help reset the nasal environment—eliminate what is present so more inhaled particles can be trapped.

Many people today attempt to artificially do a "reboot" by rinsing their sinuses with a saline solution, often using a neti pot (see figure). The aim is to relieve the congestion caused by sinusitis, colds, and allergies. According to the Food and Drug Administration (FDA), the devices are useful and can remove dust and pollen from the nose, and loosen up thick nasal mucus due to allergies, colds, and the flu. However, the FDA is concerned about the risk of infection resulting from the improper use of a nasal rinsing device. In 2011, the Louisiana Department of Health and Hospitals reported two deaths from a rare brain infection caused by *Naegleria fowleri*, a protist pathogen that might have contaminated the tap water used in a nasal rinsing device (the disease called primary amoebic meningoencephalitis is described in the chapter on diseases affecting the nervous system).

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Because some communities may have tap water containing low levels of bacterial and protist organisms, nasal rinsing devises must use a safe source of water, something the FDA says a few nasal device manufacturers don't adequately provide the consumer. Therefore, sterile or distilled water, or a filtering device with a pore size of less than 1 μm, should be purchased and used. Alternatively, one can boil the water for 5 minutes and then let it cool until it is lukewarm. So, nasal rinsing devices, like a natural sneeze, are useful for sinus conditions but make sure the artificial device has been rinsed with clean, "microbe-free" water and completely dried before use and between uses. Gesundheit and good health!

often result in infections to the middle ear (FIGURE 20.8).

In the outer ear, an inflammation referred to as **otitis externa** (*oti* = "ear") can affect the entire ear canal or just one small area, as in a boil (furuncle) or pimple. Normally, the ceruminous glands in the ear canal produce cerumen (earwax), which has antibacterial activity. However, outer ear infections commonly occur in children, especially after extended swimming in fresh water pools. Such infections, often called **swimmer's ear**, are most often caused by species of *Pseudomonas*, although *Staphylococcus* species can also cause the infection. The primary symptoms are itching followed by ear pain. Treatment involves the application of antibiotic eardrops.

A major burden to global health is middle ear infections called **acute otitis media** (**AOM**) (*media* = "middle"). Health experts state that at least 80% of children have had at least one episode of AOM by three years of age and 40% have experienced at least seven recurrences by the age of seven, even in developed nations.

AOM is typically caused by *S. pneumoniae* or *H. influenzae*, usually starting with a common cold or other viral infection of the URT. Inflammation of the Eustachian tube allows bacterial cells to infect the sterile environment of the middle ear. Fluid buildup then provides an environment for bacterial growth and **biofilm** formation, which result in the middle ear becoming inflamed. This is followed by ear pain with a red, bulging eardrum. Children with AOM may develop a fever, produce a fluid ("effusion") that drains from the ears, or have headaches. More than 80% of children with AOM get better without antibiotics. In fact, treatment with antibiotics can lead to stronger biofilms and a chronic ear infection.

Chronic otitis media (**COM**) is a condition involving long-term infection, inflammation, and damage to the middle ear. The persistent biofilm colonization of the middle ear tissue is a major global cause of morbidity, leading to hearing impairment. This can result in serious long-term effects on language, auditory and cognitive development, and educational progress.

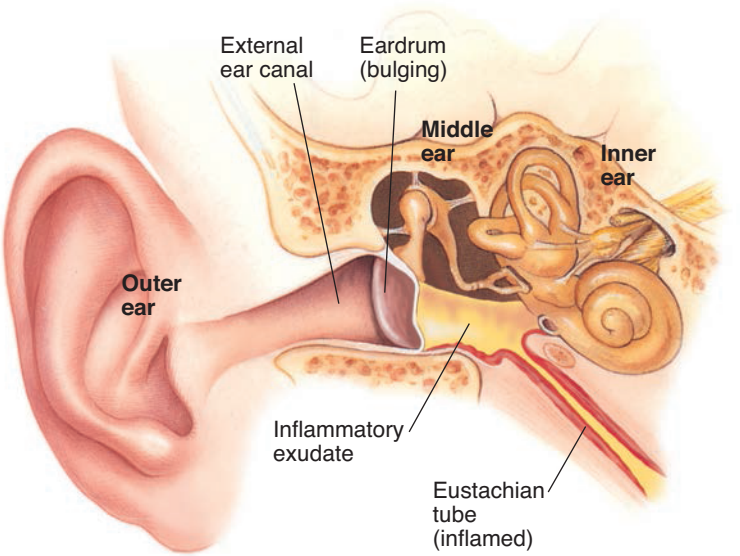
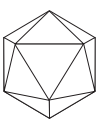


FIGURE 20.8 Ear Anatomy. The ear consists of external, middle, and inner structures. » **In a middle ear infection, how do the infecting microbes reach the middle ear?**

The Common Cold Is a Minor Inflammation of the Nose and Throat

As mentioned earlier in this chapter, the prominent position of the nose in the URT makes it the most commonly infected part of the URT and a common cold virus is usually the culprit.


Rhinovirus

Rhinoviruses. Rhinoviruses (*rhino* = "nose") are a broad group of over 100 small, naked, single-stranded (+ strand) RNA viruses with icosahedral symmetry in the family Picornaviridae (*pico* = "small"; hence, small-RNA viruses; FIGURE 20.9). The genome consists of only 10 genes. With an estimated 10^{21} rhinoviruses globally, they represent the most successful, easily transmitted viruses on the planet, although other viruses, such as some adenoviruses and coronaviruses, can also cause the **common** (**head**) **cold** (FIGURE 20.10).

Transmitted through respiratory droplets or by contact with an infected person or contaminated fomites, the portal of entry for rhinoviruses is the epithelial cells of the URT. The viruses then bind to macrophages and dendritic cells of the immune system. However, about 90% of the human rhinovirus strains cause the immune cells to produce

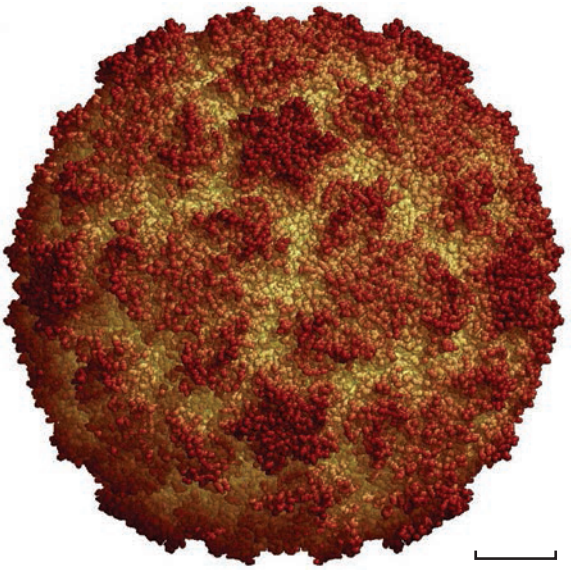


FIGURE 20.9 A Rhinovirus. A computer-generated image of the surface (capsid) of human rhinovirus 16. (Bar = 3 nm.) **What is unique about each rhinovirus that makes vaccine development impractical?**

Human rhinovirus 16: Picornaviridae; Rhinovirus; Human rhinovirus A; strain (NA). Hadfield, A.T., Lee, W.M., Zhao, R., Oliveira, M.A., Minor, I., Rueckert, R.R. and Rossmann, M.G. (1997). The refined structure of human rhinovirus 16 at 2.15 A resolution: implications for the viral life cycle. *Structure*, 5, 427–441. (PDB-ID: 1AYM)_Image by J.Y. Sgro, UW-Madison.

anti-inflammatory cytokines, which actually slows down the onset of the "common cold syndrome": sneezing, a sore throat, runny or stuffy nose, mild aches and pains, and a mild-to-moderate hacking cough. In general, the illness usually lasts 7 to 10 days. So, why do colds seem to occur much more frequently in the cooler months of early spring and fall? **MicroFocus 20.2** investigates.

Antibiotics will not prevent or cure a cold and with over 100 rhinovirus strains, a vaccine is not likely. Antihistamines can sometimes be used to treat the symptoms of a cold; however, they do not shorten the length of the illness. For other remedies, such as vitamin C, there are mixed reports on their therapeutic value. **Investigating the Microbial World 20** summarizes the findings. The bacterial and viral diseases of the URT are summarized in **TABLE 20.1**.

CONCEPT AND REASONING CHECKS 2

Bacteria: © NIAID

a. What makes *S. pyogenes* such a potentially dangerous pathogen in the upper respiratory tract?
b. In seventeenth century Spain, diphtheria was called "el garatillo" (the strangler). Why was it given this name?
c. How do acute and chronic sinusitis differ?
d. In most cases with otherwise healthy children, why is the use of antibiotics not recommended for acute otitis media?
e. Why do we get colds over and over again?

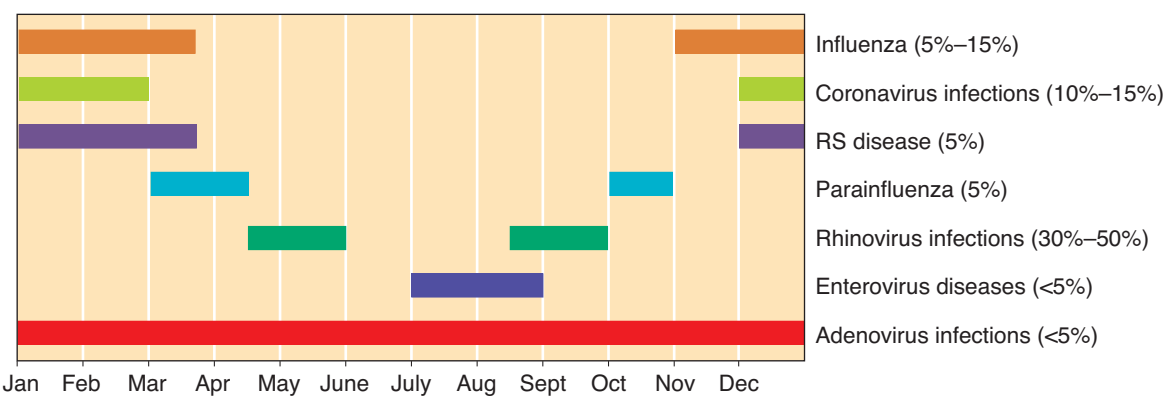


FIGURE 20.10 The Seasonal Variation and Estimated Annual Proportion of Viral Respiratory Diseases. This chart shows the seasons associated with various viral diseases of the respiratory tract (and their annual percentage). **Hypothesize why different cold viruses cause diseases at different times of the year.**

Bacteria: © NIAID

MICROFOCUS 20.2: Being Skeptical

Catching a Chill: Can It Cause a Cold?

How many times can you remember your mom or a family member saying to you, "Bundle up or you will catch a cold!" Can you actually "catch" a cold from a body chill?

© Tihis/ShutterStock, Inc.

In 2005, British researchers Claire Johnson and Professor Ron Eccles at Cardiff University's Common Cold Center published a paper reporting a drop in body temperature can allow a cold to develop. The researchers signed up 180 volunteers and split them into two groups. One group put their bare feet into bowls of ice-cold water for 20 minutes. The other group put their bare feet in similar but empty bowls.

Over the next five days, 29% of individuals who had their feet chilled reported cold symptoms, while just 9% of the control group reported symptoms.

Professor Eccles suggested chilling causes blood vessels in the nose to constrict, limiting the warm blood flow supplying white blood cells to eliminate or control any rhinoviruses a person may be exposed to. In 2013, a team at Yale University looked further into the cold temperature mystery. Using mice susceptible to a mouse-specific rhinovirus, they found that mice at warmer temperatures produced a burst of anti-inflammatory immune signals (cytokines) to help fight off the viruses. Similarly, in human cells in culture, they found a rhinovirus infection caused the cells to commit cell suicide, which would limit the spread of the virus. At cooler temperatures, fewer cytokines were produced in infected mice and the human cells in culture were not as likely to undergo cell suicide.

The verdict? The research suggests breathing in colder air will slightly drop the temperature in the upper URT, making rhinovirus survival and replication more likely. Because other studies have found no connection between temperature and rates of rhinovirus infection—as often is the case—more definitive studies are needed. But perhaps temperature is one factor important to rhinovirus spread.

CHAPTER CHALLENGE A

You have read about several diseases associated with the human URT.

Question A:
Diagnose the correct disease from the following signs and symptoms.

1. (Easy) A 2-year-old boy presents with fever, redness of the eardrum, and the presence of an effusion draining from the ear. His parents indicate their son had an upper respiratory infection 5 days ago. Disease diagnosis?
2. (Easy) A 35-year-old woman presents to a clinic in South East Asia with a sore throat, fever and chills, painful swallowing, nasal discharge, and a thick, gray membrane on the tonsils. Disease diagnosis?
3. (Medium) A 29-year-old female presents with nasal congestion, ear pain, postnasal drip with a thick, yellowish discharge from the nose. She states that she has had this condition for the last 9 weeks. Disease diagnosis?

Answers can be found in **Appendix F**.

Bacteria: © NIAID

INVESTIGATING THE MICROBIAL WORLD 20

Vitamin C and the Common Cold

In this **Investigating the Microbial World**, rather than looking at one research study, a meta-analysis is presented. The purpose of a meta-analysis is to examine many previously published, peer-reviewed research studies with the aim of developing a single, concrete conclusion from all the study results.

- **OBSERVATION:** Treating colds with vitamin C became very popular in the 1970s after Nobel laureate Linus Pauling suggested that vitamin C could prevent and lessen cold symptoms. Since then, numerous studies have looked at whether there are therapeutic benefits from taking vitamin C to prevent or reduce the length of a common cold syndrome.
- **QUESTION:** ***Does vitamin C reduce the severity, incidence, and/or duration of a common cold syndrome?***
- **OBJECTIVE:** Use a meta-analysis to systematically examine studies assessing the incidence of colds with regular vitamin C intake among study subjects reporting one or more colds during the study period. Search criteria looked for trials using more than 0.2 g per day of vitamin C and having placebo controls. The term "incidence" refers to the percentage of participants experiencing one or more colds during the study period and "duration" refers to the percentage of participants with a shorter duration of a common cold syndrome.

Data were extracted from electronic searches of: CENTRAL (a controlled trials registry), MEDLINE (biomedical literature resource), EMBASE (biomedical and pharmacological literature resource), CINAHL (Cumulative Index for Nursing and Allied Health Literature), LILACS (scientific and technical literature resource), and Web of Science (citation database). Searches were also done using the National Institutes of Health Clinical Trials registry and the World Health Organization CTRP (Clinical Trials Registry Platform).

- **SEARCH 1:** Seven studies were found that looked at the therapeutic effect and severity of symptoms (3,249 cold episodes) while taking vitamin C regularly or a placebo during the study period.
- **SEARCH 2:** Twenty-nine studies (11,306 participants) were found that examined the incidence (percentage of participants experiencing one or more colds during the study period) while taking vitamin C regularly or a placebo during the study period. These studies were separated into two subgroups: the general population and 598 participants exposed to short periods of severe physical exercise (marathon runners, skiers, and soldiers on subarctic winter exercises).
- **SEARCH 3:** Thirty-one studies were found that examined the duration (percentage of participants experiencing a shorter duration of a common cold syndrome during the study period) while taking vitamin C or a placebo. These studies were separated into two subgroups: adults and children because (a) children often have more colds due to immune system immaturity and (b) children being smaller (less body weight) means a fixed dose of vitamin C corresponds to a higher dose per body weight.
- **RESULTS:** see figures (A) and (B).
- **CONCLUSIONS:** In Search 1, no consistent effect of vitamin C could be found among the 7 studies examining the therapeutic effect (reduced severity) among participants.

