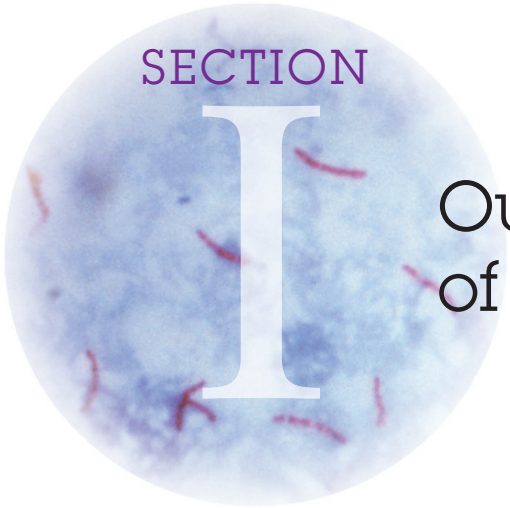

SECTION I

Outbreaks of Diseases of the Respiratory Tract

Among those who require a visit to a physician, infections of the respiratory system are the most common reason for the visit. These respiratory infections account for an average of ~80 physician visits per 100 persons each year. Infections of the lower respiratory tract, such as pneumonia and influenza, are also the leading cause of death by infectious disease worldwide. Pneumonia, influenza, and tuberculosis result in about 4.3 million deaths per year.

For full indeed is earth of woes, and full the sea; and in the day as well as night diseases unbidden haunt mankind, silently bearing ills to men.

Hesiod, *Works and Days*, ca. line 101
(Trans., J. Banks, 1856)

Containment of a respiratory outbreak can be complicated by a pathogen's ability to survive outside the body. For example, some cold-causing viruses can remain infective on an environmental surface for several hours. This makes classroom desks and doorknobs potential fomites for the spread of disease. Pathogens on the hands can be inoculated into the eyes and drain into the nose. There they can attack and initiate a respiratory tract infection. Consequently, one important way to decrease spread of respiratory pathogens is to wash hands frequently and to avoid touching the eyes.

The primary method of spread for respiratory tract pathogens is via airborne particles and mucus droplets. Airborne particles can travel over 1 meter through the air and still remain infectious, while mucus droplets travel less than 1 meter through the air. As a result, respiratory pathogens are highly contagious and spread rapidly through a community. Outbreaks of respiratory pathogens are common in colleges. Students who occupy college residence halls usually share rooms with one or more students and are in contact with hundreds of students at sporting events, in recreational facilities, and in classrooms. As a result, the number of opportunities for transmission of respiratory pathogens is greatly increased relative to others who live at home. The frequency of transmission of respiratory pathogens is significantly higher during cold-weather periods, when students are restricted to indoor activities. Therefore, annual winter outbreaks of colds, influenza, strep throat, and bronchitis in this setting are common.

Although several thousand microbes are inhaled each day, the defenses of the respiratory system are very efficient and regularly prevent infection and disease. Mucus is secreted by goblet cells within the respiratory epithelium. This mucus traps most microbes before they travel deep into the respiratory tract. It helps to inhibit attachment of microbes to host cell receptors. Microbes that are trapped in the mucus are swept out of the respiratory system by cilia on the surface of the pseudostratified epithelium. The mucus is swallowed, and the microbes are destroyed in the digestive system. In addition, the mucus has a high concentration of dissolved solutes. The hypertonic environment thus created inhibits the growth of most cellular microbes—bacteria, fungi, and protozoa. In the alveoli of the lungs, macrophages are present to phagocytize microbes that escape the other defenses.

Microbial pathogens have evolved strategies to bypass these defenses. Adhesins on the surfaces of microbes allow pathogens to attach to receptors on epithelial cells so that the microbes are not swept out of the respiratory tract. These adhesins are highly specific and at times limit infections to certain parts of the respiratory tract. For example, rhinoviruses attach to receptors located in the upper respiratory tract and are thus limited to causing a common cold. Influenza A virus, however, attaches all along the respiratory mucosa and can cause a wide range of respiratory diseases, from a common cold to life-threatening pneumonia.

Microbes that can survive in the alveoli of the lungs are the most dangerous, causing a life-threatening infection that blocks gas exchange. *Streptococcus pneumoniae* has an antiphagocytic capsule that inhibits phagocytosis by alveolar macrophages. Strains with a capsule cause pneumonia, while those without a capsule are nonpathogenic. *Mycobacterium tuberculosis*, the causative agent of tuberculosis, a chronic infection of the lungs, and *Legionella pneumophila*, the causative agent of Legionnaires' disease, avoid being digested after being phagocytized by alveolar macrophages.

The outbreaks described in this chapter emphasize the serious nature of respiratory tract infections, the difficulty in consistently and effectively implementing basic disease control measures, and the rapid spread of microbes that travel through the air.

Table I-1 Selected outbreak-causing respiratory pathogens

Organism	Key Physical Properties	Disease Characteristics
Bacteria		
Bordetella pertussis	Fastidious, Gram-negative coccobacillus	Whooping cough in unvaccinated individuals
Chlamydophila pneumoniae	Obligate intracellular bacterium; very small; Gram negative	Pneumonia, bronchitis
Corynebacterium diphtheriae	Gram-positive, club-shaped bacillus	Diphtheria in unvaccinated individuals
Streptococcus pyogenes	Gram-positive streptococcus; beta-hemolytic on blood agar; group A surface antigen	Strep throat, scarlet fever, rheumatic fever
Legionella pneumophila	Fastidious, Gram-negative bacillus	Pneumonia (Legionnaires' disease)
Mycobacterium tuberculosis	Acid-fast bacillus found in chains or cords; cell wall contains mycolic acid, which results in drug and disinfectant resistance	Tuberculosis
Mycoplasma pneumoniae	Wall-less bacterium; variable shape	Walking pneumonia
Streptococcus pneumoniae	Gram-positive diplococcus; alpha-hemolytic on blood agar	Otitis media, sinusitis, conjunctivitis, pneumonia
Viruses		
Adenovirus	Nonenveloped polyhedral capsid with double-stranded DNA	Pharyngitis, bronchiolitis, pneumonia, conjunctivitis
Epstein-Barr virus	Enveloped polyhedral capsid with double-stranded DNA	Mononucleosis
Hantavirus	Enveloped helical capsid with negative-sense single-stranded RNA	Hantavirus pulmonary syndrome; zoonotic disease carried by rodents
Influenza viruses (A, B, and C)	Enveloped pleomorphic capsid with segmented negative-sense single-stranded RNA	Influenza, pneumonia; predisposes to secondary bacterial pneumonia
Mumps virus	Enveloped pleomorphic capsid with negative-sense single-stranded RNA	Mumps
Parainfluenza viruses	Enveloped pleomorphic capsid with negative-sense single-stranded RNA	Croup, bronchiolitis, pneumonia, laryngitis
Respiratory syncytial virus	Enveloped helical capsid with negative-sense single-stranded RNA	Bronchiolitis and pneumonia, primarily in infants
Rhinoviruses	Nonenveloped polyhedral capsid with negative-sense single-stranded RNA	Common cold
Rubella virus	Enveloped polyhedral capsid with positive-sense single-stranded RNA	German measles; can cause significant birth defects when pregnant women are infected
Rubeola virus	Enveloped helical capsid with negative-sense single-stranded RNA	Measles in unvaccinated individuals
Varicella-zoster virus	Enveloped polyhedral capsid with double-stranded DNA	Chickenpox in unvaccinated individuals; shingles as a latent manifestation

OUTBREAK I-1

A Legionellosis Outbreak—Barceloneta

In the fishing neighborhood of Barceloneta, Spain, on the Mediterranean waterfront, 33 people were hospitalized in respiratory distress. Four of the victims were in serious condition. The area is predominantly inhabited by elderly people. The youngest victim was 49, while the oldest was 92. The common signs and symptoms were fatigue, malaise, high fever, shortness of breath, and coughing. Examination revealed rales (crackling sounds heard during breathing, indicating fluid in the lungs) and bilateral shadowing in the lungs on X ray (indicating fluid accumulation in both lungs).

City health officials carried out bacterial analyses of a ventilation system in the neighborhood located in a seaside building which uses a water tower as part of the cooling system for air conditioning. They isolated *Legionella pneumophila*, a Gram-negative, rod-shaped bacterium (Fig. I-1a and I-1b).

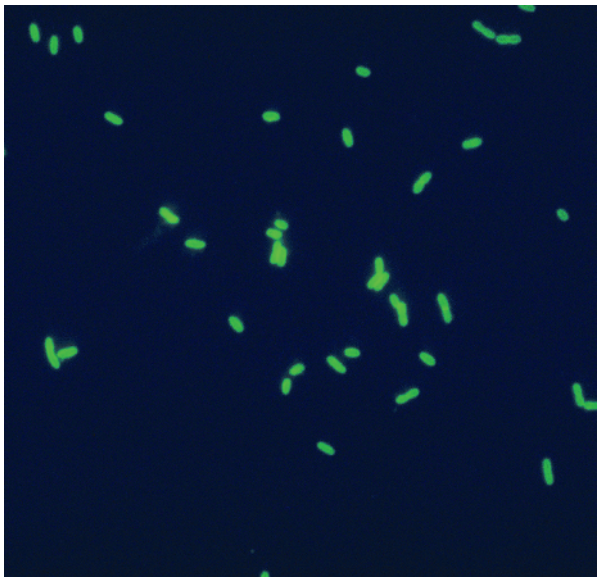

Figure I-1a Micrograph of direct fluorescent-antibody assay of *L. pneumophila* (magnification, ×400). Source: CDC/ Dr. William Cherry, PHIL, 2015, 1978.

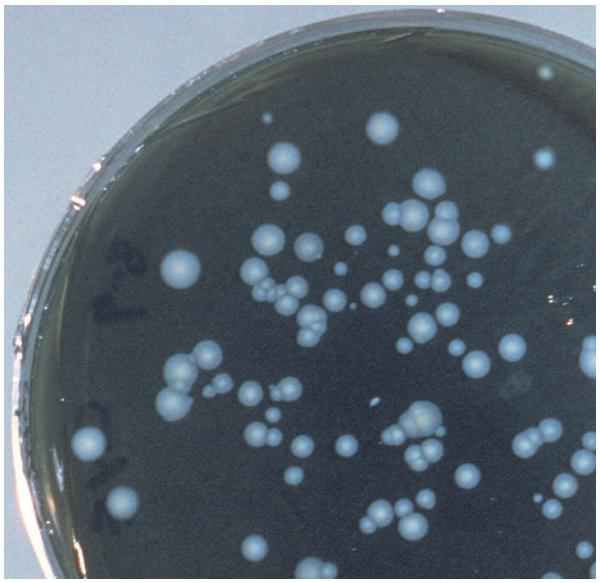

Figure I-1b *L. pneumophila* growing on charcoal-yeast extract agar. Source: CDC/ Dr. Jim Feeley, PHIL, 2137, 1978.

Content Questions

1. How is *Legionella pneumophila* transmitted?
2. What is an appropriate way to manage the disease?

Diagnosis Questions

1. How is legionellosis diagnosed?
2. What are the physical characteristics of the pathogen?

Reason It Out Questions

1. Besides *Legionella*, list four possible microbial causes of pneumonia.
2. How would you prevent future outbreaks of the disease?

An Outbreak of Respiratory Syncytial Virus Infection—Arviat, Canada

An outbreak of respiratory syncytial virus (RSV) disease sent 50 sick babies from the town of Arviat to hospitals in the south. Arviat is a remote community of 1,700 people that is located on the southwestern shore of Hudson Bay. For 2 weeks, the waiting room at the small clinic staffed by Arviat's nurses had as many as 70 sick people looking for treatment, half of them with coughing, crying infants. Nurses worked around the clock with no backup to care for the ill and to decide which children to send out, in medevac batches of three, to Churchill or Winnipeg. The disease was characterized initially as a cold or influenza, but children then developed coughing, fast breathing, wheezing, and difficulty breathing.

Lab tests of respiratory fluids were positive for RSV, an enveloped virus with a helical capsid and single-stranded RNA (Fig. I-2).

Arviat's nursing station was built in 1938 and is no longer adequate for Arviat's population. There is no resident physician in the community and no hospital facilities to treat seriously ill patients. Community leaders have called for better medical services for Arviat, including a full-time doctor, a suggestion that the hard-pressed Keewatin Regional Health Board had not yet acted on. In the year of the outbreak, Arviat was expected to see its population of 1,700 grow by 75 new babies. With a growth rate of more than 4% a year, Arviat was one of the fastest growing communities in the region.

Although the population of Arviat was small at the time of the outbreak, overcrowding was common. It was not unusual for many individuals to live in very small homes. In addition, the public schools and community center were considered too small. In addition, 82 new Nunavut government jobs were planned for Arviat. As a result, the community's population was expected to jump to more than 2,000 residents, and problems with overcrowding would worsen.

At the time of the outbreak, city officials worried that the outbreak would be compounded in the following week by hundreds of Christians from around Nunavut and Nunavik who would be traveling to the area to attend a Holy Spirit Crusade. Arviat's mayor, Mr. Hicks, expressed his concern: "Sitting elbow to elbow, with the lights on, in the heat, makes a great incubator for disease."

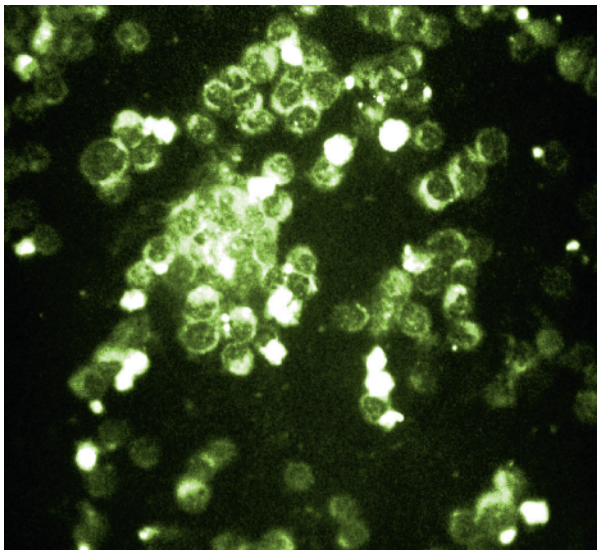

Figure I-2 Direct fluorescent-antibody assay for respiratory syncytial virus. Source: CDC/ Dr. H. Craig Lyerla, PHIL, 6484, 1977.

Outbreak I-2 continues on next page

Content Questions

1. How is this pathogen transmitted?
2. How would you treat individuals affected by this disease?

Diagnosis Questions

1. What are the physical characteristics of the pathogen?
2. What specimen is used to test for the pathogen?
3. How do you test for the pathogen in the medical science laboratory?

Reason It Out Questions

1. What public health actions should be taken to stop the outbreak and prevent future occurrences?
2. What age group is most susceptible to RSV bronchiolitis? Why?

A Tuberculosis Outbreak in a Prison Housing Inmates Infected with HIV—South Carolina

An outbreak of drug-susceptible tuberculosis (TB) occurred in a state correctional facility housing human immunodeficiency virus (HIV)-infected inmates. Before entry, inmates are tested for HIV status. They are then segregated in three dormitories of one prison, with each dormitory partitioned into right and left sides. On admission to the facility, all inmates are also screened for TB infection and disease with a tuberculin skin test and chest radiography.

In early July, an HIV-infected man aged 34 years housed in dormitory A was taken to the prison hospital with a 2-week history of fever, abdominal pain, and cough. His chest radiograph was normal; however, sputum specimens were not obtained for culture, and no acid-fast staining was done to detect acid-fast bacilli (AFB). As a result, he was not placed in respiratory isolation. The inmate was returned to the prison in mid-July without a definitive diagnosis. In mid-August, the man was evaluated at a community hospital. A lab test of his sputum was positive for AFB (Fig. I-3a), and he was diagnosed with active pulmonary TB. Later that year, the medical student who examined the inmate during the initial hospitalization developed active TB with cavities within the lungs (Fig. I-3b).

A contact investigation of dormitory A inmates identified 31 current or former inmates who had signs and symptoms of active TB. They were transferred from dormitory A to the hospital for respiratory isolation and medical evaluation. The exposed group comprised 323 men who had spent 1 to 152 days (median, 135 days) in dormitory A during that period. Of the 31 case patients, 27 (87%) resided on the right side of dormitory A during the exposure period; four (13%) resided on the left.

