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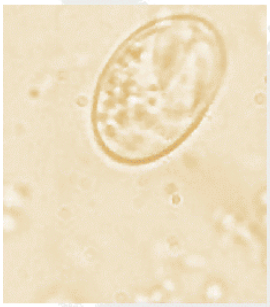
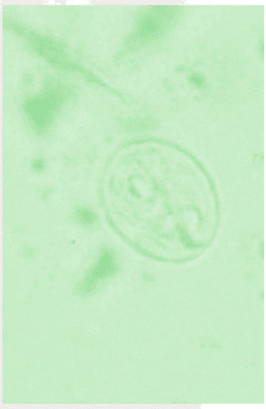
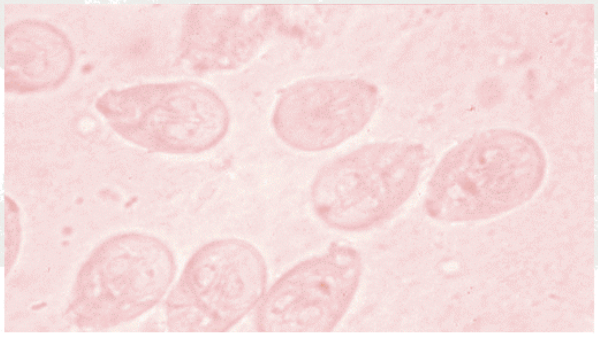
Giardia: Risk for Infants and Children







This document, which describes the childhood risks of giardiasis, was prepared as an addendum to the U.S. Environmental Protection Agency's (EPA) Drinking Water Criteria Document on *Giardia* (U.S. EPA, 1998). Section 1 presents the primary conclusions from information discussed in Section 2 Occurrence of *Giardia* Infection and Giardiasis, Section 3 Health Effects in Children, Section 4 Immunity, Section 5 Risk Factors, and Section 6 Risk Assessment. Section 7 is a summary of the information and research recommendations. Section 8 lists references used to prepare the addendum. Primary references are provided except in instances where information about *Giardia* and giardiasis has already been summarized in EPA's current Drinking Water Criteria Document on *Giardia* (U.S. EPA, 1998) or previous criteria document (ICAIR, 1984). In some instances (e.g., foreign language scientific journals), abstracts are referenced.

In this document, *Giardia* responsible for human infections will be found referred to variously as *G. duodenalis*, *G. intestinalis*, or *G. lamblia* reflecting use by those authors cited.

1. Conclusions

Giardiasis in infants and children can present as (1) asymptomatic infection; (2) acute diarrhea; (3) chronic diarrhea. *Giardia* infection is often asymptomatic for children. It is not clear whether the initial infection is acquired without producing symptoms, as infection may result in a transient, mild, diarrheal illness that passes without notice. Chronic giardiasis appears to be infrequent, but when it occurs, may persist for years, sometimes with asymptomatic periods. Symptoms include diarrhea, steatorrhea, abdominal cramps, bloating, flatulence, pale greasy and malodorous stools, weight loss, and vomiting. Giardiasis may result in malabsorption, growth impairment, or other complications for children, but rarely death.

Giardia infection tends to be more common in children than adults. The prevalence of infection among children world-wide has been found to range from 1% to 36% and occasionally may be as high as 72% depending on the age group and country. In many developing countries, *Giardia* infections are acquired in early childhood, and by the age of 5 most children have been infected at least once. This may be related to frequent opportunities for exposure. In the United States, the highest incidence and prevalence of infection is found among children under 5 years of age, especially for those attending day-care centers. In two counties of Washington State, a prevalence of 7.1% was found among children aged 1 to 3 years. Bartlett et al. (1991) found that 11% of infants and toddlers tested for admission to day care centers in Arizona were already infected. In Vermont, children aged one to four years had the highest incidence rate of any age group for symptomatic *Giardia* infection. In nine outpatient clinics in the United States, *Giardia* was detected in 15% of children (2-11

years of age) with acute diarrhea. In British Columbia, the majority of *Giardia*-positive patients were also in the 1-5 year age group. Most prevalence studies have been conducted in developing countries, and additional data are needed to better assess the current prevalence of *Giardia* infection among children in the United States.

There is no evidence that *Giardia* is transmitted from mother to fetus, but infants can acquire infections at an early age suggesting that mothers can infect their children very soon after childbirth. Breast milk has been found to contain secretory antibodies which could theoretically afford protection against *Giardia* infection. Breast milk may protect some infants from *Giardia* infection either because of protective immunity of secretory antibodies in breast milk or because of breast milk enzymes which have been found *in vitro* to release substances that kill *Giardia* trophozoites. The use of breast milk also offers fewer opportunities for the infant to become infected from other foods and water. Studies in developing countries have provided supportive evidence that breast-fed infants have a lower risk of *Giardia* infection than non-breast-fed infants, but several studies have also reported similar risks of infection or diarrhea in breast-fed and non-breast-fed infants. Further study is required to determine whether high risks for some breast-fed infants in developing countries are due to exposures from the mother, siblings, or other home or environmental sources.

Despite progress in understanding the biology of *Giardia*, there is no adequate explanation for the diverse clinical spectrum which includes asymptomatic carriage, self-limiting diarrhea, and persistent diarrhea that may fail to respond to therapy. The mechanisms by which *Giardia* produces diarrhea and malabsorption are not well understood, and the immunologic determinants for clearance of acute infection and development of protective immunity are not well defined. The epidemiology of giardiasis is also complicated by an apparent genetic heterogeneity in this species.

Development of protective immunity to *Giardia* is considered a relative lengthy process and does not necessarily develop following a single infection. Only partial protective immunity to illness from *Giardia* infection is likely to develop. Responses to a number of different *Giardia* antigens have been reported, but it is uncertain which, if any, of these responses predict a reduced risk of either infection or illness. It is likely that secretory IgA is the most important component of the antibody response to *Giardia*.

In the United States, hospitalized cases of giardiasis have occurred primarily in children under the age of five; volume depletion or dehydration (22%) was the most frequently listed co-diagnosis on admission. In Michigan, 66% of the children under 5 years of age hospitalized with a diagnosis of giardiasis were one year of age or younger. The high hospitalization rate for young children with giardiasis in the United States may reflect

the physicians' concern about a possible adverse outcome rather than the severity of illness; young children have fewer reserves and are more susceptible to fluid and nutritional losses from infection.

Although the significance of *Giardia* as a cause of growth retardation is debated, weight loss and malabsorption have been described in children infected with *Giardia* and some children have suffered from impaired growth. In Michigan, almost 19% of the children younger than 5 years of age who were hospitalized for giardiasis were diagnosed with "failure to thrive", a concern that growth is slower than expected. In Scotland, 11% of the children who were hospitalized for giardiasis were also found lacking in expected normal physiological development. The significance of impaired growth and development associated with giardiasis will differ among children in developed and developing countries, depending on capabilities for diagnosis and medical treatment and on other conditions (e.g., socioeconomic status) which may affect the ability of the child to catch-up in growth and complete pubertal development. Catch-up growth and completion of pubertal development is possible if nutrition is adequate. Additional research is needed to help clarify the association between giardiasis and growth impairment and determine other important confounding factors so that children at greatest risk of growth retardation can be identified. The role of transient or permanent immune defects in increasing the risk of growth retardation from *Giardia* infection should also be investigated.

Inflamation of the synovial membranes of major joints has been observed in some children with giardiasis; following anti-giardial chemotherapy, intestinal and synovial symptoms were abated. Although additional studies are needed to clarify a possible association between cystic fibrosis and *Giardia* infection, the clinical implications of *Giardia* infection (i.e., malabsorption of fat and fat-soluble vitamins) in cystic fibrosis patients, especially children should be recognized. "Salt and pepper" retinal changes found in a study in Italy suggest that asymptomatic, non-progressive retinal lesions may be relatively common in young children with giardiasis. The lesions were not felt to cause functional changes in the retina, but this finding should be confirmed in longer term follow-up studies. Increased risk of these lesions may reflect a genetic predisposition.

As with all diarrheas, fluid replacement is an important aspect of treatment. Anti-giardial drugs are also important in the management of individual cases of giardiasis but may not prevent the frequent re-infection of children who attend day-care centers or live in communities where *Giardia* exposures are frequent. Chemotherapeutic agents used for treatment of giardiasis in children have different effectiveness in their ability to clear *Giardia*, and side-effects should be considered. Drug resistance or re-infection may occur. Paromomycin is recommended for pregnant women, but the cure rate may be low.

Giardia is transmitted via the fecal-oral route of exposure, and both endemic and epidemic transmission are important. *Giardia* is frequently spread directly from person to person, especially among young children attending day-care centers, nurseries, institutions, or living in areas with poor sanitation and hygiene. *G. lamblia* infections in children attending day-care centers in industrialized countries are largely asymptomatic with no adverse growth effects; there is no association between infection in day-care centers and diarrhea..

Children traveling to endemic areas are at risk of infection. Siblings are also an important risk factor for infection. For preschool children, the presence of a child older than 24 months in the household is important for risk of infection. There is little epidemiological evidence that pets pose a significant risk even though dogs and cats are often found infected. Several small foodborne outbreaks of giardiasis have been associated with the contamination of ice and foods by infected food service workers, but restaurant-associated transmission of *Giardia* does not appear to be a significant public health problem for children.

Epidemiological studies in various areas of the United States have found that 7% to 54% of children attending day-care centers are infected with *Giardia*, suggesting that 155,000 to 1,198,000 children attending day-care centers in the United States may be infected with *Giardia*. Infected children in day-care centers are frequently asymptomatic. Infected infants and children, both symptomatic and asymptomatic, may infect other children and adults, especially family members or other care-givers. Secondary transmission of *Giardia* from children in day-care centers has been reported to range from 5% to 20% for household contacts and 9% to 35% for staff. This suggests an additional 15,000 to 480,000 *Giardia* infections may occur in adults from contact with children in day care settings. Secondary transmission from children who are infected from waterborne exposures may occur, but its importance could not be assessed.

In the United States, *Giardia* is the most frequently identified etiologic agent causing waterborne outbreaks, especially in unfiltered surface water systems. Higher risks found in populations using unfiltered surface water systems may be due to inadequate disinfection commonly employed before the EPA's Surface Water Treatment Rule (SWTR) became effective. It is estimated that 44.6 million children are exposed to public water systems that use unfiltered surface water. Children have been among the cases reported in waterborne outbreaks, but limited information is available on attack rates in these outbreaks. In one waterbome outbreak in Berlin, New Hampshire, 38% and 60% of children under 10 years of age and children 10-19 years, respectively, were found infected. Children are also at an increased risk of endemic waterborne infection from shallow wells and water recreational activities. Poorly maintained wading and swimming pools and heavily used swimming areas at lakes and ponds pose a risk for children, especially if the swimming areas are used by

diaper-age toddlers or other children prone to fecal accidents.

Risk assessment models have estimated the risk of waterborne *Giardia* infection in the United States. Based on levels of *Giardia* cysts found in treated drinking water in the United States, the annual risks of *Giardia* infection are estimated to be 20 x 10^{-4} (20 waterborne *Giardia* infections per 10,000 persons annually) and may be as high as 250 x 10^{-4} (250 waterborne *Giardia* infections per 10,000 persons annually). If this quantitative risk assessment can be applied to children, 155,500 to 1,944,000 waterborne infections are expected annually among children under 19 years of age. For children under the age of five, 38,000 to 474,000 cases of waterborne giardiasis may occur. These estimates assume that the dose-response curves for children and adults are similar. It is difficult to ascertain the level of accuracy that these risk estimates represent, since no comparable risk estimates are available from epidemiological studies. In addition, the interpretation of these risks depends on occurrence data for *Giardia* cysts in the environment. Methods used to date generally provide little or no information on viability, infectivity, or species identification when *Giardia* cysts are detected in environmental samples, and quantitative data may not be reliable due to low efficiency and precision of methods. Other estimates suggest that 1400 to 34,500 cases of waterborne giardiasis would be expected to occur each year in children and that 540 hospitalizations of children under 5 years of age with giardiasis each year may be due to waterborne transmission.

