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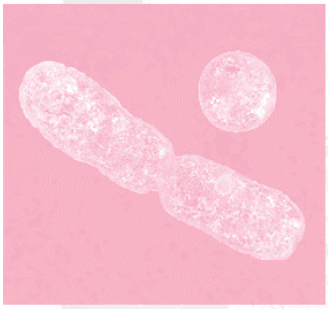
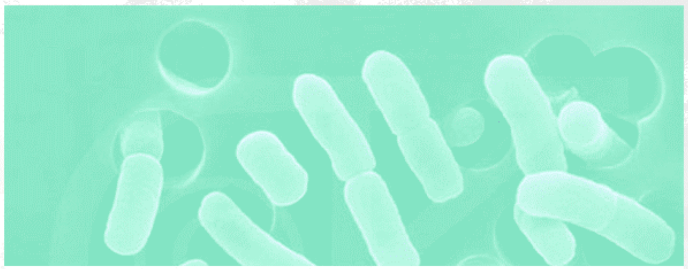
Legionella: Risk for Infants and Children





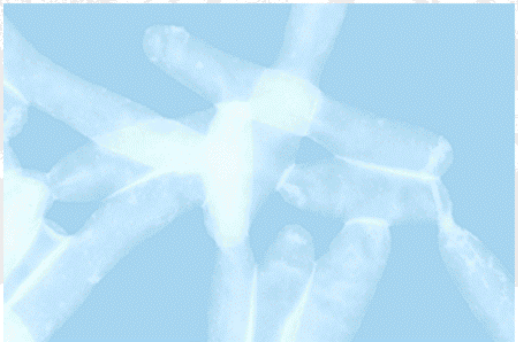


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Table of Contents

1. Executive Summary

Executive Order 13045, "Protection of Children from Environmental Health Risks and Safety Risks," requires all federal agencies to ensure that their standards take into account special risks to infants and children. Children's bodies are still developing, and therefore, their immune and metabolic systems may not be able to protect them from the effects of certain environmental health threats. Children also may have greater exposure to toxic agents than adults because, pound for pound, they breathe more air, drink more water, and eat more food than adults. In addition, children's behavior may increase their exposure to these agents (e.g., play activities, hand-to-mouth patterns).

This document is an addendum to the 1998 Legionella Human Health Criteria document, which covers all aspects of *Legionella,* except risk that may be posed to children. In response to that lack of information this document will evaluate the risk that may be posed to children. The sections of this document address: the occurrence of disease and infection caused by the bacteria (Section 2), the specific health effects exhibited by children infected with the bacteria (Section 3), the immune response in infected children and the effects of breast feeding (Section 4), risk factors for infection (Section 5), conclusions regarding the risk to children posed by the bacteria (Section 6), and recommendations for further research on children's risk from *Legionella* (Section 7). The references are listed in Section 8. There are considerable data gaps with regard to all aspects of pediatric *Legionella* infections.

2. Occurrence of Disease/Infection

In the United States, the number of reported cases of legionellosis (i.e., any disease caused by *Legionella*) is lower in children than in adults. Analysis of data collected by the Centers for Disease Control and Prevention (CDC) indicates that the annual number of legionellosis cases reported in children under the age of five is less than one percent of the total number of reported cases (CDC 1994, 1995, 1996, 1997). Similarly, the annual number of cases in children age 5-14 is less than one percent of the total number of cases (see Table 1). No information was located regarding the incidence of legionellosis in children of other countries.