All case patients were non-Hispanic black men born in the United States and were infected with HIV. The median age was 36 years (range, 23 to 56 years). All of the isolates of the pathogen tested were identical based on DNA fingerprinting analysis. Five case patients had TB diagnosed after being released from prison; all five were released before the source case patient had TB diagnosed in August.

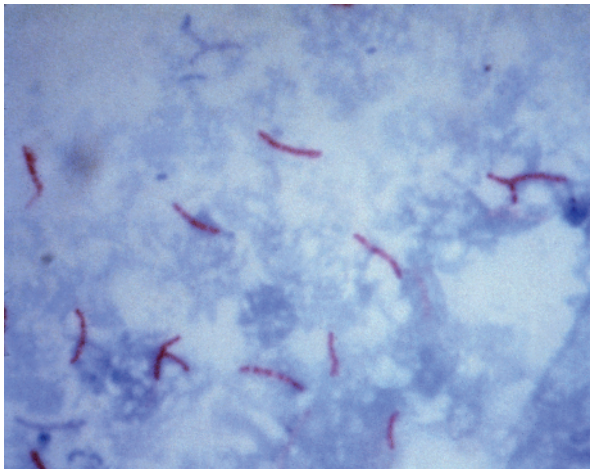

Figure I-3a Acid-fast stain of the pathogen. Source: Lewis L. Tomalty and Gloria Delisle, Queen's University.

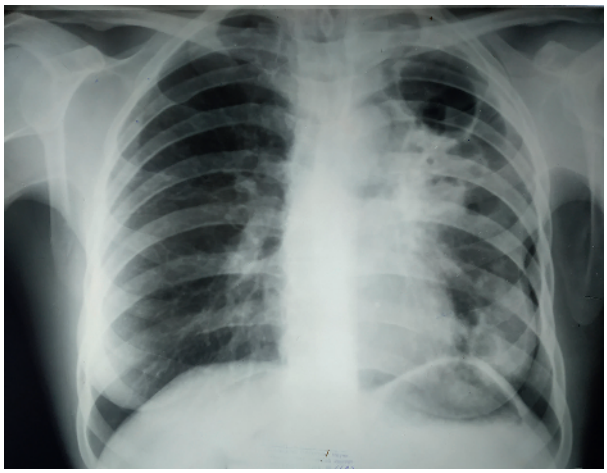

Figure I-3b Chest X ray of a patient with tuberculosis. Source: Giller Boris, Public Domain Wikimedia Commons.

Outbreak I-3 continues on next page

OUTBREAK I-3 *(continued)*

Content Questions

1. How is the pathogen transmitted?
2. What is the pathogenesis of the microbe?
3. What type of results would be expected in a chest X ray of a person who has active TB?

Diagnosis Questions

1. What color do AFB stain? Why?
2. What color do non-AFB stain? Why?
3. What is a tuberculin skin test?
4. What does a positive test indicate?

Reason It Out Questions

1. What pathogen is causing this outbreak?
2. How would you have prevented the spread of the pathogen through the prison?
3. What characteristic of AFB makes them difficult to treat?
4. What characteristics of the pathogen result in the requirement for long-term multidrug therapy?
5. How did the inmates on the opposite side of the dormitory contract TB?
6. How does a person's HIV status influence the risk of developing TB?

An Otitis Media Outbreak in a Child Care Center—Georgia

On December 18, public health officials in southwest Georgia contacted the Georgia Division of Public Health about a child aged 11 months hospitalized for otitis media. Eight days before hospitalization, a culture of drainage obtained from the child's middle ear revealed Gram-positive cocci arranged in chains. The bacteria were resistant to penicillin, clindamycin, erythromycin, trimethoprim/sulfamethoxazole, and tetracycline. The child attended a local child care center.

The child care center was located in a rural county (population, 6,318) in southwest Georgia and served approximately 54 children (age range, 9 months to 10 years). The children were divided into two groups on the basis of age (<18 months and >18 months), and the two groups had separate rooms. Nasopharyngeal (NP) swabs were collected and sent to the Centers for Disease Control and Prevention (CDC) for identification and antimicrobial susceptibility testing.

NP swabs were obtained from 5 of the 12 children who had shared a room at the child care center with the child who was hospitalized; NP swabs also were obtained from 17 of the 42 children from the other room. The pathogen was grown on blood agar under anaerobic conditions (Fig. I-4a). Alpha-hemolytic colonies were Gram stained (Fig. I-4b). The bacterium was isolated from 90% of the NP cultures; of these, 79% were penicillin nonsusceptible (i.e., they had intermediate or high-level resistance and were resistant to more than one antibiotic or class of antibiotics).

A questionnaire was distributed to evaluate risk factors that might be associated with infection. Eighty-two percent of the children in the child care center had had an illness for which they received antibiotic treatment during the 2 months preceding the questionnaire.

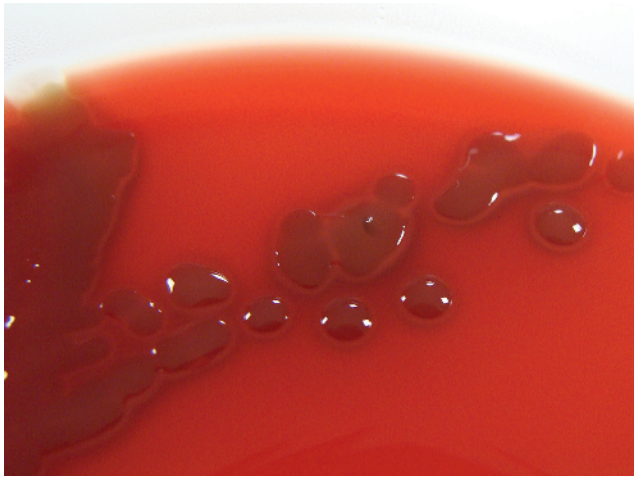

Figure I-4a Growth of the pathogen on blood agar. Source: Nathan Reading, Halesowen, UK, CC-BY 2.0.

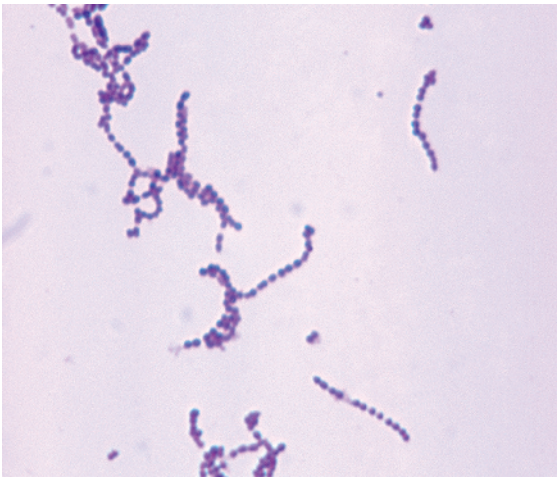

Figure I-4b Gram stain of the pathogen. Source: CDC, PHIL, 2170, 1970.

Outbreak I-4 continues on next page

OUTBREAK I-4 *(continued)*

Content Questions

1. How is this pathogen commonly transmitted in a child care setting?
2. How would you treat those infected with the multidrug-resistant pathogen?

Diagnosis Questions

1. What pathogen is most likely affecting the children at the day care center?
2. What are the physical characteristics of the pathogen?

Reason It Out Questions

1. What other disease(s) can this pathogen cause?
2. Why are children in day care and their mothers particularly susceptible to infections from drug-resistant pathogens?
3. How would you stop this outbreak and reduce the risk of similar outbreaks in the future?

An Outbreak of a Rash—Venezuela and Colombia

In January, a girl aged 7 months received medical care at a hospital near her home. Her illness started with a fever and the appearance of a maculopapular rash (a rash of flat red spots). She infected a nurse, who then transmitted the disease to several other contacts, some of whom visited a popular tourist site in Falcón, Venezuela. Of the 165 persons that were infected during this outbreak, 52% had visited the same tourist site.

The first rash case in Zulia, Colombia, occurred in a woman aged 27 years who was an auxiliary nurse in a physician's office that provided care to residents of Falcón. The nurse had had onset of rash on October 25 of the year previous to the outbreak and subsequently infected four other persons. During the next 3 months, the outbreak spread to all municipalities in Zulia; 2,074 cases had been confirmed as of July 24. For several chains of transmission, the index case was in a health care worker. Beginning in February, the outbreak spread to 14 additional states in Venezuela, including four states bordering Colombia. By July, Venezuela reported 6,380 cases.

Two years before the outbreaks, routine measles, mumps, and rubella vaccination coverage in Venezuela was 84%. By September of the year before the outbreaks, estimated coverage had decreased to 58% and was lower in Venezuelan states near the border with northern Colombia (Falcón, 44%; Zulia, 34%).

Affected persons first experienced a fever lasting about 2 to 4 days that peaked at about 104°F (40°C). This was followed by a cough, runny nose, and the outbreak of a macular rash (Fig. I-5a) that began at the hairline and then proceeded down throughout the body. In addition, tiny white dots surrounded by a red halo appeared on the inflamed mucosa inside the cheeks (Koplik spots) (Fig. I-5b). The rash lasted about 5 days.

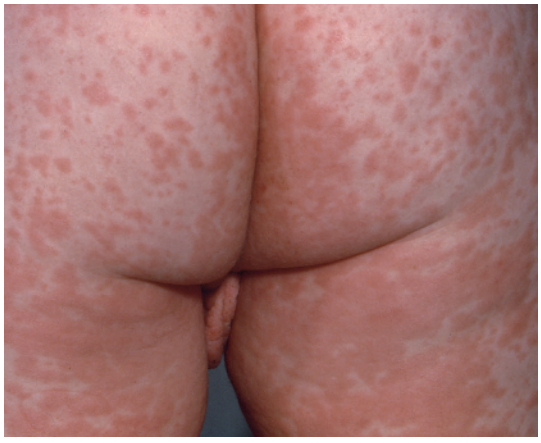

Figure I-5a Maculopapular rash. Source: CDC, PHIL, 4499, 1963.

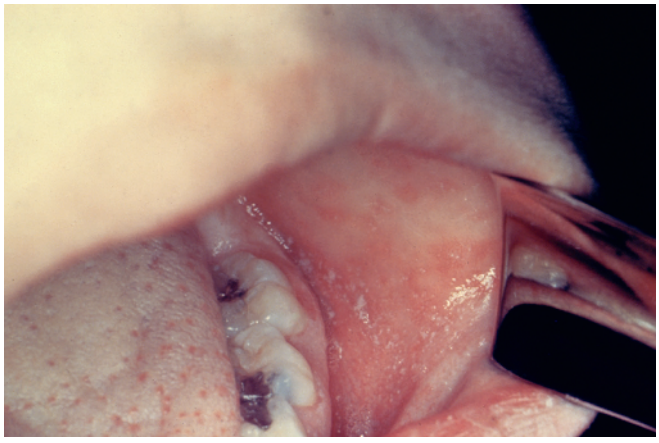

Figure I-5b Koplik spots on the buccal mucosa. Source: CDC, PHIL, 6111, 1975.

Outbreak I-5 continues on next page

Content Questions

1. How is the pathogen transmitted?
2. How does this pathogen cause a rash?
3. How would you treat a patient who contracted this disease?

Diagnosis Questions

1. What pathogen caused this outbreak?
2. What are the physical characteristics of the pathogen?

Reason It Out Questions

1. What is the disease?
2. In order to minimize the number of cases of the disease, how would you manage the outbreak?

Hantavirus Pulmonary Syndrome Outbreak—Vermont

On February 17, a 61-year-old previously healthy Vermont resident was hospitalized following three episodes of chills and fever (102°F [39°C]), nausea, vomiting, and anorexia. On examination, the lungs were clear and a 2- by 2-cm nontender lymph node was identified at the angle of the left jaw. Chest radiographs were also clear. However, 1 day after admission, the patient's condition deteriorated, with onset of respiratory failure, profound hypoxemia (lack of oxygen), and hypotension (low blood pressure), requiring mechanical ventilation. Subsequent chest radiographs revealed fluid in the lungs consistent with acute respiratory distress syndrome (Fig. I-6a). The patient also developed disseminated intravascular coagulation (blood clots forming throughout the body) and renal insufficiency.

During the 2 months preceding hospitalization, the patient, who resided in a house on four rural acres, had cleaned a mouse nest from a woodpile, observed mice in the basement, and trapped two mice under the kitchen counters.

Lab tests for bacterial pathogens, protozoal pathogens, influenza virus, adenovirus, and coronaviruses were negative. An enzyme-linked immunosorbent assay detected antibodies to Sin Nombre virus (Fig. I-6b) in the patient's serum. Forty-three rodents were trapped around the home and also tested for signs of hantavirus infection; two of five deer mice (Fig. I-6c) were positive for hantaviral antibodies, while all other rodents were negative.

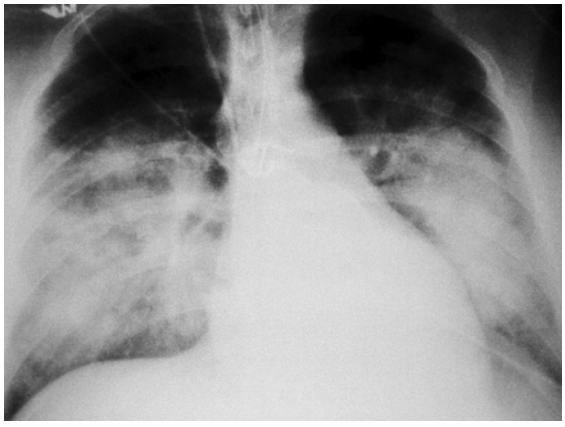

Figure I-6a Chest radiograph of a patient with hantavirus pulmonary syndrome. Source: CDC/ D. Loren Ketai, MD; PHIL, 6076, 1994.

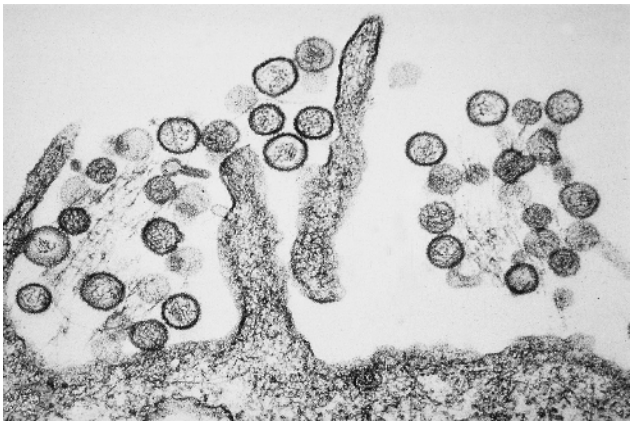

Figure I-6b Transmission electron micrograph of Sin Nombre virus. Source: CDC/ Cynthia Goldsmith, PHIL, 1136, 1993.

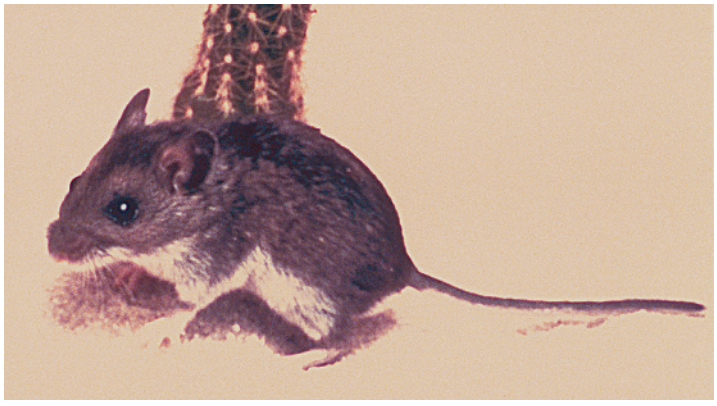

Figure I-6c A deer mouse. Source: National Center for Infectious Diseases, CDC, PHIL, 92, 1997.

Outbreak I-6 continues on next page

Content Questions

1. How does the Sin Nombre virus cause respiratory distress?
2. How is infection with this organism most commonly acquired?

Diagnosis Questions

1. What are the physical characteristics of Sin Nombre virus?
2. How does an enzyme-linked immunosorbent assay detect antibodies to a specific pathogen?