Giardiasis is common in populations living in poverty, with poor sanitation, and in areas with a high level of fecal contamination of the environment. The relative importance of waterborne transmission among other risk factors for giardiasis will vary among populations depending on general sanitation practices. For example, providing piped, high quality drinking water to some populations in developing countries may not significantly reduce the incidence of giardiasis. Although contaminated drinking water is a likely source of exposure, the variety of other exposures including personal hygiene, food hygiene, and environmental factors may overwhelm the beneficial effect of clean drinking water.

2. Occurrence of *Giardia* Infection and Giardiasis

Giardiasis is the most commonly reported intestinal protozoan infection worldwide, and human infections with *Giardia* have been reported in all of the major climatic regions from the tropics to the arctic (ICAIR, 1984). The World Health Organization estimates 200 million people are infected each year (Swarbrick et al. 1997). In the United States, United Kingdom, and Mexico, endemic *Giardia* infection most commonly occurs among children under five years of age and adults aged 25-39 years of age (Benenson, 1995). Although

Rabbani and Islam (1994) reported that breast-fed infants under 6 months of age are not likely to be infected, studies in some populations have found infections in breast-fed infants (see Section 3).

2.1. Prevalence and incidence in various countries

Based on stool positivity, the prevalence of *Giardia* infection in children has been found to range from 1% to 72%, depending on the geographic area and age group (Tables 1-5). Prevalence in children varies from country to country and among populations within countries. In some developing countries, infection among young children can be quite high. All of a birth cohort of 45 Guatemalan children had giardiasis by age three (Farthing, 1986) and 40% of Peruvian children were infected by six months of age (Ortega and Adam, 1997; Miotti et al., 1986). In the Guatemalan cohort, the mean number of infections increased from 0.7 in the first year to 3.6 in the third year (Farthing, 1986). In Israel, Fraser et al. (1997) found a 91.5% cumulative risk of infection with *G. lamblia* by age two in a birth cohort of 164 Bedouin children followed from birth. Stools specimens obtained monthly from birth to two years of age and at all diarrhea episodes showed that the detection of *G. lamblia* was higher during diarrhea episodes in children under six months of age. Afterwards, *G. lamblia* were detected less frequently in stool specimens during diarrhea episodes than in non-diarrhea stool specimens; the odds ratio (OR) = 0.8 and 95% confidence interval (CI) = 0.7-0.9. The asymptomatic detection rate for *G. lamblia* was 28.5%. In a cohort of 195 Bangladeshi infants aged 2 to 8 months at enrolment and studied for two years, 68% of children were found infected at least once (Hall, 1994).

Islam et al. (1983) followed a cohort of 33 lactating mothers and their infants in a periurban area of Bangladesh for one year and found that 82% of mothers and 42% of infants were infected with *G. lamblia* at least once. Infants became infected as early as 3 months of age, and 86% of infected infants had diarrhea, suggesting that first exposure to *G. lamblia* results in disease. Only one mother had diarrhea, suggesting partial immunity that protects against disease but not infection.

North America. In the United States, *Giardia* is the most frequently identified parasite in stool specimens submitted for ova and parasites, and the overall prevalence for all age groups ranges from 4.0% to 12% depending on the year and state (Kappus et al., 1994). In 39 states, *Giardia* was found to be the most frequently identified parasite every month of the survey periods; no information was reported specifically for prevalence in children. Harter et al. (1982) reviewed the results of randomly collected stool specimens in two counties of Washington State and found that 37 (7.1%) of 518 healthy 1- to 3-year-old children were positive for *Giardia* cysts (Table 1). Caeiro et al. (1999) determined the etiology of acute, non-dysenteric diarrhea

among 147 children between 2 and 11 years of age from nine outpatient clinics in Texas, New York, Michigan, Florida, New Jersey, Utah, and Pennsylvania. A recognized etiologic agent was detected in the stools of 89 (61%) of the children. *G. lamblia* was detected in 22 (15%) children with a spring peak; most of the cases of giardiasis were identified in Houston, Texas, and Levittown, New York.

In an epidemiological study of endemic cases of giardiasis reported from 1983 to 1986 in Vermont, children aged one to four years had the highest incidence rate for symptomatic *Giardia* infection of any age group including adults (Birkhead and Vogt, 1989). Among children aged one to four years, the incidence of symptomatic giardiasis was almost four-fold higher than for infants less than one year of age and children 5-9 years of age. Among children aged one to four years, the incidence was 50% greater for boys (approximately[1] 200 cases/100,000/year) than girls (135/100,000/year). Among infants less than one year of age, symptomatic giardiasis rates were much lower, but the incidence was 40% greater for boys (55 cases/100,000/year) than girls (40/100,000/year). Incidence rates among girls and boys were similar after the age of 4 years: 40 cases/100,000/year for ages 5 to 9 years and 18 cases/100,000/year for ages 10-19. Isaac-Renton and Philion (1992) reviewed records from 2,186 *Giardia*-positive patients in British Columbia, Canada, and also found that the majority of *Giardia* infections were in the 1 to 5 year age group. Wright et al. (1977) reported the incidence of *G. lamblia* infection in Colorado among children age 0 to 15 years was 3.05 per 100,000 per year.

Table 1. Prevalence of *Giardia* infection in children, United States

Location	Age	Prevalence
Washington State, USA (Harter et al., 1982)	1-3 years	7%
Colorado (Novotny et al., 1990)	toddlers	7%
Arizona (Bartlett et al., 1991)	infants & toddlers	11%
Nine outpatient clinics, USA (Caeiro et al., 1999)	2-11 years	15% (among cases of acute diarrhea)

Africa and the Middle East. *Giardia* prevalence for countries in Africa and the Middle East is reported in Table 2. A survey in Pikine (Senegal) of five groups of children from ecologically representative sections of the town confirmed the high prevalence of *Giardia* (43.7%) in urban areas of Africa (Salem et al., 1994 abstract). The highest prevalence for *Giardia* (56.8%) was found in children living on the outskirts of the town. Over a 12-month period random stool specimens collected from 101 children admitted to a trauma unit of a

[1] All reported incidences in Vermont children were estimated from a graph provided in the reference.

children's hospital in Cape Town, South Africa, showed that 8 (8%) were infected with *G. lamblia* (Millar et al., 1989 abstract). Esrey et al. (1989) found 23.6% of 267 preschool children in rural Lesotho, South Africa, infected with. *G. lamblia.* Studies in South Yemen found *G. lamblia* in 35% of 104 children 6-15 years old (Kopecky et al., 1992 abstract). Magambo et al. (1998 abstract) studied the prevalence of intestinal parasites among school children in southern Sudan and found children aged 6-10 years were the most frequently affected. The prevalence of *G. lamblia* was 9.8%. Mason and Patterson (1987) examined stool specimens from 3,038 children aged 3 to 14 years living in rural and urban areas near Harare, Zimbabwe, for *G. lamblia* cysts. The overall prevalence of giardial infection was 19.4% with more urban children (21.1%) passing cysts than rural children (16.7%). In urban areas the highest prevalence was in young (5-6 years of age) children; in rural areas, the highest prevalence was in older (9-10 years of age) children. Enekwechi and Azubike (1994 abstract) conducted a survey of the prevalence of intestinal parasites in primary school children in Nimo, Nigeria. Of the 1,536 stool samples collected from eight primary schools, only 0.1% were positive for *G. lamblia* examined by light microscopy after formalin ether centrifugation,.

A survey of 770 households in Behera, Egypt, selected by a random cluster sampling technique (Curtale et al., 1998), found *G. intestinalis* in 24.7% of children, aged 6 months to 12 years; fecal analyses from direct smear and the Kato-Katz examination techniques were available from 1844 and 1783 children respectively. A two-year study of the etiologic agents associated with episodes of diarrhea in a family cohort population was conducted in eight villages of rural northeastern Egypt; 3,243 stool specimens from 3,513 episodes of diarrhea were analyzed for enteropathogens (Zaki et al., 1986). The most commonly identified agent in persons with diarrhea was *G. lamblia* (44%); 60% of *Giardia*-positive stool specimens occurred in children 6 to 24 months of age. The isolation of *G. lamblia* from stool specimens was similar for persons with diarrhea and those without, and no discernible seasonal pattern was found for infection. Stazzone et al. (1996) found *Giardia* in 10.7% and 19.7% of 271 children who attended a clinic in Alexandria, Egypt, between December 1991 and July 1992 using conventional trichrome staining and immunofluorescent methods, respectively. Ahmed (1991 abstract) surveyed 1426 apparently healthy Saudi children, finding *G. lamblia* to be the most common pathogenic parasite (3.6%).

Table 2. Prevalence of *Giardia* infection in children, Africa and the Middle East

Country	Age	Prevalence
Egypt (Rabbani and Islam, 1994)	Infants	35%
Egypt (Curtale et al., 1998)	6 months-12 years	25%

Egypt, Nile Delta (Stazzone et al., 1996)	Children	11-20%
Nigeria	<5 years	2-13%
Nigeria (Enekwechi and Azubike, 1994 abstact)	primary school children	<1%
Zimbabwe (Rabbani and Islam, 1994)	7-19 years	22%
Zimbabwe (Mason and Patterson, 1987)	3 to 14 years	20%
Senegal (Salem et al., 1994 abstract)	no age provided	44-57%
South Africa (Esrey et al., 1989)	<13 months 1-2 years 2-3 years 3-4 years >4 years	2% 17% 41% 29% 26%
South Africa (Esrey et al., 1989)	preschool	24%
Sudan (Magambo et al., 1998 abstract)	6-10 years	10%
Israel, Bedouins (Fraser et al., 1997)	0-6 months 6-12 months 1-2 years	1-5% 9-23% 34-36%
South Yemen (Kopecky et al., 1992 abstract)	6-15 years	35%
Saudi Arabia (Omar et al., 1995)	1-9 years 10-24 years	22% 16%
Saudi Arabia (Ahmed 1991 abstract)	children (no age provided)	4%

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Asia. *Giardia* prevalence for countries in Asia is reported in Table 3. Ngan et al. (1992) found stool specimens positive for *G. lamblia* in 4% of 83 children under three years of age who were treated for persistent diarrhea in the gastroenterology unit of the Institute for the Protection of Children's Health in Hanoi. Kang et al. (1998) determined the prevalence of intestinal protozoal infection in 78 members of 15 families from a rural village in India. Stool specimens from all subjects were examined on alternate days for one month; the overall prevalence of parasitic infections was 97.4%, with only 2 of 78 subjects not excreting parasites in any of fifteen specimens. Eighteen (23.1%) persons had only one type of parasite, while 58 (74.3%) excreted multiple parasites. *Giardia* was the most common protozoan infection, affecting 42 (53.8%) persons. In Punjab, India, Walia et al. (1986) found 35.1% of preschool children infected with *G. lamblia*; 16.5% of those infected had diarrhea.