QUESTION 1: ***Looking at the figure (A):***

(a.) *Does vitamin C supplementation reduce the incidence of "catching a cold" in (i) the general population group and/or (ii) the severe physical exercise group? Explain.*

QUESTION 2: ***Looking at the figure (B):***

(a.) *Does vitamin C supplementation reduce the duration (length) of a common cold syndrome in adults and/or children? Explain.*
(b.) *Does the dosage of vitamin C affect the duration?*

Bacteria: © NIAID

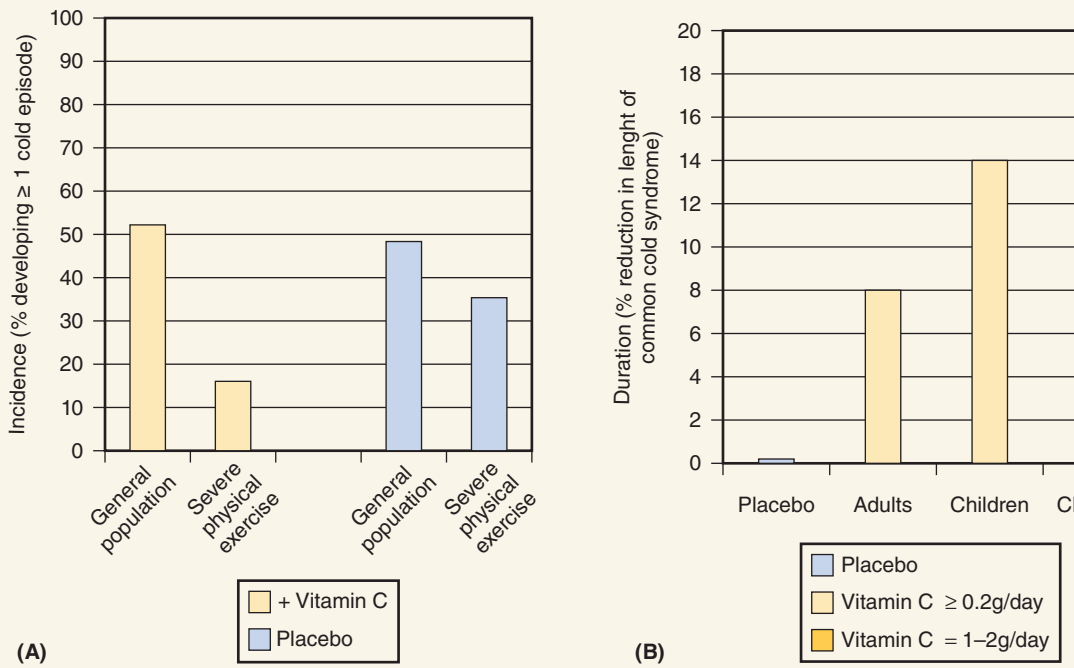
(CONTINUED)

QUESTION 3: ***What type of factors may bias the reporting of the incidence and duration of a common cold syndrome?***

QUESTION 4: ***From the meta-analysis, would you take vitamin C to prevent and treat the common cold? Explain.***

Answers can be found in **Appendix E**.

Adapted from: Hemilä, H. and Chalker, E. (2013). *Cochrane Database of Systematic Reviews* 2013, Issue 1. Art. No.: CD000980. DOI: 10.1002/14651858. CD000980.pub4.



Data from: Hemilä, H. and Chalker, E. (2013). Cochrane Database of Systematic *Reviews* 2013, Issue 1. Art. No.: CD000980. DOI: 10.1002/14651858.CD000980.pub4.

KEY CONCEPT 20.3

Bacteria: © NIAID

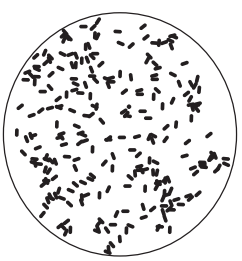
Some Pathogens Can Spread from the URT to the LRT

A few diseases, primarily pertussis and influenza, are URT infections that can progress to the LRT.

Pertussis (Whooping Cough) Is Highly Contagious

Pertussis is one of the most dangerous and highly contagious bacterial diseases and one in which there has been an increasing number of cases, as described in the chapter opener. Unfortunately, a shortcoming of the vaccine may be the cause for the disease's resurgence. Worldwide, there are more than 16 million pertussis cases annually and almost 200,000 deaths.

Causative Agent. **Pertussis** (*per* = "through"; *tussi* = "cough"), also known as **whooping cough**, is caused by *Bordetella pertussis*, a small, aerobic, gram-negative rod strictly associated with human infections. The bacilli are spread by respiratory droplets that adhere to and aggregate on the epithelial cells



Bordetella pertussis

TABLE 20.1 A Summary of the Major Infectious Diseases of the URT

Disease	Causative Agent	Signs and Symptoms	Transmission	Treatment	Prevention
Streptococcal pharyngitis	*Streptococcus pyogenes*	Sore throat, fever, headache, swollen lymph nodes and tonsils	Respiratory droplets	Penicillin	Practicing good hand hygiene
Scarlet fever	*Streptococcus pyogenes*	Pink-red rash on neck, chest, arms Strawberry-like tongue	Respiratory droplets	Penicillin Clarithromycin	Practicing good hygiene
Diphtheria	*Corynebacterium diphtheriae*	Pseudomembrane	Respiratory droplets	Penicillin Erythromycin	Vaccinating with DTaP
Sinusitis	Indigenous microbiota	Pain, tenderness, and swelling	Respiratory droplets	Nasal sprays Antibiotics	Minimizing contact with individuals with colds
Otitis externa	*Streptococcus, Staphylococcus, Pseudomonas* species	Itching and ear pain	Contaminated water	Lifestyle modifications Topical and oral medications	Keeping ears dry
Acute otitis media	*Streptococcus pneumoniae* *Haemophilus influenzae*	Ear pain Red, bulging eardrum	Airborne Direct contact	Wait and see Antibiotics	Limiting time in childcare
Common colds (rhinitis)	Rhinoviruses Adenoviruses Coronaviruses	Sneezing, sore throat, runny and stuffy nose, hacking cough	Respiratory droplets	Pain relievers Decongestants	Practicing good hygiene

in the mouth and throat. Exotoxin production paralyzes the ciliated cells and impairs mucus movement, potentially causing pneumonia.

Clinical Presentation. Typical cases of pertussis occur in three stages. The initial (**catarrhal**) stage (lasting 1–2 weeks) is marked by malaise, runny nose, low-grade fever, and a cough. An individual is most contagious and carries a high bacterial load during this stage.

During the second (**paroxysmal**) stage (lasting 2–4 weeks), disintegrating cells and mucus accumulate in the airways and cause labored breathing. Patients experience multiple **paroxysms**, which consist of rapid-fire coughs all in one exhalation, followed by a forced inhalation over a partially closed glottis. The rapid inhalation results in the characteristic "whoop" and hence the name whooping cough. Some 10 to 15 paroxysms may occur daily, some being so violent that facial injury results (FIGURE 20.11). Exhaustion usually follows each paroxysm. Adolescents and adults may not experience these characteristic symptoms.

The third (**convalescent**) stage involves sporadic coughing, which gradually decreases over several weeks of convalescence, even after the pathogen has vanished; thus, doctors call diphtheria the "100-day cough."

Treatment and Prevention. The duration and severity of the illness can be lessened when antibiotics are administered during the catarrhal stage.

Until recently, the relatively low incidence of pertussis in developed nations was the result

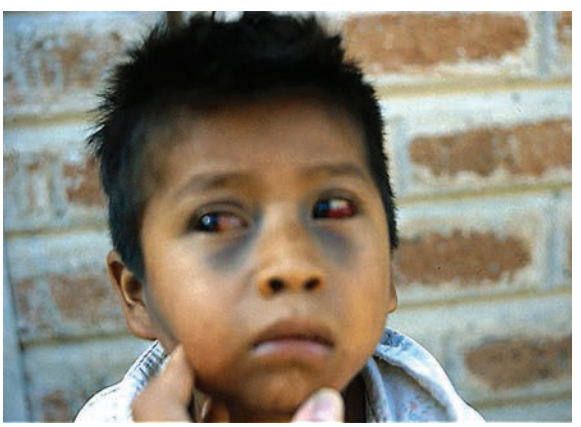


FIGURE 20.11 A Child with Pertussis. Pertussis can lead to broken blood vessels in the eyes and bruising on face. **How would pertussis lead to the facial injuries shown in the photo?**

Courtesy of Thomas Schlenker, MD, MPH, Chief Medical Officer, Children's Hospital of Wisconsin.

TABLE 20.2 Comparison of the Influenza Viruses

Characteristic	Influenza A	Influenza B	Influenza C
Reservoir	Humans, pigs, birds	Only humans	Only humans
Epidemiology			
• Epidemics	Yes	Yes	No
• Pandemics	Yes	No	No
Occurrence	Seasonal	Seasonal	Nonseasonal
Antigenic changes	Drift/shift	Drift	Drift
Potential severity of illness	Severe	Moderate	Mild
Seasonal vaccine preparation	Two subtypes	One subtype	No vaccine
Genome	Eight segments	Eight segments	Seven segments

of using a pertussis vaccine. The older vaccine (diphtheria-pertussis-tetanus, or DPT) was very effective in both preventing pertussis and stopping its transmission. However, due to vaccine reactions, a newer acellular pertussis (aP) vaccine was developed. Combined with diphtheria and tetanus toxoids, the triple vaccine has the acronym DTaP (Tripedia®). Because its ability to generate immunity slowly declines, in 2005, the U.S. Food and Drug Administration (FDA) licensed a reduced-dose acellular vaccine (Tdap), which is recommended as a booster dose for children at age 11 or 12, and as a booster every 10 years for those over 20.

This changeover to acellular vaccines might provide one reason for the resurgence in pertussis cases described in the chapter opener. The acellular vaccines appear weaker and are not as effective at preventing infection and transmission of *B. pertussis*. In addition, more than 60% of adults do not remember when, if at all, they had a Tdap booster. So, immunity may be failing due to a weak vaccine and a lack of immunization. Added to this is the fact that *B. pertussis* itself may be evolving, making the vaccine less effective.

Because unimmunized or incompletely immunized young infants are most susceptible and at risk of severe complications, it is critical that all family members in the household be vaccinated. To accomplish this, a strategy called "cocooning" is recommended. First, young children need five doses of DTaP before kindergarten. Students entering 7th grade need proof of a Tdap booster. Women should receive a Tdap booster in the third trimester of pregnancy, and healthcare workers, as well as adults in contact with infants, should have a Tdap booster every 10 years.

Influenza Is a Highly Communicable Acute Respiratory Infection

During the spring of 2009, a novel influenza virus arose in Mexico and soon spread to the United States and Canada, and within weeks the virus was a global infection. Because the global population had little or no immunity to this new strain, the infection produced the first influenza pandemic since 1968. Since the end of the pandemic in late 2010, the CDC has estimated that somewhere between 150,000 and 500,000 people died (similar to the seasonal flu). In the United States, there were an estimated 61 million cases, 275,000 hospitalizations, and an estimated 12,500 deaths.

Epidemiology. Influenza (the "flu") is a highly contagious acute disease of the respiratory tract that is transmitted by airborne respiratory droplets. Since the first recorded epidemic in 1510, scientists have described 31 pandemics. The most notable pandemic of the twentieth century was the "Spanish" flu in 1918–1919 that killed an estimated 40 to 100 million people. Today, about 20% of the global population gets the seasonal flu and 250,000 to 500,000 deaths occur from influenza complications.

Causative Agent. There are three types of influenza viruses, fittingly named **influenza A**, **influenza B**, and **influenza C**. They all belong to the Orthomyxoviridae family and share similar structural features in that they are spherical shaped in culture, enveloped, and have a segmented genome consisting of several single-stranded (– strand) RNA molecules (FIGURE 20.12). Because about 70% of human flu cases are caused by influenza A, and aquatic birds are the natural hosts for many of the influenza A subtypes, the remaining discussion will center on this type.

The genome of the influenza A virus consists of eight (–ssRNA) segments (see Figure 20.12). Each segment, which is wound helically and surrounded by a nucleocapsid, codes for one or two virus proteins. An additional structural protein, the **matrix protein**, surrounds the core of RNA segments, and an envelope covers the matrix protein.

Projecting through the envelope are some 500 protein spikes:

- **H spikes.** About 80% of the spikes are **hemagglutinin** (**H**) proteins. They recognize specific molecules on the surface of the host cells lining the nasopharynx and tracheobronchial tree, which facilitates the attachment and penetration of influenza A into the host cells.

Tracheobronchial tree: The trachea, bronchi, and bronchioles froming the airways to and in the lungs.

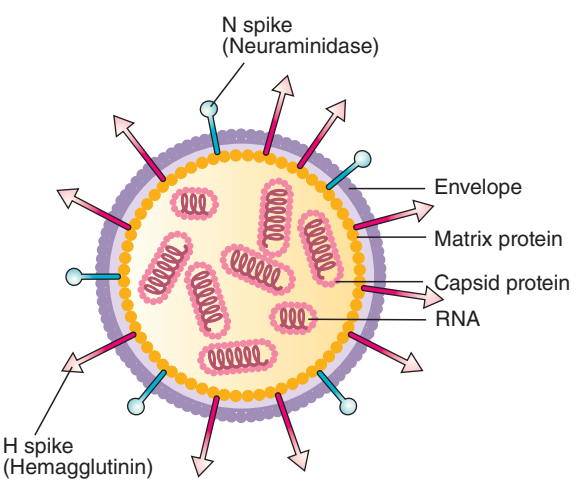


FIGURE 20.12 **The Influenza A Virus.** This diagram of the influenza A virus shows its eight single-stranded segments of RNA, matrix protein, and envelope with hemagglutinin (H) and neuraminidase (N) spikes protruding. » What is the role of the hemagglutinin and neuraminidase spikes?

- **N spikes.** The remaining spikes are **neuraminidase** (**N**) proteins. These spikes assist in the release of newly replicated viruses from the surface of the host cells.

Influenza A is divided into subtypes based on the 17 antigenically different types of H spikes (H1–H17) and 11 different N spikes (N1–N11). For example, the most common seasonal influenza A subtypes for 2015 are predicted by the WHO to be H1N1 and H3N2.

Each year a slightly different flu subtype evolves, based, in part, on changes to H and/or N spike proteins. Thus, there is a need for a new flu vaccine each year to protect individuals. Some years the new subtype is quite mild (it might be a slightly changed version of H3N2), while in other years, a predominant subtype might be more dangerous because a completely new spike protein is present (e.g., H7N2). The "Spanish" flu in 1918 was so devastating because that was the first time the H1N1 combination appeared in the human population. How do these spike changes come about? MicroInquiry 20 examines their evolution.

Clinical Presentation. The onset of influenza A is abrupt after an incubation period of 1 to 4 days. The individual with an uncomplicated illness develops sudden chills, fatigue, headache, and pain most pronounced in the chest, back, and legs. Over a 24-hour period, body temperature can rise to 40°C, and a severe, dry cough develops. Individuals may experience sore throat, nasal congestion, sneezing, and tight chest, the latter a probable reflection of viral invasion of tissues of the trachea and bronchi of the LRT. Despite these severe symptoms, influenza is normally short-lived and usually resolves in 7 to 10 days. For comparison purposes, MicroFocus 20.3 examines the similarities and differences between the common cold and seasonal flu.

Most of the annual deaths from seasonal influenza A are due to a secondary bacterial pneumonia. In fact, it appears a flu infection can trigger *S. pneumoniae* to disperse from the biofilms in the nose or throat and colonize the lung, leading to bacterial pneumonia. Influenza infection in rare cases also is associated with two other serious complications. **Guillain-Barré**

MICROINQUIRY 20

Drifting and Shifting—How Influenza Viruses Evolve

Influenza viruses evolve in two different ways. Both involve **antigenic variation**, a process in which chemical and structural changes occur periodically in such structures as hemagglutinin (H) and neuraminidase (N) spike proteins (antigens), thereby yielding new virus subtypes.

Antigenic drift involves unpredictable, but small changes to the virus (**Panel A**, below). These changes, involving minor point mutations resulting from RNA replication errors, will be expressed in the new virions produced. Although many such mutations may produce nonfunctional viruses, on occasion a mutation might confer an advantage to the virus. For example, a spike protein might have a subtle change in shape (that is, the structural shape has "drifted") so the proteins are not completely recognized by the host's immune system. This is what happens prior to most flu seasons. The virus spikes are different enough from the previous season that the host's antibodies and the immune response from the past flu season's vaccine fail to adequately recognize the new strain. Both influenza A and B viruses can undergo antigenic drift.

Antigenic shift is an abrupt, major change in structure to influenza A viruses. Antigenic shift may give rise to new subtypes that can now jump to another species, including humans (**Panel B**, below); that is, the spike structure has "shifted" such that most everyone is immunologically defenseless, and from which a pandemic may ensue (see figure).

Two mechanisms account for antigenic shift.

The "Spanish" flu was the introduction of a completely new flu subtype (H1N1) into the human population from birds. The H1N1 subtype jumped directly to humans and adapted quickly to replicate efficiently in humans (**Panels B, C**).

A second mechanism involves a process called reassortment. If a host cell has been infected with two or more flu virus subtypes at the same time, a mixing (reassortment) of genome segments from different viruses can occur (**Panel B**). Sometimes this results in a hybrid virus with completely new surface spikes. For example, the 1957 influenza virus ("Asian" influenza; H2N2) was a reassortment, where the human H1N1 subtype acquired new spike genetic segments (H2 and N2) from an avian species (**Panel D**). The 1968 influenza virus ("Hong Kong" influenza; H3N2) was the result of another reassortment; the human H2N2 subtype acquired a new hemagglutinin genetic segment (H3) from another avian species (**Panel E**).