Reason It Out Questions

1. How would you prevent an outbreak of this disease from occurring?
2. How would you reduce the risk of a similar outbreak in the future?

A Diphtheria Outbreak—Newly Independent States of the Former Soviet Union

A diphtheria epidemic began in Russia and spread to all of the other newly independent states (NIS) of the former Soviet Union. More than 150,000 cases and 5,000 deaths were reported from the NIS in 8 years. Diphtheria is caused by the bacterial pathogen *Corynebacterium diphtheriae* (Fig. I-7).

As a consequence of the fall of the Soviet Union, the health care system and public health infrastructure were extremely underfunded, resulting in the loss of health care professionals and significant interruption of health care supplies. The dire state of Russia's public health system created what President Vladimir Putin called a national emergency: during the 4-year outbreak, life expectancy at birth fell by over 5 years to 58.5, the lowest level in the developed world. Only one child in five was born healthy according to official statistics, which many experts said understated the problem. The death rate rose by 20%, an increase with no modern precedent.

After the collapse of the former Soviet Union, doctors no longer had the medicine, equipment, or money to deal with standard health care. Many physicians at the time were pessimistic about any improvements in the near future. Almost half of the medical school graduating class—doctors who are practicing throughout Russia today—could not even read an electrocardiogram on the day they got their diplomas, according to the Russian Academy of Sciences. On average during this time, doctors earned less money than drivers or baby sitters—about $145 each month.

During this period, Russia budgeted slightly less than 1% percent of its resources to health care, about the same as the poorest African nations. During the outbreak, the Russian Health Ministry said that half of the country's 21,000 hospitals did not have hot water, a quarter had no sewage systems, and several thousand had no water at all.

The collapse of the previous economic system and civil wars in parts of the former Soviet Union seriously impaired the social and health situation. During the period of the outbreak, in some of the NIS, over 65% of the population were estimated to be below the poverty level. Health services at this time were free of charge only for emergency situations; otherwise, drug treatment and hospital care had to be paid for by the patient.

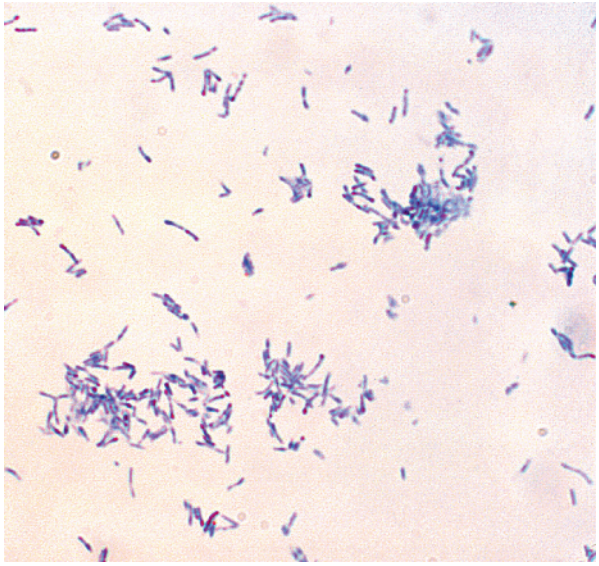

Figure I-7 Gram stain of the pathogen. Source: CDC, PHIL, 1943.

Outbreak I-7 continues on next page

Content Questions

1. What are the clinical features of diphtheria?
2. How can the disease be fatal?
3. How is diphtheria usually prevented?

Diagnosis Questions

1. What specimen is used to test for the pathogen?
2. What laboratory test(s) is used to identify the pathogen?

Reason It Out Questions

1. How would you prevent the disease from spreading to tourists and travelers to the NIS?
2. Why are infants particularly at risk for acquiring diphtheria?
3. How would you arrest this outbreak?

An Outbreak of Mycoplasmal Pneumonia—Ohio

From June 15 through September 5, an acute respiratory illness caused by *Mycoplasma pneumoniae* occurred among 47 (12%) of 403 staff members and clients of a sheltered workshop for developmentally disabled adults in Ohio. The disease was characterized by acute onset of cough and fever. The median age of patients was 35 years (range, 20 to 60 years); seven (15%) required hospitalization, and 31 (66%) had chest X rays showing fluid in the lungs—evidence of pneumonia. One workshop participant died on June 30 from complications of pneumonia.

Specimens of blood, sputum, and nasopharyngeal secretions were analyzed in the clinical laboratory.

Results of the Gram stain of a sputum sample were inconclusive; however, abundant cells that fight off infection (polymorphonuclear leukocytes) were observed. Serologic and microbiologic studies were negative for acute viral infections. No bacteria were present in the blood sample. An antigenic test was able to identify the pathogen as *Mycoplasma pneumoniae* (Fig. I-8).

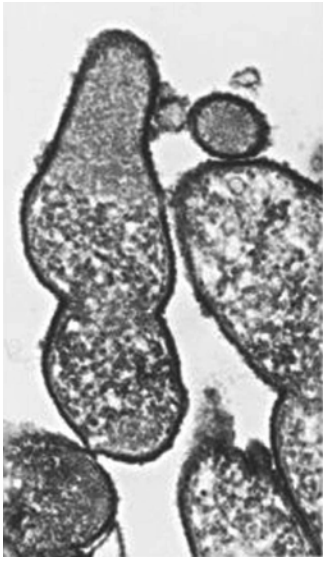

Figure I-8 Transmission electron micrograph of *Mycoplasma*.
Source: Reprinted from Yanez A, et al, *Emerg Infect Dis* **5:**164–167, 1999.

Content Questions

1. How is *Mycoplasma pneumoniae* transmitted?
2. How would you treat those affected by this pathogen?

Diagnosis Questions

1. What are the physical characteristics of *Mycoplasma pneumoniae*?
2. What specimen is used to test for the pathogen?
3. What laboratory test(s) is used to identify the pathogen?

Reason It Out Questions

1. What are three other viral or bacterial pathogens that can cause primary pneumonia?
2. Why is an institutional setting a common place for such an outbreak?
3. What physical property makes *Mycoplasma* different from all other pathogens that cause bacterial pneumonia?
4. To which group of antibiotics would *Mycoplasma pneumoniae* be resistant?
5. How would you reduce the risk of future outbreaks?

OUTBREAK I-9

A Pneumonia Outbreak in a Nursing Home—New Jersey

On April 24, nine cases of pneumonia among residents of a nursing home were investigated by the Hamilton Township Department of Health, New Jersey. Illness onset among the residents occurred from April 3 to24. Four residents died. Pneumonia was characterized by one or more lobes filled with fluid and pleural effusions (pus in the pleural space) (Fig. I-9a).

The nursing home is a 114-bed facility that employs approximately 200 staff, including nurses, restorative aides, and other administrative and support personnel. None of the employees was known to have pneumonia during this period.

Seven of the residents lived in the same wing of the nursing home. All nine patients had blood cultures that grew alpha-hemolytic colonies on blood agar (Fig. I-9b). Sputum samples were Gram stained to identify the pathogen. All isolates were penicillin sensitive and resistant to erythromycin.

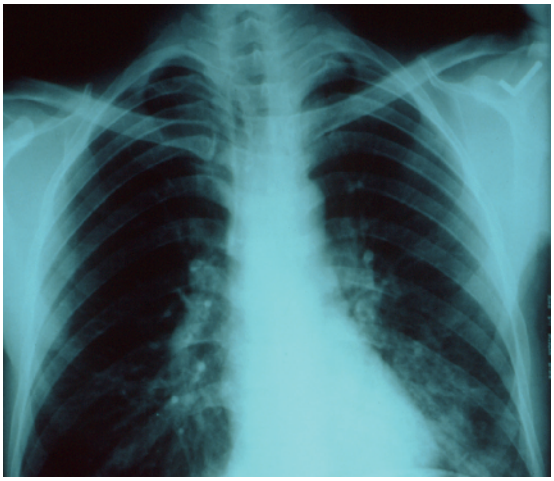

Figure I-9a Chest X ray of a patient with pneumonia. Source: CDC/ Dr. Thomas Hooten, PHIL, 5803, 1973.

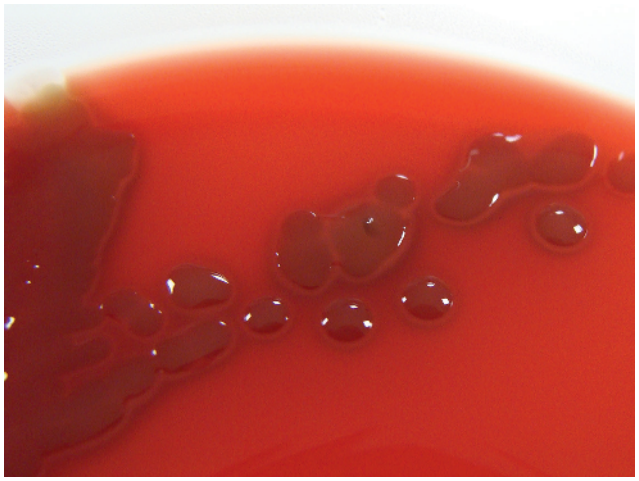

Figure I-9b Growth of the pathogen on blood agar. Source: Nathan Reading, Halesowen, UK, CC-BY 2.0.

Content Questions

1. How would you treat a patient who contracted this disease?
2. What physical property does this pathogen have that enables it to avoid phagocytosis by the macrophages in the lungs?
3. How is the pathogen transmitted?

Diagnosis Questions

1. What pathogen is causing this outbreak?
2. What are the physical characteristics of the pathogen?

Reason It Out Questions

1. In order to minimize the number of cases of the disease, how would you manage the outbreak?
2. How would you reduce the risk of a similar outbreak in the future?

Past and Future Pandemics of Influenza A—Worldwide, 1918 to Present

The golden age of microbiology began with Louis Pasteur and his development of the anthrax and rabies vaccines and saving of the French wine industry. It continued with Robert Koch, who established the germ theory of disease and discovered the causative agents of anthrax, cholera, and tuberculosis. The first time knowledge from the new field of microbiology was practically applied to attempt to control a major epidemic was the influenza pandemic of 1918, probably the world's worst epidemic of all time.

Some modern epidemiologists estimate that the influenza pandemic caused 50 to 100 million deaths, with about one-half occurring in men and women in their 20s and 30s. The flu killed 8% of all young adults then living. The 2-year epidemic spread rapidly, with two-thirds of deaths occurring in 24 weeks and over half occurring from mid-September to early December of 1918 (Fig. I-10).

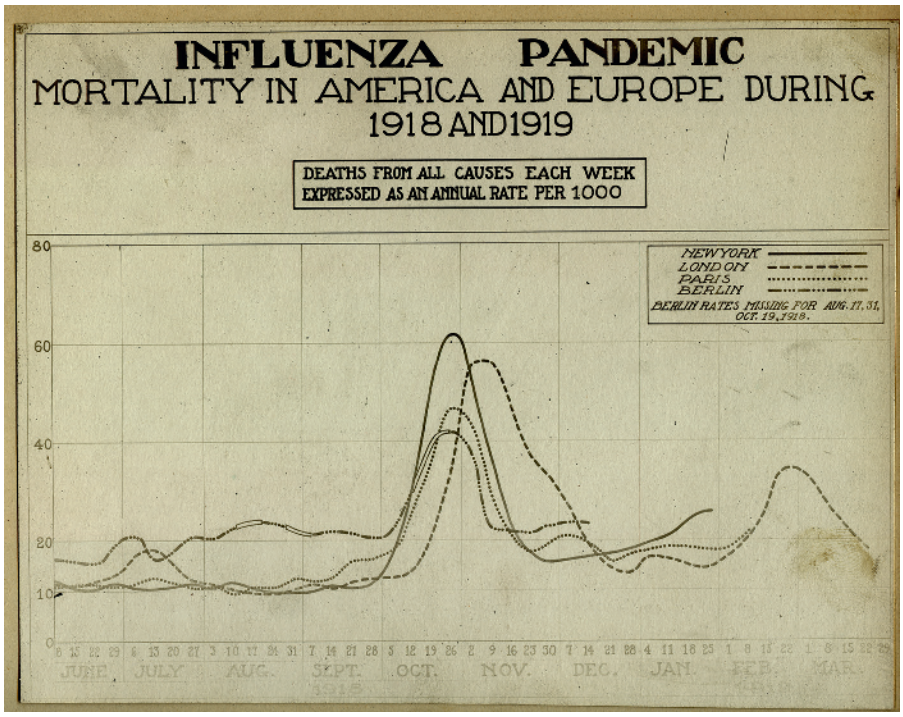

Figure I-10 1918 influenza pandemic record. Source: National Museum of Health and Medicine, Armed Forces Institute of Pathology, Washington, DC; Reeve, 3143.

Past and present plagues fall far short of the influenza pandemic of 1918. The flu killed more people in 24 weeks than AIDS has killed in 24 years. It killed more people in a year than the Black Death of the Middle Ages killed in a century.

In 1997, the partial sequences of five influenza virus genes were recovered from the preserved lung tissue of a U.S. soldier who died from influenza in 1918. The sequence data now suggest that the hemagglutinin gene (coding for the H antigen) of the 1918 virus was a composite of a stretch of nucleotides from a pig virus flanked by nucleotides from a human virus.

The current version of the bird flu also has a unique combination of H and N antigens (H5N1) found in no other version of the virus. Fortunately for the world, this version of influenza A virus has not been

Outbreak I-10 continues on next page

effectively spread via respiratory droplets. In most cases, it has been spread by direct contact with infected birds. Like the 1918 version, this new strain appears to result in extremely high mortality. Over 50% of those who are infected die.

In an interview with author Michael Spector (February 28, 2005, issue of *The New Yorker*), Scott Dowell, the director of the Centers for Disease Control and Prevention's Thailand office, stated, "The world just has no idea what it's going to see if this thing comes. When, really. It's when. I don't think we can afford the luxury of the word 'if' anymore. … The clock is ticking. We just don't know what time it is."

John S. Marr, M.D., former director of the Bureau of Preventable Diseases and a principal epidemiologist in the New York City Department of Public Health, is also concerned about a future influenza pandemic. In a 1999 interview, he stated, "The spread of the 'Spanish Flu' in 1918–19 took four months to circle the world. A new strain of influenza could cause a pandemic in four days. … Sadly, many people believe that 'flu', a household word, is nothing much to be concerned about, but a new strain could kill tens of millions of people quite easily, within weeks. That is the one I worry about."

When Tommy Thompson announced his resignation as Secretary of Health and Human Services in December of 2004, he cited a bird flu epidemic as one of the greatest dangers the United States faces. Governmental estimates of the cost of an influenza epidemic have been made. Without large-scale immunization, the estimates of the total economic impact in the United States of an influenza pandemic range from 71.3 billion to 166.5 billion dollars.

Content Questions

1. How is the influenza virus transmitted?
2. How can influenza be treated?

Diagnosis Questions

1. What are the physical characteristics of the influenza A virus?
2. What laboratory test(s) is used to identify an infection by an influenza virus?

Reason It Out Questions

1. How can a virus that primarily attacks birds be changed into a pathogen that effectively infects humans?
2. Given the increase in worldwide travel and population since 1918, could a human version of this influenza virus that was spread by respiratory droplets be contained? Explain your reasoning.
3. Given the advances in vaccine production and medicine since 1918, could modern health care prevent tens of millions of deaths if the current bird flu was effectively spread by respiratory droplets? Explain your reasoning.

A Pharyngitis Outbreak in the Marine Corps—San Diego

An outbreak of an infectious disease sent more than 100 recruits to the hospital at San Diego's Marine Corps Recruit Depot (MCRD) in 1 week. Fifty Marines were hospitalized with an upper respiratory tract infection. One was in critical condition, and one died. The outbreak was confined to four of the base's seven companies. All of the ill recruits arrived for training before the outbreak.

Sore throat was the most common symptom, but more serious complications developed. Maj. Gen. Jan Huly, commander of MCRD, stated that no one expects casualties in recruit training. Maj. Gen. Huly said, "We take every one of those deaths personally, as if there were some way we could have prevented it, and we're going to find a way we can prevent it."

The initial onset of the clinical signs and symptoms of the disease included fever, pharyngitis (inflammation of the pharynx and tonsils), and headache. Later signs included exudative tonsillitis (creamy yellow pus produced on tonsils). Some patients suffered from complications such as peritonsillar abscesses, where the infection invaded into deeper tissue, or a high fever and bright red rash.