Table 3. Prevalence of *Giardia* infection in children, Asia

Country	Age	Prevalence
Thailand (Janoff et al., 1990a)	<5 years (includes infants)	20%
Thailand (Rabbani and Islam, 1994)	7-19 years	21%
Bangladesh (Hall, 1994)	<2 years	68%
Bangladesh (Rabbani and Islam, 1994)	5-9 years	21%
India (Walia et al., 1986)	preschool children	35%
Rural south India (Kang et al., 1998)	0-5 6-10 11-15	72% 70% 65%
Clinic, Hanoi, Vietnam (Ngan et al., 1992)	<3 years	4% (among cases of diarrhea)

Europe. *Giardia* prevalence for countries in Europe is reported in Table 4. Gray and Rouse (1992 abstract) found that 23.7% of index cases of giardiasis in Bristol, England, were in preschool children; the remainder in travelers abroad and persons aged 10 years or more engaged in water recreation. Olszok and Kucharz (1996 abstract) found about 10% of adults and 20% of children in Poland infected with *G. lamblia*; only a small percentage of infected persons were symptomatic. Skorochodzki et al. (1998 abstract) studied a sample of 112 children hospitalized with chronic abdominal pain from 1992 to 1993 in northeastern Poland; based on the results of the duodenal fluid examination, *G. lamblia* infection was diagnosed in 77 (68%) children. Nikolic et al. (1998 abstract) surveyed intestinal parasitism among 5981 schoolchildren in central Serbia during the period 1984-1993. The study included 2887 females and 3094 males, 7-11 years old representing 10% of the total age-matched population in the region. *G. lamblia* was detected in 6.8% of the children.

Table 4. Prevalence of *Giardia* infection in children, Europe

Country	Age	Prevalence
Spain (Garcia et al., 1989 abstract)	0-2 years	4%
Spain (Jarabo et al., 1995 abstract)	5-14 years	36%
Spain (Perez Armengol et al., 1997 abstract)	6-10 years	5%
Spain (Buchrieser et al., 1988 abstract)	6-14 years	29%
England (Gray and Rouse, 1992 abstract)	preschool	24%
Poland (Olszok and Kucharz, 1996 abstract)	no age provided	20%
Poland (Skorochodzki et al., 1998 abstract)	no age provided	68% (among children hospitalized with chronic abdominal pain)
Serbia (Nikolic et al., 1998 abstract)	36351	7%

To study the prevalence of intestinal parasites in school-age children of Centro de Salud de Mota del Cuervo, Cuenca, Spain, Jarabo et al. (1995 abstract) analyzed fecal samples from healthy children, 5-14 years old, randomly selected by stratified sampling. The study included 297 children of whom 133 (44.8%) were found infected with parasites. *G. lamblia* was the parasite most frequently detected (36.4%). There was no difference in prevalence between boys and girls. During 1994 to 1996, Perez Armengol et al., (1997 abstract) found the overall prevalence of intestinal parasites (27.1%) in 1,917 children without symptoms, 6 to 10 years of age, living in 20 villages in the Guadalquivir valley of Spain to be similar to that found in other regions of Spain; *G. lamblia* (5.1%) was the second most commonly identified parasite in these children. Garcia et al. (1989 abstract) studied diarrhea and the prevalence of enteropathogens for a one-year period in a group of 144 children (31 newborn infants, 62 aged 1 year and 51 aged 2 years) randomly selected from the registrar's office of Seville, Spain. Two stool specimens were obtained, one at the beginning of the study and the second midway through the study. The prevalence rate of *G. lamblia* infection was 4%. Buchrieser et al. (1988 abstract) identified *G. lamblia* in 28.7% of stool specimens collected on the Cape Verde Islands; 90% of the samples came from children aged between 6 and 14 years.

Latin America. *Giardia* prevalence for Latin America countries is reported in Table 5. In a prospective study of 318 children, aged 3 to 14, without symptoms, attending school in eight villages in the eastern part of the province of Avila, Brazil, Pedraza et al. (1994 abstract) found a 4.4% prevalence of *G. lamblia* during 1992-93. No statistically significant differences in prevalence were found between girls and boys or between children over or under 10 years of age. Lindo et al. (1998) conducted a cross-sectional epidemiologic study of *G. lamblia* and *Cryptosporidum* infections in Jamaica. Three hundred twenty eight stool samples from patients less than one to 81 years of age were examined. In contrast to *Cryptosporidum* infections, which were most frequently diagnosed in children less than five years old and prevalence decreased with age, the prevalence of *Giardia* infection was highest among children aged 7-8 and infection increased as children became older.

Table 5. Prevalence of *Giardia* infection in children, Latin America

Country	Age	Prevalence
Guatemala (Gupta et al., 1982; Farthing, 1986)	0-6 month	<2%
	6-12 months	7%
	1-2 years	16%
	2-3 years	20%
	2-5 years	22%

Jamaica (Lindo et al.; 1998)	<3 years 3-4 years 5-6 years 7-8 years 11-12 years	5% 8% 14% 32 % 13%
Costa Rica	3 years	20%
Brazil (Pedraza et al., 1994 abstract)	3-14 years	4%
Peru (Ortega & Admans, 1997; Miotti, 1986)	<6 months	40%
Peru (Lanta et al., 1992)	<3 years	23-31% (among children with diarrhea)

2.2. Prevalence and incidence in day-care centers, nursery schools, other institutions

Day-care centers. A high prevalence of infection has been reported in settings where infants and young children in diapers are collectively cared for. As many as 54% of children attending child care centers in developed countries can be infected with attack rates of 50% or more occurring in outbreaks (Adam, 1991; Hall, 1994; Ortega and Adam, 1997; Steketee et al., 1989). The prevalence of infection may also be high in young children who intend to enroll in day-care centers. Bartlett et al. (1991) found *Giardia* infection in almost 11% of 6,761 new infants and toddlers tested for admission to 31 day care centers.

In an epidemiological study of endemic cases of giardiasis reported from 1983 to 1986 in Vermont, Birkhead and Vogt (1989) found that children attending child-care facilities had an incidence rate 50% greater than non-attendees (300.0/100,000/year versus 194.7/100,000/year). Steketee et al. (1989) described three outbreaks of giardiasis that occurred over a 19-month period in a Wisconsin facility that cared for a daily average of 115 children aged 1 month to 6 years. Estimated attack rates in the three outbreaks were: 47%, 17%, 37% for children; 35%, 13%, 9% for staff; and 18%, 9%, 5% for household contacts. In a day-care center in Washington, D.C., Polis et al. (1986) investigated an outbreak of giardiasis where 35% of the children were infected. In two prevalence studies of 660 children enrolled in 30 day care centers, Pickering et al. (1984) found *Giardia* cysts in 21% and 26% of children who provided stool specimens. No association was found between diarrheal episodes and *Giardia* detection, and asymptomatic infection did not affect monthly height and weight (Pickering et al., 1984). Fraser (1994) reported that *G. lamblia* infections in children attending day-care centers in Israel have been largely asymptomatic with no adverse growth effects and no association with higher rates of diarrhea.

Thompson (1994) found prevalence rates of *Giardia* infection in Australia to range between 2% and 46% and to be highest among children 1-5 years of age who attended preschool care. In three day-care centers in Atlanta, Georgia, the infection rate ranged from 29% to 54% compared to 2% among children not attending day-care centers (ICAIR, 1984). In two day-care centers in metropolitan Toronto, Canada, infection rates of 17% and 39% were reported (ICAIR, 1984); the most susceptible children were 1 to 3 years old.

A two-year prospective study of diarrheal illness in children up to 36 months of age in 22 day care centers in Maricopa County, Arizona, identified 465 sporadic cases and 170 outbreak-associated cases of diarrhea (Bartlett et al., 1991). *G. lamblia* and rotavirus were the most commonly isolated enteropathogens in children with diarrhea. *Giardia* infection was more common in toddlers than in infants.

In 1989 and 1990, a survey of stool specimens from 292 diapered children attending 17 randomly selected day-care centers in Fulton County, Georgia, found that 21 (7%) children in seven centers were infected with *Giardia* (Addiss et al., 1991). Infected children ranged in age from 3 to 30 months, and only 57% of *Giardia*-positive children had symptoms. In 1986 the prevalence of infection in these same centers was 11% (Addiss et al., 1991). Both of these prevalence rates, however, are lower than the 16% to 38% infection reported in other studies of children attending day centers where outbreaks had not occurred (Addiss et al., 1991). The percentage (41%) of day-care centers with one or more infected children was also lower than the 66% to 85% reported in other studies (Addiss et al., 1991). Cody et al. (1994) collected specimens from 80 of 231 children 2 to 3 years of age in six commercial day care centers and found that 13 (16%) were infected with *Giardia*; only seven (54%) of the infected children had diarrhea.

Novotny et al. (1990) surveyed a sample of children in the toddler age group in Denver, Colorado, to determine the prevalence of *G. lamblia*. The sample consisted of 236 children who were attending day-care centers and 79 who were not. Thirty-eight (16%) of the children who attended day-care centers and 7 (9%) who did not attend day-care centers were found to be infected with *G. lamblia*. Seventy-five children (42 girls and 33 boys, aged from 6 to 65 months) attending a day care center in Montreal, Quebec, Canada, were surveyed for excretion of *G. lamblia* cysts (Varga and Delage, 1990 abstract). *G. lamblia* was found in 17 (23%) of the children, 9 of whom were still positive six months later. Rodriguez-Hernandez et al. (1996) identified *G. intestinalis* in 25% of the children studied in eight day care centers in Salamanca, Spain.

Franco and Cordeiro (1996 abstract) studied the prevalence of *G. duodenalis* infections in 310 children, 2-60 months old, enrolled in eight day-care centers in Campinas, Brazil. *Giardia* was found in 42 (13.5%) of the

children and was most frequent in the age group 19-24 months old; infants during the first six months of life also had positive stool specimens. The prevalence of *Giardia* infection did not differ between boys and girls.

A parasitological survey conducted in three municipal day-cares from Botucatu, Brazil, found the prevalence of *Giardia* infection to range from 52.7% to 69.6% (Guimaraes and Sogayar, 1995 abstract). Three separate stool specimens were collected from 147 children, <1 to 72 months old and from 20 staff members. *G. lamblia* was found mainly in children between 12 to 47 months old; only one employee was positive.

Schools, institutions. Analysis of fecal specimens obtained from 722 of 820 children attending seven nursery schools and one primary school in the city of Santiago, Chile, showed that 33% of the children were infected with *G. lamblia* (Goldin et al., 1990). *G. lamblia* infection prevalence among primary school students aged 5 to 10 years (38%) was higher than among nursery school students aged 3 months to 5 years (29%). There was no apparent association between socio-economic status and *G. lamblia* infection, and a privately owned nursery school had the highest prevalence (40%) of infection. Golinska et al. (1997 abstract) reported *Giardia* infection in 12.5% of 588 children attending four kindergartens in Warsaw, Poland. Derylo et al. (1994) detected *Giardia* in 1% to 2% of 96 Polish children aged 7 to 14 years and attending a private school.

G. lamblia was identified in 72% of the fecal specimens examined from 92 institutionalized Romanian children (Brannan et al, 1996). Janoff et al. (1990a) conducted a point prevalence survey for enteric protozoa in 205 institutionalized orphans, 1-61 months of age, in Bangkok, Thailand. *G. lamblia* was identified in 42 (20%) children. At the time of diagnosis, diarrheal symptoms were present in only 10% of the children with *G. lamblia*. Children living in institutions such as orphanages are more exposed to intestinal parasities, since crowding and behavioral patterns contribute greatly to the spread of parasitic infection. However, the prevalence of *G. lamblia* was found to be 10% among 100 children living in orphanages in Cairo, Egypt, compared to 15% among 20 children living outside the orphanages under better conditions (Makhlouf et al., 1994 abstract). Ages of the children ranged from 6-12 years.

HIV-positive children. Del Aguila et al. (1997) conducted a prospective study of parasites in 83 HIV-positive pediatric patients (mean age of 6.3 years, mean CD4 count of 504.7/mm^3) from three hospitals in Madrid, Spain. Forty-eight children suffered from diarrhea at the time of the study. Enteric parasites were identified in 32.5% of the children. *Cryptosporidium* sp. was the most common (14.4%) parasite detected in these children followed by *Blastocytis* sp. (9.6%) and *G. duodenalis* (8.4%). *Giardia* was detected twice as often in stool specimens from children with diarrhea (10.4%) than children without diarrhea (5.7%). In a study

of 92 institutionalized Romanian children 12 to 52 months of age, Brannan et al. (1996 abstract) found that HIV seropositivity ($p<0.02$) was predictive of *Giardia* infection; *G. lamblia* cysts were detected in 72% of the children.