In this second transmission mechanism, pigs usually are the reassortment "vessels" because they can be infected by both avian and human flu viruses. In fact, the 2009 swine flu is another example, involving reassortment of swine, avian, and human virus segments (**Panel F**). In late 2013, the first human cases of H7N9 and H5N1 (gene reassortments in poultry between domestic ducks and wild bird subtypes) were reported in China. Generating a virus with a functional reassortment is rare, but as you can see from the graph, they do occur with some regularity.

Discussion Point

The current avian (or bird) flu subtype (H5N1) is lethal to domestic fowl but is transmitted very inefficiently from fowl to human. Since 2003, of the approximately 650 reported human infections (as of January 14, 2014), 60% have died. In late 2011, two research groups, one at the University of Wisconsin, Madison and the other from the Erasmus Medical Center in the Netherlands, each identified the few mutations needed to make H5N1 readily transmissible to humans. Both reports were initially blocked from publication because critics feared that making the methodology and resulting mutation sequences publically available might give terrorists the "recipe" to make a "doomsday weapon;" or the virus might escape from a research lab. Proponents for publication say knowing what mutations must occur would allow epidemiologists to "be on the lookout" for such naturally occurring mutations in H5N1 and to test the efficacy of existing vaccines and antiviral drugs. Both papers have now been published. Was this a good idea?

(*Continued*)

Bacteria: © NIAID

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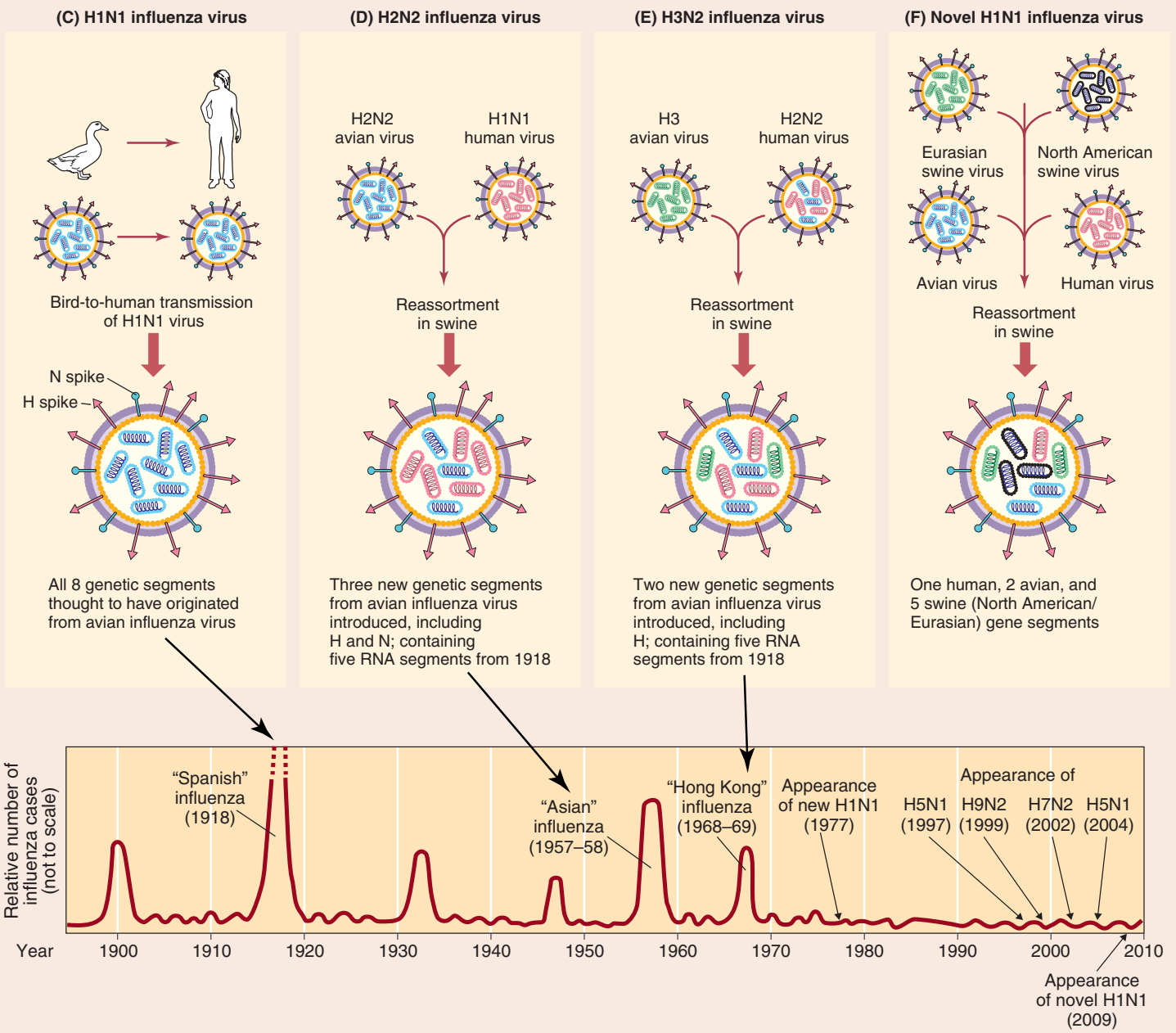


The Major Influenza Pandemics in Humans. The four pandemics were the result of antigenic shifts.

Bacteria: © NIAID

MICROFOCUS 20.3: Public Health

Is It a Cold Or the Flu?

Do you know the differences in symptoms between a cold and flu? As described in this chapter, both are respiratory illnesses but are caused by different viruses. Yet both often have some similar symptoms. In general, the flu has a sudden onset (3–6 hours) while a cold comes on more gradually. Flu symptoms are more severe than cold symptoms (see table). In addition, colds generally do not progress to more serious complications, such as pneumonia and bacterial infections, nor do they usually require hospitalization.

TABLE **Is It a Cold Or the Flu?**

Symptoms	Cold	Flu
Fever	Uncommon	Common; lasts 3 to 4 days
Headache	Uncommon	Common
Chills	Uncommon	Fairly common
General aches and pains	Slight	Common and often severe
Fatigue and weakness	Sometimes	Usual and can last up to 2–3 weeks
Extreme exhaustion	Uncommon	Usual
Stuffy nose	Common	Sometimes
Sneezing	Common	Sometimes
Sore throat	Common	Sometimes
Cough	Mild to moderate hacking, productive cough	Dry, unproductive cough that can become severe

Adapted from National Institute of Allergy and Infectious Diseases website http://www.niaid.nih.gov/topics/Flu/Pages/coldOrFlu.aspx

syndrome (**GBS**) occurs (1 case per 100,000 flu infections) when the body's immune system mistargets the infection and instead damages peripheral nerve cells, causing muscle weakness and sometimes paralysis. **Reye syndrome** usually makes its appearance in young people after they are given aspirin to treat fever or pain associated with influenza. It begins with nausea and vomiting, but the progressive mental changes (such as confusion or delirium) may occur. Very few children develop Reye syndrome (less than 0.03–1 case per 100,000 persons younger than 18 years).

Treatment and Prevention. Treatment of uncomplicated cases of influenza requires bed rest, adequate fluid intake, and aspirin (or acetaminophen in children) for fever and muscle pain. Two antiviral drugs, zanamivir (Relenza®) and, in the United States, oseltamivir (Tamiflu®), are available by prescription. These drugs interfere with the neuraminidase spikes, blocking the release of new virions. If given to otherwise healthy adults or children early in disease onset, these drugs may reduce the duration of illness by half a day. However, these drugs should not be taken in place of vaccination, which remains the best prevention strategy and is about 75% effective. Today, there are several different forms of the vaccine available for just about anyone, as **MicroFocus 20.4** illustrates.

CONCEPT AND REASONING CHECKS 3

Bacteria: © NIAID

a. Why have reported cases of pertussis been increasing in the United States and some other countries?

b. From MicroInquiry 20, why does the influenza A virus cause most human flu epidemics and pandemics?

Bacteria: © NIAID

MICROFOCUS 20.4: Public Health

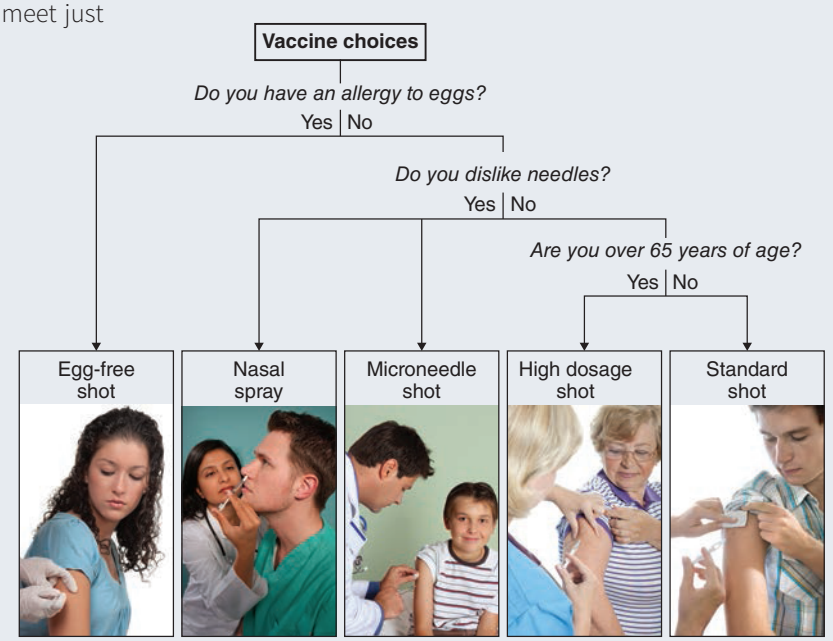
Which Flu Vaccine Is for Me?

Until recently, there were few options for getting vaccinated against the flu. You could get the standard shot in the arm, which is a vaccine containing two inactivated type A viruses and one type B virus. FluMist, an attenuated flu virus vaccine, was introduced as a nasal spray in 2003. Then, for the first time, in 2013 six different flu vaccines became available to meet just about anybody's need (see figure). These include:

- An **egg-free vaccine** (for people 18–49 years of age with egg allergies) is produced in caterpillar cells rather than chicken eggs.
- The **nasal spray** (FluMist®) **vaccine** (for healthy individuals 2–49 years of age).
- The **microneedle vaccine** delivers the standard vaccine via a microneedle syringe to produce a less painful jab in the arm.
- The **high dosage vaccine** (for people over 65 years of age) provides a 24% stronger immune response (more antibodies produced).
- The **standard vaccine** (for anyone 6 months and older).

The standard and the nasal spray vaccines also come in a quadrivalent form (two type A and two type B subtypes).

Hopefully, with the multiple types of vaccines, most Americans will get an annual vaccination. And it might not be long before there is a universal flu vaccine for protection against all strains of the flu viruses.



(A) © Brian Chase/ShutterStock, Inc.; (B) Courtesy of James Gathany/CDC; (C) © Leah-Anne Thompson/ShutterStock, Inc.; (D) © Alexander Raths/ShutterStock, Inc.; (E) © Alexander Raths/ShutterStock, Inc.

CHAPTER CHALLENGE B

You have read about a couple of diseases associated with the URT and LRT.

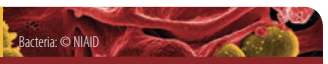
Question B:

Identify the correct pathogen from the following diseases signs and symptoms.

1. (Easy) A 30-year-old woman presents with sudden symptoms of chills, fever, dry cough, fatigue, and headache. Her son had an upper respiratory infection 5 days ago. Pathogen diagnosis?
2. (Moderate) A 14-year-old boy presents with a runny nose, nasal congestion, a mild fever, and a persistent, severe cough. Pathogen diagnosis?

Answers can be found in **Appendix F**.

KEY CONCEPT 20.4



Several Bacterial, Viral, and Fungal Pathogens Target the LRT

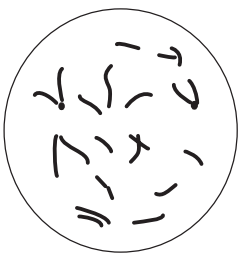
Drug-Resistant Tuberculosis Is a Significant Public Health Threat

The human population has had to deal with tuberculosis for thousands of years and the pathogen continues to evolve and resist most, if not all, antibiotics.

Causative Agent and Epidemiology. **Tuberculosis** (**TB**) is caused by *Mycobacterium tuberculosis*, the "tubercle" bacillus. It is a small, aerobic, nonmotile rod whose cell wall forms a waxy cell surface providing resistance to drying, chemical disinfectants, and many antibiotics.

Over the centuries, TB has continued to be a "slate wiper" in the human population. During the first half of the twentieth century, TB was called "consumption" or "white plague" because the disease wasted away the body and made the patient look pale. Although the CDC reported less than 10,000 cases in the United States in 2013 (half in California, Florida, New York, and Texas), globally the WHO estimated there were more than 9 million new active cases (FIGURE 20.13). Today, some 2 billion individuals, almost one-third of the world's population, are infected with the TB bacillus and 1.4 million die each year.

Clinical Presentation. Tuberculosis is primarily an airborne disease and, as such, the bacilli may be transmitted from person to person in small, aerosolized droplets when a person with active pulmonary disease sneezes, coughs, or even spits. The infectious dose is quite small, perhaps only one to three bacilli. However, individuals with prolonged, frequent, or intense contact with a diseased individual are most at risk of becoming infected, with an estimated 30% infection rate. Consequently, people who live in overcrowded, urban ghettoes often contract TB.



Mycobacterium tuberculosis

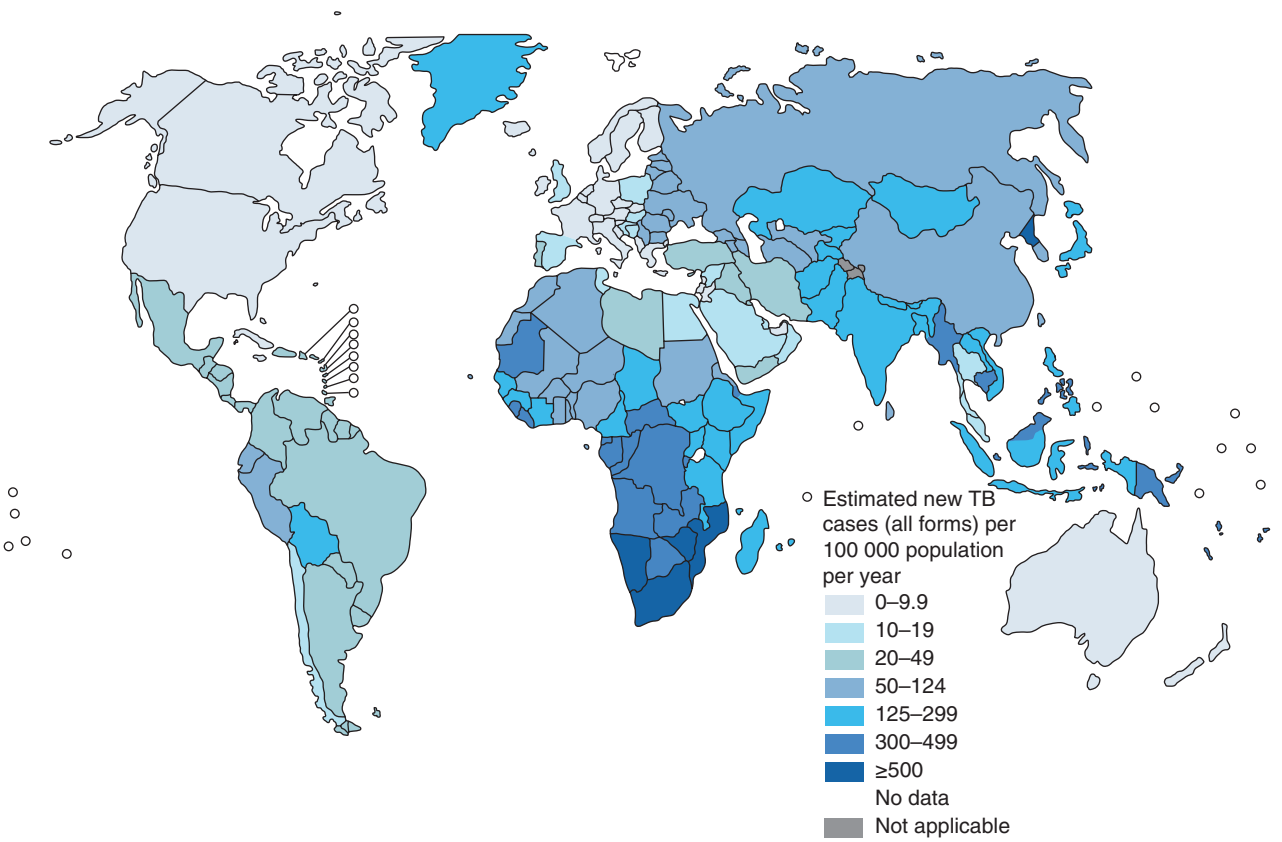


FIGURE 20.13 **Estimated Global Incidence of Tuberculosis, 2012.** The incidence of TB cases varies widely around the world.
» Where was the highest burden of new TB cases?