Table 1. Summary of Reported Cases of Legionellosis in the United States, by Age, 1993-1996

Age Group	**Number of Cases (Percentage of Annual Total)**			
	1993	**1994**	**1995**	**1996**
<5	9 (<1%)	11 (<1%)	4 (<1%)	7 (<1%)

5-14	7 (<1%)	7 (<1%)	10 (<1%)	5 (<1%)
15-24	29 (2%)	47 (3%)	30 (2%)	32 (3%)
25-39	171 (13%)	209 (13%)	255[a] (21%)	142 (12%)
>39	1014 (79%)	1303 (81%)	915[b] (74%)	1000 (83%)
Age Not Stated	50 (4%)	38 (2%)	27 (2%)	12 (1%)
Total	1280	1615	1241	1198

[a]Reported age range is 25-44
[b]Reported age range is >44
Sources: CDC 1994, 1995, 1996, 1997

A seroepidemiological study of Taiwanese children suggests that the prevalence of past exposure to *Legionella* is lower in children aged 12-18 months than in older children (aged 7-18 years) (Hsu et al. 1996). Serum samples from the children were tested against *Legionella pneumophila* serogroups 1-6 by the indirect immunofluorescence antibody (IFA) test. The IFA test used polyvalent *L. pneumophila* antigen (supplied by Organon Teknika). An IFA titer of 1:32 was established as the cut-off value for seropositivity in this study (in contrast to the 1:64 titer that has been established by the CDC). The cut-off value used in this study was based on sera from individuals in the youngest age group (12-18 months old and presumably unexposed), of whom 90% had negative titers (i.e., titers less than or equal to 1:16). In 240 apparently healthy children and young adults aged 12-18 months, 7-8 years, 12-13 years, and 17-18 years (60/group), the prevalence of antibodies to *L. pneumophila* indicative of a prior exposure was 10, 30, 28.4, and 35 percent, respectively. The potential contribution of other cross-reacting antibodies (to other Gram-negative bacterial antigens) was not addressed by the study authors.

The study results also indicate that the rate of exposure to *Legionella* is higher than the rate of legionnaires' disease (Hsu et al. 1996). The study identified 53 children ranging in age from 6 months to 18 years (mean 6.1 ± 4.5 years) and exhibiting community-acquired, atypical pneumonia. In these 53 children, the prevalence of past *L. pneumophila* exposure was 34 percent, whereas the frequencies of confirmed and presumptive acute legionnaires' disease were 0 and 5.7 percent, respectively.

No information was located regarding the incidence of legionellosis among pregnant women. Tewari et al. (1997) reported that legionnaires' disease is rarely diagnosed in pregnancy and offered the following explanations: (1) pneumonia in pregnancy may be aggressively treated without identification of a specific pathogens; (2) subclinical infection may be overlooked.

3. Health Effects in Children

In adults, legionellosis is an infecton caused by the bacterium legionella pneumophila . The diease has two distinct forms: Legionnaire's diease, the more severe form of infecton which includes pneumonia and pontiac fever the milder illness. Both conditions have been documented in children, and the clinical effects resemble those seen in adults.

Goldberg et al. (1992) examined the clinical manifestations of an outbreak of Pontiac fever in which 31 children were known to be affected. The incubation period and duration of illness in the children were similar to those in the adults, the median incubation period in children was three days compared to two days in adults, and median duration of the illness in children was two days compared to four days in the adults. The study authors noted that the mean duration of symptoms in the children (3.23 days) was slightly, but significantly, shorter compared to that of the adults (4.28 days). Similar symptoms (e.g., headache, tiredness, pyrexia, myalgia) were noted in both children and adults. Only two symptoms occurred at a significantly different incidence in the two populations: arthralgia and breathlessness occurred with a significantly lower incidence in the children compared to the adults. The study authors, however, noted that these differences were probably not clinically significant because the differences were small. Furthermore, these differences could have arisen simply from difficulties in collecting reliable case histories for children. The study authors concluded that the clinical manifestations of Pontiac fever in children closely resemble those observed in adults.