3. Health Effects in Children

3.1. Symptoms and Clinical Features

Asymptomatic infection. *Giardia* infection is often asymptomatic. This is the most common outcome of infection, especially for children. It has been estimated that as many as 50% to 75% of *Giardia*-infected persons may be asymptomatic (U.S. EPA, 1998). Factors in the host-parasite relationship that allow infection but prevent expression of diarrheal disease have not been defined (Farthing, 1996).

It is not clear whether the initial infection is acquired without producing symptoms; infection may result in a transient, mild, diarrheal illness that passes without notice. Islam et al. (1983) found infants in Bangladesh became infected as early as 3 months of age, and 86% of infected infants had diarrhea, suggesting that first exposure to *G. lamblia* results in disease. In a cohort study of 45 Guatemalan children followed from birth to age 3 years, Farthing et al. (1986) found no diarrheal disease associated with *Giardia* infection in the first four months of life, even though all children became infected at least once during the first three years of life. At ages 6 to 11 months, the incidence of infection with diarrhea in the cohort was 3.3 episodes per 100 child months, increasing approximately two fold in the next two years (Table 6). At ages 12 to 23 months, the incidence of *Giardia* infection with diarrhea was almost twice the incidence of infection without diarrhea. During ages of 24 to 29 months, the incidence of infection with and without diarrhea was similar; during the age 30 to 35 months the incidence of infection without diarrhea was higher. More than 40% of infections lasted 2 to 6 weeks or longer (Farthing, 1986).

Table 6. Incidence of *Giardia* episodes associated with diarrhea in a cohort of Guatemalan children followed from birth to age three years (Farthing et al., 1986)

Episodes* per 100 child months	0-5 months	6-11 months	12-17 months	18-23 months	24-29 months	30-35 months
with diarrhea	0	3.3	7.8	8.2	7.3	6.6
without diarrhea	3.2	3.7	4.1	4.5	7.3	7.5

Giardia-positive weeks separated by at least two *Giardia*-negative weeks and at least 3 negative stool exams; adjusted for specimens not collected.

In a cohort of 164 Bedouin children in Israel followed from birth to 2 years of age, Fraser et al. (1997) found that after the age of 6 months, *G. lamblia* was more frequently detected in routine non-diarrhea stool specimens than in specimens obtained during a diarrhea episode. Overall the prevalence of asymptomatic infection was 28.5% only slightly higher than the 22.3% prevalence for infection during diarrheal episodes; however, the proportion of *Giardia*-infected children with and without diarrhea varied according to age. For infants aged 3 months or younger, a higher proportion of stool specimens were positive for *G. lamblia* during diarrheal episodes, but during ages 10 to 12 months, a higher proportion of stool specimens were positive for *G. lamblia* during routine sampling (Fraser et al., 1997). A cohort of Egyptian infants followed by Mahmud et al. (1995) from birth through their first year found that infants less than six months of age were at special risk for developing their first symptomatic infection. Mahmud et al. (1995) noted that in previous studies infants acquired infection during weaning when they were more likely to be exposed to a variety sources of infection, but in their current study, *Giardia* was detected in the stool of three infants as early as the first weeks of life (Mahmud et al., 1995). In a cohort of 195 Bangladeshi infants aged 2 to 8 months at enrolment and studied for two years, it was found that 68% of children had been infected at least once (Hall, 1994). Among a cohort of 58 Kenyan children, the average period between infections was about one month (Hall, 1994).

In a family cohort population in eight villages of rural northeastern Egypt, Zaki et al. (1986) found the most commonly identified pathogen in persons with diarrhea was *G. lamblia* (44%); 60% of positive stool specimens occurred in children 6 to 24 months of age. Also isolated were heat stable enterotoxin (ST)-producing enterotoxigenic *Escherichia coli* (ETEC) (15%), heat labile toxin-producing ETEC (12%), enteropathogenic *E. coli* (4%), rotavirus (3%), *Shigella* (2%) and *Salmonella* (1%). Isolation of *G. lamblia* from persons with diarrhea and those without diarrhea was similar, and no discernible seasonal pattern was found for *Giardia* infection. In a longitudinal study of acute and persistent diarrhea in 677 children less than three years old in a peri-urban community of Lima, Peru, during 27 months of surveillance, stools were cultured at the beginning of each diarrheal episode and on each subsequent week of illness (Lanata et al., 1992). Analyzing stool cultures only from children who had not received antibiotic treatment in the 48 hours prior to the culture, no association was found between *G. lamblia* and persistent diarrhea. The isolation rate for *G. lamblia* (23-31%) was similar during the first, second, third or later week of illness.

Asymptomatic *Giardia* infection for children may be epidemiologically significant (ICAIR, 1984). Children with asymptomatic *Giardia* infection serve as unidentified carriers and may be responsible for

transmission of the infection. Secondary transmission among family members may occur. In a study on 132 families in Spain where a case of giardiasis was diagnosed, Arancon Viguera et al. (1990 abstract) found an additional 30 of 405 (7.4%) persons who were positive for *G. lamblia*. Among people younger than fifteen years of age, 14.7% were positive, while after this age the rate of infection was 4.2%.

Asymptomatic infections may last for months or years (ICAIR, 1984). Farthing et al. (1986) found that infections lasted 2 to 6 weeks or longer in more than 40% of his cohort of Guatemalan children. In one longitudinal study of children in a day-care center, almost 15% excreted cysts for a mean of six months. Varga and Delage (1990 abstract) found that over half (53%) of the infected children attending a day care center in Quebec were still *Giardia* positive six months later. In a longitudinal study, Pickering et al. (1984) found that 12 children in day-care centers excreted *Giardia* cysts for a mean of 6.2 months (SD=1.2 months).

Acute giardiasis. Infection may result in a variety of intestinal symptoms including diarrhea, steatorrhea, abdominal cramps, bloating, flatulence, pale greasy and malodorous stools, and weight loss; nausea or vomiting may also occur (U.S. EPA, 1998). The severity of symptoms and the duration of *Giardia* infection are highly variable. In some patients, symptoms last for only 3 or 4 days, while in others the symptoms last for months. A study of experimental human infections of adults with a single *Giardia* strain found the severity and duration of giardiasis bore no apparent relationship to the magnitude of the serum or secretory antibody responses (Nash et al., 1987). Gillin et al. (1990) felt the variability in the severity of giardiasis symptoms may be due in part to trophozoite interactions with non-immune elements of intestinal milieu.

Farthing et al. (1986) found that the incidence of diarrheal disease in his cohort of Guatemalan children peaked at age 12 to 23 months. In a family cohort population in eight villages of rural northeastern Egypt, Zaki et al. (1986) found the incidence of *Giardia*-associated diarrhea was highest during ages 6 to 24 months but decreased significantly among older children and adults. At age 0 to 5 months the incidence (1.4 *Giardia*-associated diarrhea episodes per person year) was about half that seen at ages 6 to 24 months. After age 24 months, the incidence of *Giardia*-associated diarrhea per person year decreased: 1.2 at ages 2 to 3 years, 0.5 at 3 to 4 years, 0.3 at 4 to 5 years, 0.1 at 5 to 15 years, and <0.1 at ages greater than 15 years (Zaki et al., 1986).

The epidemiology of giardiasis is complicated by an apparent genetic heterogeneity in the species of *Giardia*. Differences in virulence, pathogenicity, infectivity, growth, drug sensitivity, and antigenicity of *Giardia* have been reported. In endemic areas of Australia where extensive heterogeneity exists, mixed infections with more than one genotype has been found in children (Upcroft et al., 1995). Chavez et al. (1995)

studied axenic trophozoites of 10 strains of *G. lamblia* isolated from children with infections in Mexico City and concluded that the variable clinical course of human giardiasis in these children may be due in part to differences in the virulence of the various strains.

Giardia trophozoites are principally found in the small intestine, and in severe giardiasis, duodenum and jejunal mucosal cells may be damaged (U.S. EPA, 1998). Under *in vitro* conditions, isolates of *G. lamblia* trophozoites derived from symptomatic or asymptomatic human infections were found to damage epithelial cultured cells mainly by depleting their microvilli; none showed evidence of an invasive effect (Chavez et al., 1995 abstract). Savidge et al. (1996) investigated epithelial cell turnover in children with food intolerance (cows' milk protein intolerance and celiac disease) after infection with *G. lamblia*; levels of epithelial cell proliferation suggested a hyperplastic crypt response.

Burke (1975) reported that giardiasis can mimic celiac disease, but few studies have studied the incidence and possible effect of *G. lamblia* in children with celiac disease (Carswell et al., 1973). In a study of 93 hospitalized children suspected of having celiac disease, Carswell et al. (1973) found a similar incidence of *G. lamblia* infection in 58 children with celiac disease and 35 children without the disease. The mean age of patients with *Giardia* infection was 35 months compared to a mean age 53 months for patients without infection. Carswell et al. (1973) also examined jejunal biopsies of celiac patients and found that *Giardia* was more commonly found in children with less severe histological changes.

Pesce et al. (1992) reported an 8-year-old boy with hypertrophic gastropathy associated with duodenal *G. lamblia* infection. Viral (cytomegalovirus) and bacterial (*Helicobacter pylori*) infections have also been associated with hypertrophic gastropathy, and the role of *G. lamblia* and these agents in the pathogenicity of hypertrophic gastropathy requires additional study.

Lactose intolerance is common during active infection and may persist for several months after clearance of the parasite (Wolfe, 1992). In 67 well-nourished African children in Gabon, Africa, Gendrel et al. (1992 abstract) found that *Giardia* infection was associated with an increased, but not statistically significant, lactose intolerance; 10 of 12 infected children (83.3%) showed lactose malabsorption.

In the United States from 1979 to 1988, an estimated 4,600 persons (an incidence of 2.0 hospitalizations per 100,000 persons per year) were hospitalized annually with giardiasis; the median length of the hospital stay was 4 days (Lengerich et al., 1994). The estimated hospitalization rate was highest for children less than 5

years old (4.6 per 100,000 per year). In Michigan the hospital admission rate for giardiasis from 1983 to 1987 was 1.4 per 100,000 persons; the incidence (4.0 per 100,000) was greatest among children younger than 5 years of age (Lengerich et al., 1994). Of 139 hospitalizations in children younger than 5 years of age, 30 (22%) occurred among children younger than 1 year of age and 61 (44%) occurred among children one year of age. In Scotland, hospitalized cases of giardiasis were also primarily observed for children under the age of five (Robertson, 1996).

Lengerich et al. (1994) reported that volume depletion or dehydration (22%) was the most frequently listed co-diagnosis on admission. In Scotland, dehydration did not occur as frequently with giardiasis, either because of *Giardia* strain differences or because rehydration treatments are more widely self-administered in Scotland (Robertson, 1996).

Deaths due to giardiasis are rare (ICAIR, 1984; Bennett et al., 1987). In the United States in 1982, giardiasis was listed as the underlying cause of death for only four deaths; the age at death was not provided (ICAIR, 1984). In a family cohort population in eight villages of rural northeastern Egypt (Zaki et al., 1986) 12 diarrhea-related deaths occurred in two years; *G. lamblia* was identified in 4 of these fatal cases. In 2 fatal cases, *G. lamblia* and *Shigella flexineri* were identified, and in one case, *G. lamblia* and (ST)-producing ETEC were identified. Brannan et al. (1996) reported *G. lamblia* infection was common (72% of 92 children studied) in institutionalized Romanian children and may play a role in causing morbidity and mortality in this high-risk group of children.