Gram stains revealed Gram-positive cocci (Fig. I-11a). Other lab tests of sputum samples and throat swabs showed beta-hemolytic colony growth on blood agar (Fig. I-11b). Antigen tests indicated that the pathogen carried group A antigens on its surface.

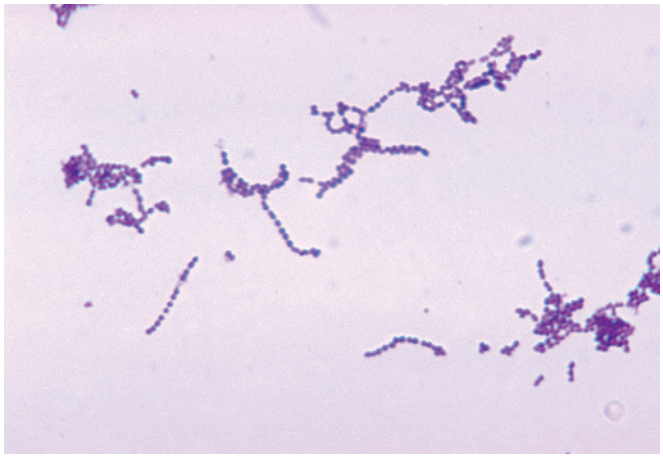

Figure I-11a Gram stain of the pathogen. Source: CDC, PHIL, 2170**,** 1970.

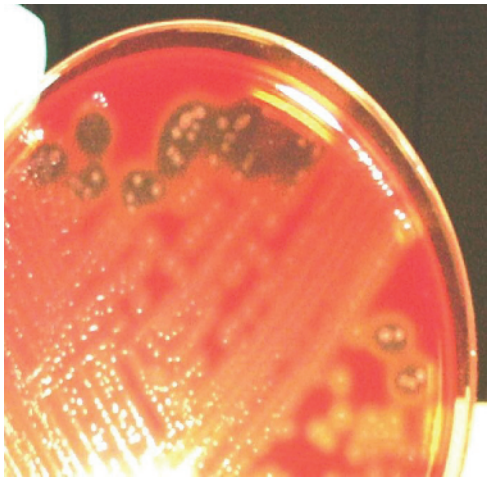

Figure I-11b Growth of the pathogen on blood agar. Source: Nathan Reading, Halesowen, UK, CC-BY 2.0.

Outbreak I-11 continues on next page

Content Questions

1. How would you treat those affected by the disease?
2. If the disease is not treated, what potential serious complications can result?
3. How is the pathogen transmitted?

Diagnosis Questions

1. Given the lab test results, what are the pathogenic agent and the disease it causes?
2. What are the physical characteristics of the pathogen?

Reason It Out Questions

1. What features of the pathogen enable it to cause abscesses?
2. What features of the pathogen enable it to cause a bright red rash?
3. How could this outbreak be quickly arrested?

A Measles Outbreak in Kosovar Refugee Children—Albania

Extensive ethnic conflict within the Kosovo region of the Federal Republic of Yugoslavia and an organized bombing campaign by the North Atlantic Treaty Organization led to mass population displacement. Approximately 500,000 Kosovar Albanians fled into the Yugoslavian Republic of Montenegro and the neighboring countries of Albania, Bosnia-Herzegovina, and the Former Yugoslav Republic of Macedonia.

Of the estimated 130,000 refugees who fled to Macedonia, approximately 65,000 were housed in seven refugee camps. A major public health concern in these camps was the prevention of vaccine-preventable diseases. Vaccination against preventable microbial diseases is a major public health priority in the acute phase of any emergency involving large-scale displacement of a population. In past emergencies, up to 50% of deaths were attributed to vaccine-preventable disease.

In response, the Macedonian health ministry, in collaboration with UNICEF and the International Medical Corps, planned a mass vaccination campaign. The vaccination campaign needed to overcome several significant obstacles. First, there were substantial fluctuations in the population. On a weekly basis, thousands of refugees were both leaving and entering the camps as they fled additional fighting, looked for relatives, tried to return to their homes, or looked for better living conditions. For example, in the Macedonian camps, 44,417 refugees left and 46,492 refugees arrived in 1 week. Second, vaccination at the time of entry was not feasible. There was a lack of access to refugees at the camp borders, and the timing of their arrival and movement in the camps were unpredictable. Finally, there was a concern that vaccination immediately upon entering the camps would be psychologically traumatic to children.

An outbreak of measles broke out in one of the camps that had a large population of undernourished children. Examination of those affected showed a high fever, a macular rash, and Koplik spots on the inside of the cheeks of the mouth (buccal mucosa).

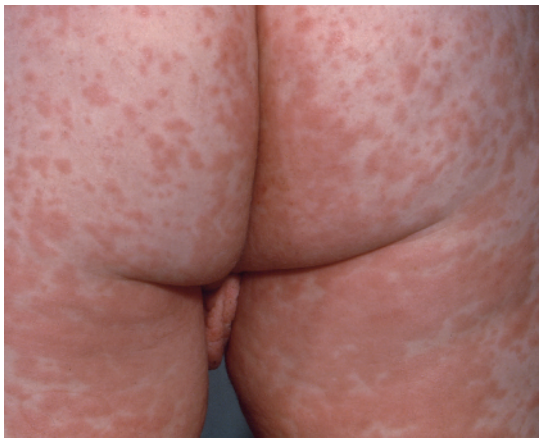

Figure I-12a Maculopapular rash. Source: CDC, PHIL, 4499, 1963.

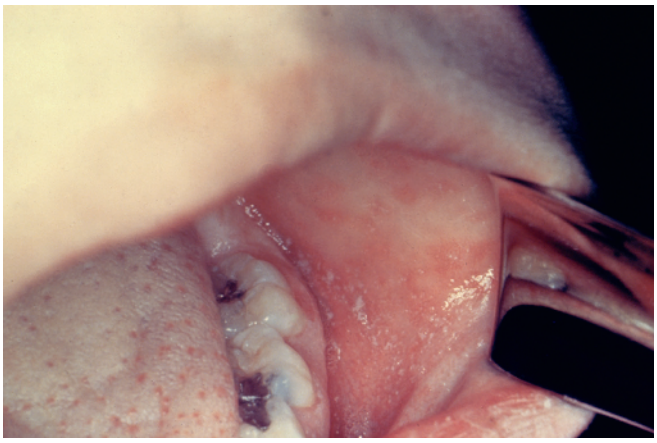

Figure I-12b Koplik spots on the buccal mucosa. Source: CDC, PHIL, 6111, 1975.

Outbreak I-12 continues on next page

Content Questionsm

1. To what complications from measles are the undernourished children especially susceptible?
2. How is the measles virus transmitted?

Diagnosis Questions

1. How is measles diagnosed?
2. What are the physical characteristics of the measles virus?

Reason It Out Questions

1. Why is a measles outbreak of significant concern in a mass refugee setting?
2. How would you prioritize the expenditure of funds and resources in order to minimize the number of deaths caused by measles and other vaccine-preventable diseases?
3. List five vaccine-preventable diseases that could be a threat to the health of the refugee population.

A Swimming Pool-Related Outbreak of Pharyngitis and Conjunctivitis—Spain

The swimming pool in Oñati in the province of Gipuzkoa was often the center of summertime activities for families with children. However, summer activities were interrupted in early July when children began coming down with a fever, sore throat, a headache, and conjunctivitis. Since there was a large number of cases in a short period of time, an investigation was undertaken to identify the risk factors associated with the illness to help in determining the possible source of the disease so an intervention could be made.

To identify cases of pharyngitis or pharyngoconjunctival fever, local physicians' practices and a referral hospital in the area were monitored. Between 16 June and 11 August, 59 children were identified. Affected patients were interviewed in order to record the following variables: place of residence, age, sex, date of symptom onset, symptoms, presence of complications, swimming pool use, and other potential exposures.

Forty-three of the children had recently used the municipal swimming pool. Fifteen of the children had been in close contact with one of the children who had been ill after pool use. The first case occurred in a patient who had not visited the swimming pool. The epidemic curve confirmed an outbreak consistent with the hypothesis of a persistent common source and several more isolated cases, resulting from person-to-person transmission, mainly in a family environment (Fig. I-13).

Adenovirus was detected in five of the six pharyngeal swabs collected. For adenovirus detection, a real-time polymerase chain reaction (PCR) method was used. The virus was identified as adenovirus type 4 by sequencing the amplified portion of the virus.

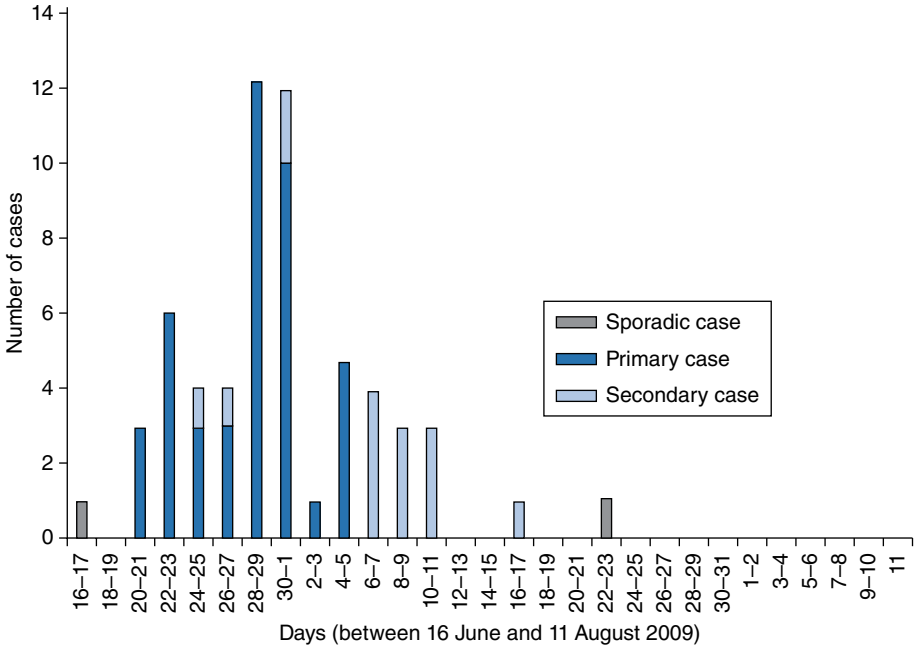

Figure I-13 Cases of pharyngoconjunctival fever by date of disease onset (active surveillance was ongoing until 11 August). Source: Adapted from Artieda J, et al, *Euro Surveill* **14:**19125, 2009.

Outbreak I-13 continues on next page

OUTBREAK I-13 *(continued)*

There were numerous electrical system failures after the swimming pool opened. This caused intermittent failure of the water circulation and bromine dosing pumps. The disinfectant concentrations registered on 3 July were insufficient in the small children's pool (0.45 mg of total bromine per liter) and were adequate in the remaining pools.

Content Questions

1. What pathogens are known for causing outbreaks in swimming pools?
2. What other pathogens besides adenovirus can cause acute pharyngitis?
3. What pathogen causes strep throat?
4. How would you treat viral pharyngoconjunctival fever?
5. Which case(s) would be considered a sporadic case?
6. Which case(s) would be considered a primary case?
7. Which case(s) would be considered a secondary case?

Diagnosis Questions

1. What is PCR?
2. How does real-time PCR differ from PCR?
3. What did the real-time PCR analyze in order to identify adenovirus 4 in the sample?

Reason It Out Questions

1. What was the source of the outbreak?
2. Why did the investigators ask about place of residence, age, sex, date of symptom onset, and symptoms?
3. Describe how the pathogen was transmitted in this outbreak?
4. Which viral cause of pharyngitis and fever is also often associated with conjunctivitis?
5. How would you stop this outbreak and prevent future outbreaks by this pathogen?

A Cruise Ship-Associated Legionnaires' Disease Outbreak

The number of ocean cruise passengers has increased steadily for several decades, including passengers traveling on pleasure cruises departing from North American ports. The potential for rapid spread of a variety of diseases is high on cruise ships. Thousands of people are transported for days together in a closed environment where they eat and are entertained in large groups. In addition, travelers from different parts of the world mix, and during the cruise ship's stops where passengers disembark, they mix with individuals at different ports of call.

The CDC investigated eight cases of Legionnaires' disease (LD) that occurred during November to May among persons who had recently traveled on cruise ships. Cases were defined as a person having LD that had been confirmed by laboratory testing and having traveled by cruise ship during the 10 days before symptom onset.

There were seven different voyages and five different cruise ships associated with the eight cases of LD (Table I-14). Two cases occurred during one cruise. Two cases occurred at different times on the same cruise ship. Two cases were fatal.

Most passengers with LD were diagnosed after disembarking from their ships, since the duration of the cruises was from 7 to 10 days, while the mean time from cruise ship boarding to onset of symptoms was 10.4 days (range, 4 to 16 days). Although two passengers had symptoms before the end of their respective cruises, only one had LD diagnosed while still aboard the ship.

Table I-14 Cases of cruise ship travel-associated Legionnaires' disease[a]

Ship	Age (yrs)	Sex	Cruise Duration (days)	Day of Illness Onset	Complicating Conditions	Outcome
A	53	F	7	9	Smoker	Recovered
A	45	F	7	11	Diabetes	Died
B	23	F	7	11	None	Recovered
B	51	M	7	4	History of lymphoma	Recovered
C	76	M	10	11	COPD	Died
D	68	M	9	9	Diabetes, recent lung disease	Recovered
E	65	M	11	16	History of heart disease	Recovered
E	65	M	14	12	Unknown	Recovered

[a] COPD, chronic obstructive pulmonary disease.

Source: Adapted from Centers for Disease Control and Prevention, *MMWR Morb Mortal Wkly Rep* **54:**1153–1155, 2004.

Outbreak I-14 continues on next page

Content Questions

1. What are three pathogens that you would you expect to cause outbreaks of respiratory infections on cruise ships?
2. What pathogen causes LD?
3. What are the characteristics of the pathogen that causes LD?
4. What are the signs and symptoms of LD?
5. How is the LD pathogen transmitted?
6. What is the reservoir for the LD pathogen?

Diagnosis Questions

1. What lab tests can be used to identify the pathogen?
2. What specimen would you take to test for the LD pathogen?

Reason It Out Questions

1. Why was this case definition used?
2. What risk factors did patients have for acquiring LD?
3. Are family members who were not on the cruise at risk of contracting LD? Explain.
4. How would LD most likely be spread on a cruise ship?
5. Although reporting of LD is required and followed up with an investigation, what factors would contribute to the difficulty of detecting an LD outbreak on a cruise ship?

A Pertussis Epidemic—Washington State

From January to March of the year of the outbreak, the number of cases of pertussis in the state of Washington significantly exceeded those from the first quarter of the year from each of the previous 5 years. The increase began in the middle of the previous year. As a result of the rapid increase in pertussis cases, a pertussis epidemic was declared on April 3 by the Washington state Secretary of Health. In the first 6 months of the year previous to the outbreak, only 180 cases of pertussis were reported. In the first 6 months during the epidemic, there were 2,520, the highest number of reported cases since 1942, which was before a pertussis vaccination was available (Fig. I-15).

