of symbiotic microorganisms, including algae, amebas, ciliated protozoa, and other water-dwelling bacteria, promotes the growth of *Legionella*. The organisms can invade and multiply within free-living protozoa.

Heavy rainfall and flooding can result in the entry of high numbers of legionellae into water-distribution systems, leading to an upsurge of cases. Large buildings over three stories high are commonly colonized with *Legionella*. Sporadic community-acquired Legionnaires' disease has been linked to colonization of hotels, office buildings, factories, and even private homes. Drinking-water systems in hospitals and extended-care facilities have been the source for health care–associated Legionnaires' disease.

In contrast, cooling towers and evaporative condensers have been overestimated as sources of *Legionella* causing human illness. Early investigations that implicated cooling towers antedated the discovery that the organism could also exist in drinking water. In many outbreaks attributed to cooling towers, cases of Legionnaires' disease continued to occur despite disinfection of the towers; drinking water was found to be the actual source. Koch's postulates have never been fulfilled for *Legionella* links to cooling tower–associated outbreaks as they have been for hospital-acquired Legionnaires' disease. Nevertheless, cooling towers have, in rare instances, been implicated in community-acquired outbreaks, including an outbreak in Murcia, Spain. As mentioned above, *L. longbeachae* infections have been linked to potting soil, but the mode of transmission remains to be clarified.

Multiple modes of transmission of *Legionella* to humans exist, including aerosolization, aspiration, and direct instillation into the lungs during respiratory tract manipulations. Aspiration is now known to be the predominant mode of transmission, but it is unclear whether *Legionella* enters the lungs via oropharyngeal colonization or directly via the drinking of contaminated water. Oropharyngeal colonization with *Legionella* has been demonstrated in patients undergoing transplantation. Nasogastric tubes have been linked to hospital-acquired Legionnaires' disease; microaspiration of contaminated water was the hypothesized mode of transmission. Surgery with general anesthesia is a known risk factor that is consistent with aspiration. Especially compelling is the reported 30% incidence of postoperative Legionnaires' disease among patients undergoing head and neck surgery at a hospital with a contaminated water supply; aspiration is a recognized postoperative complication in such cases. One observational study showed that patients with hospital-acquired Legionnaires' disease underwent endotracheal intubation significantly more often and for a significantly longer duration than patients with hospital-acquired pneumonias of other etiologies.

Aerosolization of *Legionella* by devices filled with tap water, including whirlpools, nebulizers, and humidifiers, has been linked to cases in patients. An ultrasonic mist machine in the produce section of a grocery store has been the source in community outbreaks. Pontiac fever has been linked to *Legionella*-containing aerosols from water-using machinery, a cooling tower, air conditioners, and whirlpools.

EPIDEMIOLOGY

Community-Acquired Pneumonia The incidence of Legionnaires' disease depends on the degree of contamination of the aquatic reservoir, the immune status of the persons exposed to water from that reservoir, the intensity of exposure, and the availability of specialized laboratory tests on which the correct diagnosis can be based. Numerous prospective studies have ranked *Legionella* among the top four microbial causes of community-acquired pneumonia, finding that it accounts for 2–13% of cases. (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Chlamydia pneumoniae* are usually ranked first, second, and third, respectively.) On the basis of a multihospital study of community-acquired pneumonia in Ohio, the Centers for Disease Control and Prevention (CDC) estimated that only 3% of community-acquired cases of Legionnaires' disease are diagnosed as such. Observational studies of community-acquired pneumonia showed that Legionnaires' disease was largely unrecognized unless *Legionella* diagnostic testing was routinely applied to all patients with pneumonia; such studies in Spain and Germany resulted in detection of increased numbers of cases throughout Europe. It is likely that observational studies in Taiwan and Australia will have a similar result, with more cases identified throughout Asia as the index of suspicion rises.

Hospital-Acquired Pneumonia *Legionella* is responsible for 10–50% of cases of nosocomial pneumonia when a hospital's water system is colonized with the organism. The incidence of hospital-acquired Legionnaires' disease depends on the degree of contamination of drinking water, as defined by the rate of positivity of distal water sites; in contrast, the use of quantitative criteria of the number of colony-forming units per milliliter has proven useless.

Proactive culture of the hospital water supply has increased the detection of hospital-acquired Legionnaires' disease and simultaneously allowed expeditious diagnosis resulting in early administration of antibiotic therapy. In the early years after its recognition, Legionnaires' disease was documented primarily in the United States. As diagnostic modalities (especially the urinary antigen test) became more widely used, cases were documented in European hospitals. Likewise, following the enactment of public health guidelines in Taiwan, cases attributable to hospital tap water were found in Taiwanese hospitals. Risk factors for Legionnaires' disease include cigarette smoking, chronic lung disease, advanced age, prior hospitalization with discharge within 10 days before onset of pneumonia symptoms, and immunosuppression. Immunosuppressive conditions that predispose to Legionnaires' disease include transplantation, HIV infection, and treatment with glucocorticoids or tumor necrosis factor α antagonists. However, in a large prospective study of community-acquired pneumonia, 28% of patients with Legionnaires' disease did not have these classic risk factors. Hospital-acquired cases are now being recognized among neonates and immunosuppressed children.

Pneumonia in Transplant Recipients Transplant recipients appear to be at unusually high risk of *Legionella* pneumonia. This elevated risk may be due to diagnostic bias, given the extensive workup for opportunistic pathogens with pneumonic symptoms as well as the long-standing immunosuppression in this population of patients. Legionnaires' disease usually occurs in the 3 months after transplantation. Cavitation is seen on chest radiograph more frequently in transplant recipients, and mortality rates are higher.

Pontiac Fever Pontiac fever occurs in epidemics. The high attack rate (>90%) reflects airborne transmission.

PATHOGENESIS AND IMMUNITY

Legionella enters the lungs through aspiration or direct inhalation. Attachment to host cells is mediated by bacterial type IV pili, heat-shock proteins, a major outer-membrane protein, and complement. Because the organism possesses pili that mediate adherence to respiratory tract epithelial cells, conditions that impair mucociliary clearance, including cigarette smoking, lung disease, or alcoholism, predispose to Legionnaires' disease.

Both innate and adaptive immune responses play a role in host defense. Toll-like receptors mediate recognition of *L. pneumophila* in alveolar macrophages and enhance early neutrophil recruitment to the site of infection. Alveolar macrophages phagocytose legionellae by a conventional or a coiling mechanism. After phagocytosis, *L. pneumophila* evades intracellular killing by inhibiting phagosome–lysosome fusion. Although many legionellae are killed, some proliferate intracellularly until the cells rupture; the bacteria are then phagocytosed again by newly recruited phagocytes, and the cycle begins anew. The role of neutrophils in immunity appears to be minimal: neutropenic patients are not predisposed to Legionnaires' disease. Although *L. pneumophila* is susceptible to oxygen-dependent microbiologic systems in vitro, it resists killing by neutrophils. The humoral immune system is active against *Legionella*. Type-specific IgM and IgG antibodies are measurable within weeks of infection. In vitro, antibodies promote killing of *Legionella* by phagocytes (neutrophils, monocytes, and alveolar macrophages). Immunized animals