Lüttichau et al. (1998) investigated an outbreak of Pontiac fever involving six children (ages 4-9) and seven adults (ages 30-38) residing in a Denmark. *Legionella* was established as the cause of their illness based on cultures and serological tests. The source of the *Legionella* could not be determined definitively, although circumstantial evidence pointed to a whirlpool. The authors compared the clinical effects in the children and adults. Although the children had a shorter incubation period and longer duration of illness compared to the adults, these differences were not significant. Arthralgia, dizziness, low back pain, myalgia, and chest pain were significantly more common in the adults, whereas ear pain and rash were significantly more common in the children. Children and adults exhibited no significant differences in the frequency of fever, headache, cough, tiredness, abdominal pain, nausea, poor concentration, dry and/or sore throat, or vomiting. Sequelae, consisting mainly of chest pain and poor concentration, were more common among the adults. None of the children nor adults presented with leukocytosis, and chest radiographs of both the adults and children were normal. The authors noted that due to the lack of characteristic symptoms and sequelae in children with Pontiac fever, many unrecognized cases may occur.

Brady (1989) reviewed seven cases of nosocomial legionnaires' disease that occurred in patients whose ages ranged from 9 months to 20.5 years (mean 12.3 years). Similar to adults, common symptoms included fever (defined as greater than 38.5°C), cough, headache, dyspnea, pleuritic chest pain, abdominal pain, and diarrhea. Unlike adults, these patients did not exhibit myalgias or neurological abnormalities. The study author, however, noted that assessment of symptoms in three patients was difficult due to neurological impairment or age (i.e., one patient was 9 months old). Similar to adults, the chest radiographs of these patients varied. Three patients exhibited lobar consolidation, while three exhibited diffuse bilateral infiltrates. Three patients exhibited pleural effusions. Four patients required mechanical ventilation, and six patients recovered after erythromycin therapy. The study author noted the consistency of these findings with those reported from legionnaires' disease outbreaks in adult patients.

Levy and Rubin (1998) reviewed nine cases from the U.S., Europe, and Japan of nosocomial legionnaires' disease in neonates and infants younger than three months old. Four patients were preterm infants, and five had been full-term. Eight of the nine cases had potential risk factors including prematurity, congenital heart disease, congenital immunodeficiency, bronchopulmonary dysplasia, or corticocosteroid therapy. All nine infants exhibited acute respiratory distress and required mechanical ventilation. Chest radiographs were available for five infants. As with adults, the chest radiographs of these patients varied. Two infants exhibited lobar infiltrate, two exhibited bilateral lobar or bronchopneumonia, and one infant exhibited pleural effusions. In all nine cases, *Legionella* were isolated from lung tissues and/or pulmonary fluids. Of the four infants who received erythromycin, three survived, whereas all five infants who did not receive erythromycin died. The authors concluded that, as with adults and children, the most important determinants of the prognosis of legionnaires' disease in neonates are early recognition and institution of appropriate treatment.

These reports indicate that legionellosis in children resembles that in adults; nevertheless, Holmberg et al. (1993) cautioned that "the full spectrum of manifestations in children is unknown." Based on the substantial number of normal children (i.e., 20-50%) that exhibit antibody titers (cut-off values for seropositivity of 1:64 to 1:256) to *Legionella pneumophila* by the age of five, a subclinical or atypical infection may be common in children. Although not specifically stated by the study authors, exposure to *Legionella* without an actual infection (i.e., multiplication of organisms in the body) may be sufficient to cause the rise in antibody titers. In addition, the study authors acknowledged that nonspecific, cross-reacting antibodies may be responsible for the observed antibody titer levels.

Pregnancy

Three case reports were located that reported legionnaires' disease in pregnant women (Eisenberg et al.

1997, Soper et al. 1986, Tewari et al. 1997). These reports indicate that, like many other illnesses, legionnaires' disease during pregnancy may result in pre-term delivery, and effects in the newborn may be secondary to pre-term delivery. In one case (Tewari et al. 1997), the neonate had a bowel perforation that may have been associated with intrauterine infection. No conclusive findings can be made about the effects of *Legionella* infection during pregnancy based on these few case reports.

