There are only a few infections that warrant airborne isolation precautions in the conventional hospital setting: tuberculosis, measles, and varicella. While most patients with these diseases may not require hospitalization, airborne transmission of these pathogens has been described in hospital settings. Airborne isolation strategies (including well-ventilated rooms, negative room air pressure relative to the corridor, and use of respirators by health care workers) have been successful in mitigating transmission risk.

**Tuberculosis**

Tuberculosis (TB) is a chronic bacterial infection most commonly caused by *Mycobacterium tuberculosis*. TB infects a third of the world’s population and is the single leading cause of death by an infectious agent. Humans are the only reservoir, and a third of infected patients are undiagnosed. Prior infection does not confer immunity. The highest TB incidence is in sub-Saharan Africa and Asia.

Infection of the lung or airway (e.g., larynx) allows aerosolization of bacilli with coughing or speaking. Inhalation of small infectious droplets (<5 microns) into alveoli leads to uptake by macrophages, which migrate outside the lung. A cell-mediated immune response takes 2–10 weeks and is usually effective in containing primary infection within granulomas.
KEY CLINICAL FEATURES

Latent (asymptomatic) TB represents 90% of infections and reflects a small burden of bacilli contained within granulomas. Active disease develops in 10%, but more frequently in those with HIV or on TNF-alpha inhibitor therapy, and usually represents reactivation from prior infection. Typical pulmonary TB involves upper lobe cavitation associated with chronic cough, hemoptysis, fevers, unintentional weight loss, and/or night sweats. Atypical pulmonary involvement presents with lower lobe infiltrates (with or without cavitation), pleural effusions, and hilar lymphadenopathy and is more frequent in the immunosuppressed. Patients with extrapulmonary TB (e.g., vertebral involvement) should always be evaluated for pulmonary disease.

Diagnosis of TB remains a significant challenge. Both PPD skin testing and interferon-gamma release assays (IGRA) assess cell-mediated response to TB antigens and are used to diagnose latent TB with similar sensitivity, but false negative results occur in 20%.

Culture is the diagnostic gold standard but takes 3–8 weeks. Nucleic acid amplification tests (NAATs) can allow for rapid identification (i.e., hours) of TB and resistance mutations that predict multidrug-resistant (MDR) TB with sensitivity and specificity similar to culture.

Sputum smears allow rapid quantification of bacilli, the burden of which correlates with contagiousness. Approximately 10,000 bacilli/mL are required for smear positivity. A single sputum AFB smear is approximately 60% sensitive compared to culture; two additional smears increase sensitivity an additional 12%. Smear-negative, culture-positive patients represent 30–60% of pulmonary TB cases and are less infectious but still responsible for 10–20% of transmission events.

Standard treatment requires multidrug therapy for at least 6 months. MDR TB is defined as resistance to isoniazid and rifampin and is responsible for >450,000 infections/year; treatment relies on second-line agents that may be less reliable. Extensively drug-resistant (XDR) TB is additionally resistant to a fluoroquinolone and a second-line injectable drug and carries high mortality. Given the limited treatment options, high mortality rate, and public health implications, some experts advocate that patients hospitalized with XDR-TB be managed in a biocontainment unit (see chapter 13). Bacille Calmette-Guerin
vaccine (BCG) is a live attenuated vaccine for tuberculosis that can reduce the severity of childhood TB infections, but it does not protect against primary infection or reactivation, making it marginally useful in limiting transmission.

**KEY INFECTION PREVENTION CONCEPTS**

TB is exhaled in small aerosol droplets from patients with symptomatic disease affecting the lungs or respiratory tract, particularly through coughing, sneezing, or talking. TB is not transmitted by large respiratory droplets or direct contact. Patients with latent TB or exclusive extrapulmonary involvement are not considered infectious with rare exception (such as aerosolization from a cutaneous TB infection). Ultraviolet light readily inactivates TB bacilli, making transmission in outdoor settings very inefficient.