Reproduced from WHO Global Tuberculosis Report 2013 (p. 14) http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf.

Unlike many other infectious diseases where an individual becomes ill after several days or a week, the incubation period for TB is much longer (2–12 weeks). In addition, the illness has two separate stages: an infection stage and a disease stage (FIGURE 20.14). If a person has a pulmonary infection (85% of infections are respiratory), the bacterial cells enter the alveoli, where pathogen interactions occur (FIGURE 20.15). This individual is now said to have a **primary TB infection.** If tested, the person would have a positive tuberculin reaction, but a chest X ray often is negative and a sputum test would be negative (see Disease Detection, below).

In the alveoli, macrophages respond to the infection by ingesting the bacilli. Unfortunately, the bacilli often are not killed by the macrophages and as more macrophages arrive, they too phagocytize bacilli but are incapable of destroying them. An inflammatory condition ensues. After about four weeks, the cell-mediated immune response localizes the infection, forming a central area of large, multicellular giant cells. Recruited lymphocytes and fibroblasts surround the mass in the lung, forming a type of granuloma called a **tubercle** (hence the name tuberculosis). In 90% of primary TB infections, the infection becomes arrested and the individual is said to have a **latent TB infection** (see Figure 20.14) and is carried by 2 billion people worldwide. Of these, 90% will never develop active disease and will not be infectious.

Up to 10% of individuals who have a primary or latent TB infection will develop a clinical disease. Primary TB infections can develop into **primary active TB disease** in one to two years. The disease usually becomes extrapulmonary and is disseminated through the body. Also, due to immune system dysfunction, a latent TB

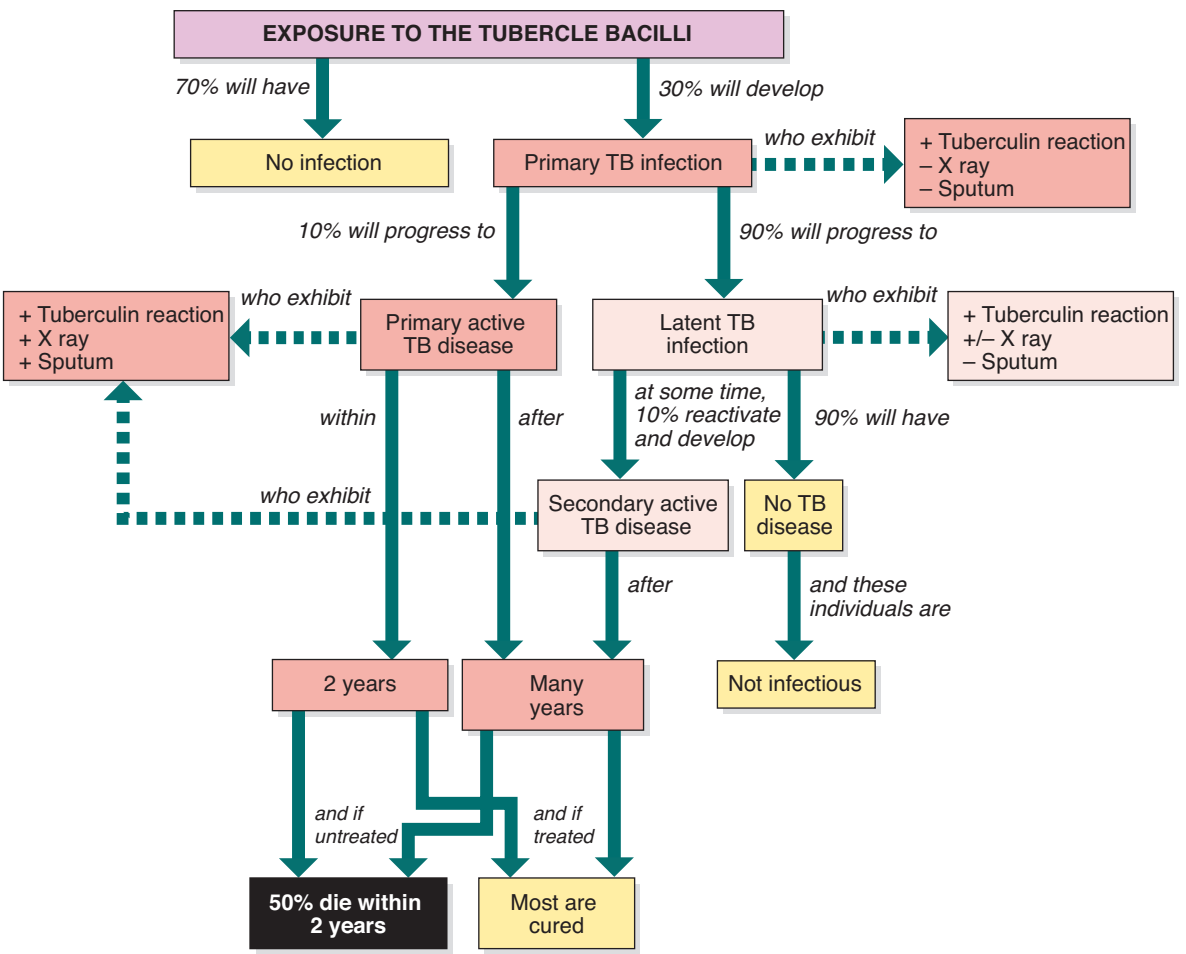


FIGURE 20.14 A Concept Map for Tuberculosis. The stages of tuberculosis infection and disease are shown. ("+" or "-" represents positive or negative test results.) **How does TB infection differ from active TB disease?**

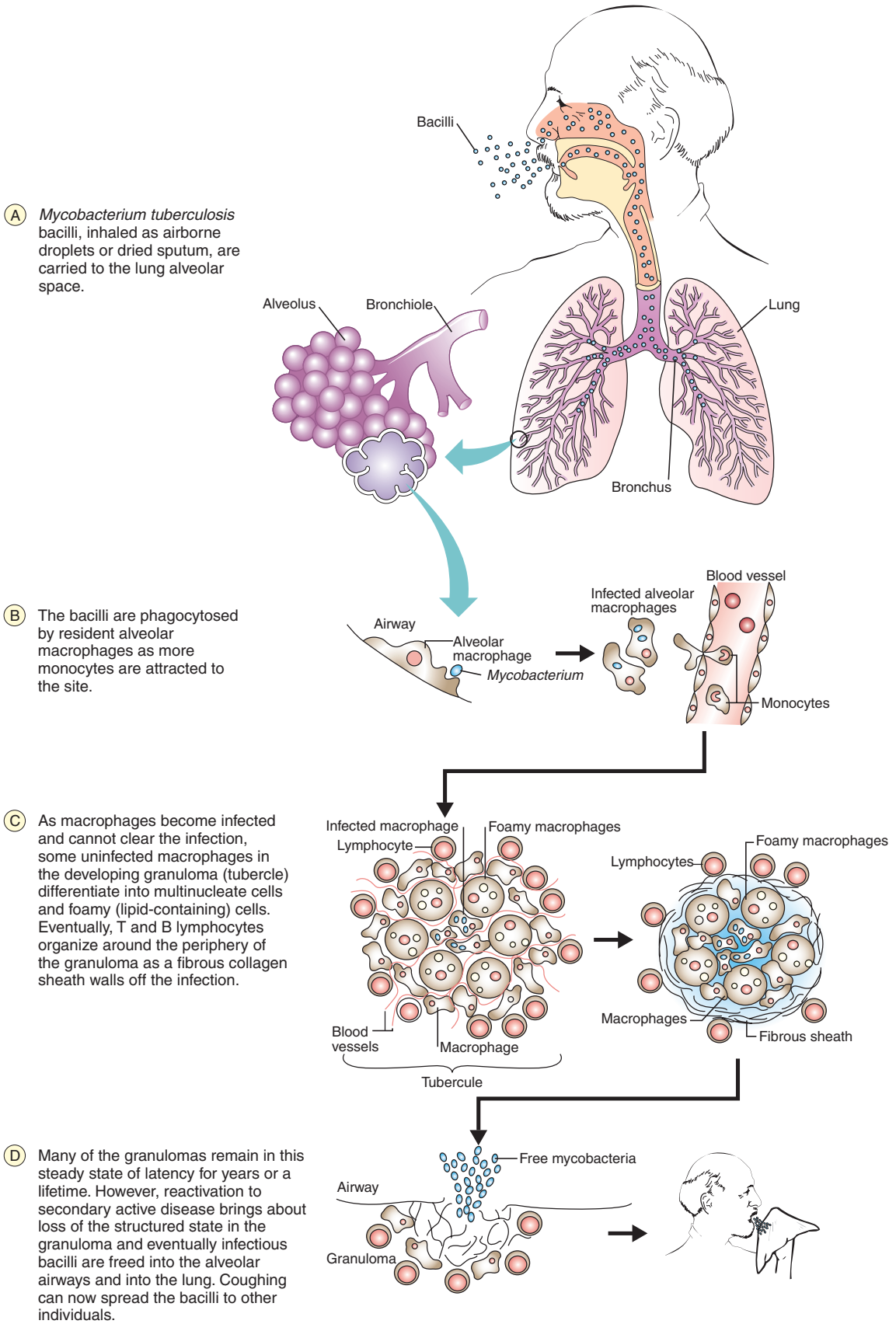
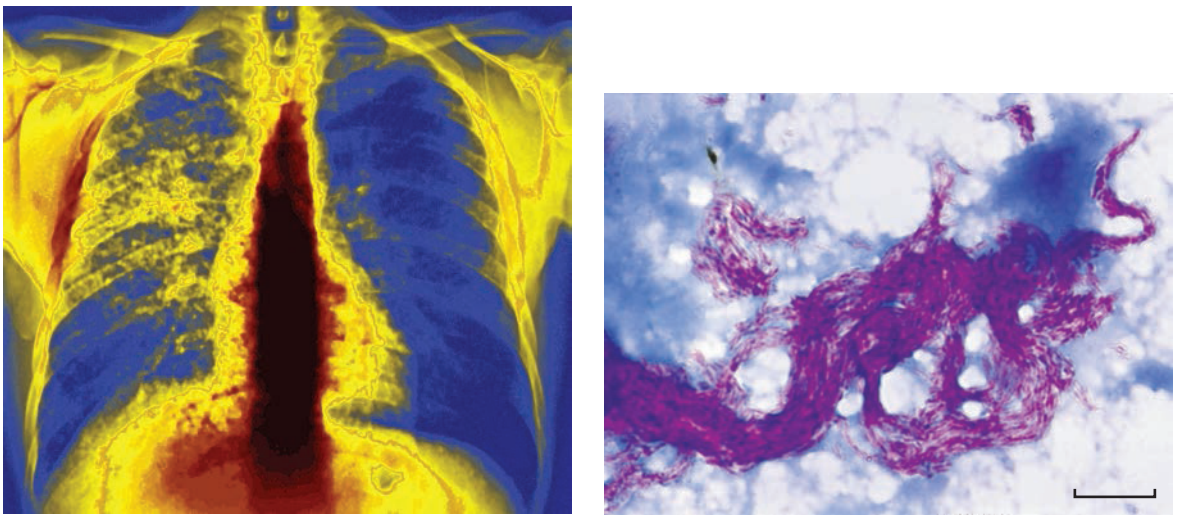


FIGURE 20.15 **The Progress of Tuberculosis.** Following invasion of the alveoli, the tubercle bacilli are taken up by macrophages and the cell-mediated immune system attempts to "wall off" the bacilli. **What is the immune system attempting to do by forming tubercles?**



(A) (B)

FIGURE 20.16 Pulmonary Tuberculosis. (A) This false color X ray shows the extensive fibrosis (fuzzy yellow color in the lung cavity) typical in patients with advanced, active tuberculosis. **(B)** This light microscope image shows *M. tuberculosis* cells stained with the acid-fast procedure. In sputum samples, the bacterial cells often exhibit growth in thick strings. (Bar = 10 μm.) **Why isn't the Gram stain used to identify *M. tuberculosis*?**

infection can undergo reactivation developing into **secondary active TB disease**. Individuals will become ill within three months; experience chronic cough, chest pain, and high fever; and continue to expel sputum, which is rust colored, indicating blood has entered the lung cavity.

In active TB disease, the immune defenses cannot keep the tubercle bacilli in check. These individuals will now have a positive tuberculin reaction, chest X ray, and sputum test, and they can transmit the disease to others (FIGURE 20.16).

Because the bacilli in individuals with primary active TB disease are not killed, tubercle erosion can allow the bacterial cells to spread through the blood and lymph to other organs such as the liver, kidney, meninges, and bone. If active tubercles develop throughout the body, the disease is called **miliary (disseminated) tuberculosis** (*milium* = "seed"; in reference to the tiny lesions resembling the millet seeds in bird food). Tubercle bacilli produce no known toxins, but growth is so unrelenting and the immune reaction so damaging that the respiratory and other body tissues are literally consumed, a factor that gave tuberculosis its alternate name of "consumption."

Meninges: The membranes surrounding and protecting the brain and spinal cord.

Disease Detection. Early detection of tuberculosis is aided by the tuberculin reaction, a delayed hypersensitivity test involving the application of a purified protein derivative (PPD) of *M. tuberculosis* to the skin. One method of application, called the **Mantoux test**, uses an injection of PPD intradermally into the forearm. Depending on the patient's risk of exposure, the skin becomes thick, and a raised, red welt, termed an **induration**, of a defined diameter develops (FIGURE 20.17). In 2010, a TB test system was introduced that could

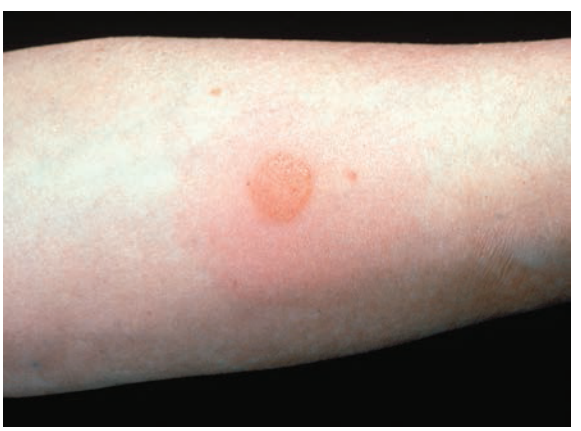


FIGURE 20.17 Tuberculin Skin Test for Tuberculosis. This is an example of a positive reaction to the Mantoux skin test. An induration of less than 15 mm is considered negative. **What basic immunological process is responsible for the red and thickened swelling typical of an induration?**

identify a TB infection in less than two hours versus the two to three months required to verify a positive sputum test. Because this test is expensive and requires specialized equipment, in 2014 a cheap TB test was introduced that can detect TB bacilli in less than 30 minutes. It is almost 75% accurate.

Treatment. Standard TB can be treated with such first-line antibiotics as isoniazid and rifampin. However, there is now a growing epidemic of TB strains that are resistant to these antibiotics. Globally, in 2014, there were an estimated 450,000 cases and 170,000 deaths due to **multidrug-resistant tuberculosis** (**MDR-TB**). This has necessitated a switch to a group of second-line drugs, including fluoroquinolones and kanamycin. Because the organism multiplies at a very slow rate (its generation time is about 18 hours), MDR-TB individuals must undergo intensive antimicrobial drug therapy, involving daily injections and swallowing of more than 10,000 drug pills over a two-year period. The treatments can be very toxic and make patients quite ill.

If that wasn't bad enough, there is now an increasing incidence of **extensively drug-resistant tuberculosis** (**XDR-TB**). In 2013, almost 10% of MDR-TB cases were actually XDR-TB. This form of TB is resistant to almost all drugs used to treat the disease and few treatment options remain for these individuals. Although MDR-TB and XDR-TB make up a very small fraction of the total drug-resistant forms of TB, they consume up to 35% of the funds available for TB treatment.

In 2014, the FDA approved the first drug in a new class of anti-TB medications in 40 years. Called bedaquiline, it can be used for up to 24 weeks in combination with other antibiotics to which the TB bacillus is susceptible.

Patients in developing nations who have a weakened immune system due to AIDS are especially vulnerable to TB. In 2012, 13% of the people who contracted TB were HIV-positive and accounted for 320,000 of the HIV deaths. In these co-infected patients, the T lymphocytes that normally mount a response to *M. tuberculosis* are being destroyed by HIV, and the patient cannot respond to the bacterial infection. Unlike most other TB patients, those with HIV usually develop miliary tuberculosis in the lymph nodes, bones, liver, and numerous other organs.