Chronic giardiasis. Chronic infections often present with recurrent, persistent, brief episodes of loose, foul-smelling stools which may be yellowish and frothy in appearance (ICAIR, 1984). In selected populations, chronic giardiasis may be as common as the acute illness (Keating, 1992). In some cases, symptoms may persist for years (ICAIR, 1984). Immunodeficiency with varying degrees of hypogammaglobulinemia or agammaglobulinema predisposes to the acquisition of giardiasis and is the most commonly reported form of immunodeficiency associated with chronic giardiasis (Farthing, 1996).

A loss of appetite is a commonly reported symptom, and nausea or vomiting, abdominal cramps and bloating may occur (Hopkins and Juranek, 1991). Symptoms are likely to contribute to reduced appetite and food intake (Hall, 1994).

Farthing (1996) reported that a proportion (30-50%) of symptomatic patients have chronic diarrhea, often with steatorrhea and about 50% of patients may have biochemical evidence of fat malabsorption. When daily losses of fat in feces are greater than 7 grams, the condition is classified as steatorrhea (Hall, 1994). Weight loss can be significant under these circumstances with a loss of 10 to 20% of usual or ideal body weight (Farthing, 1996). Prolonged malabsorption of fat and its excretion in stools can lead to a significant loss of potential dietary energy, especially as a result of chronic infection. This will be of greater consequence for young children since they have greater requirements for energy than adults and have small stomachs. Burke (1975) reported that giardiasis was second to cystic fibrosis as a cause of childhood steatorrhea at the University of Kentucky Medical Center. Intestinal malabsorption of fat soluble vitamins including vitamin A and B_{12} has also been reported. Casterline et al. (1997) found subnormal fractional absorptions of folate and vitamin B_{12} in one-sixth and one-third, respectively, of 29 Swedish children, age 8 months to 13.5 years, with chronic giardiasis.

In a study of 93 patients evaluated for symptoms of malabsorption in Scotland, giardiasis was the second most common diagnosis (Carswell, et al. 1973). Chronic malabsorption has been described in children infected with *Giardia*; most reported patients have been toddlers (Keating, 1992). Frequently described signs are protuberance of the abdomen, spindly extremities, and retardation of growth (Keating, 1992). Increased stool fat excretion, decreased serum carotene, abnormal xylose absorption are common, and peripheral or generalized edema and pallor may occur (Keating, 1992). Bali (1998) reviewed malabsorption syndromes that commonly result from a pathological interference of the normal digestive process. The review focuses on some clinical aspects of malabsorption, and diagnostic testing regarding malabsorption. Celiac disease, Whipple's disease, giardiasis, tropical sprue, malabsorption of oligo- and disaccharides, vitamin B_{12} and bile salts are discussed.

The incidence and host determinants of chronic giardiasis are not well known. The energy density of the diet and its efficient absorption are important, and persistent malabsorption of fat due to *Giardia* could lead to protein-energy malnutrition (Hall, 1994). In severe infection, increased protein loss with associated hypoalbuminemina has been reported, but a study in The Gambia suggests this is not a common phenomenon even in severely malnourished infants and children (Farthing, 1996).

3.2. Consequences and Complications of Giardiasis

Case reports and epidemiological studies suggest several conditions or complications that may be associated with *Giardia* infection, however, the evidence for a causal role of *Giardia* is limited. Few well-

designed epidemiological studies have been conducted. Anecdotal evidence from case reports is important, especially when patients respond to medical treatment, but case reports are often difficult to evaluate because of the lack of a comparison population. The epidemiological studies reported have differed in the amount and quality of information about exposures and heath effects. Guidelines are available for assessing the causality of associations observed in cohort, cross-sectional, or case-control epidemiological studies, and these include an evaluation of results to rule out confounding and bias, the consistency of observed results, the plausibility of a cause-effect from biochemical studies of disease mechanisms, and a reversal of signs and symptoms with prescribed drug treatment for giardiasis. The evidence for the reported complications in children is discussed in this section.

Failure to thrive or impairment of growth. The most often reported and a potentially serious consequence of giardiasis is nutritional insufficiency and its consequences. In adults this rarely produces serious sequelae, especially if the infection is treated promptly or spontaneous remission occurs, but in infants and young children, nutritional insufficiency can have profound effects on growth and development (Farthing, 1996). The principal forms of nutritional impairment associated with *Giardia* are weight loss or in children a 'failure to thrive", a term reflecting the concern that growth is slower than expected (Hall, 1994). The importance of impaired growth and development for children depends on capabilities for diagnosis and medical treatment and on other conditions (e.g., socioeconomic status) which may affect the ability of the child to catch-up in growth and complete pubertal development.

Although recurrent gastrointestinal infection can retard growth in children and *Giardia* has been epidemiologically associated with growth impairment, the importance of *Giardia* itself as a cause of growth impairment continues to be debated, especially for children who are asymptomatic (Farthing, 1996). Reasons that *Giardia* is thought to be capable of affecting the growth and development of children include: it can impair the growth of some young animals; it may cause intestinal malabsorption, infection may persist for many months, and its peak prevalence is in infants and children during the preschool years (Farthing, 1996). However, Hall (1994) notes that the epidemiological association between malnutrition and *Giardia* infection is not consistent, and it is not clear whether *Giardia* is a cause of malnutrition or whether malnutrition predisposes people to *Giardia*.

Since Perkins first reported the association between chronic giardiasis and growth impairment in 1921, a number of investigators have reported impaired growth in children who have severe manifestations of infection (i.e., chronic giardiasis or hispitalized) departments (Farthing, 1996). In Michigan, almost 19% of the children

younger than 5 years of age who were hospitalized for giardiasis were diagnosed with "failure to thrive" (Lengerich et al., 1994). In Scotland, 11% of the children who were hospitalized for giardiasis were also found lacking in expected normal physiological development (Robertson, 1996). Burke (1975) studied seven children aged 2 months to 7 years 10 months of age who were hospitalized with giardiasis in Kentucky; weight loss and growth failure were reported but reversed after treatment of giardiasis with metronidazole. In a study of 144 children (31 newborn infants, 62 aged 1 year and 51 aged 2 years) randomly selected from the registrar's office of Seville, Spain, Garcia et al. (1989 abstract) found that children with low body weight had a six-fold higher detection rate of *G. lamblia.*

Epidemiological studies have been conducted in developing countries where many infants and children who are infected with *Giardia* are asymptomatic and are often infected with more than one pathogenic agent. Thus, it may also be difficult to establish whether any observed complications are caused by *Giardia* infection or by other infections. For example, in Cairo, Egypt, Shukry et al. (1986) conducted a one-year study of the etiology of acute diarrhea complicated by severe dehydration, active bleeding, shock and cardiovascular collapse, pneumonia, acute renal failure, or seizures in infants under 18 months of age. Of 19 infants who died or left the hospital moribund and 126 infants who had a potentially fatal illness, 35% were found infected with *G. lamblia*. However, Shukry et al. (1986) felt that the etiologically important agents of this severe diarrhea were not *Giardia* but rotavirus (33%), heat-stable enterotoxin-producing *Escherichia coli* (20%), heat-labile enterotoxin-producing *E. coli* (11%), enteropathogenic *E. coli* (8%), and *Salmonella* spp. (5%). The authors felt the high prevalence of *G. lamblia* probably represented the high endemic rate in this population, and the observed association may not be causal. Observed epidemiological associations may reflect interactions between *Giardia* infection and behavioral, environment, socioeconomic, or demographic factors.

Community-based longitudinal studies in The Gambia and Guatemala suggest that giardiasis can reduce weight gain in children of developing countries. Farthing et al. (1986) conducted a prospective study of 45 children from birth to age 3 years in Guatemala. During the first and third years of life there was no difference in terms of weight gain between *Giardia*-infected and uninfected infants, but in the second year of life, the rate of weight gain was statistically significantly lower ($p=0.03$); height gain was similar in children with and without infection during the study. Children who suffered more prolonged *Giardia* infection (>2 weeks duration) tended to have lower median weight and height gain; 20% of the children who had prolonged infection had weight and height gain below the lower limits of normal. Gupta et al. (1982) also conducted a prospective study of 159 Guatemala children aged 24 to 61 months with 60% ascariasis prevalence and 22% giardiasis prevalence. The children were divided into 4 groups based on age, gender, socioeconomic status, and past

growth experience and randomly assigned to either a placebo or treatment (metronidazole, piperazine, or both of these drugs) group. Administration of metronidazole decreased the prevalence of giardiasis to less than 3% and was accompanied by increased growth as judged by weight and height gain. Although piperazine decreased ascariasis prevalence, it did not affect growth. Cole and Parkin (1977) studied growth and infection in a longitudinal study of 152 children (mean age=1.62 years) in The Gambia and 45 (mean age=1.80 years) children in Uganda. Giardiasis was found to be associated with a lower weight gain (decrease of 7 gm/ month; $p<0.05$) in the Gambia. In Uganda a lower weight gain was also found (decrease of 1 gm/month) but was not statistically significant. In The Gambia, more malnourished infants were found to be infected with *Giardia* than healthy controls, but there was no difference in the prevalence of *Giardia* infection between malnourished children with or without persistent diarrhea (Hall, 1994).

Valencia et al. (1995) studied the effects of mild giardiasis on energy intake and energy expenditure both at rest and in activity in ten boys aged 6 to 10 years living in low-income areas of an urban Mexican population. The children were generally well nourished, as weight for age and height were above the National Center for Health Statistics (NCHS) 50th centile. Energy intake, basal metabolic rate, and total free-living expenditure were determined for seven days during both infection and after treatment. There was no significant difference in recorded energy intake between the two periods. The mean weight change in the *Giardia*-infected period was +0.17 kg and -0.06 kg in the *Giardia* free period. Body weight and fat-free mass were higher at the start of the Giardia-free period than at the start of the *Giardia*-infected period ($P<0.05$). Although two mothers reported that their child had a diminished appetite during the *Giardia*-infected period, no significant difference was seen in recorded energy intake between the infected and uninfected period for the two boys. The basal metabolic rate showed no significant change in response to treatment for the ten boys. The mean energy expenditure increased in the *Giardia*-free period in 8 of the 10 boys. The overall energy expenditure of the boys while infected was 12% lower than when free of infection, but this overall change was not statistically significant ($P=0.08$). The authors noted that the children studied were older than those in whom growth impairment secondary to gastrointestinal infestation has been studied and were able to eat as much as desired from a selection of food of sufficient quality to meet their nutritional requirements. Thus, the study results do not exclude the possibility that either younger or malnourished children, or children with more severe giardiasis, could have more pronounced effects on energy intake and expenditure.

Herzog et al. (1998 abstract) described growth impairment in a 10-year-old, previously healthy Swiss boy who suffered from repeated episodes of watery diarrhea for months following a summer camp holiday. No etiology was found for the gastroenteritis, and except for treatment of symptoms, no other therapy was

provided. At age 15, he was evaluated for failure to grow and found to have a bone age of 11.5 years. He was again evaluated at the age of 20 because of persistent growth failure at which time he was found to have a bone age of 14 years and *G. lamblia* trophozoites found microscopically on the surface of duodenal mucosa biopsy specimens. Dysgammaglobulinemia, which may have predisposed the gastrointestinal tract to chronic giardiasis, was also detected. After a 10-day course of metronidazole treatment for giardiasis, the patient experienced catch-up growth and completed his pubertal development. The dysgammaglobulinemia persisted after therapy. This case report suggests that catch-up growth and completion of pubertal development are possible even after the age of 20 years if nutritional supply is sufficient.

In a study of 112 children hospitalized with chronic abdominal pain from 1992 to 1993 in northeastern Poland, Skorochodzki et al. (1998 abstract) reported that failure to thrive and recurrent episodes of the loose stools were significantly more frequent in infected children compared with uninfected children.