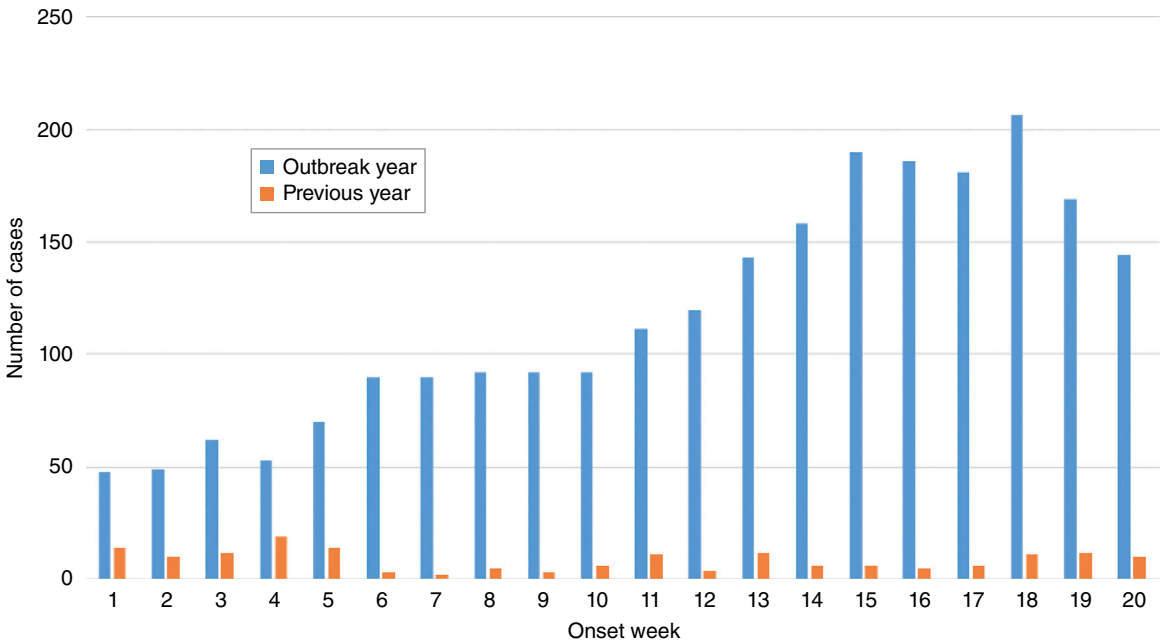

Figure I-15 Pertussis cases reported for the first weeks of the outbreak year and previous year. Source: Adapted from Centers for Disease Control and Prevention, *MMWR Morb Mortal Wkly Rep* **61:**517–522, 2012.

High incidence rates of pertussis were observed among pediatric patients that were less than 1 year old. This was not unexpected, given that infants do not begin being immunized against the pertussis pathogen until 2 months of age. The immunization schedule continues at 4 months, 6 months, 15 months, 4 to 6 years, and 11 years. As a result, very young infants have no or only partial immunity to the pathogen. However, the highest incidence rates of pertussis were observed in 10-year-old children and adolescents that were 13 to 14 years old.

The outcome of the disease varies significantly with age, with infants being more likely to have serious complications that require hospitalized care. Hospitalization was required for 34 of 155 infants less than 1 year old. Fourteen of the 34 infants hospitalized were less than 2 months of age.

For older children (more than 1 year old) and adolescents, the risk of hospitalization is much lower. Only 14 of 2,360 pertussis patients more than 1 year old were hospitalized.

No fatalities occurred in Washington state associated with this outbreak.

Approximately 76% of pertussis patients aged 3 months to 10 years for which vaccination status could be determined were up to date. Vaccination does not always prevent someone from developing pertussis. Developing disease is the result of a complex interaction between a person's current immunity

Outbreak I-15 continues on next page

level, his or her current health status, the infectious dose, the virulence factors of the pathogen, etc. Although vaccinated children can develop pertussis, they are less infectious, have milder symptoms and shorter illness duration, and are at reduced risk for severe outcomes, including hospitalization.

During the year of and the year preceding the outbreak, 4.5% of school children in the state of Washington were exempted from vaccinations normally required to attend public schools. Washington state law allows medical, philosophical, and religious exemptions from vaccination for school and day care attendance. This is obtained by completing a form by checking a box for exemption status, signing the form, and having it also signed by a physician, physician assistant, osteopath, naturopath, or advanced registered nurse practitioner licensed in Washington state. If there is an epidemic of a vaccine-preventable disease, children who are not vaccinated may be required to stay home from school until the epidemic is over.

Content Questions

1. What pathogen causes pertussis?
2. What are the characteristics of the pathogen that causes pertussis?
3. Which week reported the highest number of cases?
4. What is a toxoid vaccination?
5. What other toxoids are included with the diphtheria-pertussis-tetanus (DPT) vaccination?
6. What is an incidence rate?
7. What was the risk of hospitalization for infants less than 2 months of age?
8. What was the risk of hospitalization for infants less than 1 year old?
9. What was the risk of hospitalization for older children and adolescents?
10. Who is at highest risk for serious complications?
11. What was the mortality risk?
12. How would you treat a child with pertussis?

Diagnosis Questions

1. What specimen is taken to identify the pathogen?
2. What laboratory test can be used to identify the pathogen?

Reason It Out Questions

1. With school beginning in August, do you expect the number of cases to increase or decrease?
2. What age group would potentially be the most easily infected by the pertussis pathogen?
3. Why were the highest incidence rates of pertussis observed in 10-year-old children?
4. What are the benefits of vaccination?
5. Why do some people choose not to get their children vaccinated?
6. How would you prevent the spread of the pathogen to family members?

COLLEGE PERSPECTIVE

A Mumps Outbreak on a University Campus—California

Western Europe has periodic mumps epidemics. These can be caused in part by segments of the population lacking the recommended two doses of the measles-mumps-rubella (MMR) vaccination, or it may be that immunity wanes after vaccination. As a result, traveling to Western Europe can result in exposure to the mumps virus.

The index patient was a 21-year-old male college student who had traveled to Western Europe. After returning, he experienced a headache, muscle aches, and a slight fever. He went to the university health service with a fever; one side of his face and jaw ached and was very swollen. Health services diagnosed him with cellulitis, a bacterial infection of the subcutaneous tissues under the skin that causes pain and swelling. They prescribed appropriate antibiotics for the diagnosis.

Six days later, he returned to the health service because his testicles had developed pain, swelling, and redness. His current orchitis and earlier symptoms combined with his lack of vaccination and his travel history resulted in the presumptive diagnosis being revised to mumps. The index patient was referred to the hospital for a blood test to confirm his diagnosis, but he did not follow through. His suspected case of mumps was not reported to the local health department.

Before widespread vaccination, mumps was a childhood disease. Typically, childhood diseases increase in severity with age. Infection with the mumps virus is often asymptomatic when infecting small children, as are about one-third of other respiratory pathogens. In vaccinated populations, the percentage of asymptomatic infections is high even in older patients. However, older individuals, even those who have been vaccinated, can get mumps. Postpubescent males who get mumps have a significantly higher risk of suffering from complications. The probability of developing orchitis is 25% for postpubescent males.

Three weeks after suspected diagnosis of the first case, the index patient's roommate, a 21-year-old male, became ill. He had a swollen neck and jaw even though he had received the recommended two doses of the MMR vaccine as a child. He received a diagnosis of parotitis. A blood sample was taken for serological testing for infection with the mumps virus. He was advised to isolate himself in his room for 5 days. Shortly after, three additional cases of mumps among students were confirmed by PCR analysis and an outbreak investigation was initiated.

The investigation revealed that the outbreak involved 27 students and one close contact of a student (Fig. I-16). All of the viral specimens that were analyzed were genotype G, the predominant type circulating in Western Europe. Twenty-two of the cases occurred among persons previously vaccinated with the recommended two doses of the MMR vaccine. Seventeen of the cases occurred in students living in the college dormitories. The university moved some early patients to alternative housing, but as the outbreak spread, those who developed the disease later were not moved.

Because at least two generations of transmission had occurred before public health officials were notified of the mumps outbreak, the MMR vaccine was recommended to all students regardless of current vaccination status in order to avert a larger outbreak. The university had 36,000 enrolled students, and ~9,300 were living in university housing. Vaccination clinics were held during a 4-week period, and 3,631 persons received a dose of the MMR vaccine. One of the public health staff members who assisted during a mumps vaccination clinic was infected and got mumps.

Outbreak I-16 continues on next page

OUTBREAK I-16 *(continued)*

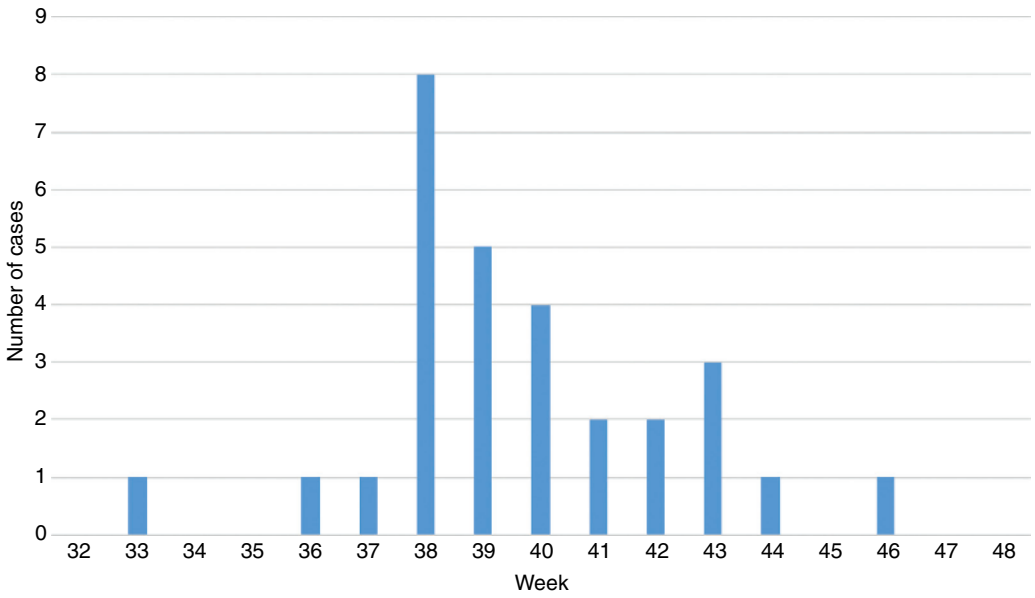

Figure I-16 Number of mumps cases by week of illness onset. Source: Adapted from Centers for Disease Control and Prevention, *MMWR Morb Mortal Wkly Rep* **61:**986–989, 2012.

Content Questions

1. What is herd immunity?
2. Does herd immunity protect everyone from disease? Why or why not?
3. How is mumps normally prevented?
4. What serious complications can occur with mumps?
5. What are the physical characteristics of the mumps virus?
6. Are individuals with the mumps infectious before signs and symptoms appear?
7. How long after the onset of parotitis does an individual with mumps remain infectious?
8. How does the mumps virus cause disease?
9. What is the efficacy of the mumps vaccination?
10. What type of epidemic curve is shown in the figure?

Diagnosis Questions

1. What sample would be used to test for a mumps virus infection?
2. What lab tests can be used to positively test for infection by the mumps virus?
3. How is serological testing for acute mumps virus infection done in a vaccinated individual?
4. What does the PCR assay measure when testing for the mumps virus in a clinical sample?

Reason It Out Questions

1. Why do individuals who have had all their childhood vaccinations get childhood diseases such as mumps?
2. How should public health workers be protected from the mumps virus while giving vaccinations?
3. Why did the majority of mumps cases occur in students who lived in the dormitories?
4. Why do many schools require proof of vaccination before children can enter elementary school?
5. Why is the incidence of mumps higher in Western Europe than in the United States?
6. List three reasons why parents may not have their children vaccinated and provide a logical/factual argument that would encourage someone to choose to be vaccinated.

OUTBREAK I-17

GLOBAL PERSPECTIVE

A Diphtheria Outbreak—Colombia

Santiago de Cali is the capital of the Valle del Cauca province in Colombia. It has a population of 2 million people, with marked differences in their socioeconomic levels and living conditions. For a decade, the diphtheria-pertussis-tetanus (DPT) vaccination coverage for children less than 1 year old in Cali varied widely (Fig. I-17). Coverage was nearly 100% in some years but at one time declined to below 60%. The decline in vaccination coverage was probably the result of an economic crisis that affected the national and local health sector, along with a major reorganization of the health care system.

The DPT vaccine contains diphtheria and tetanus toxoids and killed whole cells of the bacteria that cause pertussis. The primary series of DPT vaccines should be given in three doses to all infants, starting at a minimum age of 6 weeks and given at 4-week intervals. One or two booster doses are given for better protection against the disease, the first at 16 to 24 months of age and the second at 4 to 7 years of age.

When vaccine coverage was the lowest, an outbreak of diphtheria occurred in Cali, with eight confirmed cases. The first reported patient was a 3-year-old girl. Hers was the only fatal case. Of the eight confirmed patients, six were 10 years old or less. One was vaccinated, five had had an incomplete series of vaccinations, and two were unvaccinated.

The 3-year-old girl who had the lethal case was part of a household of 26 family members living in the southeast part of the city. They all shared the same overcrowded dwelling and lived in extreme poverty. Over the next 4 weeks, four of the girl's brothers were diagnosed with the disease. Ten weeks later, two additional but unrelated people developed the disease. However, there was no obvious link to the previous cases. The new cases occurred in the northeast area of the city. The last case of the outbreak appeared a week later, in a 19-year-old residing in a community in the southeastern area of the city. It also did not have any epidemiological link with any of the previous cases.

All the patients with diphtheria, regardless of location in the city, belonged to the same socioeconomic stratum. They lived in overcrowded dwellings, had inadequate disposal of excreta and difficult access to drinking water and sewerage services, and had unmet basic needs associated with dire poverty.

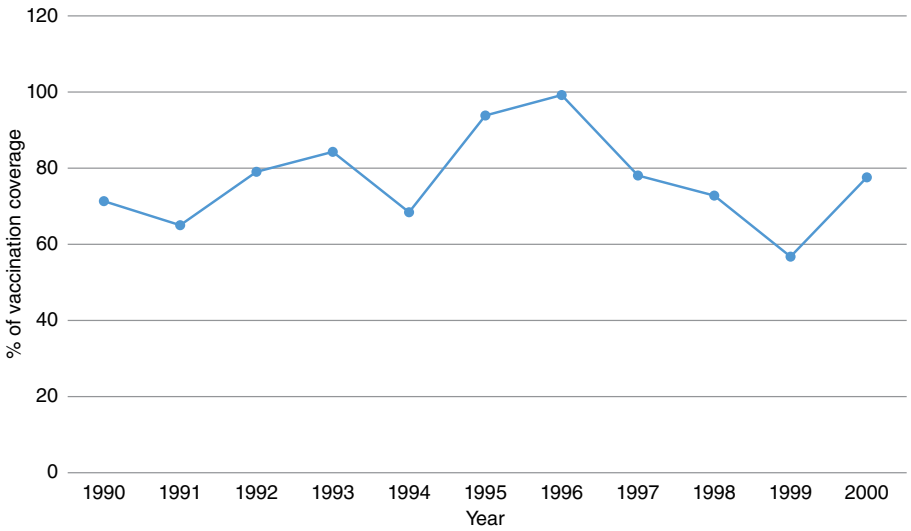

Figure I-17 DPT vaccination coverage in Cali for children <1 year old. Source: Adapted from Landazabal García N, et al, *Epidemiol Bull* **22:**13–15, 2001.

Content Questions

1. What pathogen causes diphtheria?
2. How does the diphtheria toxin damage cells?
3. What are the clinical signs and symptoms of diphtheria?
4. What was the average DPT vaccination coverage from 1990 to 2000?

Diagnosis Questions

1. What specimen would be taken for a microbiological test for diphtheria?
2. What laboratory tests are required to confirm a case of diphtheria?

Reason It Out Questions

1. What is a booster vaccination?
2. What checkpoints are in place in the United States to ensure widespread coverage of the childhood vaccinations?
3. Why was the vaccinated individual able to get the disease?
4. Why was it significant that the last case did not have any epidemiological link with any of the previous cases?
5. Explain why each of the factors below increases the risk for the spread of infectious disease.

   Overcrowded dwellings

   Inadequate excreta disposal

   Difficult access to drinking water and sewerage services

   Unmet basic needs associated with dire poverty

REFERENCE MATERIAL

Chickenpox

Since the introduction of the varicella vaccine in 1995, the number of new cases of chickenpox has declined by an estimated 95%. As a result, the CDC predicts that the varicella vaccine prevents more than 3.5 million cases of chickenpox, 9,000 hospitalizations, and 100 deaths each year in the United States. As vaccine coverage remains high for children, the epidemiology of chickenpox will change, and the proportion of individuals who get the disease as adults will increase. Adults are more likely than children to die or have serious complications if they get chickenpox.

Cause

Varicella-zoster virus (VZV), a member of the herpes family of viruses, is the causative agent of chickenpox. It is an enveloped virus with a polyhedral capsid which contains double-stranded DNA as genetic information.