Prevention. Vaccination against TB may be rendered by intradermal injections of an attenuated strain of *Mycobacterium bovis,* a species causing tuberculosis in cows as well as humans. The attenuated strain is called **Bacille Calmette-Guérin** (**BCG**) and is used in parts of the world where the disease causes significant mortality and morbidity. It is not recommended in the United States because it was thought to have limited effectiveness for preventing TB in adults. In fact, recent studies suggest the BCG vaccine administered in childhood may be more effective in adults than previously thought. More than a dozen new antimicrobial compounds, consisting of subunits, molecules of DNA, and attenuated strains of mycobacteria, are currently being tested and developed as new vaccine candidates.

Other Mycobacterium Species. Several other species of *Mycobacterium* deserve a brief mention. Another pathogenic species, *M. chelonae*, is frequently found in soil and water. Infection can cause lung diseases, wound infections, arthritis, and skin abscesses. *M. haemophilum* is often found in immunocompromised individuals, including those with AIDS. Cutaneous ulcerating lesions and respiratory symptoms are typical in these patients. Found in the central United States, *M. kansasii* causes infections indistinguishable from *M. tuberculosis*. Finally, a group known as *M. avium* complex (MAC) tends to cause a disseminated disease in immunocompromised individuals. In the United States, MAC represents an opportunistic infection responsible for most cases of miliary TB in AIDS patients. For all these species mentioned, there is no evidence for spread between individuals; rather, infection comes from contacting soil, or ingesting food or water contaminated with the organism.

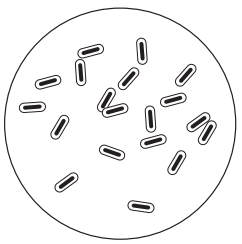
Inhalational Anthrax Is an Occupational Hazard

Anthrax is caused by *Bacillus anthracis,* a spore-forming, aerobic, gram-positive rod. The disease is primarily associated with large,

Bacillus anthracis

domestic herbivores, such as cattle, sheep, and goats. Thus, humans acquire **inhalational anthrax** from contaminated animal products or dust. For example, workers who tan hides, shear sheep, or process wool may inhale the spores and contract a pulmonary infection also called **Woolsorters' disease**. It initially resembles a common cold (fever, chills, cough, chest pain, headache, and malaise). After several days, the symptoms may progress to severe breathing problems and shock. Inhalation anthrax is usually fatal without early antibiotic treatment.

Anthrax also is considered a biological weapon for bioterrorism and biological warfare. The seriousness of using biological agents as a means for bioterrorism was underscored in October 2001 when *B. anthracis* spores were distributed intentionally as a powder through the United States mail. In all, 22 cases of anthrax (11 inhalation and 11 cutaneous) were identified. In the end, five individuals with inhalational anthrax died, while the six other individuals with inhalation anthrax and all the individuals with cutaneous anthrax recovered.



Klebsiella pneumoniae

Pneumonia Can Be Caused by Several Bacterial Pathogens

The term **pneumonia** refers to microbial disease of the bronchial tubes in the lungs. There are some 2 to 3 million cases annually in the United Sates, resulting in 45,000 deaths. **Acute pneumonia** develops over a 24 to 48 hour period, while **chronic pneumonia** progresses over several weeks. A variety of bacterial species may cause pneumonia. For discussion purposes, we can divide bacterial pneumonia into healthcare-acquired and community-acquired infections.

Healthcare-Acquired Pneumonia. The second most common healthcare-acquired infection after urinary tract infections is pneumonia. **Healthcare-acquired pneumonia** (**HCAP**) is defined as an inflammation of one or both lungs that develops at least 48 hours after admission to a hospital or other healthcare facility for another health reason. In the United States, 86% of HCAPs are associated with mechanical ventilation (endotracheal intubation) to assist patient breathing. Several bacterial species are responsible for most cases of HCAP and these species are showing increased antibiotic resistance.

- **Staphylococcal pneumonia.** The most common gram-positive cause of HCAP results from an infection by *Staphylococcus aureus*. The pathogen is most often spread to others by contaminated hands and infants, young children, and immunocompromised patients who have invasive medical devices are particularly vulnerable to infection. Symptoms of **staphylococcal pneumonia** include a short period of fever followed by rapid onset of respiratory distress, which may include rapid breathing and bluish skin. With increased antibiotic resistance, infections can be difficult to treat and can progress to life-threatening infections because there are fewer effective antibiotics available.
- ***Klebsiella* pneumonia.** *Klebsiella pneumoniae* is a gram-negative rod with a prominent capsule. The pathogen, which is responsible for up to 15% of gram-negative infections in hospitals, is acquired by respiratory droplets as often it occurs naturally in the nasopharynx. ***Klebsiella* pneumonia** may be a primary infection or a secondary infection in alcoholics or people with impaired pulmonary function. As a primary pneumonia, it is characterized by sudden onset and gelatinous reddish-brown sputum. The bacterial cells grow over the lung surface and rapidly destroy the tissue, often causing death of the individual. In its secondary form, *K. pneumoniae* occurs in already ill individuals and is a hospital-acquired disease spread by such routes as clothing, intravenous solutions, foods, and the hands of healthcare workers. In addition, scientists have reported the discovery of multidrug-resistant *K. pneumoniae* strains resistant to most all available antibiotics. MicroFocus 20.5 relates a recent, frightening outbreak of this secondary form in one of the nation's leading research hospitals.
- ***Pseudomonas* pneumonia**. *Pseudomonas aeruginosa,* a gram-negative, aerobic rod, is one of the most dangerous opportunistic pathogens because of its ability to cause severe or fatal nosocomial infections, especially in

MICROFOCUS 20.5: Public Health

"*We Never Want This to Happen Again*"

NIH Clinical Center.

The 243-bed National Institutes of Health (NIH) Clinical Center, the nation's leading research hospital in the suburbs of Washington, DC, is a unique hospital, only treating people enrolled in government research studies. On June 13, 2011, a 43-year-old study participant critically ill with a rare pulmonary disease was admitted with a medical record of having multidrug-resistant *Klebsiella pneumoniae*, termed KPC. The woman was put in strict isolation, all staff entering her room donned a protective gown and gloves and rigorously washed their hands, and all medical equipment was thoroughly decontaminated. All other patients in the ICU were tested regularly to make sure KPC was not spreading. All seemed fine.

On July 15, the woman (patient 1) had recovered and was sent home. But on August 5, a man with cancer, who never had contact with patient 1, was identified as having KPC. Then, on August 15, a woman with a primary immune deficiency fell ill to KPC. Patients 2 and 3 died. From then on, almost a patient a week was getting infected with KPC. The hospital locked down patients, disinfected everything with bleach, ripped out potentially-contaminated plumbing, and still patients contracted KPC. Over six worrisome months, KPC spread. By the end of the outbreak in mid-December, 19 people had been infected, and seven died of bloodstream infections from KPC.

Where was the KPC coming from and how was it traveling about the hospital? Epidemiologists were called into action to solve the mystery. It would require sequencing the bacterium's genome in trying to solve the CSI-like investigation.

By comparing DNA sequences from all KPC patients, the isolate from the first patient matched the isolates taken from the other patients, making it highly likely the first patient (index case) was the origin of the KPC outbreak. In fact, fine differences in sequences suggested the KPC cells came from three sites on her body (lungs, groin, and throat) and so there were at least three separate transmission events. Undoubtedly, some form of intrahospital transmission had occurred, but the specific form(s) and/or vehicle(s) remain a mystery.

But where was the *K. pneumoniae* hiding out after the index patient was released from the hospital? Genetic sleuthing provided a few clues. *K. pneumoniae* stayed alive in sink drains and even on a ventilator that had been thoroughly cleaned with bleach, providing a few potential modes of transmission for the pathogen.

Since then, the NIH Clinical Center has made changes: all ICU patients undergo extensive invasive testing, using rectal swabs to identify any "silent" pathogens; a wall now partitions off the ICU; all ICU staff, including janitors, work nowhere else in the hospital; and monitors are paid to ensure everyone follows the rules. As Dr. Tara Palmore, deputy hospital epidemiologist at the NIH Clinical Center, said, "*We never want this to happen again*."

immunocompromised patients. ***Pseudomonas* pneumonia** is the second most common cause of HCAP, accounting for more than 10% of all cases. In addition, it is often resistant to commonly used antibiotics. The *P. aeruginosa* cells can be transmitted via aspiration from contaminated ventilator tubing or other healthcare devices, such as bronchoscopes, mechanical ventilators, and nebulizer equipment. Symptoms in immunocompromised patients include breathing problems, productive cough, fever, chills, and bluish skin. The treatment of this condition may include a combination of antibiotics.

■ ***Acinetobacter* pneumonia.** *Acinetobacter* species are gram-negative, aerobic rods that frequently colonize the respiratory tract. Called the *Acinetobacter calcoaceticus-A. baumannii* complex (Abc), it accounts for up to 80% of clinical infections and is becoming a major cause of HCAP in intensive care units. ***Acinetobacter* pneumonia** occurs in outbreaks and, like *P. aeruginosa*, is usually associated with contaminated respiratory-support equipment or fluids. The Abc is becoming increasingly resistant to antibiotics, presenting a significant challenge in treating these infections.

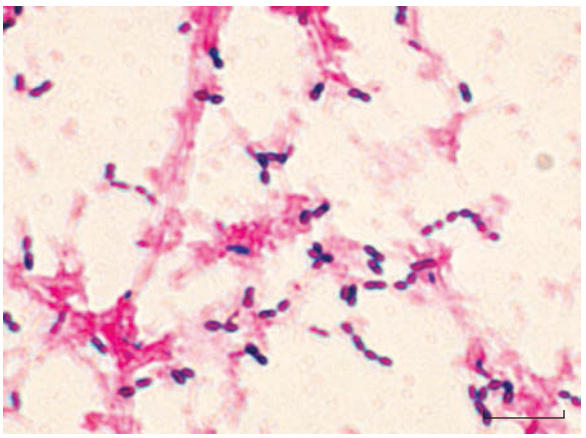
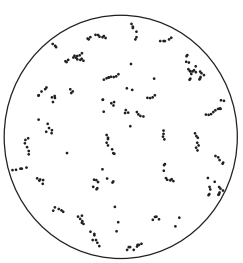


FIGURE 20.18 ***Streptococcus pneumoniae.*** False-color transmission electron micrograph of *S. pneumoniae* (dark rods), the cause of pneumococcal pneumonia. (Bar = 10 µm.) **How would you describe the arrangement of *S. pneumoniae* cells?**

Courtesy of Dr. Mike Miller/CDC

Insidious: Refers to a disease that progresses gradually and without obvious symptoms.



Mycoplasma pneumoniae

Community-Acquired Pneumonia. In the United States, between 350,000 and 620,000 cases of **community-acquired pneumonia** (**CAP**) occur each year in the elderly.

■ **Pneumococcal pneumonia**. The leading cause of CAP is *Streptococcus pneumoniae*, a gram-positive, encapsulated chain of diplococci (FIGURE 20.18). **Pneumococcal pneumonia**, being community acquired, exists in all age groups, although the mortality rate is highest among the elderly, those with underlying medical conditions, and young children, the latter accounting for 500,000 deaths primarily in low- and middle-income nations worldwide.

S. pneumoniae is usually acquired by aerosolized droplets or aspiration of oral microbiota in many individuals. Because mucociliary clearance is at work and the natural resistance of the body is high, pneumococcal pneumonia usually does not develop until the defenses are compromised. Malnutrition, smoking, viral infections, and treatment with immune-suppressing drugs most often **predispose** one to *S. pneumoniae* infections.

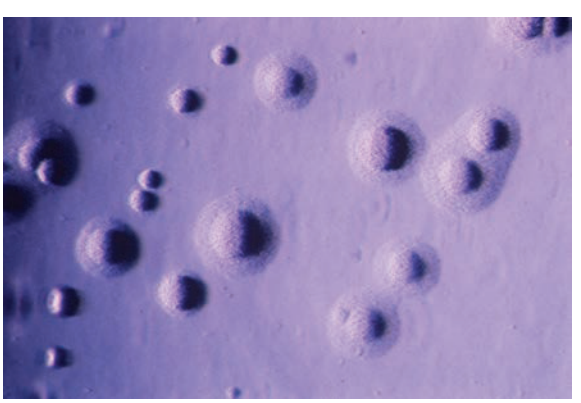
Predispose: To make an individual susceptible to a condition.

Patients with pneumococcal pneumonia experience high fever, sharp chest pains, difficulty breathing, and rust-colored sputum. The color results from blood seeping into the alveolar sacs of the lung as bacterial cells multiply and cause the tissues to deteriorate. The involvement of an entire lobe of the lung is called **lobar pneumonia**. If both left and right lungs are involved, the condition is called **double pneumonia**. Scattered patches of infection in the respiratory passageways are referred to as **bronchopneumonia**.

With appropriate antibiotic therapy, recovery is likely. Unfortunately, recovery from one serotype does not confer immunity to another serotype (over 90 capsular serotypes are known). A pneumococcal conjugate vaccine is recommended for all children younger than 5 years old. For adults, a polyvalent polysaccharide vaccine effective against the 23 serotypes responsible for almost 90% of pneumococcal pneumonia cases is recommended.

A more **insidious** form of CAP is not caused by the typical pathogens described above.

■ **Primary atypical pneumonia. Primary atypical pneumonia** occurs in previously healthy individuals and is caused by *Mycoplasma pneumoniae*, the cells of which are among the smallest, lack a cell wall, and form distinctive "fried-egg" colonies on agar (FIGURE 20.19). This community-acquired disease causes about 20% of pneumonias.



(B)

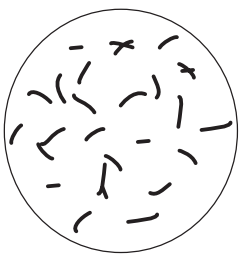
FIGURE 20.19 ***Mycoplasma pneumoniae.*** Colony morphology on agar shows the typical "fried egg" appearance. **What structural feature is missing from the mycoplasma cells that allows for the pleomorphic shape of the individual cells?**

© Michael Gabridge/Visuals Unlimited

Most *M. pneumoniae* patients, who are usually between 6 and 20 years old, first experience symptoms of headache, fever, fatigue, and a characteristic dry, hacking cough with a sore throat. About 30% of infections then progress to pneumonia. Often it is called **walking pneumonia** (even though the term has no clinical significance) and the disease is rarely fatal. However, epidemics are common where crowded conditions exist, such as, military bases, urban ghettoes, and college dormitories. In the fall of 2012, the largest *Mycoplasma* pneumonia outbreak at a university in 35 years occurred at Georgia Institute of Technology, where 83 students were infected. Erythromycin and tetracycline are commonly used as treatments.

■ **Legionnaries' disease.** Another form of CAP first surfaced in July 1976, after an American Legion convention in Philadelphia. What would become known as **Legionnaries' disease** affected 140 conventioneers and 72 other people who became ill with headaches, fever, coughing with bloody mucus, chest pain, and shortness of breath. Thirty-four individuals died of the disease or its complications. The causative agent, *Legionella pneumophila,* is an aerobic, gram-negative rod found where water collects, such as cooling towers, industrial air-conditioning systems, and stagnant pools (FIGURE 20.20). After breathing the contaminated aerosolized droplets into the respiratory tract, the bacterial cells infect alveolar macrophages where they survive and continue to reproduce. Older adults and individuals with weak immune systems are most susceptible to infection. Erythromycin is effective for treatment, and prevention requires that water sources be kept chlorinated. Another milder infection called **Pontiac fever** causes an influenza-like illness lasting 2 to 5 days but does not cause pneumonia. The term "legionellosis" encompasses both Legionnaires' disease and Pontiac fever.

Community-Acquired Pneumonia Is Also Caused by Intracellular Parasites

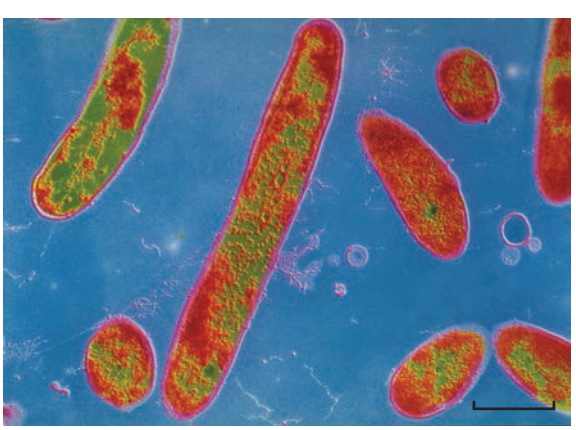


Legionella pneumophila

Pneumonia also can be caused by some of the smallest bacterial organisms, the chlamydiae. Most are obligate, intracellular parasites, meaning they only grow inside host cells.