Prolonged exposure to shared airspace is typically required for transmission. Transmission risk varies by case and depends on: (1) contagiousness of the patient; (2) burden of exposure; (3) host susceptibility; and (4) strain type. Patients are considered more contagious if they are sputum smear-positive, have an active cough, have cavitary lung disease on chest X-ray or involvement of the larynx, or are not on effective treatment. Factors affecting the burden of exposure include exposure duration, room size and ventilation, and cough-inducing procedures (such as bronchoscopy or intubation). Children, the immunocompromised, or those with a high exposure burden are more likely to develop active disease.

Health care workers (HCWs) are at higher risk of contracting TB than the general population, and unrecognized TB patients pose the highest risk to these workers. The annual HCW TB acquisition incidence varies from ~5% in low-income countries to 1% or less in high-income countries. A three-tiered approach significantly reduces HCW TB infection rates. Administrative controls aim to reduce the number of TB exposures and include a TB program that facilitates the prompt recognition and isolation of suspect TB patients. Engineering controls reduce the concentration of airborne TB and involve well-ventilated rooms for TB suspects (minimum 12 air exchanges/hour) with negative air pressure relative to the corridor. Finally, personal protective equipment (PPE) in-
cludes use of a respirator (such as a fit-tested N95 mask) to minimize TB inhalation.

Airborne isolation precautions should be used for inpatients suspected of pulmonary TB, including use of a well-ventilated negative-pressure airborne infection isolation room (AIIR) and respirator use. Outside the room, patients should wear a surgical mask to minimize spread of respiratory droplets. In patients determined unlikely to have TB, airborne isolation may be discontinued when three sputum samples, collected at least 8 hours apart with one early morning sample, are negative. NAAT performed on at least one sputum sample may reduce time to diagnosis.

For patients with confirmed TB, airborne isolation should be continued until three consecutive sputum smears are negative. Treatment of drug-susceptible TB rapidly reduces transmissibility over several days. However, since results of susceptibility testing take weeks, isolation should be continued until the patient has completed 2 weeks of treatment with signs of clinical improvement. Discharge home requires coordination with the local health department to ensure that treatment is continued and to evaluate household contacts.

Patients with suspected or proven MDR TB are managed more conservatively given the significant consequences of transmission. While inpatient, airborne isolation may be continued either for the entire treatment duration or until sputum cultures finalize as negative.

Exposure investigations emphasize identifying those with the highest exposure burden (e.g., household contacts or HCWs performing an aerosol-generating procedure) and at highest risk of developing active infection (e.g., children or the immunocompromised). Exposed contacts should have a baseline PPD or IGRA test and repeat testing 8 or more weeks after exposure. Treating those with conversions may reduce risk of active disease by 60%.

**Measles**

Measles virus (rubeola) is one of the most contagious human pathogens and was responsible for 2 million deaths annually prior to vaccine availability in 1963. Dramatic reductions in global measles incidence over the last several decades represent a tremendous public health achievement,
though areas of endemic transmission remain, particularly in Africa and Asia.

Measles is caused by an enveloped RNA virus member of the *Paramyxoviridae* family. In endemic areas, 95% have been infected by age 15 years. Measles virus is transmitted through respiratory droplets and aerosols. Inhalation or direct inoculation of the upper respiratory tract with infectious virus leads to viral replication in respiratory epithelium, followed by spread to local lymphatic tissue, subsequent viremia, and involvement of a wide range of organs. A robust humoral and cellular immune response confers lifelong immunity.

**KEY CLINICAL FEATURES**

The incubation period is typically 10–14 days, though it may be longer in adults. Initial symptoms include a prodrome of fever, malaise, conjunctivitis, cough, and coryza. Koplik’s spots (bluish or grey “grains of sand” on a red base frequently seen on the buccal mucosa) are pathognomonic and may develop prior to the rash. Low suspicion for measles and lack of clinician experience may contribute to misdiagnosis of measles as Kawasaki’s disease, scarlet fever, infectious mononucleosis, parvovirus, or enterovirus.