Transmission

- **Reservoir:** Infected humans
- **Mode of transmission:** Droplet mode during coughing and sneezing, direct contact with infected lesions or contaminated fomites

Pathogenesis

- **Entry:** Respiratory route via mucus droplets
- **Attachment:** A protein on the envelope of the virus attaches to the epithelium of the respiratory tract
- **Spread:** Infected leukocytes carry the virus to lymphoid tissues. Virus released from lymphoid tissue is disseminated throughout blood and lymph. The virus is carried through the blood to sites outside capillaries under the skin.
- **Avoidance of host defenses:** VZV is an intracellular pathogen which initially avoids destruction by circulating antibodies and cells of the immune system. During primary infection, the virus is carried to reticuloendothelial organs for viral amplification, causing a secondary viremia. It is during this phase that the virus is seeded into the skin. Also, VZV forms a provirus in the cell bodies of nerve cells near the spinal cord (dorsal root ganglia) of sensory neurons. A provirus forms when a virus incorporates its DNA into the chromosome of the host cell. In this state, the provirus can remain dormant. If it becomes active, a secondary outbreak known as shingles can occur.
- **Damage:** The virus induces formation of syncytia (large multinucleated fused cells) under the skin and induces a local inflammatory response.

Clinical Features

Incubation is 10 to 23 days. The distinguishing feature of chickenpox is a vesicular rash on the scalp, head, and trunk which progresses to the extremities. Other signs and symptoms include a fever, headache, fatigue, sore throat, anorexia (loss of appetite), irritability, and pruritus (itching). The vesicles turn pustular (filled with pus), form a crust, form a scab, and then heal. A secondary outbreak of VSV called shingles can also occur and typically affects the elderly. Shingles result when the dormant provirus becomes active, resulting in a vesicular/pustular rash breaking out along the ends of the cranial or spinal nerve that the virus infected. Shingles causes intense pain.

Diagnosis

Diagnosis of VZV infection is done by clinical presentation alone. No lab specimens or tests are necessary.

Treatment

The primary treatment for chickenpox is supportive care. Over-the-counter medications are often used, such as antihistamines to reduce itching, calamine lotion to help dry vesicles, and ibuprofen or acetaminophen to reduce fever. Fluids and electrolytes are given to prevent dehydration from the fever. It is also important to monitor and treat secondary bacterial infections.

Rare complications such as herpes encephalitis are treated with acyclovir, a herpesvirus-specific agent. Acyclovir is a nucleoside analog of guanosine that blocks DNA synthesis in herpesvirus-infected cells.

Prevention

- An effective vaccine is available.
- Unvaccinated individuals should wash their hands regularly and avoid touching their eyes and nose. Avoiding contact with infected individuals can be difficult, since individuals are infectious several days before the rash appears. Infected individuals can help prevent spread by covering their mouths when coughing and sneezing.
- For shingles, an effective vaccination is available and is given to people at ~60 years of age. If an individual develops shingles, injection of local anesthetic early following breakout results in pain relief and accelerated healing.

Diphtheria

Diphtheria is a serious, life-threatening disease. Even with treatment, 1 of 10 people who contract this disease die. Although diphtheria has been brought under control in the developed world by widespread use of an effective childhood toxoid immunization, political turmoil, wars, mass refugee migrations, and large natural disasters can result in the collapse of the health care structure and the long-term interruption of vaccination programs. Consequently, there can be a dramatic increase in the number of cases of diphtheria that develop.

Cause

Corynebacterium diphtheriae, a Gram-positive bacillus that can produce a potent cytotoxin when carrying a prophage with the *tox* gene, is the causative agent of diphtheria.

Transmission

- **Reservoir:** Symptomatic and asymptomatic carriers of the pathogen
- **Mode of transmission:** Contact mode via respiratory droplets, fomites, or direct contact

Pathogenesis

- **Entry:** The pathogen is principally spread from person to person via the respiratory tract.
- **Attachment:** *C. diphtheriae* attaches to the epithelial tissue of the tonsils and the pharynx.
- **Avoidance of host defenses:** *C. diphtheriae* infects the epithelial layer and initially avoids circulating antibodies and cells of the immune system.
- **Damage:** The cytotoxin that is produced by bacteriophage-infected organisms inhibits cellular protein synthesis, causing cell death. This leads to necrosis of the infected and surrounding tissues. This also allows entry into the bloodstream, leading to damage of internal organs.

Clinical Features

The disease begins with pharyngitis. The cytotoxin causes tissue death, leading to a bluish gray and then black membrane of necrotic (dead) tissue on the soft palate (diphtheritic membrane). The intense inflammatory response results in extensive swelling of the cervical lymph nodes, giving a "bull neck" appearance. The toxin enters the blood and lymph vessels, causing the systemic effects of the disease, including low-grade fever, exhaustion, electrocardiographic changes, and possible cardiac failure. The toxin can also damage motor neurons, causing paralysis of the soft palate, which results in the regurgitation of fluids, and paralysis of the muscles of the diaphragm.

Diagnosis

- **Clinical:** Physical features include a bull neck appearance from enlarged cervical lymph nodes and the presence of the diphtheritic membrane, a bluish-gray membrane on the pharynx that becomes black and necrotic.
- **Laboratory**
  - **Specimen:** Pharyngeal swab of any discolored areas or ulcerations.
  - **Cultural tests:** Growth on serum tellurite agar is selective for *Corynebacterium*, giving characteristic gray or black colonies. Gram staining of isolated colonies shows multiple club-shaped forms that look like Chinese character writing. The production of toxin is detected by using immunoelectrophoresis is required to demonstrate that the *Corynebacterium* isolate is pathogenic.

Treatment

Patients are typically kept in isolation until they have been on erythromycin or penicillin for 48 hours and elimination of the pathogen has been documented by culture. Patients also receive diphtheria antitoxin, which is administered as soon as diphtheria is suspected, without waiting for laboratory confirmation. The antitoxin inactivates the toxin in the bloodstream.

Prevention

- To prevent diphtheria, a highly effective vaccination series is administered to children. It begins with a combination vaccine, the DPT vaccine. The vaccine contains denatured toxins that protect against diphtheria, tetanus, and an acellular pertussis vaccine. The denatured toxins are called toxoids. They stimulate a protective immune response but are not pathogenic.

- Diphtheria is a highly contagious disease that requires strict isolation to reduce the risk of spreading the infective bacillus.

Hantavirus Pulmonary Syndrome

Hantavirus pulmonary syndrome was first characterized during an outbreak in 1993 in the Four Corners area of the United States. Although most cases are found in the southwestern United States, the pathogen is more widely distributed with its rodent hosts.

Cause

Sin Nombre virus (hantavirus), a virus with an enveloped, icosahedral capsid (a protein shell with 20 sides) and single-stranded RNA for genetic information, is the cause of hantavirus pulmonary syndrome.

Transmission

- **Reservoir:** The disease is a zoonosis. Four species of rodents are the reservoir for the virus: the deer mouse, the cotton rat, the rice rat, and the white-footed mouse.
- **Mode of transmission:** The virus is airborne and typically transmitted by inhaling aerosols from dried rodent urine or feces from rodents that were infected by the virus. The pathogen is not transmitted from person to person.

Pathogenesis

- **Entry:** The virus enters the lungs as an airborne pathogen.
- **Attachment:** The pathogen attaches to alveolar macrophages and endothelial cells.
- **Avoidance of host defenses:** The pathogen is an intracellular pathogen, so it initially avoids circulating antibodies and cells of the immune system.
- **Damage:** The damage caused by the virus results in a complex pathophysiology. One key to the damage is that the virus destroys endothelial cells, causing hemorrhaging and fluid loss. When the virus is concentrated in the lungs, this causes a sudden life-threatening pneumonia.
- **Exit:** The disease is not spread from person to person.

Clinical Features

Early signs and symptoms include fever, fatigue, and muscle aches and can include headaches, dizziness, chills, and abdominal problems. Hantavirus pulmonary syndrome is a difficult disease to recognize from early symptoms, since they resemble those of common illnesses which are treatable. The fever, headaches, and myalgia are rapidly followed by a nonproductive cough with rapid onset of respiratory failure. The disease progresses rapidly after early symptoms develop, necessitating hospitalization and often ventilation.

Diagnosis

- **Specimen:** Blood serum sample.
- **Test:** The CDC uses an enzyme-linked immunosorbent assay (ELISA) to detect hantaviral infections.

Treatment

Intense supportive care in the hospital is needed to manage fluid loss and lung damage. Broad-spectrum antibiotics have been used to prevent secondary bacterial infections that may complicate the disease further.

Prevention

- Prevention focuses on reducing suitable environments for rodents in and around homes.
- Food should be stored in tightly closed, rodent-proof containers.
- All garbage should be discarded in rodent-proof containers and disposed of regularly.
- Habitats for rodents, such as brush or woodpiles, near homes should be eliminated or moved.
- Traps can be set both inside and outside the home.
- Since sweeping or vacuuming can aerosolize dried rodent urine or feces, contaminated areas should be first wetted with disinfectant.

Influenza

Worldwide, pneumonia is the number one cause of death from infectious disease, causing about 3 million deaths per year. Influenza is the most common cause of viral pneumonia.

Tens of millions of people are infected by an influenza virus each year in the United States. Influenza is the leading reason for a physician's visit for all infectious diseases. Depending on the strain of influenza circulating and the effectiveness of the vaccine, there are about 20,000 to 80,000 deaths from influenza each year.

Cause

Influenza is caused by the influenza viruses (A, B, and C). Influenza A and B viruses cause the most serious illnesses. Influenza A and B viruses are enveloped viruses belonging to the orthomyxovirus family ("*myxo*" is Greek for "mucus"). The viruses have a pleomorphic capsid and multiple segments of single-stranded, negative-sense RNA for genetic information. The virus is classified based on two different proteins embedded in the envelope: hemagglutinin (H protein) and neuraminidase (N protein).

Transmission

- **Reservoir:** The reservoir for influenza A virus is humans but also includes birds and a variety of mammals, including swine. The reservoir for influenza B virus is primarily humans.
- **Mode of transmission:** The influenza viruses are spread by respiratory droplets produced during coughing and sneezing. They can also be spread via fomites, i.e., by touching contaminated objects and then touching the nose or eyes.

Pathogenesis

- **Entry:** The virus enters by fomites or inhaling mucus droplets carrying the pathogen.
- **Attachment:** The virus uses the H protein to attach to the ciliated respiratory epithelium.
- **Avoidance of host defenses:** The pathogen is intracellular, and infection is restricted to the surface of the respiratory tract, resulting in the pathogen initially avoiding circulating antibodies and cells of the immune system.
  - Both influenza A and B viruses can undergo antigenic drift, whereby they accumulate point mutations in the H and N proteins. Over time, these key antigens change their structure sufficiently that the immune response from previous infections of a host will not provide immunity. Influenza A virus undergoes antigenic drift more rapidly than influenza B virus.
  - Influenza A virus can also undergo antigenic shifts. These occur when a human and animal virus recombine in a single host, typically swine. If the resulting unique recombinant virus can be easily spread between humans, it can cause a pandemic.
- **Damage:** Influenza viruses destroy the tissue lining the respiratory epithelium. The tissue damage induces an inflammatory response that accounts for the clinical features of the disease. Tissue damage also makes an infected host more susceptible to secondary bacterial pneumonia.
- **Exit:** The virus exits through respiratory droplets.

Clinical Features

The average incubation period for influenza is 2 days. Influenza usually starts suddenly and may include these symptoms: fever (usually high), headache, tiredness (can be extreme), cough, runny or stuffy nose, body aches, and sore throat. Diarrhea and vomiting also can occur but are more common in children. Influenza results in pneumonia and death primarily as a result of the infection compromising the normal defenses of the respiratory tract, increasing the risk for secondary bacterial infections. Older adults (>65 years old) account for ~90% of deaths attributed to influenza.

Diagnosis

- **Specimen:** Throat swab, nasal wash, or nasal swab, depending on the type of test used.
- **Test:** Rapid ELISA detects influenza viruses within 30 minutes.

Treatment

- There are three classes of antivirals for treating influenza virus infections. Neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir) prevent release of the virus from the host cell, while baloxavir marboxil is a polymerase acidic endonuclease inhibitor. These antivirals are active against both influenza A and B viruses. M2 protein channel inhibitors (amantadine and rimantadine) block uncoating of the virus. They are specific for influenza A virus, and resistance is widespread. All are effective at reducing the severity and duration of influenza if given within the first 48 hours of clinical signs and symptoms.
- Therapy for symptoms includes bed rest, drinking plenty of fluids to prevent dehydration, and using analgesics to reduce pain and fever. (Aspirin is not used as a pain reliever because of an increased risk of Reye's syndrome in children and adolescents.)

Prevention

- The influenza vaccine consists of inactivated and attenuated live viruses that are prepared from the two dominant variants of influenza A virus and the one dominant version of influenza B virus from the previous year. As a result, the vaccine is effective if the virus does not undergo significant genetic drift or an antigenic shift.
- Other prevention strategies include covering one's mouth when coughing or sneezing, avoiding others with the flu, frequent and thorough handwashing, and avoiding touching the eyes and nose.

Legionnaires' Disease

A serious pulmonary infection attacked 235 people who were attending a convention of the American Legion in Philadelphia during the U.S. Bicentennial celebration in July 1976; 34 people died.

Cause

Legionella pneumophila, a bacterial pathogen, causes Legionnaires' disease. It is a Gram-negative, aerobic bacillus that contains a capsule and has fastidious growth requirements.

Transmission

- **Reservoir:** Free-living in soil and stagnant water (25 to 42°C). *Legionella* can contaminate large air-conditioning systems that use water in cooling towers.

- **Mode of transmission:** Inhalation of aerosolized droplets containing *Legionella*. The pathogen is not spread from person to person. Most infections occur in patients who have compromised immunity and pulmonary function.

Pathogenesis

- **Entry:** Inhalation of aerosols containing *Legionella*
- **Attachment:** *Legionella* attaches to alveolar sacs.
- **Avoidance of host defenses:** *Legionella* is phagocytized by alveolar macrophages but avoids destruction by preventing fusion with lysosomes. *Legionella* replicates inside the macrophage and causes cell lysis.
- **Damage:** *Legionella* causes direct damage through cell lysis and indirect damage by inducing an inflammatory response and producing damaging enzymes and toxins. After lysing macrophages, the bacteria spread and continue to cause damage and inflammation, resulting in bronchial hemorrhaging and abscesses.
- **Exit:** *L. pneumophila* is rarely transmitted from person to person; therefore, exit from the lungs is rare.

Clinical Features

- Most infections are asymptomatic or produce only mild symptoms.
- The incubation period is 2 to 10 days, normally being 5 to 6 days.
- Symptoms include fever and chills, a nonproductive cough, difficulty breathing, confusion, headache, and muscle pain.

Diagnosis

- **Clinical:** Evidence of pneumonia including rales (crackling sounds in the lungs indicating fluid accumulation) and a chest X ray showing fluid in the lungs.
- **Laboratory testing**
  - **Sample:** Sputum, urine
  - **Culture testing:** Grows slowly on a buffered cysteine-containing charcoal yeast extract agar.
  - **Nonculture testing:** Urinary antigen test detects serogroup 1. Positive tests are confirmed by culture. Tests for other serogroups include indirect immunofluorescence microscopy, rapid microagglutination tests, and DNA analysis.

Treatment

Macrolides and respiratory fluoroquinolones are used to treat Legionnaires' disease. Respiratory therapy is often required for the seriously ill patient.

Prevention

- Regular maintenance and adequate chlorination of ventilation systems and other potential reservoirs
- Maintaining water reservoir temperature at >60°C or <20°C
- Avoiding water stagnation
- Avoiding smoking and excessive alcohol consumption, which can lower resistance to the pathogen

Measles

Measles is probably the greatest killer of children in history. Despite the availability of an effective vaccine that was developed more than 50 years ago, the measles virus remains the leading cause of vaccine-preventable deaths worldwide. In the United States, occasional measles outbreaks occur as a result of cases imported from abroad. Most of these cases occur in unvaccinated U.S. residents who are exposed while traveling. These individuals return and infect susceptible contacts.

Cause

Measles virus, a member of the paramyxovirus family, causes measles. It is an enveloped virus with a helical capsid which contains single-stranded RNA with a negative-sense polarity as genetic information.