Q fever. Q fever (the "Q" is derived from "query," originally referring to the unknown cause of the disease) is caused by *Coxiella burnetii,* which does not have to exist as a strict intracellular pathogen (FIGURE 20.21). This form of CAP represents a **zoonotic** disease, where the organisms are transmitted to humans

Zoonotic: Refers to a disease transmitted from animals to humans.



(A)

FIGURE 20.20 ***Legionella pneumophila.*** A false-color transmission electron micrograph of *L. pneumophila* cells. (Bar = 1 μm.) **What do the false-colored red and green areas in the cells represent?**

© Phototake/Alamy

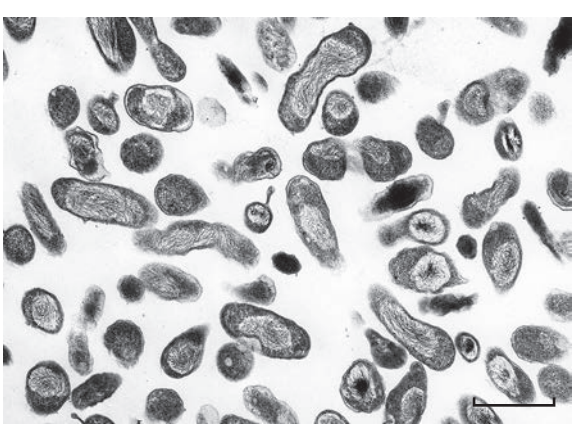


FIGURE 20.21 ***Coxiella burnetii.*** An electron micrograph of *C. burnetii,* the agent of Q fever. Note the oval-shaped rods of the organism. (Bar = 1 μm.) **What does it mean to say *C. burnetii* is an obligate, intracellular pathogen?**

Courtesy of Rocky Mountain Laboratories, NIAID, NIH.

from livestock, especially dairy cows, sheep, and goats. Therefore, human outbreaks may occur even some distance from where infected animals are raised, housed, or transported. In 2009, almost 4,000 cases of Q fever, including six deaths, were reported in the Netherlands, where intense goat farming occurs. In addition, humans may acquire the disease by consuming raw or improperly pasteurized milk or cheese infected with *C. burnetii*. Although most cases are asymptomatic, some patients experience a bronchopneumonia characterized by severe headache, high fever, dry cough, and occasionally, lesions on the lung surface. The mortality rate is low, but antibiotic treatment should not be delayed.

Psittacosis. Another zoonotic disease, **psittacosis**, is caused by *Chlamydophila* (formerly *Chlamydia*) *psittaci*. This obligate, intracellular pathogen is transmitted to humans by infected parrots, parakeets, canaries, and other members of the psittacine family of birds (*psittakos* = "parrot"). The disease also occurs in pigeons, chickens, turkeys, and seagulls, and some microbiologists prefer to call it **ornithosis** (*ornith* = "bird") to reflect the more widespread occurrence in bird species. Humans acquire *C. psittaci* by inhaling airborne dust or dried droppings from contaminated bird feces. Sometimes the disease is transmitted by a bite from a bird or via the respiratory droplets from another human. The symptoms of psittacosis include fever, headache, dry cough, and scattered patches of lung infection. Antibiotics are commonly used in therapy.

Chlamydial pneumonia. A mild form of CAP is caused by *Chlamydophila pneumoniae*, which is transmitted human-to-human by respiratory droplets, principally in young adults and college students. The disease is clinically similar to primary atypical pneumonia and is characterized by a sore throat, headache, and nonproductive cough. Treatment with antibiotics hastens recovery from the infection.

CONCEPT AND REASONING CHECKS 4

Bacteria: ©NIAID

a. Explain how a primary or latent tuberculosis infection is different from primary or secondary tuberculosis disease.
b. What cellular factor makes *B. anthracis* a dangerous pathogen and bioterror agent?
c. What are the common characteristics to all forms of HCAP?
d. Hypothesize why some pneumonia-causing species are community acquired and others are hospital acquired?
e. Summarize (1) the unique characteristics and (2) the mode of transmission of the intracellular pathogens causing CAP.

CHAPTER CHALLENGE C

In this section we have examined several forms of pneumonia.

Question C:
Diagnose the form of pneumonia from the following signs and symptoms.

1. (Medium) A 45-year-old man presents with high fever, severe headache, and a dry cough. He reports that he works with livestock and does animal research. Pneumonia form diagnosis?
2. (Hard) A 75-year-old man presents with headache, fever, cough with bloody mucus, and chest pain. The patient also reports he has had a shortness of breath since returning from an ocean cruise. Pneumonia form diagnosis?
3. (Medium) A 65-year-old female presents with breathing difficulties, sharp chest pain, rust-colored sputum, and a fever. Microscopy identifies gram-positive diplococci in the sputum. Pneumonia form diagnosis?

Answers can be found in **Appendix F**.

Some Viruses Also Cause CAP

Viruses, other than the influenza, can cause CAP, some being life threatening.

Respiratory syncytial disease. The respiratory syncytial virus (RSV), a member of the Paramyxoviridae family, causes **respiratory syncytial (RS) disease**. RS disease is the most common lower respiratory tract illness affecting infants and children. Some virologists believe that up to 95% of all children have been infected by 2 years of age, and CDC epidemiologists estimate that RSV causes 51,000 to 82,000 hospitalizations and 4,500 deaths in infants and children each year in the United States. On a global scale, there are some 34 million RSV infections and 200,000 deaths each year.

Community outbreaks of RSV are spread by respiratory droplets or virus-contaminated hands. When the virus infects ciliated epithelial cells of the airways, it causes the epithelial cells to fuse together, forming giant multinucleate cells called **syncytia**, and the disease is often described as **viral pneumonia**. Although most children and adults develop mild cold-like signs and symptoms, infants with severe cases may develop a high fever, severe cough, rapid, short breathing, and a bluish color of the skin.

Human metapneumovirus pneumonia. An RSV-like illness is caused by the human metapneumovirus (hMPV), another member of the Paramyxoviridae. Just about every child in the world has been infected by age 10 and hMPV is responsible for up to 15% of CAP. The disease also can occur in adults, as evidenced by two outbreaks of hMPV in skilled nursing facilities in West Virginia and Idaho in 2011–2012. Among the 57 cases, 6 patients died.

Parainfluenza infection. Infection by human parainfluenza viruses 1 and 3, also highly contagious members of the Paramyxoviridae, accounts for 40% of acute pneumonia in children. Although as widespread as influenza, parainfluenza is a much milder disease and is transmitted by direct contact or via aerosolized droplets. It is characterized by minor upper respiratory illness, often referred to as a cold. However, pneumonia and **bronchiolitis** may accompany the disease, which is most often seen in children under the age of six. No approved vaccines exist for these three Paramyxoviridae-caused diseases, so hand washing, along with disinfection of surfaces, are the best transmission prevention methods.

Bronchiolitis: An inflammation of the bronchioles.

Severe Acute Respiratory Syndrome. In the spring of 2003, an infectious disease quickly spread through Southeast Asia and to Canada, as reported in Clinical Case 20. During the epidemic, the WHO identified 8,100 cases from 29 countries with the majority of the 774 deaths being in China, Taiwan, Vietnam, Singapore, and Canada. The disease, which became known as **severe acute respiratory syndrome (SARS)**, is caused by the SARS coronavirus (SARS-CoV), a single-stranded (+ strand) RNA virus with helical symmetry and a spiked envelope (FIGURE 20.22).

SARS is spread through close person-to-person contact by touching one's eyes, nose, or mouth after contact with SARS-CoV. Spreading also comes from contact with objects contaminated through coughing or sneezing

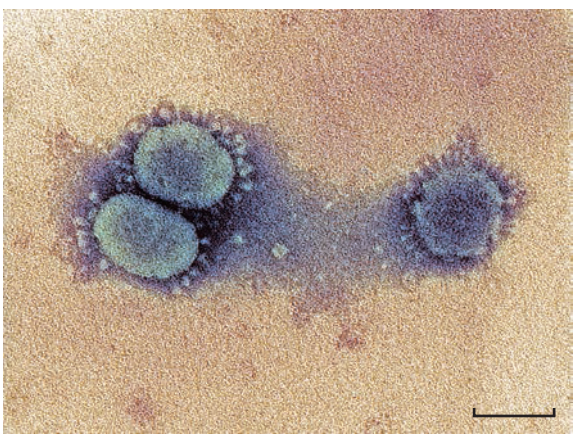
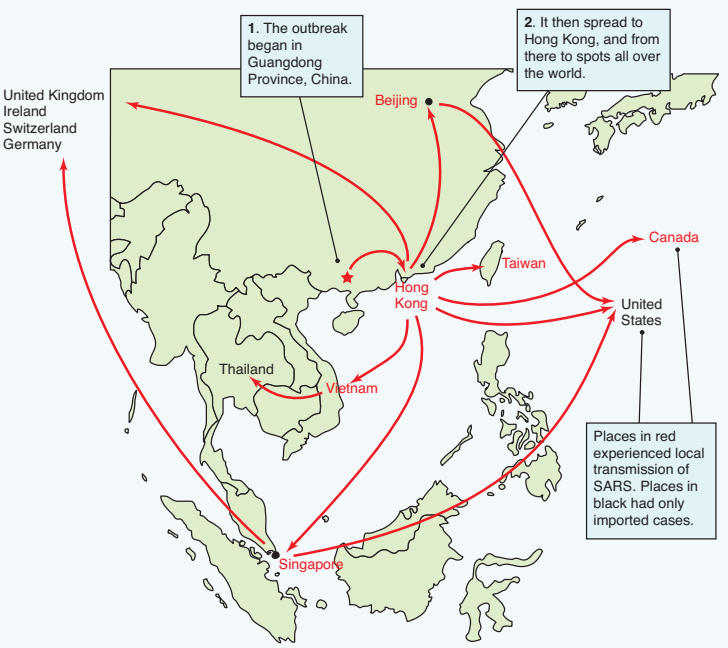


FIGURE 20.22 **Coronaviruses.** False-color transmission electron micrograph of three human coronaviruses. The spikes can be seen clearly extending from the viral envelope. Viruses similar to these are responsible for severe acute respiratory syndrome (SARS). (Bar = 100 nm.) **» By looking at the micrograph, explain why the virus is referred to as a "corona" virus.**

CLINICAL CASE 20

The Outbreak of SARS: 2002–2003

1. On February 11, 2003, the Chinese Ministry of Health notified the World Health Organization (WHO) of a mystery respiratory illness that had been occurring since November 2002 in Guangdong province in southern China. However, officials of China refused to allow WHO officials to investigate.
2. February 21, a 64-year-old doctor from Guangdong came to Hong Kong to attend a wedding. He stayed at a Hong Kong hotel, infecting 16 people, who spread the disease to Hanoi, Vietnam; Singapore, and Toronto, Canada (see figure).
3. February 23, a Canadian woman tourist checked out of the same Hong Kong hotel and returned to Toronto, where her family greeted her. She died 10 days later as five family members were hospitalized.
4. February 28, a WHO doctor in Hanoi, Carlo Urbani, treated one of the people infected in Hong Kong and realized this was a new disease, which he named "severe acute respiratory syndrome" (SARS). He died of the disease 29 days later.
5. March 15, the WHO declared SARS a worldwide health threat. To block the chain of transmission, isolation and quarantine were instituted. Over half of those infected were healthcare workers.
6. April 16, the identification was made by 13 laboratories around the world that a new, previously unknown, coronavirus caused SARS.
7. June 30, the WHO announced there had been no new cases of SARS for two weeks. During the 114-day epidemic, more than 8,000 people from 29 countries were infected and 774 died.



Spread of SARS.

Questions

(Answers can be found in **Appendix E**.)

A. Why might Chinese officials be reluctant to allow a WHO investigation into the mystery illness?

B. Justify the use of quarantine and isolation to break the chain of SARS transmission.

C. Propose an explanation as to why there was such a disproportionately high number of infections in healthcare workers.

D. How could such a large number of infections in healthcare workers have been prevented?

E. Why is SARS a textbook case for an emerging infectious disease?

For additional information see http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5226a4.htm.

with infectious droplets by a SARS-infected individual. Bats are the primary reservoir of SARS-CoV.

Many people remain asymptomatic after infection. However, in individuals developing SARS, a dry cough occurs and patients have trouble breathing. In those patients progressing to a severe respiratory illness, pneumonia develops with insufficient oxygen reaching the blood. In 10% to 20% of cases, patients require mechanical ventilation. Because this is a newly emerging disease, treatment options remain unclear.

In 2012, a dangerous disease similar to SARS was reported in Saudi Arabia. Called the **Middle East respiratory syndrome** (**MERS**), by September 2014 the disease had infected more than 855 individuals and killed at least 330 (mostly in Saudi Arabia). There have been three reported cases in the United States involving individuals who had worked and lived in Saudi Arabia. Most of the fatalities have been in patients with other medical conditions. The infection by MERS-CoV produces symptoms similar to SARS but progression to respiratory failure is much faster with MERS. Transmission may be person-to-person, and camels and/or bats may be the reservoir.

Hantavirus Pulmonary Syndrome. In the spring of 1993, a cluster of sudden and unexplained deaths in previously healthy young adults occurred in the Four Corners region of the American Southwest. The CDC identified a hantavirus, now called Sin Nombre virus (SNV), as the infectious agent and termed the outbreak **hantavirus pulmonary syndrome** (**HPS**). Since 1993, there have been more than 2,000 cases throughout the Americas (600 in the United States) and about 35% of reported cases have resulted in death. In 2012, an outbreak in tent cabins at Yosemite National Park in California may have exposed 1,700 to the disease. It did sicken at least six people and took the lives of three.

The hantaviruses are enveloped, single-stranded, (–strand) RNA viruses in the Bunyaviridae family (FIGURE 20.23). The deer mouse is the reservoir and it sheds the virus in saliva, urine, and feces. Humans usually are infected by breathing the infectious aerosolized dried urine or feces. Several weeks after exposure, early symptoms of infection include fatigue, headache, fever, and muscle aches. About half of all HPS patients experience dizziness, difficulty breathing, and low blood pressure, which can lead to respiratory failure as the lungs fill with fluid. Prevention consists of eliminating rodent nests and minimizing contact with them. There is no vaccine available.

TABLE 20.3 summarizes the bacterial and viral forms of pneumonia affecting the LRT.

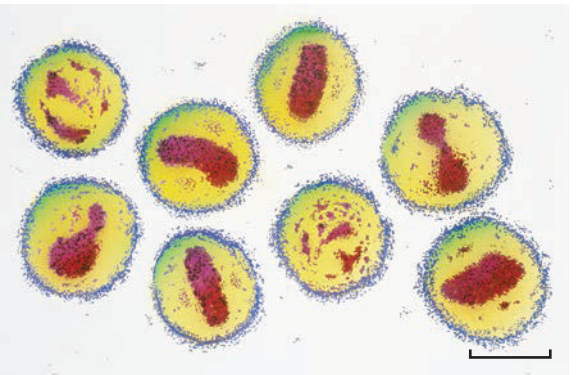


FIGURE 20.23 The Hantavirus. False-color transmission electron micrograph of hantaviruses. (Bar = 90 nm.) **What do the red geometric shapes represent in the hantaviruses?**

CONCEPT AND REASONING CHECKS 5

Bacteria: © NIAID

a. Identify the common relationships between paramyxoviruses causing CAP.

b. How do the SARS coronavirus and the hantavirus differ in their spread between individuals?

CHAPTER CHALLENGE C

In this section, we identified several forms of pneumonia caused by viruses.

Question C:

Diagnose the virus from the following signs and symptoms.

1. (Medium) An 8-month-old infant presents with high fever, cough, shallow breathing, and a bluish color on the lips. Virus diagnosis?
2. (Medium) A 25-year-old man presents with headache, fever, muscle aches. He reports he has had difficulty breathing and has been dizzy. The patient also reports he returned from a camping trip in a wilderness area 5 day ago. Virus diagnosis?

Answers can be found in **Appendix F**.