Janoff et al. (1990a) studied the nutritional status of 202 institutionalized orphans 1 to 61 months of age in Bangkok, Thailand; 39 children (19%) were infected with *Giardia* and 14 (7%) infected with *Cryptosporidium*. Of 144 children less than 24 months age, 21 (14%) were found infected with *G. lamblia*; 34% of children aged 24 to 60 months were found infected. The weight/height ratio, which the authors felt most accurately reflected acute nutritional status, was significantly lower among children infected with *Cryptosporidium* compared with children infected with *Giardia* or children not infected with either protozoan. In contrast, measurements of height to age ratio, which reflects chronic nutritional status, were similar among children infected with *Cryptosporidium*, *Giardia*, or not infected with either protozoan. Chronic or severe diarrhea was not a consistent feature of *Giardia* infections.

Studies have not found evidence of growth failure in children in day care centers of developed countries where infection is usually asymptomatic (Farthing, 1996). Varga and Delage (1990 abstract) reported little or no nutritional impact associated with *G. lamblia* infection in Quebec. Among 75 children (42 girls and 33 boys, aged from 6 to 65 months) attending a day care center in Quebec, 17 (23%) were found to be infected. Weight, height and arm skinfold thickness of each child were obtained and compared to normal values in the Quebec population; a questionnaire concerning gastrointestinal symptoms was filled out for each child. No difference in weight, height, skinfold thickness or in frequency of gastrointestinal symptoms was found between children positive for *Giardia* and children with a negative stool examination. Pickering et al. (1984) also found that asymptomatic *Giardia* infection did not affect monthly height and weight among children in day-care centers.

Malabsorption of iron. The etiology of iron deficiency, with or without anemia, is a multifactorial problem (Filer, 1996). Intestinal malabsorption may be responsible for iron deficiency that can contribute to anemia, and 43% of the world's children under 4 years of age may be anemic (Filer, 1996). Malabsorption of iron was reported in a 1985 study of children with symptomatic giardiasis (Filer, 1996). De Morais et al. (1996) recently evaluated intestinal absorption of iron in children aged 1-6 years with asymptomatic giardiasis and iron deficiency anemia in Brazil. Iron malabsorption was not found in these children, and they had a positive hemoglobin response to oral iron therapy. Based upon results of blood hemoglobin and stool examination, two groups were studied (asymptomatic giardiasis and anemia; anemia without *Giardia* infection) similar in age, weight, height, and iron nutritional status. Intestinal absorption of iron was evaluated using the iron tolerance test and the hemoglobin response to iron therapy. The serum iron tolerance test was based on the fasting iron level and the increment of iron levels two hours after administering an iron load. Hemoglobin response to oral iron therapy was determined by the increment of hemoglobin on day 30 of therapy with ferrous sulfate (5 mg/kg/day of elemental iron). Asymptomatic giardiasis did not affect the intestinal absorption of iron or the hemoglobin response to oral iron therapy in the iron-deficient anemic children. No statistical difference was found between the asymptomatic giardiasis and control groups with reference to the iron tolerance test results or the hemoglobin response to iron therapy. The children's intestinal absorption of iron was not associated with the presence or absence of trophozoites of *G. lamblia* in duodenal aspirates.

Because a significant increase in weight gain has been observed in iron-deficient children after four weeks of oral iron therapy, De Morais et al. (1997) evaluated whether asymptomatic giardiasis interferes with the expected weight gain. After four weeks of oral iron therapy, no detrimental effect on weight gain was found in children with asymptomatic giardiasis (De Morais et al., 1997).

Hematological alterations/allergies. A study of Egyptian children found significantly lower hemoglobin levels in those infected with *Giardia*, and the infected children showed a significant increase in hemoglobin levels after treatment with metronidazole (Hall (1994). Curtale et al. (1998) conducted a survey of 770 households selected by a random cluster sampling in Behera, Egypt, to evaluate the role of intestinal parasites in the epidemiology of anemia among school age children. Fecal and hemoglobin analyses were available from 1238 children aged 6-12 years. The prevalence of anaemia (Hb <12 g/dl) in the study area was high (90%), but only two children had severe anemia (Hb <7 g/dl). Multiple regression analyses showed that the intensity of infection with two helminths (*Fasciola* and *Schistosoma mansoni*) and *G. intestinalis* was correlated ($p<0.05$) with low hemoglobin levels but explained only a very small fraction ($r^2=0.05$) of the variability in hemoglobin levels. *G. intestinalis* can adversely affect hemoglobin, probably through impaired

absorption of vitamin B_{12} and folate, and *S. mansoni* can cause blood loss in stools, but since *Fasciola* was found to be the most important determinant of anemia in this area, Curtale et al. (1998) recommend additional studies of longitudinal design.

Dos Santos and Vituri (1996 abstract) evaluated erythrometric and leucometric parameters in 55 patients infected with *G. lamblia* and 55 sex and age matched parasite-free persons. Hematological parameters evaluated were mean corpuscular volume, hemoglobin concentration, eosinophils and lymphocytes. No significant differences was detected between the two groups in the mean values of corpuscular volume, hemoglobin levels and absolute relative lymphocyte numbers. When the analysis considered age (0-18 years old and older than 18 years), a significant difference in both relative and absolute number of eosinophils was observed among persons over the age of 18. No differences, either in relative and absolute number of eosinophils, were observed in those 18 years or younger. The authors suggest that during *G. lamblia* infection in adults, but not children, a parasite allergen(s) may be secreted causing an increase of eosinophil counts.

Di Prisco et al. (1993 abstract, 1998) studied *G. lamblia* infection, specific IgE responses, and skin test reactivity in Venezuelan children; an enhanced IgE antibody was found in allergic children with giardiasis in response to common environmental allergens. Results suggested that children with giardiasis may be exposed to greater amounts of intestinally absorbed antigens. A group of 125 children (mean age: 6.0 years, SD=3.6 years) who attended a Children's Outpatient Clinic in Caracas, Venezuela, where both allergies and giardiasis are commonly seen was studied, but no information was presented on how the children were selected for study. Three consecutive stool samples were examined from each child for intestinal parasites, and serum was collected for measurement of total IgE, specific IgE antibody against inhalant and food allergens and anti-*G. lamblia* IgE. Sixty percent of the children were free of parasites, 24% were positive for parasites other than *G. lamblia*, and 16% were positive for *G. lamblia*; 20% of the children positive for *G. lamblia* were also positive for other parasites. Seventy percent of the children infected with *G. lamblia* had presented with symptoms of allergy in the previous six months in contrast to 43% of the non-*Giardia* parasitized group and the non-parasitized group ($p<.05$). Allergic rhinitis or upper respiratory tract allergy (33%) was the most common allergenic disease was followed by asthma (23%), atopic dermitis (18%), and chronic urticaria and/or angiodema (6%). In addition, the *Giardia*-infected children had higher levels of total serum IgE (1194 IU/mL) than the non-*Giardia* group (822 IU/mL) ($p<.005$). Children infected with *G. lamblia* showed higher levels of specific serum IgE antibody against food allergens compared with the non-parasitized group ($p <.0001$) and children infected with parasites other than *Giardi*a ($p <.05$). In contrast, IgE responses were similar in all the groups studied for an inhaled allergen, *Dermatophagoides pteronyssinus*. The investigators suggest that

Giardia infection may enhance sensitization towards food antigens because of increased antigen penetration through damaged intestinal mucosa.

Wasilewska et al. (1995 abstract) reported an allergic reaction in a group of 81 children infected with *G. lamblia*. Skorochodzki et al. (1998 abstract) reported the frequency of allergic skin lesions was similar among *G. lamblia* infected and uninfected children hospitalized with chronic abdominal pain in northeastern Poland.

In a group of 518 children evaluated for chronic diarrhea over a six-year period in a speciality clinic in Boston, Perlmutter et al. (1985) found that the 55 case-patients with hypogammaglobulinemia had a statistically higher incidence of small intestinal histological injury, carbohydrate malabsorption, and infection with *G. lamblia* (34%) or *Clostridium difficile* (24%) compared to a control group. The role of *Giardia* in these children with hypogammaglobulinemia was not clear.

Synovitis. Inflammation of the synovial membranes of major joints has been seen in children with giardiasis, but following anti-giardial chemotherapy, intestinal and synovial symptoms were abated (U.S. EPA, 1998). Although uncommon, giardiasis can cause severe synovitis that may be confused with a septic joint. Few reports of synovitis secondary to giardiasis exist in the literature. Arthropathy secondary to giardiasis is uncommon, but may be under diagnosed. In a study by Letts et al. (1998), *Giardia* synovitis was diagnosed in two children at a major children's hospital over a 20-year period. Both were boys, aged 7 years, 6 months and 1 year, 8 months at the time of presentation. The knee was the affected joint in both patients, and both cases were initially misdiagnosed as septic arthritis. The synovitis subsided with treatment of the giardiasis, one with cefuroxime and the other with cefuroxime and metronidazole. The diagnosis of *Giardia* synovitis should be suspected by the presence of *Giardia* cysts in the stool, similar symptoms in other family members, a synovial white count under 40,000, and an increase in the eosinophil count.

Ocular changes. Case reports have described ocular complications including iridocyclitis, choroiditis, retinal hemorrhages in patients with giardiasis, and associations have been reported between *Giardia* infection and uveitis and retinal vasculitis (Corsi et al., 1998). A “salt and pepper” form of degeneration in children involving the retinal pigmented epithelium has also been described (Corsi et al., 1998). Corsi et al. (1998) recently evaluated ocular manifestations in 141 Italian children with current and past giardiasis and 300 children without giardiasis. “Salt and pepper” retinal changes were diagnosed in 20% of the children with giardiasis (mean age was 4.7 years) but in none of the children without giardiasis. The development of this retinal change did not depend on the severity of the infection. Corsi et al. (1998) suggested that small children may be more

susceptible to this type damage because of the immaturity of the retinal epithelium cells. Because electroretinographic findings were normal in all children, Corsi et al. (1998) felt the lesions likely do not cause functional changes in the retina but recommended that this finding be confirmed in longer term follow-up. This study suggests that asymptomatic, non-progressive retinal lesions may be common in young children with giardiasis; the risk does not seem to be related to the severity of infection, its duration, or use of metronidazole but may reflect a genetic predisposition (Corsi et al., 1998). The mechanisms underlying the ocular lesions associated with giardiasis are not known, but Corsi et al. (1998) suspected they are related to immune function.

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Pancreatic and hepatic disease, cystic fibrosis. An association between symptomatic giardiasis and pancreatic or hepatic disease has been suspected, as several case reports have seen these disorders in adults with giardiasis (Carroccio et al., 1997; Nakano et al., 1995; Roberts et al., 1988). This association has not been systematically studied. Roberts et al. (1988) suggested that if such an association exists, the relatively common occurrence of pancreatic insufficiency or hepatic cirrhosis in persons with cystic fibrosis might predispose them to infection with *Giardia*. Roberts et al. (1988) studied the prevalence of *Giardia* in 107 patients with cystic fibrosis and a control group of 64 persons without cystic fibrosis in households of patients with cystic fibrosis. The cystic fibrosis group had a significantly higher rate of infection than the control group (28% vs 6%, $p=0.0006$), and the disparity between the two groups increased with age ($p=0.005$). Although not statistically significant, a higher rate of *Giardia* infection was seen in children under 5 years of age (24% vs 11%) and children 5 to 10 years of age (27% vs 9%). Among the risk factors examined, only the presence of household members under 5 years of age and cystic fibrosis were found associated with increased prevalence of giardiasis. These results suggest that patients with cystic fibrosis may have an increased prevalence of giardiasis, but whether *Giardia* plays a role in the disease is not clear. Cystic fibrosis patients may have increased duration of exposures that cause increased prevalence of *Giardia* infection, or the disease may predispose persons to infection with the predisposition increasing with age (Hall, 1994). Predisposing factors may be a deficiency of pancreatic enzymes or change in small bowel pH from decreased pancreatic bicarbonate excretion (Roberts et al., 1988). Additional studies are needed to clarify the observed association between cystic fibrosis and *Giardia* infection. However, the clinical implications of *Giardia* infection (i.e., malabsorption of fat and fat-soluble vitamins) in cystic fibrosis patients, especially children should be recognized.