4. Immunity

No information was located regarding the immune response in infected infants or children or any possible protective immunity provided by breast feeding. Silberg et al. (1987) provided evidence that maternal *L. pneumophila* antibodies cross the placenta into the fetal circulation. Sera from 199 mothers and their newborn infants (cord blood samples) were analyzed with an indirect immunofluorescence antibody (IFA) test using a polyvalent *L. pneumophila* antigen of serogroups 1-4. An IFA titer of 1:64 was established as the cut-off value for seropositivity. A total of 71 of the 199 mothers (35.7%) and 28 of the 199 infants (14.1%) were seropositive for *L. pneumophila.* Seropositive infants were born to 26 of the 71 seropositive mothers (36.6%). In contrast, among the128 seronegative mothers, 2 (1.6%) gave birth to seropositive infants. These two seronegative mothers had antibody titers of 1:32, and therefore, the results in these two mother-infant pairs could have been analytical artifact or cross-reactions to other antigens. The study findings suggest the need for caution in using antibody titers to diagnose legionellosis in children younger than one year of age.

5. Risk Factors

In the U.S., the occurrence of legionellosis in children is relatively uncommon and represents just 1 percent of the total legionellosis cases reported to the Centers for Disease Control and Prevention (CDC 1994, 1995, 1996, 1997). (Data are reported for age groups under 5 and 5-14 years.) These data are in agreement with current knowledge of the risk factors that influence *Legionella* infection in adults, and no additional risk factors have been reported that are specific to children. Based on large case series among the general population, the demographic factors most commonly associated with an increased susceptibility to legionnaires' disease include age over 50 years, adult behaviors such as heavy alcohol consumption, and underlying diseases in adults such as chronic obstructive pulmonary disease, end-stage renal disease, or diabetes (Marston et al. 1994, England et al. 1981). Even though pneumonia is common in the general pediatric population, legionnaires' disease in otherwise healthy infants and children is extremely rare (Carlson et al. 1990, Abernathy-Carver et al. 1994,

Famiglietti et al. 1997).

The published literature contains several reports of nosocomial legionnaires' disease in children whose medical treatment or underlying medical condition placed them at increased risk. As for adults, pediatric patients at risk for contracting legionnaires' disease in the hospital setting include those who require intubation or other ventilation assistance (including surgery patients), those who receive respiratory therapy, or those whose care includes the use of aerosol generators such as nebulizers or humidifiers (England et al. 1981, Marston et al. 1994, Stout and Yu 1997). Brady (1989) reported seven cases of nosocomial legionnaires' disease in children seen at a tertiary care pediatric hospital in Ohio during a three-year period. Each of the seven children had at least one known risk factor, including high-dose corticosteroid therapy or other immunosuppressive treatment and underlying chronic lung and/or kidney disease. Carlson and colleagues (1990) reported three nosocomial cases of legionnaires' disease in children, but again, each of the children was at increased risk of infection due to a history of intubation or use of respiratory therapy equipment, as well as the use of corticosteroids. Corticosteroid therapy has also been identified as a risk factor in children who developed legionnaires' disease following bone marrow transplantation (Harrington et al. 1996).

The association between corticosteroid use (and the resulting immunosuppression) and risk of infection with *Legionella* is also apparent in the large population of children with asthma who receive corticosteroid therapy. Boldur and colleagues (1986) compared *Legionella*-seropositive rates among 184 asthmatic children (ages 2-15 years) with 80 age- and sex-matched controls. The number of seropositive children (titers 1:256) was significantly higher ($p<0.001$) in the asthmatic group, although no association was found between corticosteroid treatment and antibody titer. The authors also noted that the apparent susceptibility of asthmatic children to legionnaires' disease may also be attributable in part to the children's increased contact with hospital environments and their use of respiratory equipment including medication nebulizers.

Another population that could be at particularly high risk for *Legionella* infection and legionnaires' disease is neonates due to their underdeveloped lung and immune defenses, as well as the intensive medical treatments (including ventilation assistance and humidified incubators) and corticosteroid therapy they may receive. Only a small number of cases of legionnaires' disease have been reported in neonates (Horie et al. 1992, Holmberg et al. 1993, Famiglietti et al. 1997, Levy and Rubin 1998). Nevertheless, these sporadic cases have served to bring *Legionella* to the attention of neonatologists and other medical personnel.