TABLE 20.3 A Summary of the Major Bacterial and Viral LRT Diseases

Disease	Causative Agent	Signs and Symptoms	Transmission	Treatment	Prevention
Bacterial					
Tuberculosis	*Mycobacterium tuberculosis*	Active TB: Cough, weight loss, fatigue, fever, night sweats, chills, breathing pain	Respiratory droplets	Combination therapy with antibiotics	Preventing exposure to active TB patients BCG vaccine
HCAP		Severe breathing and shock can develop	Respiratory droplets	Antibiotics	Annual flu vaccination Practicing good hand hygiene
Pneumococcal pneumonia	*Streptococcus pneumoniae*	High fever, sharp chest pains, difficulty breathing, rust-colored sputum	Respiratory droplets	Penicillin Cefotaxime	Vaccinating Hand hygiene
Other "typical" pneumonias	*Staphylococcus aureus* *Klebsiella pneumoniae* *Pseudomonas aeruginosa* *Acinetobacter species*	Chills, high fever, sweating, shortness of breath, chest pain, cough with thick, greenish or yellow sputum	Respiratory droplets	Antibiotics	Practicing good hand hygiene
"Atypical" pneumonia	*Mycoplasma pneumoniae* *Legionella pneumophila*	Headache, fever, fatigue, dry hacking cough	Respiratory droplets Via water systems, whirlpool spas, air conditioning systems	Antibiotics	Extreme cleaning and disinfecting of water systems, pools, and spas
Q fever	*Coxiella burnetii*	Headache, fever, dry cough	Dust particles Contact with infected animals	Doxycycline	Vaccine for high-risk occupations
Psittacosis	*Chlamydophila psittaci*	Headache, fever, dry cough	Contact with infected psittacine birds	Doxycycline	Keeping susceptible birds away from the infecting agent
Chlamydial pneumonia	*Chlamydophila pneumoniae*	Headache, fever, dry cough	Respiratory droplets	Doxycycline Erythromycin	Practicing good hygiene
Inhalational anthrax	*Bacillus anthracis*	Fever, chills, cough, chest pain, headache, and malaise	Airborne endospores	Penicillin Ciprofloxacin	Avoiding contact with infected livestock and animal products
Viral					
Respiratory syncytial (RS) disease	Respiratory syncytial virus (RSV)	Influenza-like	Respiratory droplets Hand contact	Fever-reducing medications Ribavirin for severe cases	Practicing good hygiene
Parainfluenza	Human parainfluenza viruses 1 and 3	Cold-like	Respiratory droplets Direct contact	No specific therapy	Practicing good hygiene
RSV-Like illness	Human metapneumovirus	Cold-like	Respiratory droplets Direct contact	Fever-reducing medications Ribavirin for severe cases	Practicing good hygiene
SARS	SARS coronavirus (SARS CoV)	Fever, headache, body aches, dry cough, and breathing difficulty	Respiratory droplets Direct contact	No specific treatment	Practicing good hygiene Standard precautions
Hantavirus pulmonary syndrome	Hantavirus (Sin Nombre virus)	Fatigue, fever, muscle aches, headache, dizziness, breathing difficulty	Aerosolized droplets of rodent saliva, urine, feces	Supportive care	Eliminating rodent nests Minimizing contact

Several Fungal Pathogens Cause Lower Respiratory Tract Diseases

Several fungi can affect the respiratory system, often with a primary infection in the lungs followed by spread to other body areas. These systemic mycoses often are opportunistic, causing life-threatening disease in individuals with a weakened immune system.

Histoplasmosis. A lung disease endemic in the Ohio and Mississippi River valleys is **histoplasmosis**, often called "summer flu." The causative agent is *Histoplasma capsulatum*.

Infection usually occurs from the inhalation of spores (conidia) present in dry, dusty soil or found in the air of chicken coops and bat caves (FIGURE 20.24). Being a dimorphic fungus, it grows as a yeast form at 37°C and causes chronic pneumonia. However, the infection in immunocompromised individuals causes a systemic infection, forming tuberculosis-like lesions in the lungs and other internal organs. Health experts estimate that up to 25,000 people in the Midwest develop life-threatening complications every year. Antifungal drugs may be used in treatment.

Blastomycosis. Caused by *Blastomyces dermatitidis*, **blastomycosis** occurs principally in Canada, the Great Lakes region, and areas of the United States from the Mississippi River to the Carolinas. The largest outbreak in United States history occurred in central Wisconsin in 2010 when 55 people were infected. All recovered.

The fungus is dimorphic and is associated with enriched, dusty soil and bird droppings, particularly in moist soils near barns and sheds. When the conidia are inhaled, they germinate as a yeast form. A persistent cough, fever, and chest pains in immunocompromised patients, leading to chronic pneumonia is the most common manifestation. A progressive, systemic form of blastomycosis may involve the skin and many internal organs (bones, liver, spleen, or nervous system), which could prove fatal. Amphotericin B is used in therapy.

Coccidioidomycosis. Known more commonly as "valley fever" or "desert fever," **coccidioidomycosis** is caused by *Coccidioides immitis* and *C. posadasii*. During most of the 1980s, about 450 annual cases were reported to the CDC. In 1991, the number jumped to over 1,200 cases, and in 2013, the number of reported cases was over 10,000, the majority occurring in California and Arizona.

In the soil, the ascomycete fungus produces highly infectious arthrospores by a unique process of spherule and endospore formation (FIGURE 20.25). When inhaled into the human lungs, the arthrospores become lodged in the terminal bronchioles and develop into large spherules. Infection induces an influenza-like disease, with a dry, hacking cough, chest pains, and high fever. Although some 40% of cases develop a self-limiting pulmonary disease, a small number of cases become disseminated via endospore-ingested macrophages and involve skin, bone, and the central nervous system, including the meninges of the spinal cord. Recovery brings lifelong immunity. Amphotericin B is prescribed for severe cases. Another drug, nikkomycin, and a vaccine are in development.

Cryptococcosis. An oval-shaped yeast known as *Cryptococcus neoformans*, a member of the Basidiomycota, causes **cryptococcosis**. The organism is found in the soil of urban

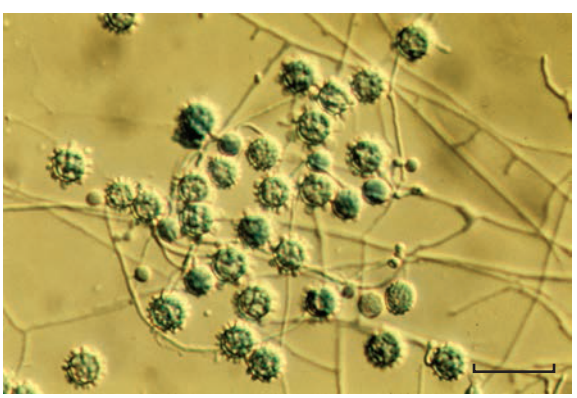
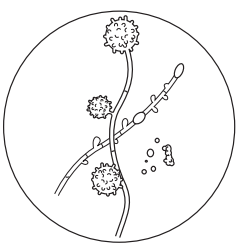
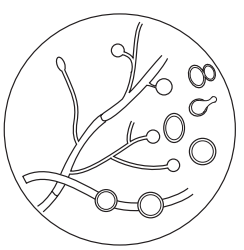


FIGURE 20.24 ***Histoplasma* Mycelium and Spores.** *H. capsulatum* grows as a mycelium in soil enriched by animal excrement. The spores are produced from the hyphal tips. (Bar = 20 μm.) **Which dimorphic form of this fungus is associated with human infections?**

Dimorphic: Refers to fungi that usually grow as a yeast form in human tissue and as a filamentous form in their natural environment.



Histoplasma capsulatum



Blastomyces dermatitidis

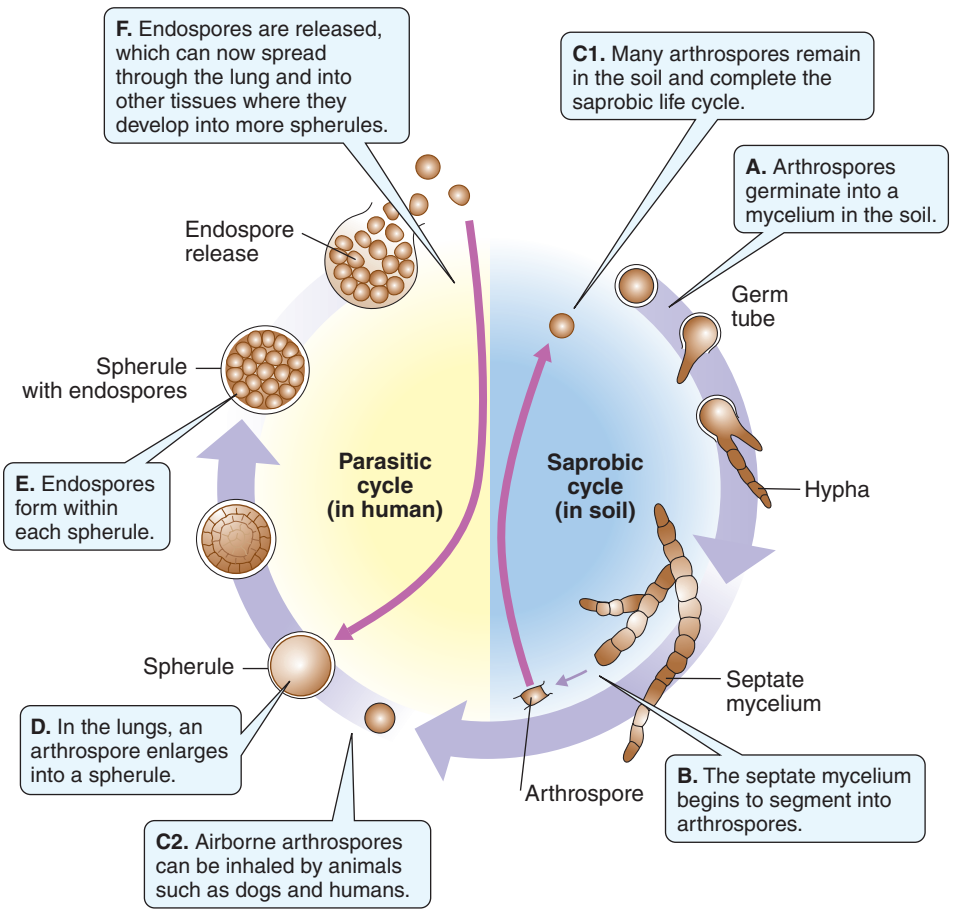
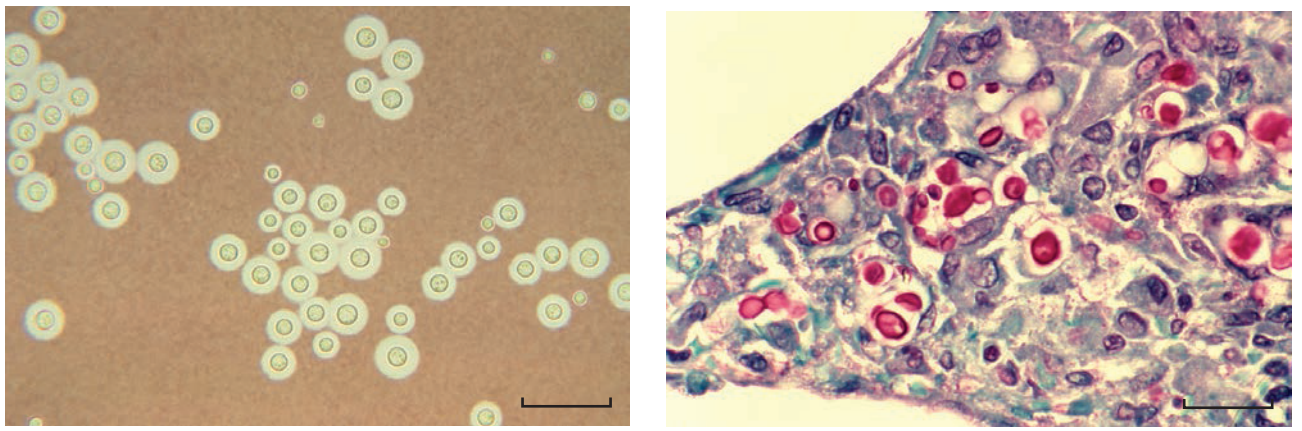


FIGURE 20.25 The Life Cycle of *Coccidioides*. Outside the body, the fungus goes through a saprobic cycle. However, the arthrospores in the respiratory tract go through a parasitic cycle, producing endospores capable of forming more spherules and infecting other tissues such as the skin, bone, and central nervous system. **Explain why *Coccidioides* is considered a dimorphic fungus.**

environments and grows actively in the droppings of pigeons, but not within the pigeon tissues. Cryptococci may become airborne when dried bird droppings are stirred up by gusts of wind, and the organisms subsequently enter the respiratory passageways of humans. Cryptococcosis is the most prevalent invasive fungal infection in the world, accounting for more than 25% of all deaths from fungal diseases.

The *C. neoformans* yeast cells are embedded in a thick, gelatinous capsule that provides resistance to phagocytosis (FIGURE 20.26). Infection usually produces a mild asymptomatic pneumonia. However, in immunocompromised patients, the cryptococci pass into the bloodstream and localize in the meninges and brain. The patient experiences piercing headaches, stiffness in the neck, and paralysis. Left untreated, the ensuing meningoencephalitis may be fatal. However, intravenous treatment with the antifungal drug amphotericin B is usually successful.

Another species of *Cryptococcus*, *C. gattii*, emerged in British Columbia in 1999 and soon spread to the Pacific Northwest (Washington, Idaho, Oregon, and California). This subtropical fungus, which may have originated in Brazil, has thus adapted to a more temperate climate. However, unlike *C. neoformans*, this species is not associated with bird droppings but rather is found in the soil around eucalyptus, pine, and Douglas fir trees. The fungal spores are inhaled, where they can cause a lung infection and



(A) (B)

FIGURE 20.26 ***Cryptococcus neoformans*.** **(A)** A light microscope photomicrograph of *C. neoformans* cells. The capsules (white halos) are prominent. (Bar = 20 μm.) **(B)** A photomicrograph of stained *C. neoformans* cells (red) from lung tissue of an AIDS patient. The capsule surrounding the cells provides resistance to phagocytosis and enhances the pathogenic tendency of the fungus. (Bar = 20 μm.) **Why would *C. neoformans* be a serious health threat to AIDS patients?**

(A) Courtesy of Dr. Leanor Haley/CDC; **(B)** Courtesy of Dr. Edwin P. Ewing, Jr./CDC.

pneumonia in 70% to 80% of otherwise healthy (immunocompetent) individuals. Symptoms include chest pain, a persistent cough, fever, and weight loss. Blindness can be an outcome in *C. gattii*-infected individuals.

With the ability to distinguish *C. gatti* from *C. neoformans*, *C. gatti* infections are being reported in places beyond the Pacific Northwest. There have been more than 25 cases reported in California, Florida, Georgia, and most recently, New York.

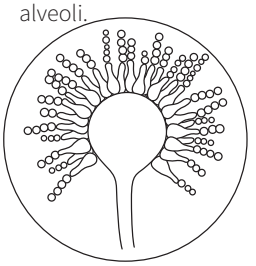
***Pneumocystis* pneumonia.** The most common form of nonbacterial pneumonia in Americans with AIDS is ***Pneumocystis* pneumonia** (**PCP**), caused by *Pneumocystis jiroveci* (previously called *Pneumocystis carinii*). Person-to-person transmission of *P. jiroveci* is by droplets from the respiratory tract, although transmission from the environment also can occur. A wide cross-section of individuals harbors the organism without symptoms, mainly because of the control imposed by the immune system. In the lung alveoli, cysts form and, when mature, they open and liberate the sporozoites, which enlarge and undergo further reproduction and maturation to trophozoites.

Trophozoites and cysts fill the alveoli and occupy all the air spaces. A nonproductive cough develops, with fever and difficult breathing. Progressive deterioration leads to **consolidation** of the lungs and, eventually, death. The current treatment for PCP is trimethoprim-sulfamethoxazole (co-trimoxazole; TMP-SMX) and corticosteroid therapy.

Aspergillosis. A few species of *Aspergillus*, primarily *A. fumigatus*, cause **aspergillosis**. These opportunistic molds, which are ubiquitous in soil, air, and decaying vegetation, produce spores that when inhaled, initiate the pulmonary illness.

In the lung alveoli, a **pulmonary aspergilloma**—a tangled ball of fungal mycelium—forms. At first, the "fungus ball" may not produce any symptoms. However, eventually symptoms do develop and include a bloody cough, chest pain, and wheezing with a shortness of breath. The most deadly form of aspergillosis—**invasive aspergillosis**—occurs when the fungal infection spreads beyond the lungs to the other organs, such as the skin, heart, kidneys, or brain. Signs and symptoms depend on which organs are affected, but, in general, include headache, fever with chills,

Consolidation: Formation of a firm dense mass in the alveoli.



Aspergillus fumigatus

bloody cough, shortness of breath, and chest or joint pain.

Treatment usually involves antifungal drugs and surgery may be needed to remove the fungus ball. It can be difficult to avoid *Aspergillus* spores in the environment. Staying away from obvious sources of mold, such as compost piles and damp places, can help prevent infection in susceptible individuals.