3.3. Therapy

As with all diarrheas, fluid replacement is an important aspect of treatment; anti-giardia drugs are also important in the management of giardiasis. Chemotherapeutic agents used for treatment of giardiasis include

metronidazole, tinidazole, quinacrine, furazolidone, albendazole, and ornidazole. Various doses and treatment periods are recommended for each drug. The drugs may have different effectiveness in their ability to clear *Giardia*; drug resistance and relapses may occur, and the drugs have side-effects that should be considered. Chemotherapeutic agents used for treatment of giardiasis are discussed in greater detail in the EPA's Drinking Water Criteria Document for *Giardia* (U.S. EPA, 1998).

Metronidazole or tinidazole has been the drug of choice for giardiasis probably because the treatment period is short and compliance good (Farthing, 1996; Benenson, 1995). Quinacrine and furazolidone have also been commonly used (Freeman et al., 1997). Metronidazole appears to have fewer side effects than furazolidone and quinacrine, but nausea, metallic taste, and headache may occur (Turner, 1985). Metronidazole and furazolidone have been found to be mutagenic and carcinogenic in animal experiments (Turner, 1985). Misra et al. (1995) found that albendazole is as effective as metronidazole for treating giardiasis in children and does not produce the anorexia that is often seen with metronidazole treatment. In addition, albendazole is less expensive and has fewer side-effects than metronidazole (Bulut et al., 1996). Tinidazole is reported to be as or more effective than metronidazole (Freeman et al., 1997) and has fewer side-effects (Rabbani and Islam, 1994). A single dose has been effective in children (Rabbani and Islam, 1994; Nahmias et al., 1991). Ornidazole has also been effective when administered as a single dose.

Turner (1985) recommended pharmacological treatment of giardiasis be avoided in pregnancy unless symptoms cannot be controlled by conservative measures. Because it is poorly absorbed, paromomycin has been used to treat giardiasis in pregnant women, but the cure rate is variable and may be as low as 55% (Rabbani and Islam, 1994; Farthing, 1996).

Pharmacological treatment of all asymptomatic *G. lamblia* infections in a developing country hyperendemic for the disease is of questionable value because of rapid re-infection. Lanata et al. (1992) believes that frequent re-infections with enteropathogens prevalent in the population, such as *G. lamblia,* may be one reason for prolonged illnesses in developing countries with a high incidence of diarrheal diseases. In a peri-urban shanty town in Lima, Peru, that was hyperendemic for *G. lamblia*, 44 children aged between 0.9 months and 10 years were effectively treated for *G. lamblia* with tinidazole, and stools were examined weekly in the 6 months after treatment to determine the rate of reinfection (Gilman et al., 1988). Almost all the children (98%)became reinfected with *G. lamblia* within 6 months, and after reinfection stool excretion of the parasite lasted a mean of 3.2 (SD=3.3) months. In this study the children's mean stool fat index was unaffected by *G. lamblia* re-infection. In a cohort of 195 Bangladeshi infants aged 2 to 8 months at enrolment and studied

for two years, it was found that 45% of the children had become re-infected after treatment (Hall, 1994). Follow-up examination of children in Zimbabwe treated with a metronidazole-diloxanide combination drug therapy also showed a relatively high rate of re-infection; 29.6% were found to be excreting cysts during the year following their treatment (Mason and Patterson, 1987). Younger children were more likely to be reinfected than older children. Over half of infected, but untreated, children had undergone apparent "self-cure".

In three outbreaks of giardiasis in Wisconsin, Steketee et al. (1989) found that infections recurred in outbreak proportions even though a variety of control measures were instituted, including pharmacological treatment with a cure rate of >90%, better case identification, follow-up testing of stools, and improved personal and environmental hygiene practices. In a prospective randomized trial comparing three strategies for control of *Giardia* in infant-toddler day care centers, Bartlett et al. (1991) found that more strict intervention (exclusion and treatment of both symptomatic and asymptomatic infected children) did not result in the elimination of infections. An initial *Giardia* prevalence of 18-22% in the three intervention groups was, however, reduced to 7-8% in each group at six months intervention (Bartlett et al., 1991).

4. Immunity

The role of immune responses to *Giardia* infection has been studied in relation to resistance to infection or reinfection, duration of infection, and resistance to or severity of illness from subsequent infections. Information on the immune response to infection comes from clinical and epidemiological studies of humans, experimental infection of humans and other animals and laboratory studies of the interaction of *Giardia* trophozoites and immune cells.

Animals studies of mice and gerbils with specific immune defects were conducted to determine the contribution of various components of normal immune responses to infection and illness. These studies have demonstrated that T-cell function is necessary for development of resistance to infection (Roberts-Thompson et al., 1976). Furthermore, helper/inducing T-cells rather than suppressor/cytotoxic T lymphocytes are necessary for *Giardia muris* clearance (Heyworth et al., 1987). In mice treated with anti-IgM antisera and exposed to *G. muris*, high trophozoite counts and prolonged cyst excretion, were observed, indicating the need for IgM in the clearance of *Giardia* infections (Snider et al., 1988).

Induced immune suppression has also been used to demonstrate the existence of chronic *Giardia* infections. Mice previously infected with *G. muris* and then given corticosteroids will begin excreting

detectable numbers of cysts at levels higher than the original infection (Ferguson et al., 1990). Since this was only observed in mice previously infected and not in identically treated mice without a prior infection, the results suggest that chronic low level infections may continue in mice following recovery. At least in this animal model, *Giardia* excretion may be eradicated following symptomatic recovery, however, the immune system may not eliminate the infection but only control the level of infection to prevent adverse health effects.

Immunosuppression as a risk factor for chronic *Giardia* infections in humans has also been suggested. A high incidence of giardiasis in immunoglobulin-deficient individuals suggests a role for the humoral immune response in resistance to *Giardia* infection or illness from infection (Granot et al., 1998). In a study of 100 children with chronic giardiasis, 50 children with acute giardiasis, and 50 with no giardiasis, Rajeswari et al. (1996 abstract) found that humoral immune defects in the host was the major determinant of whether the giardial infection would be symptomatic or not.

The role of immune response to infection is also supported by the occurrence of severe and prolonged giardiasis in human patients with hypogammaglobulinemia (Adam, 1991). It is accepted that secreted immunoglobulin IgA and IgM antibodies play a role in both controlling, as well as eradicating, the parasites (Wolfe, 1992). The appearance of IgA in the intestinal secretions of *G. muris* infected mice has been associated with the resolution of infection (Snider et al., 1988). In humans, serological response to *Giardia* antigens appears to be uncommon below 12 months of age (Abdel Fattah et al., 1991; Shetty et al., 1992), but the intensity of response of *Giardia*-specific IgG, IgM and IgA increases with increasing age of children after age 12 months in both developed and developing countries (Janoff et al., 1990b; Abel Fattah et al., 1991; Shetty et al., 1992).

Lower antibody titers to a specific *Giardia* antigen were found in persistently infected pediatric cases compared to children who cleared the infection (Kumkum et al., 1988; Vinayak et al., 1989). The investigators felt that some of the deficits were temporary and the children would eventually return to a normal immune state. They also found that, after adolescence, IgM levels did not increase, perhaps reflecting exposures early in life. This agrees with a study by Granot et al. (1998) who found that infected children from developing countries did not show an IgM response. Infected day-care children, however, showed an IgM response suggesting a primary infection. In children with chronic giardiasis and persistent diarrhea, a strong IgM response, but no elevated response to IgA and IgG, has been detected (Char et al., 1993). Conversion from IgM to IgG and IgA response may be necessary to clear an infection. Lack of serological response to a 57-kDa antigen may predict individuals at risk of chronic infection (Char et al., 1993).

As suggested in animal models, immune responses to *Giardia* infection appear to control the number of cysts excreted and thereby control symptoms. However, Danciger and Lopez (1975) found wide variations in the number of oocysts excreted by asymptomatic children. Although children may develop resistance to symptomatic giardiasis, development of this resistance may be very slow. A prospective cohort study of Guatemalan children provides evidence that protective immunity develops slowly in children (Farthing et al., 1986). In the first and second year of life, diarrhea-associated *Giardia* infections outnumbered asymptomatic infections by a factor of two; it was not until age 30 to 35 months that infections without diarrhea were more frequent than infections with diarrhea. In a cohort of 164 Bedouin children sampled monthly from birth to two years of age and at all diarrhea episodes, Fraser et al. (1997) also found detection of *G. lamblia* was higher in diarrhea episode samples obtained before six months of age; after that age, detection of *G. lamblia* was lower in diarrhea episodes than in non-diarrhea stool specimens (OR=0.8; 95% CI=0.7-0.9).

In Bangladesh, a survey of persons in an urban slum found a decline in the prevalence of *Giardia* with increasing age (Hall, 1994). Because other protozoan infection continued, Hall (1994) argued that this suggested some degree of protective immunity as a result of repeated infections. Another study in Bangladesh which considered both the prevalence of infection and serum antibodies to *Giardia* found that the decrease in prevalence of infection after the age of 8 years was associated with a subsequent increase in seroprevalence into adulthood (Gilman et al., 1985). Even if previous infection confers some protection against symptomatic illness, Steketee et al. (1989) found that previous *Giardia* infection may not provide immunity for subsequent re-infections in children.

Breast milk has been found to contain secretory antibodies which could theoretically afford protection against *Giardia* infection (Hall, 1994). Islam et al. (1983) failed to find evidence that antibodies protected breast-fed infants, but Nayak et al. (1987) found that significantly fewer infants were infected if mothers had high titers of antibodies in breast milk. In a family cohort studied in eight villages of rural northeastern Egypt, Zaki et al. (1986) did not find a protective effect against diarrhea for breast-fed infants from either all causes or diarrhea or from *G. lamblia*. Among infants less than 6 months of age with diarrhea, 37% of stool specimens from breast-fed infants were found positive for *G. lamblia*; 36% of stool specimens were *G. lamblia* positive from infants who were not breast-fed (Zaki et al., 1986). In another cohort study, Mahud et al. (1995) found Egyptian infants of less than 6 months of age were at special risk for acquiring *Giardia* infection. These two studies suggest some infants may lack passively acquired immunity from mothers' placenta before birth or from IgA in breast milk after birth. The infants may also have been exposed to high levels of *Giardia* from their home environment from the mother or siblings.

In Scotland, marked differences were found in the age distribution of hospitalized cases of giardiasis and cryptosporidiosis (Robertson, 1996). The median age for hospitalization for giardiasis was 30 years of age, significantly older than the median age of hospitalization for cryptosporidiosis which was 5 years of age. In addition, the median age of persons spending more than 5 days in the hospital was 31 years of age for giardiasis compared with 7 years of age for cryptosporidiosis, and the proportion of hospitalized cases for children under five was greater for cryptosporidiosis (49%) than giardiasis (28%). The median length of stay for giardiasis was longer for children less than five years of age than for adults aged 18-38 years. Impaired immunity was frequently listed as a co-diagnosis with cryptosporidiosis and associated with extended hospitalization. Robertson (1996) felt these age-group risk differences for giardiasis and cryptosporidiosis may be due to host immunity, host behavior, or parasite factors and suggested that the development of protective immunity to *Giardia* infection may be more prolonged than it is to *Cryptosporidium* infection. Development of protective immunity to *Giardia* is considered a relative lengthy process and not necessarily developed following a single infection (Farthing, 1994).