The characteristic morbilliform (maculopapular) rash develops 2–4 days after initial prodrome symptoms and is usually present with fever. It begins at the hairline and spreads downward to the face, trunk, and then extremities, and may become confluent. The rash resolves in the same order it appeared and may desquamate. Transient leukopenia may occur. Most patients fully recover 7–10 days after symptom onset. Rash may be absent in immunocompromised patients. Treatment is supportive; vitamin A may reduce complications.

Complications occur in 30% of cases and are more common in the malnourished or immunosuppressed. These include pneumonia (primary or secondary bacterial infection) or sight-threatening ocular involvement. Additionally, neurologic complications include acute measles encephalitis (with or without a rash) or fatal subacute sclerosing panencephalitis that begins insidiously 7–10 years after infection. Functional immunosuppression may follow measles infection and increase risk for bacterial pneumonia or tuberculosis.
Diagnosis is often made clinically. Elevated IgM antibody titers are diagnostic of acute measles, though they may not be detectable until several days after rash onset. False negative and positive IgM results may occur. RT-PCR can detect measles directly from throat, nasopharyngeal, or urine samples within the first several days of rash onset.

KEY INFECTION PREVENTION CONCEPTS

Measles virus is highly transmissible through large respiratory droplets and smaller aerosols that may remain suspended in the air for up to 2 hours after the patient has left the area. Patients are considered infectious 4 days prior to the onset of rash, exacerbated by the cough of escalating prodromal symptoms. Rash onset heralds peak viral replication and the beginning of the adaptive immune response, though patients remain infectious for an additional 4 days.

Suspect measles patients should be masked and avoid waiting rooms; triage staff should be trained to promptly isolate suspect patients. Inpatients should be placed in negative-pressure isolation rooms; outpatients should be seen as the last case of the day and use alternative entrances. Health care providers caring for measles patients should have evidence of measles immunity, although respirators (i.e., N95 masks) are still recommended to prevent breakthrough infections.

All eligible HCWs should demonstrate evidence of measles immunity. Two doses of vaccine confer 99% protection. Breakthrough infections can occur but are less severe and are less infectious. Given its ease of transmissibility, a high level of population immunity is required to interrupt transmission.

Postexposure management consists of vaccination for those nonimmune. Given that measles is one of only a few infections that may be contagious prior to symptom onset, quarantine of exposed individuals can be considered for those who are nonimmune (such as those who decline or have contraindications to vaccination). The CDC defines evidence of immunity as written documentation of one or more measles vaccine after age 1 (two or more for high-risk individuals such as HCWs), lab evidence of immunity or prior measles infection, or born before 1957. Measles vaccination given within 72 hours of exposure may provide some protection. Immune globulin should be offered to patients at high risk of
complications or with contraindication to vaccine (including pregnant women, infants <12 months, or immunocompromised patients). Nonimmune HCWs should not return to work through the duration of the incubation period, regardless of prophylaxis given.

Measles only infects humans, is vaccine preventable, is not transmitted by asymptomatic carriers, and confers lifelong immunity; these factors make it an attractive target for global eradication.

**Varicella and Zoster**

Varicella zoster virus (VZV) is an enveloped DNA virus and member of the *Herpesviridae* family that is ubiquitous and exclusive to humans. Primary varicella infection is characterized by a self-limited febrile rash syndrome (chicken pox), leading to viral latency and reactivation later in life as zoster (shingles). In temperate climates, primary infection is most common in children younger than 10 years.

Primary infection occurs when a susceptible individual inhales aerosolized virus, infecting respiratory mucosa. Viremia with infected T-lymphocytes may precede rash onset by up to 10 days and disseminates infection to the skin and other organs. Robust cell-mediated immunity develops, which can be lifelong, although mild breakthrough infections do occur.

**KEY CLINICAL FEATURES**

The symptoms of primary varicella begin 14–16 days (range 10–21) following exposure. A pruritic rash is often the first symptom in children, although a mild prodrome (low-grade fever, malaise, and headache) may precede rash onset by 1–2 days. The rash rapidly evolves from maculopapular to vesicular (“dewdrops on a rose petal”), then pustular before scabbing over. Multiple stages of evolution are present at any given time and may involve the entire body, including mucosal surfaces. Skin lesions will scab within 1 week, heralding the end of infectivity.