TABLE 20.4 summarizes the fungal diseases of the LRT. The **Summary Map of Key Concepts and Diseases** presents the bacterial, viral, and fungal diseases of the respiratory system by causative agent and site.

CONCEPT AND REASONING CHECKS 6

a. How does histoplasmosis differ in "healthy" individuals versus in an immunocompromised individual?
b. Why is blastomycosis a dangerous disease in immunocompromised individuals?
c. What is the unique feature of a coccidioidomycosis infection?
d. Explain why cryptococcosis is such a dangerous fungal disease.
e. What are the unique features of *P. jiroveci*?
f. Summarize the unique features of aspergillosis.

TABLE 20.4 A Summary of the Major Fungal LRT Diseases

Disease	Causative Agent	Signs and Symptoms	Transmission	Treatment	Prevention
Histoplasmosis	*Histoplasma capsulatum*	Mild influenza-like illness Can disseminate to other organs	Airborne spores	Amphotericin B or ketoconazole for systemic disease	Wearing facemask in contaminated areas
Blastomycosis	*Blastomyces dermatitidis*	Persistent cough Chest pains Chronic pneumonia	Airborne spores	Amphotericin B	Wearing facemask in contaminated areas
Coccidioidomycosis	*Coccidioides immitis* *Coccidioides posadasii*	Dry, hacking cough Chest pains High fever	Airborne arthrospores	Amphotericin B	Limiting exposure where infection is highest
Cryptococcosis	*Cryptococcus neoformans* *Cryptococcus gattii*	Asymptomatic Opportunistic infection leads to severe headache, stiff neck, paralysis	Airborne yeast cells	Amphotericin B	Maintaining strong immune system
Pneumocystis pneumonia	*Pneumocystis jiroveci*	Nonproductive cough Fever Breathing difficulty	Airborne droplets	Trimethoprim-sulfamethoxazole	Maintaining strong immune system
Aspergillosis	*Aspergillus fumigatus*	Bloody cough Chest pain Wheezing Shortness of breath	Airborne spores	Voriconazole	Staying away from sources of mold

CHAPTER CHALLENGE E

Our final challenge deals with the fungal diseases of the LRT.

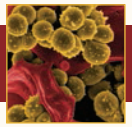
Question E:

Diagnose the correct fungal disease from the following signs and symptoms.

1. (Medium) A 56-year-old man presents with chest pain, a shortness of breath with a wheezing sound, and a bloody cough. The patient reports he has had asthma and 3 days ago he did extensive yard work. Disease diagnosis?
2. (Medium) A 27-year-old woman presents with headache, fever, muscle aches, chills, a dry cough, and chest discomfort. She reports she returned 10 days ago from a trip to Costa Rica where she was researching bats. Disease diagnosis?

Answers can be found in **Appendix F**.

In conclusion, we have seen that the respiratory system can be a major portal of entry and infection site for bacterial, viral, and fungal pathogens. With the number of pathogens that exist, it is surprising that our respiratory system is not subjected to more infections. The ability to limit the number of infections reflects on the strong immune defenses present in healthy individuals. Should those defenses not be fully developed, as in infants and children, or become weakened, such as in immunocompromised people or older individuals, then the infectious agents, especially opportunistic pathogens, may gain the upper hand. Thankfully, we also have a vibrant and active resident microbiota that usually successfully competes with eliminate most pathogenic "visitors."



Bacteria: © NIAID

SUMMARY OF KEY CONCEPTS

20.1 The Respiratory System Has a Resident Microbiota

- The **respiratory system** is divided into the **upper respiratory tract (URT)** (nose, sinus cavities, pharynx (throat), and larynx), and the **lower respiratory tract (LRT)** (trachea, bronchi, and lungs). The lungs contain the alveoli where gas exchange occurs. Mechanical and chemical defenses of the URT include: **mucociliary clearance** to trap microbes in a layer of **mucus**; the presence and activity of several antimicrobial substances, including lysozyme and other antimicrobial peptides, IgA and IgG antibodies, and human defensins. The microbiota of the URT includes *Streptococcus, Neisseria* (in the nasopharynx), *Haemophilus, Staphylococcus* (primarily in the anterior nares of the nose). (Fig. 20.2, 20.3)

20.2 Bacterial and Viral Diseases of the URT

Bacterial:

- Streptococcal pharyngitis
  1. *Streptococcus pyogenes*
- Scarlet fever
  2. *Streptococcus pyogenes*
- Diphtheria
  3. *Corynebacterium diphtheriae*
- Sinusitis
  4. Various bacterial species
- Otitis externa
  5. *Streptococcus, Staphylococcus, Pseudomonas* species
- Otitis media
  6. *Streptococcus pyogenes, Haemophilus influenzae*

Viral:

- Common colds
  7. Rhinoviruses

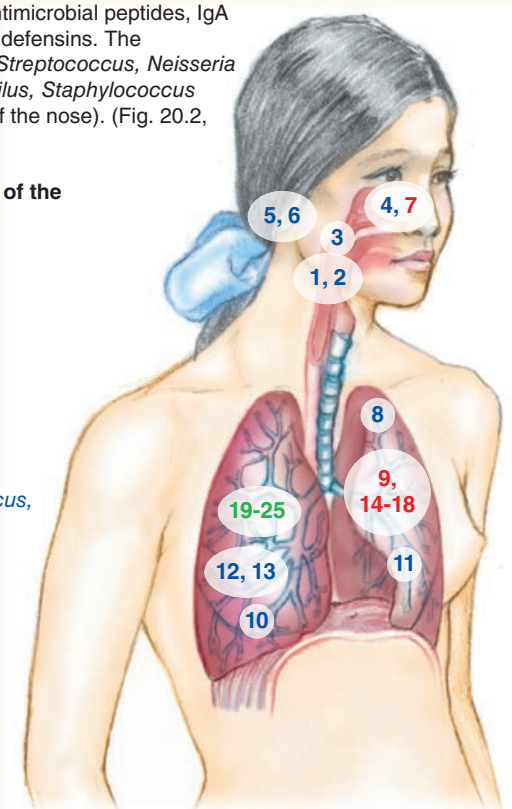
20.3 Bacterial and Viral Diseases of the URTand LRT

Bacterial:

- Pertussis
  8. *Bordetella pertussis*

Viral:

- Influenza
  9. Influenza A virus, influenza B virus



20.4 Bacterial, Viral, Fungal Diseases of the LRT

Bacterial:

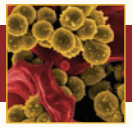
- Tuberculosis
  10. *Mycobacterium tuberculosis*
- Inhalational anthrax
  11. *Bacillus anthracis*
- HCAP
  12. *Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter* species
- CAP
  13. *Streptococcus pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila, Coxiella bumetii, Chlamydophila psittaci, Chlamydophila pneumoniae*

Viral:

- Respiratory syncytial (RS) disease
  14. Respiratory syncytial virus
- Parainfluenza
  15. Human parainfluenza viruses 1 and 3
- RSV-like illness
  16. Human metapneumovirus
- SARS
  17. SARS coronavirus
- Hantavirus pulmonary syndrome (HPS)
  18. Hantavirus

Fungal:

- Histoplasmosis
  19. *Histoplasma capsulatum*
- Blastomycosis
  20. *Blastomyces dermatitidis*
- Coccidioidomycosis
  21. *Coccidioides immitis, Coccdioides posadasii*
- Cryptococcosis
  22. *Cryptococcus neoformans*
  23. *Cryptococcus gattii*
- *Pneumocystis* pneumonia
  24. *Pneumocystis jirovecii*
- Aspergillosis
  25. *Aspergillus fumigatus*



Bacteria: © NIAID

CHAPTER SELF-TEST

For STEPS A–D, answers to questions and problems can be found in **Appendix D**.

STEP A: REVIEW OF FACTS AND TERMS

Multiple Choice

Answer each of the following questions by selecting the ***one*** answer that best fits the question or statement.

1. Which one of the following is NOT part of the lower respiratory tract?
   A. Alveoli
   B. Pharynx
   C. Bronchi
   D. Trachea
2. Which one of the following is a complication of strep throat?
   A. Rheumatic fever
   B. Pseudomembrane blockage
   C. Strawberry tongue
   D. Chest, back, and leg pain
3. A prominent feature of diphtheria is _____.
   A. rheumatic fever
   B. a pseudomembrane
   C. strep throat
   D. tubercle formation
4. Which one of the following illnesses is characterized by yellow or green pus discharged from the nose?
   A. Pertussis
   B. Diphtheria
   C. Bronchitis
   D. Acute sinusitis
6. Swimmer's ear is a common name for a _____ infection of the _____ ear.
   A. bacterial; outer
   B. viral; outer
   C. bacterial; middle
   D. viral; inner
7. There are more than _____ different rhinoviruses, which belong to the _____ family.
   A. 50; Orthomyxoviridae
   B. 100; Adenoviridae
   C. 30; Paramyxoviridae
   D. 100; Picornaviridae
8. A catarrhal and paroxysmal stage is typical of which one of the following bacterial diseases?
   A. Tuberculosis
   B. Pneumonia
   C. Pertussis
   D. Q fever
9. Which one of the following statements is NOT true of the influenza viruses?
   A. They have a segmented genome.
   B. The genome is double-stranded DNA.
   C. The viruses have an envelope.
   D. Spikes project from the virus surface.
10. The Mantoux test is one method of detection for which one of the following pathogens?
    A. *Haemophilus influenzae*
    B. *Streptococcus pneumoniae*
    C. *Klebsiella pneumoniae*
    D. *Mycobacterium tuberculosis*
11. Inhalational anthrax _____.
    A. is usually fatal without early treatment
    B. results from inhaling endospores
    C. is caused by an aerobic, gram-positive rod
    D. All the above (A–C) are correct.
12. Which one of the following is a bacterial species commonly causing healthcare-acquired pneumonia?
    A. *Streptococcus pneumoniae*
    B. *Klebsiella pneumoniae*
    C. *Staphylococcus aureus*
    D. *Chlamydophila pneumoniae*
13. Humans can acquire which one of the following diseases from the droppings of infected birds?
    A. Q fever
    B. Legionellosis
    C. Tuberculosis
    D. Psittacosis
14. Which one of the following is NOT a member of the Paramyxoviridae?
    A. Human metapneumovirus
    B. SARS-CoV
    C. Parainfluenza virus
    D. Respiratory syncytial virus
15. Deer mice are reservoirs for which disease?
    A. SARS
    B. RS disease
    C. HPS
    D. Q fever

16. This disease develops after inhaling arthrospores and is commonly called "valley fever."
    A. Blastomycosis
    B. Coccidioidomycosis
    C. Cryptococcosis
    D. Histoplasmosis
17. Which one of the following fungi would most likely be found in pigeon droppings?
    A. *Histoplasma*
    B. *Cryptococcus*
    C. *Coccidioides*
    D. *Aspergillus*

Term Selection

For each choice, circle the word or that best completes each of the following statements.

18. Rhinoviruses are a collection of (RNA, DNA) viruses having (helical, icosahedral) symmetry and the ability to infect the (air sacs, nose) causing (mild, serious) respiratory symptoms.
19. Respiratory syncytial disease is caused by a (DNA, RNA) virus infecting the (URT, LRT) of (adults, children) and inducing cells to (fuse together, cluster) and form giant cells called (syncytia, tumors).
20. SARS is caused by a (coronavirus, orthomyxovirus), a/an (naked, enveloped) virus spread by (sexual, person-to-person) contact.
21. Scarlet fever is caused by a species of *(Staphylococcus, Streptococcus)* that often produces a (strawberry tongue, pseudomembrane) in children.
22. Middle ear infections called (otitis media, otitis externa) are common in children and often are caused by a species of *(Bartonella, Streptococcus)* following a cold that inflamed the (Eustachian tube, larynx).
23. A person with secondary active TB disease would have a positive (sputum, urine) test, while someone with a latent TB infection might have only a positive (sputum, tuberculin) test. The dissemination of TB bacilli throughout the body is called (latent, miliary) TB.
24. A systemic mycosis is (aspergillosis, blastomycosis), which grows in the lungs as a (yeast, filamentous) form and is transmitted by diseased or contaminated (cattle, bird droppings).

STEP B: CONCEPT REVIEW

25. Explain (a) how the URT maintains sterility in the LRT and (b) what portions of the URT are normally colonized by indigenous microbiota. (**Key Concept 1**)
26. Summarize the clinical aspects **strep throat** and the complications arising from **streptococcal pharyngitis**. (**Key Concept 2**)
27. Name the bacterial species responsible for, and describe the clinical aspects of treatment and prevention of, **diphtheria**. (**Key Concept 2**)
28. Distinguish between **acute** and **chronic sinusitis**. (**Key Concept 2**)
29. Recognize the symptoms of outer and middle ear infections. (**Key Concept 2**)
30. Explain why a vaccine against rhinoviruses is not feasible. (**Key Concept 2**)
31. Justify why **pertussis** is viewed as one of the more dangerous contagious diseases. (**Key Concept 3**)
32. Identify (a) the major influenza viruses and the structures involved in generating subtypes and (b) explain the genetic mechanisms by which influenza A subtypes evolve.
33. Summarize (a) the clinical aspects of *Mycobacterium tuberculosis* as an infection and disease, and (b) the problems concerning antibiotic resistance. (**Key Concept 4**)
34. Assess the potential danger caused by the inhalation of *Bacillus anthracis* endospores. (**Key Concept 4**)
35. Distinguish between the bacterial species responsible for **healthcare-acquired** and **community-acquired pneumonia**. (**Key Concept 4**)
36. Summarize the mode of transmission and types of pneumonia caused by the intracellular pathogens. (**Key Concept 4**)
37. Describe the LRT infections caused by the paramyxoviruses. (**Key Concept 4**)
38. Distinguish how **SARS** differs from other LRT infections. (**Key Concept 4**)
39. Assess the seriousness of **histoplasmosis**, **blastomycosis**, and **coccidioidomycosis** to an immunocompromised individual. (**Key Concept 4**)
40. Describe the opportunistic mycoses **cryptococcosis**, ***Pneumocystis* pneumonia**, and **aspergillosis**. (**Key Concept 4**)

STEP C: APPLICATIONS AND PROBLEMS

41. One of the major world health stories of 1995 was the outbreak of diphtheria in the New Independent and Baltic States of the former Soviet Union. If you were in charge of this international public health emergency, what would be your plan to help quell the spread of *Corynebacterium diphtheriae*?
42. The CDC reports that an estimated 40,000 people in the United States die annually from pneumococcal pneumonia. Despite this high statistic, only 30% of older adults who could benefit from the pneumococcal vaccine are vaccinated (compared to over 50% who receive an influenza vaccine yearly). As an epidemiologist in charge of bringing the pneumonia vaccine to a greater percentage of older Americans, what would you do to convince older adults to be vaccinated?
43. In a Kentucky community, a crew of five workers demolished an abandoned building. Three weeks later, all five required treatment for acute respiratory illness, and three were hospitalized. Cells obtained from the patients by lung biopsy revealed oval bodies and epidemiologists found an accumulation of bat droppings at the demolition site. As the head epidemiologist, what disease did the workers contract?

STEP D: QUESTIONS FOR THOUGHT AND DISCUSSION

44. A bacteriophage is responsible for the ability of the diphtheria bacillus to produce the toxin that leads to disease. Do you believe that having the virus is advantageous to the infecting bacillus? Why or why not?
45. A children's hospital in Salt Lake City reported a dramatic increase in the number of rheumatic fever cases. Doctors were alerted to start monitoring sore throats more carefully. Why do you suppose this prevention method was recommended?
46. A Boeing 737 bound for Kodiak, Alaska, developed engine trouble and was forced to land. While the airline rounded up another aircraft, the passengers sat for 4 hours in the unventilated cabin. A passenger, it seemed, was in the early stages of influenza and was coughing heavily. By the week's end, 38 of the 54 passengers on the plane had developed influenza. What lessons about infectious disease does this incident teach?
47. In a suburban community, a group of residents obtained a court order preventing another resident from feeding the flocks of pigeons that regularly visited the area. Microbiologically, was this action justified? Explain.
48. Residents of a New York community, unhappy about the smells from a nearby composting facility and concerned about the health hazard posed by such a facility, had the air at a local school tested for the presence of fungal spores. Investigators from the testing laboratory found abnormally high levels of *Aspergillus* spores on many inside building surfaces. Is there any connection between the high spore count and the composting facility? Is there any health hazard involved?
49. On January 17, 1994, a serious earthquake struck the Northridge section of Los Angeles County in California. From that date through March 15, 170 cases of coccidioidomycosis were identified in adjacent Ventura County. This number was almost four times the previous year's number of cases. What is the connection between the two events?