Transmission

- **Reservoir:** Symptomatic humans
- **Mode of transmission:** Airborne and contact mode. Airborne viral particles are stable for 2 hours when suspended in air but are quickly inactivated upon landing on surfaces.

Pathogenesis

- **Entry:** Inhalation of airborne particles or mucus droplets
- **Attachment:** Envelope proteins attach to the CD150 receptor on host cells in the respiratory epithelium. The virus infects dendritic cells or $CD150^+$ myeloid or lymphoid cells in the mucociliary epithelium or the alveoli.
- **Spread:** The measles virus-infected myeloid cells migrate to the draining lymph nodes, where the virus replicates and causes a secondary viremia. Virus-infected cells migrate systemically to other organs, including tissues under the skin.
- **Damage:** The measles virus damages the host cells it infects. After infecting lymphocytes and dendritic cells, cells of the respiratory epithelium are infected are destroyed and shed infectious virus particles. Damage results in an inflammatory response and fluid accumulation, which can restrict gas exchange. Replication of the virus in lymphoid tissues results

in depletion of lymphocytes and significant but transient immunosuppression. Infection of tissues under the skin results in a local inflammatory response, causing the rash formation.

- **Exit:** The pathogen exits via respiratory route. The virus continues to be shed for 3 to 4 days once the rash is gone.

Clinical Features

The incubation period is typically 10 to 14 days and is followed by an acute respiratory illness, including runny nose, fever, conjunctivitis, and cough. The fever rises steadily until the appearance of the rash 2 to 4 days later. A maculopapular rash (red, slightly raised spots) begins on the face and spreads down to the trunk and outward toward the extremities. Koplik spots (pinpoint blue-white spots on a red background) appear on the inside of the cheeks (buccal mucosa) of the mouth 1 to 2 days before the rash

Serious complications such as pneumonia and encephalitis occur in about 4% of cases.

Diagnosis

Clinical features are used to diagnose the disease. Koplik spots, a maculopapular rash spreading from the head down, fever, and conjunctivitis indicate measles.

Treatment

There are no antiviral medications for inhibiting the measles virus. Treatment addresses symptoms and commonly includes bed rest, intake of fluids and electrolytes to replace those lost because of the fever, and over-the-counter medications for fever and headache, such as acetaminophen or ibuprofen.

Prevention

- A highly effective live attenuated (immunogenic but not pathogenic) measles vaccine given most commonly to children as the MMR vaccine protects against measles, mumps, and rubella.
- Infected individuals should be isolated due to the highly contagious nature of the disease.

Mononucleosis

Development of mononucleosis is associated with socioeconomic status. The poor are typically infected when young and develop only a mild disease. However, higher socioeconomic groups are more likely to become infected as adults or adolescents. This has been attributed to children in lower socioeconomic groups living in more crowded conditions as opposed to growing up with a room to themselves.

Cause

Epstein-Barr virus (EBV), a herpesvirus with an envelope with a polyhedral capsid and double-stranded DNA as genetic information, is the cause of mononucleosis.

Transmission

- **Reservoir:** Infected humans; symptomatic and asymptomatic individuals can shed virus for months after disease.
- **Mode of transmission:** Direct contact with infected saliva or contaminated fomites

Pathogenesis

- **Entry:** Oral entry via direct contact with infected saliva
- **Attachment:** Proteins in the envelope of EBV attach to receptors on the epithelium of the oropharynx and to B lymphocytes.
- **Avoidance of host defenses:** EBV is an intracellular pathogen which is not initially exposed to circulating antibodies and other cells of the immune system.
- **Damage:** Activated T lymphocytes attack infected B lymphocytes, resulting in a large amount of cytokines, which are released systemically and cause the symptoms of the disease.
- **Exit:** Virus is shed in saliva from infected epithelial cells and lymphocytes in salivary glands and the pharynx.

Clinical Features

Children most often have asymptomatic infections. Adolescents and adults present with mononucleosis. The infection has a 4- to 7-week incubation period followed by a fever for 1 to 3 weeks, with tonsillitis, swollen lymph nodes (lymphadenopathy), enlarged liver and spleen (hepatosplenomegaly), and extreme fatigue.

Diagnosis

The presence of atypical lymphocytes in the blood in conjunction with the clinical signs and symptoms

Treatment

Antibiotics are not effective against a viral disease and can cause complications. Therefore, mononucleosis is treated with supportive care, including bed rest, fever, ibuprofen or acetaminophen to reduce fever, throat lozenges for sore throat, and fluids and electrolytes to prevent dehydration.

Prevention

- Prevention is very difficult because EBV is a ubiquitous pathogen which is shed for long periods of time by asymptomatic carriers.
- Risk can be decreased by frequent handwashing.

Mumps

Mumps is a highly contagious disease. Without immunization, between 1 out of every 100 and 1 out of every 1,000 people are affected per year. Mumps remains

a common disease in parts of Europe, Asia, the Pacific, and Africa. Those who travel internationally should be protected against mumps.

Cause

The mumps virus, an enveloped virus with a polyhedral capsid and negative-sense single-stranded RNA, is the cause of mumps.

Transmission

- **Reservoir:** Humans only
- **Transmission:** Contact mode via respiratory droplets, fomites, or direct contact

Pathogenesis

- **Entry:** Mucus droplets enter the pharynx or conjunctiva.
- **Attachment:** The HN protein on the virus envelope connects to the sialic acid glycoprotein receptor on cell surfaces.
- **Avoidance of host defenses:** The virus replicates intracellularly to avoid contact with circulating antibodies and cytotoxic T cells.
- **Damage:** The pathogen replicates in the nasopharynx and regional lymph nodes. Viremia results when lymph circulates throughout body. Viral damage causes inflammation in salivary glands, meninges, and potentially the pancreas and the testes or ovaries.
- **Exit:** Virus is present in salivary secretions. Six days before the onset of symptoms, the virus is detectable in salivary gland secretions. This continues for 5 days after symptoms start.

Clinical Features

Symptoms begin 16 to 18 days after exposure and resolve after 7 to 10 days. Early symptoms include headaches, malaise, myalgia, anorexia, ear pain, and low-grade fever. One to 2 days later, one or both parotid glands become painful and swollen. The submandibular and sublingual glands may also be involved. Other common symptoms include fever, chills, nausea, vomiting, lower abdominal pain, meningitis, and inflammation of the testis (orchitis)/ovaries (oophoritis) and pancreas (pancreatitis).

Diagnosis

- **Specimen:** Buccal swab
- **Test:** Reverse transcriptase PCR is used to amplify the mumps virus DNA for analysis.

Treatment

Only therapy for symptoms is available. This includes rest, ice to reduce swelling, acetaminophen or ibuprofen to reduce fever and relieve pain, and fluids to prevent dehydration.

Prevention

The MMR vaccine is about 90% effective with two doses. Frequent handwashing is recommended. Avoid touching the eyes and face.

Mycoplasmal Pneumonia

Mycoplasma pneumoniae infections are the second most common cause of pneumonia-related hospitalization in adults with community-acquired pneumonia. Over 2 million *M. pneumoniae* infections occur each year in the United States. This disease is known as walking pneumonia because the illness begins with an extended period of milder symptoms before serious illness. The incubation period averages 3 weeks, in contrast to that of other bacterial pneumonias and influenza, which generally develop in a few days. Only about 3% of infections with *M. pneumoniae* result in pneumonia, with most of the rest causing upper respiratory tract infections. Transmission of *Mycoplasma* requires prolonged exposure to an infected individual; consequently, epidemics of mycoplasmal pneumonia tend to occur more frequently within closed populations, such as in military and institutionalized populations, prisons, and colleges.

Cause

Mycoplasma pneumoniae, a very small, wall-less bacterial pathogen that has a pleomorphic shape (many different forms), is the cause of mycoplasmal pneumonia.

Transmission

- **Reservoir:** Infected humans
- **Mode of transmission:** Contact mode via respiratory droplets and direct contact.

Pathogenesis

- **Entry:** The pathogen enters the respiratory system after prolonged, close exposure to an infected host.
- **Attachment:** The pathogen uses gliding motility to reach the epithelial cell surface, where it attaches to fibronectin using its tip structure, where adhesion proteins are concentrated.
- **Avoidance of host defenses:** Gliding motility facilitates penetration of the pathogen through the mucus of the respiratory tract. The pathogen lodges between microvilli and cilia, preventing phagocytosis. Intracellular localization may be responsible for protecting the pathogen from antibodies. The pathogen uses antigenic variation of surface adhesins.
- **Damage:** Tissue damage is caused by the community-acquired respiratory distress syndrome toxin. Tissue damage promotes the production of proinflammatory cytokines and acute inflammatory response.
- **Exit:** The pathogen exits the respiratory tract in mucus droplets.

Clinical Features

About two-thirds of the respiratory infections caused by *M. pneumoniae* result in bronchitis. Onset of pneumonia occurs slowly about 2 to 4 weeks after infection. There is a gradual onset of fever, headache, and a constant, nonproductive cough. As the disease progresses, rales (crackling sounds in the lungs indicating fluid) are detected, and chest X rays reveal fluid accumulation in one or more lobes of the lungs.

Diagnosis

- **Specimen:** Sputum or a nasopharyngeal swab is used as a sample.
- **Test:** Real-time PCR using *M. pneumoniae*-specific primers or PCR-based nucleic amplification in commercially available systems that test for many different respiratory pathogens simultaneously.

Treatment

Doxycycline, azithromycin, and fluoroquinolones are effective at treating the disease.

Prevention

- Avoid close contact with acutely ill individuals.
- Practice frequent and thorough handwashing.

Otitis Media (Middle Ear Infection)

Otitis media is the most common reason parents bring their children to the doctor. Because Eustachian tubes are smaller and more level in children than they are in adults, drainage of the fluid in the ear is more difficult. Also, if the Eustachian tubes are swollen or blocked with mucus due to a cold or other respiratory illness, fluid is even less likely to drain. However, with the introduction of the pneumococcal conjugate vaccine, otitis media has decreased, with 20% of children in the U.S. having an episode before their first birthday and 60% of children having one by their third birthday.

Cause

- Bacteria are responsible for most (~85%) cases of acute otitis media. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, and *Staphylococcus aureus* are bacterial pathogens commonly associated with acute otitis media.
- Acute otitis media frequently occurs with respiratory infections, as the nasal membrane and the Eustachian tube become swollen and congested.

Transmission

- **Reservoir:** Pathogens that cause upper respiratory tract infections that lead to middle ear infections are found in many environments. Individuals at highest risk are young children in day care.
- **Mode of transmission:** Contact mode via respiratory droplets, direct contact, and fomites (nonliving intermediates that can be contaminated with the pathogen, such as tissues and children's toys).

Pathogenesis

- **Entry:** Acute otitis media is caused by bacteria (or viruses) that enter the nose or throat and ascend the Eustachian tube to reach the middle ear. Since the Eustachian tube in young children is short, pathogens are likely to be able to spread to the middle ear.
- **Attachment:** The pathogens can attach to the tissues of the pharynx or nasal cavity.
- **Avoidance of host defenses:** Infection is restricted to the epithelium, an environment that is initially protected from circulating antibodies and cells of the immune system.
- **Damage:** Children's Eustachian tubes are easily blocked by swelling caused by the infection, leading to an increase in fluid, pus, and mucus, causing pressure and pain in the middle ear.
- **Exit:** The pathogen most likely exits by mucus droplets.

Clinical Features

Older children often complain about ear pain, ear fullness, or hearing loss. Younger children may demonstrate irritability, fussiness, or difficulty in sleeping, feeding, or hearing. They may pull at their ears. Fever may be present in a child of any age. These symptoms are frequently associated with signs of upper respiratory infections, such as a runny or stuffy nose or a cough. Severe ear infections may cause the eardrum to rupture.

Diagnosis

A physician examines the ears with an otoscope. This allows the doctor to check for redness and fluid behind the ear drum. If the eardrum ruptures, a specimen of pus may be taken for culture and identification.

Treatment

- For acute otitis media cases caused by bacteria, antibiotics may be prescribed. Common antibiotics used to treat otitis media include the following.
  - **Amoxicillin:** Amoxicillin is a semisynthetic penicillin that is highly effective for treating susceptible Gram-positive cocci (*Streptococcus pneumoniae*).
  - **Amoxicillin and potassium clavulanate:** The addition of potassium clavulanate inhibits the activity of a penicillinase produced by many penicillin-resistant bacteria (*Staphylococcus aureus*).

- **Azithromycin:** Since allergic reactions to β-lactams are common, the macrolide azithromycin serves as an alternative. Azithromycin is used to treat *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.
- For viral pathogens, antibiotics are not effective. Therapy for symptoms using over-the-counter medications can help reduce the pain and congestion.

Prevention

- Breast feeding helps to pass IgA, an antibody class that prevents otitis media.
- If bottle feeding is necessary, the child should be held in an upright position. This prevents pooling of milk in the child's throat, which can lead to a buildup of bacteria that can travel into the ear.
- Children involved in large groups, such as day care, develop more frequent colds and therefore more earaches. Frequent handwashing and disinfection of toys can help reduce the spread of the pathogens.
- Second-hand tobacco smoke is also associated with otitis media and should be avoided.

Pertussis

Pertussis is an endemic disease worldwide, with approximately 15 million new infections per year mostly in the developing world. Although there is a vaccine that effectively prevents pertussis in children, protection begins to decrease after 3 to 6 years. Currently, those most commonly infected are adolescents, adults, and infants that have not received three doses of the vaccine. The CDC estimates that only 5 to 10% of pertussis cases are recognized and reported. In reported studies, 12 to 32% of adults with prolonged cough (1 to 4 weeks) have been found to have pertussis.

Cause

- Pertussis is caused by *Bordetella pertussis*, a bacterial pathogen.
- *Bordetella pertussis* is a Gram-negative coccobacillus. It is fastidious, requiring special media to grow in the laboratory.

Transmission

- **Reservoir:** *B. pertussis* is found only in humans. In the vaccine era, asymptomatic carriers transmit the pathogen.
- **Mode of transmission:** Pertussis is highly communicable and is transmitted by airborne particles and mucus droplets.

Pathogenesis

- **Entry:** The pathogen enters the respiratory tract by inhalation of infective droplets.
- **Attachment:** The pathogen uses fimbriae to attach to the ciliated respiratory epithelium.
- **Avoidance of host defenses:** Tracheal cytotoxin causes tissue death of the respiratory epithelium, preventing removal of the pathogen. Adenylate cyclase toxin inhibits leukocyte action. Since the infection is limited to the epithelial surface, the pathogen initially avoids circulating antibodies and cells of the immune system.
- **Damage:** Tracheal cytotoxin causes tissue death of the respiratory epithelium. The damage allows the pertussis toxin to enter the bloodstream, where it induces the systemic effects of the disease. Inflammation of the alveoli can cause pneumonia.
- **Exit:** The pathogen exits via coughing and sneezing of the host.

Clinical Features

- After infection, there is a 5- to 10-day incubation period.
- There are three stages to the disease in children. Adolescents and adults have milder disease.
  - The first stage (prodromal phase) is the initial symptomatic period, which lasts from 1 to 2 weeks and includes only mild cold-like symptoms.
  - The second stage (paroxysmal phase) lasts from 1 to 6 weeks and is characterized by a progressively worsening cough. The cough progresses to paroxysm in which 5 to 20 forcible hacking coughs are produced in 15 to 20 seconds, terminating with production of mucus or vomiting. The sudden inspiration of air produces a characteristic whooping. Death can result from lack of oxygen caused by the paroxysmal coughing.
  - During the third stage (convalescent phase), the cough still persists for several months.

Diagnosis

- **Clinical:** Paroxysmal coughing
- **Laboratory**
  - **Specimen:** Nasopharyngeal swab.
  - **Tests:** PCR to identify *B. pertussis*-specific DNA and culture of the organism for confirming diagnosis, strain identification, and antimicrobial resistance testing.

Treatment

- The macrolide antibiotics erythromycin, clarithromycin, and azithromycin are preferred for treatment. They kill the pathogen and eliminate

carriage in the nasopharynx. The earlier the treatment, the less severe the disease. Treatment after 3 weeks following onset of symptoms does not alter the course of the disease.

- Symptomatic therapies include avoiding respiratory irritants, such as smoke, that can trigger coughing; using a cool-mist vaporizer to help loosen mucus and soothe the cough; drinking plenty of fluids to prevent dehydration; and eating small meals every few hours to help prevent vomiting.