Children whose cellular immune systems have been compromised by AIDS could be at increased risk for developing infections caused by opportunistic intracellular pathogens such as *Legionella*. The incidence of

pneumonia caused by *Legionella*, however, is extremely low in this population (Chaisson 1998, Stout and Yu 1997). This low incidence may be due in part to increased infection control vigilance when these children are hospitalized. Another factor may be the likelihood that children with AIDS are receiving prophylactic antibiotic treatment (e.g., trimethoprim-sulfamethoxazole) to reduce their risk of *Pneumocystis carinii* pneumonia, as recommended by the American Academy of Pediatrics (1997). These antibiotics are also effective against *Legionella.*

Pediatric cases of community-acquired legionnaires' disease have also been reported in the published literature (Stout and Yu 1997), but these cases typically entail scenarios in which both adults and children were exposed to *Legionella* and a small percentage of the exposed adults and children contract legionnaires' disease. For example, Jernigan et al. (1996) reported an outbreak of legionnaires' disease in adults and children that was associated with an improperly maintained whirlpool spa filter on a cruise ship (Jernigan et al. 1996). No reports were located concerning outbreaks that were apparently restricted to children, and the sporadic occurrence of this disease in the community does not allow discernment of risk factors that are specific to children.

The environments in which children spend the majority of their day -- at home, in daycare, in school, or playing outside -- have not been associated with increased risk of exposure to *Legionella*. While scientists have determined that *Legionella* may be present in home and small building water supply systems (Straus et al. 1996), the vast majority of environmental research and available literature on *Legionella* has focused on this organism's presence in complex water systems and cooling towers of large buildings, especially hospitals. No information was located concerning the occurrence of *Legionella* in association with disease outbreaks in schools, day care centers, or recreational areas.

Certain behaviors in children (e.g., hand-to-mouth or fingers-to-eyes/nose contact, or playing in close proximity to each other) place them at increased risk for many infectious diseases that are transmitted from person-to-person. Because *Legionella* are not transmitted person-to-person as are many other bacterial and viral agents causing pediatric pneumonia, children's play behavior is not expected to increase their risk of exposure to *Legionella*. There are no available reports that have compared the occurrence of *Legionella* (or the incidence of legionnaires' disease) in areas with poor sanitation to areas with adequate sanitation. No information was located regarding the influence of socioeconomic factors on the risk of legionnaires' disease, although poor nutritional status that compromises a child's immune defenses (e.g., severe vitamin D or zinc deficiencies) or limitations in access to health care could influence a child's prognosis. There was no information located regarding the influence of a country's economy (i.e., developed or developing) on this disease.

6. Conclusions

Considerable knowledge gaps persist in the literature with regard to potential risk factors specific to the pediatric population. Based on the literature reviewed in this report, there appear to be no specific factors that place children at increased risk for diseases caused by *Legionella*, and there is no evidence that children are more likely to be exposed to these bacteria. It is widely agreed that *Legionella* have a very low virulence in the general population, which is apparently true for children based on the very low numbers of reported cases of legionellosis in children. There are also knowledge gaps regarding the behavior of *Legionella* in the environment and inside the human body (e.g., the infective dose). Thus, the available literature does not support a formal risk assessment on this group of microbial pathogens. However, compared to the general population, children and infants do not appear to be an especially vulnerable population in terms of either the risk of exposure or the risk of developing clinical disease from *Legionella.*

7. Research Recommendations

The available literature suggests that children and infants are not at increased risk of exposure to *Legionella* or developing legionellosis; however, considerable knowledge gaps exist regarding the effects of *Legionella* in this subpopulation. Research should focus on improved diagnostic testing so that we may better understand the spectrum of pediatric disease and the risk factors associated with *Legionella* infection. An additional research need is prospective studies of the incidence of legionnaires' disease in children hospitalized with either community-acquired pneumonia or nosocomial pneumonia.

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