Complications of primary varicella infection are infrequent but are more likely to occur in the immunocompromised, neonates, or adults. These include secondary bacterial infection of the lung or skin (e.g., group A *Streptococcus*), severe varicella (prolonged viral replication), or
encephalitis. Primary varicella during pregnancy is associated with potentially life-threatening varicella pneumonia, and if it develops during the first two trimesters of pregnancy can cause severe congenital defects. Neonatal varicella is associated with high mortality (30%).

Zoster incidence becomes more common after age 50 and reflects waning cell-mediated immunity. It typically presents as a unilateral painful vesicular rash along a single (or neighboring) neurologic dermatome(s). Disseminated zoster may occur in the immunosuppressed and involves noncontiguous dermatomes.

Diagnosis is often clinical. PCR of vesicular fluid is highly sensitive. Direct immunofluorescence performed on cells from an active (non-crusted) vesicle may provide a rapid diagnosis. Viral culture has lower yield than PCR. Serology can be used to screen for immunity but has limited utility in diagnosing active infection.

Treatment of primary varicella is primarily supportive. Concomitant aspirin use is associated with Reyes syndrome and should be avoided. Acyclovir (or its analogues) is recommended for patients with severe disease or at increased risk for complications. IV acyclovir is recommended for immunosuppressed patients or those with severe disease and is most beneficial when given within the first 24 hours after rash onset. Acyclovir is recommended to reduce severity and duration of zoster symptoms.

**KEY INFECTION PREVENTION CONCEPTS**

Transmission of VZV within health care settings is well recognized. Although all forms of VZV are potentially infectious, primary varicella is considered the most infectious with a 90% attack rates for susceptible household contacts.

Patients with primary varicella are considered infectious 1–2 days prior to rash onset until all lesions are crusted, and the degree of infectivity correlates with the severity of skin involvement. Virus is aerosolized from vesicular fluid in skin lesions and possibly from the respiratory tract and may spread through either the airborne route or through direct contact. Both airborne and contact precautions are recommended until all lesions have crusted. All HCWs should demonstrate immunity (documentation of 2 doses of vaccine or confirmatory serology), and only those with confirmed immunity should care for patients with primary varicella.
Isolation precautions are still recommended for immune HCWs given the possibility of breakthrough infections.

Zoster is common in health care settings and is significantly less infectious than primary varicella. Transmission may occur from direct contact with active skin lesions and may cause primary varicella in susceptible persons. For otherwise immunocompetent patients with localized zoster, standard precautions should be used. Aerosolization and airborne transmission from localized zoster lesions has been reported (rarely) in health care settings, emphasizing the importance of covering active lesions. Patients with disseminated zoster should be managed like primary varicella. Immunosuppressed patients with localized zoster are at higher risk for disseminated infection and should also be managed like primary varicella until disseminated infection has been ruled out.

Managing exposures includes rapid assessment of immunity in exposed individuals and administration of vaccine or varicella-zoster immune globulin (VZIG) to those susceptible. As people may become infectious prior to symptom onset, quarantine of individuals who are exposed but nonimmune may be considered, particularly for people in contact with those at risk for VZV complications (such as health care workers). The definition of exposure in hospital settings includes face-to-face contact for at least 5 minutes or presence in the same room for at least 1 hour. Exposed but immune HCWs should undergo daily monitoring for symptoms between postexposure days 8–21 and immediately removed from patient care if symptoms develop. Nonimmune HCWs should be removed from patient care areas during postexposure days 8–21; vaccination within 5 days of exposure may reduce disease severity. Exposed nonimmune individuals at risk for severe disease who have contraindication to vaccination should receive VZIG as soon as possible, within 10 days of exposure.

Vaccination (live attenuated Oka strain) is safe and has reduced primary varicella incidence by 97% in the United States. Vaccination leads to subclinical infection and subsequent latency similar to wild type virus, but the Oka strain is very unlikely to cause rash or secondary transmission. Zoster vaccines (live virus and inactivated subunit) are now available.