Prevention

- The DPT vaccine is safe and effective.
- Infants under 2 years old who have not been immunized can be given immune serum globulin.
- Close contacts of individuals who have pertussis should be given prophylactic macrolide antibiotics and a booster immunization.
- Good handwashing and avoiding touching the eyes and face are recommended.

Pharyngoconjunctival Fever

The adenoviruses are extremely stable infectious agents that cause infections of the respiratory tract, the eye, and the gastrointestinal tract. Adenoviruses are unusually stable to disinfectants, physical agents, and adverse pH conditions, allowing prolonged survival outside the body on surfaces and in water. Adenoviruses represent the largest nonenveloped viruses. The virus encodes around 1 million amino acid residues.

Cause

Pharyngoconjunctival fever is most frequently is caused by adenovirus serotypes 3 and 7. Adenoviruses are nonenveloped viruses with a polyhedral capsid and double-stranded DNA.

Transmission

- **Reservoir:** Adenovirus serotypes 3 and 7 are human-only pathogens.
- **Mode of transmission:** Contact mode via respiratory droplets, fomites, and direct contact

Pathogenesis

- **Entry:** The virus enters the pharynx via respiratory droplets or drains into the pharynx through the tear ducts.
- **Attachment:** The spike protein at each corner of the capsid attaches to host cell receptors.
- **Avoidance of host defenses:** The virus is an intracellular pathogen, and infection is initially restricted to the surface epithelium, allowing the virus to avoid circulating leukocytes and cytotoxic T cells.
- **Damage:** The virus replicates using a lytic cycle. Cell destruction results in tissue damage, causing an inflammatory response.
- **Exit:** The virus exits in mucus droplets during coughing and sneezing.

Clinical Features

The incubation period after exposure is 5 to 12 days. Pharyngoconjunctival fever is characterized by pharyngitis and a fever lasting up to 10 days. Myalgia, malaise, and gastrointestinal disturbances are frequently associated with the fever. Symptoms of conjunctivitis range from slight itching and burning to significant irritation. Swelling of the lids may occur within 48 hours after infection.

Diagnosis

Diagnosis of pharyngoconjunctival fever is generally based on clinical presentation alone.

Treatment

Treatment is mainly symptomatic. Antipyretics and analgesics are used to reduce fever and pain. Conjunctivitis is treated using cold compresses and artificial tears to relieve itching and burning eyes.

Prevention

- Avoid infected individuals.
- Use proper handwashing.
- Avoid touching eyes and face.

Pneumococcal Pneumonia

In the United States, *Streptococcus pneumoniae* was the most common cause of community-acquired pneumonia before the widespread use of the pneumococcal vaccines in adults, the routine use of pneumococcal conjugate vaccines in children, and a reduction in cigarette smoking. *S. pneumoniae* is now responsible for approximately 10% of cases in the United States but a higher proportion of cases in some other countries. Influenza infection greatly predisposes an individual to secondary pneumococcal pneumonia. It is estimated that in the United States, about 5% of those who develop pneumococcal pneumonia die from the disease.

Cause

Streptococcus pneumoniae, a Gram-positive, alpha-hemolytic, facultatively anaerobic diplococcus, is the cause of pneumococcal pneumonia. The bacteria are catalase negative and show optochin susceptibility and bile solubility. *S. pneumoniae* can express one of over 90 different polysaccharide capsule types that are serologically and biochemically distinct.

Transmission

- **Reservoir:** *Streptococcus pneumoniae* is a human pathogen. About 40% of children younger than 10 years of age carry the pathogen asymptomatically, but this number declines progressively with age, and the rate is 1 to 10% among adults. Nasopharyngeal colonization is a prerequisite for pneumococcal disease.
- **Mode of transmission:** Pneumococcal infections are spread from person to person via droplets and aerosols.

Pathogenesis

- **Entry:** The pathogen enters through respiratory droplets.
- **Attachment:** Pili are the major adhesion factors. They also influence colonization, virulence, and the inflammatory response to the pathogen.
- **Avoidance of host defenses:** Neuraminidase cleaves mucin and uncovers cell receptors. The polysaccharide capsules are antiphagocytic and also enhance biofilm production, making the pathogen more invasive for the lungs and brain.
- **Damage:** The pore-forming toxin pneumolysin and hydrogen peroxide are released in copious amounts by the bacteria. This disrupts the alveolar epithelium and edema fluid accumulates in the alveolar space
- **Exit:** The pathogen exits the respiratory tract in mucus droplets.

Clinical Features

Pneumococcal pneumonia is characterized by a sudden onset of illness featuring shaking chills, fever, shortness of breath or rapid breathing, chest pain that is worsened by breathing deeply, and a productive cough. Upon examination, rales (crackling sounds in the lungs indicating fluid) are detected, and chest X rays reveal fluid accumulation in one or more lobes of the lungs.

Diagnosis

- **Sample:** High-quality sputum sample (<10 squamous epithelial cells and >25 polymorphonuclear cells at a magnification of ×100).
- **Test:** Gram stains and culture are the first diagnostic steps for identifying pneumococcal pneumonia and provide information on antibiotic susceptibility. Enzyme-linked immunosorbent assays to detect *S. pneumoniae* teichoic acids are used for rapid results.

Treatment

The standard treatment for pneumococcal infections is penicillin. However, antibiotic-resistant outbreaks have been occurring in some areas.

Prevention

- Avoiding close contact with acutely ill individuals
- Frequent and thorough handwashing
- Pneumococcal vaccination
  - Adults 65 years and older should get the 23-valent pneumococcal polysaccharide vaccine.
  - Children up through 5 years of age routinely receive four doses of 13-valent pneumococcal conjugate vaccine, PCV13. The seven-valent vaccine was introduced into the childhood vaccination program in the United States in 2000. Since then, a tremendous decrease has been observed in vaccine-related invasive pneumococcal disease in children.

Respiratory Syncytial Virus Bronchiolitis and Pneumonia

Respiratory syncytial virus (RSV) is extremely infectious. By 18 months of age, 87% of children have antibodies to RSV, and by the age of 3 years, virtually all children have been infected. RSV is the most common cause of lower respiratory tract infections in children and the leading cause of hospitalization for infants younger than 1 year. Those at highest risk for severe complications of RSV are children less than 1 year old and adults more than 65 years old. Each year, RSV disease results in more than 225,000 hospitalizations.

Cause

RSV, an enveloped virus with a helical capsid and single-stranded RNA with negative-sense polarity, is the cause of RSV bronchiolitis and pneumonia.

Transmission

- **Reservoir:** Infected humans.
- **Mode of transmission:** Contact mode via respiratory droplets, fomites, or direct contact.

Pathogenesis

- **Entry:** Infection occurs through contact of infectious material with mucous membranes of eyes, mouth, or nose or inhalation of droplets from an infected person's cough or sneeze.
- **Attachment:** The envelope contains surface proteins (G proteins) which attach to tissues in the nasopharynx, bronchioles, and alveoli.
- **Avoidance of host defenses:** RSV initially avoids host defenses as an intracellular pathogen. Although the immune system defenses are able to destroy the pathogen, reinfection by RSV is common.
- **Damage:** RSV infection causes fusion of infected cells, resulting in large multinucleate cells (syncytia). Damage to bronchioles may be caused by viral replication and cytotoxicity and/or the immunological response to RSV infection.

Clinical Features

Symptoms begin most frequently with a runny nose, sneezing, coughing, and fever, much like the common cold. The infection can spread to the lower respiratory tract, causing difficulty breathing, and cyanosis (a blue color due to the lack of oxygen). In premature infants, RSV has a high mortality rate.

Laboratory Diagnosis

- **Sample:** Nasal washings
- **Test:** Enzyme-linked immunosorbent assays are highly sensitive in children but not in adults. RSV RNA can be detected using real-time reverse transcriptase PCR.

Treatment

Most cases of RSV are mild and no treatment is necessary other than the treatment of symptoms using over-the-counter medications. Common treatments include ibuprofen or acetaminophen to reduce fever and cough syrups to suppress cough and relieve symptoms of sore throat. Most children recover naturally from RSV in 8 to 15 days, although a small proportion of children, usually under 6 months of age, require hospitalization for respiratory support due to reduced gas exchange. For premature infants, a monoclonal antibody is used to provide passive immunity. Treatment of severe pediatric cases can include the antiviral medication ribavirin.

Prevention

- RSV is unstable in the environment (it survives for only 2 to 3 hours) and readily inactivated with soap or disinfectants. The best prevention is careful and frequent handwashing and good hygiene practices, such as disposal of tissues used to clean nasal secretions, frequent disinfecting of toys, and not sharing cups, glasses, eating utensils, etc.
- Excluding children with known RSV infection from contact with asymptomatic siblings and friends does not significantly reduce the transmission of the disease, because viral shedding occurs 3 to 4 days before symptoms are visible, allowing spreading during early stages of illness.
- Palivizumab is a monoclonal antibody which can be administered to high-risk infants and young children.

Strep Throat

The pathogen of strep throat causes 10% of all adult pharyngitis and about 25% of pediatric cases. Strep throat is more common in children than adults. It is most common in children 5 through 15 years old. One in 400 cases of untreated strep throat can be expected to result in acute rheumatic fever, a serious complication of the pathogen.

Cause

- *Streptococcus pyogenes,* a bacterial pathogen, is the cause of strep throat.
- The pathogen is a Gram-positive coccus arranged in chains and pairs. It has a fermentative metabolism and an antiphagocytic capsule made of hyaluronic acid. It produces a toxin, hemolysin, that lysis erythrocytes. The pathogen contains the group A antigen on its surface and produces beta-hemolysis on blood agar.

Transmission

- **Reservoir:** Infected humans and asymptomatic carriers
- **Mode of transmission:** Droplet mode via secretions sprayed from the air passages by sneezing or coughing, usually spreading the infection via the respiratory route. The organism may also be transmitted by fomites.

Pathogenesis

- **Entry:** The pathogen enters by respiratory droplets or by contaminated fomites.
- **Attachment:** The pathogen attaches to the mucosal cells of the upper respiratory tract. The bacterial F protein attaches to fibronectin receptors found on the pharyngeal cells.
- **Avoidance of host defenses:** The capsule of *S. pyogenes* inhibits phagocytosis; streptolysin is cytotoxic to white blood cells.
- **Damage:** Enzymes (protease, DNase, hemolysins, and streptokinase) secreted by *S. pyogenes* contribute to tissue damage. The tissue damage causes an intense inflammatory response. In addition, peptidoglycan fragments and teichoic acids induce a cytokine response. Cytokines are signaling proteins that also stimulate an inflammatory response.

Clinical Features

Strep throat is characterized by fever, sore throat (pharyngitis), swollen lymph nodes, and pus discharge from the tonsils (exudative tonsillitis). Headache is usually associated with the disease in older adolescents and adults. While these symptoms are common with strep throat, many other bacterial and viral infections demonstrate similar signs. For this reason, it is very important to contact a physician to determine the definite cause of illness. Proper treatment is effective at preventing several serious complications that can result from strep throat. Complications can include peritonsillar abscesses resulting from the invasion of the pathogen into deeper tissue. Scarlet fever is a rare complication from the release of a toxin that indirectly causes a blanching bright red rash followed by

peeling of the surface of the skin (desquamation). Other rare complications include rheumatic fever, rheumatic heart disease, and acute glomerulonephritis (which causes kidney failure).

Diagnosis

- **Specimen:** Because it is not possible to tell if pharyngitis is viral or bacterial by clinical means, a throat swab and antigenic test and possibly a culture are the best way of confirming the presence of group A streptococci (GAS).
- **Tests:** Rapid enzyme-linked immunosorbent assays (ELISAs) are used to provide fast results; however, about 15% of GAS-positive samples test negative. It is common to streak swabs that have tested negative in rapid ELISAs onto blood agar plates, since this is a significantly more sensitive assay for GAS. Beta-hemolytic colonies that are Gram-positive streptococci that also show sensitivity to bacitracin are identified as *S. pyogenes*.

Treatment

Streptococcal pharyngitis is self-limiting and usually lasts only 5 to 7 days without therapy; however, antibacterial treatment is important to prevent the development of serious complications. Sensitive strains are treated with penicillin or amoxicillin. Erythromycin is used if the patient is allergic to penicillins. Drugs are given orally for 10 days to avoid relapse due to regrowth of antibiotic-resistant bacteria and prevent the development of rheumatic fever.

Prevention

- There is no vaccine for the prevention of GAS infections.
- Good personal hygiene habits, such as covering the mouth when sneezing or coughing and washing hands after wiping or blowing the nose, coughing, or sneezing, are important.
- Prophylactic antibiotic therapy can be used to arrest the spread of *S. pyogenes* during epidemic outbreaks.

Tuberculosis

The prevalence of latent tuberculosis (TB) infection is about 1.7 billion persons—25% of the world's population. New cases number about 10 million yearly, and annual mortalities worldwide are estimated at 1.6 million. Approximately 1 in 30 new cases of TB is caused by resistant strain, and 1 in 6 of previously treated cases is multidrug resistant (MDR). Among MDR TB cases, 1 in 12 are extensively drug resistant. TB is fatal for up to 50% of untreated patients, and MDR TB cases have a reported fatality rate of more than 70%

Cause

- *Mycobacterium tuberculosis*, a bacterial pathogen, is the cause of tuberculosis.
- The pathogen is an acid-fast, rod-shaped streptobacillus. It is aerobic and grows very slowly. The waxy, acid-fast cell wall restricts diffusion of many chemicals, making it resistant to disinfectants and many antibiotics.

Transmission

- **Reservoir:** Infected humans
- **Mode of transmission:** Airborne and droplet mode. The bacterium is resistant to temperature change and drying and survives as suspended particles in the air for several hours.

Pathogenesis

- **Entry:** Airborne particles or respiratory droplets containing *M. tuberculosis* are inhaled.
- **Attachment:** The organism attaches to alveolar macrophages after entering the lungs.
- **Avoidance of host defenses:** The organism is engulfed by alveolar macrophages but avoids fusion with lysosomes, resulting in its being protected within the host cell.
- **Damage:** Replication within the macrophage results in cell lysis. Other macrophages are drawn to the site of infection and are layered around the infected cells, forming tubercles or small granulomas. The tubercles can block alveoli and bronchioles. If the immune system cannot contain the mycobacteria in the tubercles, the pathogen spreads within the lungs and to other organs.

Clinical Features

Approximately 10% of those with latent TB infections go on to develop active TB. The lungs are the most commonly affected organ. Clinical signs and symptoms of pulmonary TB include a bad cough that produces bloody sputum, chest pain, chronic fever, weakness or fatigue, chills, night sweats, weight loss, and loss of appetite.

Diagnosis

Diagnosis of a person with suspected latent TB disease is made by using a Mantoux tuberculin skin test. A Mantoux skin test is performed by injecting a small amount of purified protein derivative of tuberculin intradermally in the skin of the forearm. The test is read 48 to 72 hours later; if the site of injection shows an area of swelling and redness larger than 15 mm in a healthy person, the test is considered positive. A positive skin test is followed up with a chest radiograph. Those with only latent TB have no lesions in the lungs. Individuals with active TB have a positive Mantoux skin test, usually sputum containing

acid-fast bacilli (or a positive test for *M. tuberculosis*-specific DNA using PCR), an abnormal chest radiograph and one or more signs of the disease.

Treatment

Because the pathogen grows so slowly and has the waxy coating covering its cell wall, long-term therapy with antibiotics that can penetrate into the *Mycobacterium* cell is required. For latent TB in those who have been exposed to an individual with drug-susceptible TB, the recommended treatment is isoniazid and rifapentine for 12 weeks to prevent development of tuberculosis. Treatment for drug-susceptible active tuberculosis is a combination of four drugs—isoniazid, rifampin, pyrazinamide, and ethambutol—for 6 to 9 months. The combination of drugs is used to prevent the mycobacteria from becoming resistant to any single drug.

Prevention

- The BCG (*M. tuberculosis* bacille Calmette-Guérin) vaccine is used for prevention in countries with a high rate of TB.
- Health care workers and others who work where TB is common must be tested regularly to ensure that they are not infected.
- Those with active TB should be isolated so as not to spread the disease to others.
- Antibiotic prophylaxis with isoniazid can be used to prevent development of active tuberculosis.