The value of serological tests in studies of giardiasis has been debated. Rojas et al. (1989) found that serum antibodies to the entire trophozoite were elevated in young children (ages 1-5 years) who had been recently infected. They concluded that antibody tests can be a useful in diagnosing giardiasis in young children and can be an alternative to duodenal aspiration for difficult diagnoses.

Findings from antibody studies in adults have been less conclusive. Jokipii et al. (1988) found a relationship between antibody titer and prior infection. Titers in adults were higher than in children and titers in women were higher than in men. Although higher titers were also observed for people with stool confirmed *Giardia* infections, the levels overlapped levels observed in stool negative individuals, suggesting that serological tests will not be useful for diagnosis of giardiasis in adults. The finding of high levels of antibody responses to *Giardia* antigens in individuals who had not recently experienced symptomatic giardiasis suggested to some authors that cross-reactions with other non-giardial immunogens were common. The alternative explanation that asymptomatic *Giardia* infections may be common or that the antibody response may be very long lived was not considered.

In summary, only partial protective immunity to illness from *Giardia* infection is likely to develop. Responses to a number of different *Giardia* antigens have been reported, but it is uncertain which, if any, of these responses predict a reduced risk of either infection or illness. It is likely that secretory IgA is the most important component of the antibody response to *Giardia*. Other factors, such as intestinal mucus layer,

motility and breast milk consumption for infants may also play a role in altering the risk of infection or illness. Various immune deficiencies may identify individuals at risk of adverse health effects from infection. Further studies of serological response to *G. lamblia* are needed to evaluate the utility of using these responses for epidemiological studies of populations with different exposures to the parasite. Even though the serological response may not provide a reliable means for diagnosing current or recent infections, it is possible that these responses, adjusted for age and sex, can provide valuable information on populations exposures, such as an unfiltered surface water supply.

5. Risk Factors

Giardia is frequently spread directly from person to person, especially among young children attending day-care centers, nurseries, institutions, children living in areas with poor sanitation and hygiene, and children with siblings. In institutions, crowding, fecal incontinence, and poor personal hygiene may promote the transmission of infections among children (Hall, 1994). Children can also become infected from ingestion of contaminated drinking water and the accidental ingestion of water while swimming or other water recreation. Infected infants and children, either symptomatic or asymptomatic, may transmit infection to other children or adults, especially family members or other care-givers. Higher incidence rates of symptomatic giardiasis (Birkhead and Vogt, 1989) and hospitalized cases of giardiasis (Lengerich et al., 1994) in women of childbearing age may be related to increased exposure to infected children. There is no evidence that *Giardia* is transmitted from mother to fetus (Hall, 1994), although infants can acquire infections at an early age suggesting that mothers can infect their children very soon after childbirth (Farthing et al., 1986).

Cross-sectional surveys of infection in developing countries show that *Giardia* tends to be more common in children than adults, and this may be related to greater opportunities for exposure to sources of infection. In many developing countries, *Giardia* infections are acquired in early childhood and by the age of 5 years most children have been infected at least once (Hall, 1994). In the United States and Canada, studies have found that the highest incidence of giardiasis is in children under the age of 5 (Birkhead and Vogt, 1989; Isaac-Renton and Philion, 1992).

Socio-environmental factors. Like other gastrointestinal infections, giardiasis is very common in populations living in poverty, with poor sanitation, and a high level of fecal contamination of the environment. Mason et al. (1986) indicated that even providing piped, high quality drinking water may not significantly reduce the incidence of giardiasis in developing countries. Although contaminated drinking water may be an

important source of exposure in developing countries, the variety of other exposures including personal hygiene, food hygiene, and environmental factors may overwhelm the beneficial effect of clean drinking water. In a study of preschool children in rural Lesotho, South Africa, Esrey et al. (1989) found that the use of low amounts of water for personal hygiene was associated with *G. lamblia* infection (OR=2.4; 95% CI=1.1-5.2). The use of traditional, unimproved drinking water sources or lack of latrines was not associated with infection. This study suggests that to prevent waterborne *Giardia* infection in some populations in developing countries the amount of water used for domestic hygiene may be more important than its quality.

In a study of 1417 inhabitants (81.4% of the total) of nine villages in a rural area of southwest Saudi Arabia where the *G. lamblia* prevalence was 18.9%, Omar et al. (1995) found that socio-demographic factors including age, sex, degree of education, intrafamilial clustering and crowding index were not associated with infection. The source of domestic water was the sole factor significantly associated with the high prevalence rates of infection in the community. A high risk of contracting the infection was observed among individuals who drank jar water (OR=3.0; 95%CI=1.5-4.4) or well water (OR=2.2; 95%CI=1.2-3.9). Those who used desalinated water for drinking were protected against infection (OR=0.7; 95%CI= 0.5-0.9). These results indicate that the use of improved water supply can reduce the rate of infection in some communities.

Mahmud et al. (1995) found that the primary determining factors that predispose newborn infants to the first symptomatic *Giardia* infection among infants in rural Egypt were: poverty, low levels of education, poor access to or underutilization of antenatal and perinatal care, poor sanitation, and inadequate environmental conditions. These also appear to be responsible for the continuing high level of endemicity of giardiasis in Egypt (Mahmud et al., 1995).

Children living in urban and rural areas may have different levels of risk of *Giardia* infection, but both can be at a high risk of infection, especially in developing countries. In Zimbabwe, the annual incidence of the disease in urban children was 22%, compared to 12% for rural children (Rabbani and Islam, 1994). In urban Glasgow, 13% of native Scots children aged 6 months to 16 years from a poor socioeconomic background were found infected (Hall, 1994). High population density in urban areas, overcrowding, poverty, and poor sanitation of the urban slum areas may contribute to the high rate of infection.

Gamboa et al. (1998) found the prevalence of intestinal parasites in children up to 14 years old in La Plata, Argentina, to vary according to socioeconomic conditions. The respective prevalences of intestinal parasites was 73%, 54%, and 35.1% in each of three areas within the city, a 'marginal' zone, a lower-income

suburb, and a middle-income urban district. *G. lamblia* was the most frequent parasite found. Prevalence was highest within the population group having poor sanitary and environmental conditions. The prevalence of infection was associated with age in all three of the neighborhoods and school attendance in the two suburban districts. In Washington State, Harter et al. (1982) found no correlation between socioeconomic status of the families and the presence of *Giardia* infection in children. In a study of 92 institutionalized Romanian children, Brannan et al. (1996) found that normal nutritional status ($p<0.01$) was predictive of *Giardia* infection. Walia et al. (1986) also found no difference in risk between nourished and undernourished preschool children in two endemic areas of Punjab, India.

Day-Care Centers. Outbreaks at day care centers have been caused by *Giardia* and other enteropathogens, and a high prevalence of *Giardia* infection have been reported in settings where infants and young children in diapers are collectively cared for. Steketee et al. (1989) found that attack rates were highest among the ambulatory children in diapers, children who attended a day-care center for 40 or more hours per week. The most susceptible were children 1 to 3 years old.

Pickering et al. (1986) reviewed studies that show diarrhea occurs more frequently among children enrolled at day-care centers than among age-matched children cared for at home or in family day care. Children in day-care centers commonly excrete enteropathogens in the absence of symptoms. In two prevalence studies of 660 children enrolled in 30 day care centers, Pickering et al. (1984) found that children who had attended the centers for more than 3 months were more likely to be excreting *Giardia*. Positive stool specimens were more frequent in the 13 to 30 month old children than in children younger than 12 months. There was no association with diarrheal episodes and finding *Giardia*, suggesting most *Giardia*-infected children were asymptomatic. A two-year prospective study of diarrheal illness in children up to 36 months of age in 22 day care centers in Maricopa County, Arizona, identified 465 sporadic cases and 170 outbreak-associated cases of diarrhea (Bartlett et al., 1991). *Giardia* was significantly more common in toddlers than in infants.

Ortega and Adam (1997) reported that no seasonal pattern has been observed for *Giardia* infection in day-care situations; however, Rodriguez-Hernandez et al. (1996) observed a higher frequency of giardiasis in the autumn season in a study of eight day care centers in Salamanca, Spain, where *G. intestinalis* was identified in 25% of the children studied. In Arizona, Bartlett et al. (1991) found that the seasonal pattern of diarrhea, frequency of pathogen isolation, and relative frequency of individual pathogens were similar in households that used day care and those that did not.

In seven nursery schools and one primary school in Santiago, Chile, where 33% of the children were infected with *G. lamblia*, Goldin et al. (1990) found no apparent association between socio-economic status and *G. lamblia* infection. In a parasitological survey conducted in three municipal day-care centers (one in the downtown area, one in the city periphery, and the third in a rural area) in Botucatu, Brazil, three stool specimens were collected from 147 children ranging from 0 to 72 months old and 20 staff members (Guimaraes and Sogayar, 1995 abstract). The frequency of *G. lamblia* detected in the children of downtown, periphery and rural day-care centers was 69.6%, 52.7% and 69.6%, respectively. *G. lamblia* was found mainly in children between 12 to 47 months old. A survey of children from 2 to 5 years old in two day nurseries in Aracaju, Brazil, found the prevalence of *G. lambia* in children of higher socioeconomic status to be lower (50%) than children of lower socioeconomic status (63.3%) (de Sa Cardoso et al., 1995 abstract). Eating vegetables was the only risk factor associated with giardiasis in the day nursery of children of higher socioeconomic level. Risks among children in the other day nursery included no potable water in their residences, inappropriate garbage disposal, vegetable eating habits, and shared bedrooms.

An outbreak in elderly residents of a Minnesota nursing home was associated with physical contact with children at the day care facility through an adopted grandparent program (White et al., 1989). An epidemiological study in Vermont found that person-to-person transmission in child-care facilities was important in the transmission of non-outbreak cases of giardiasis (Birkhead and Vogt, 1989). Novotny et al. (1990) studied a sample of children in the toddler age group in Denver, Colorado to determine the prevalence of *G. lamblia* and identify risk factors. The sample consisted of 236 children attending day-care centers and 79 who were not attending. Infection was not found to be associated with symptoms. Risk factors for infection among children attending day-care centers included an increased duration of attendance, hours per week in attendance, low family income, and large family size. In a case-control study, Chute et al. (1987) found that day-care was associated with a higher risk of giardiasis (OR=2.2; 95% CI= 1.3-3.7) in New Hampshire. Harter et al. (1982), however, found no differences in prevalence of infection between children who normally attended day-care centers and those who did not.

Pickering et al. (1986) reported higher rates of diarrhea in day-care centers were associated with selected characteristics of centers, the most important of which was the presence of non-toilet-trained children. The contamination of hands, communal toys, and other classroom objects played a role in the transmission of enteropathogens in outbreaks of diarrhea in day care centers. The spread of infection from non-toilet-trained children in centers to their families was common. Cody et al. (1994) developed and evaluated a method for recovering *Giardia* cysts from environmental surfaces, and field tested the method in six commercial child day-

care centers. Cysts were recovered from Formica® surfaces inoculated with 10 to 190 cysts on a surface area of 50 cm^2 or with 10 to 20 cysts/400 cm^2 and from stainless steel surfaces inoculated with 20-186 cysts/400 cm^2. Cysts were not recovered from wood and fiberglass surfaces inoculated with 190 cysts/400 cm^2. In the field test, cysts were detected on surfaces in two of the six day-care centers where samples were collected. A total of 53 chairs and tables were examined; two fiberglass chairs (6%) and one Formica® table (2%) surface were found to be positive for *Giardia* cysts. Although laboratory studies found that *Giardia* cysts survive for less than 24 hours on dry environmental surfaces, children may be frequently exposed in institutional and day-care settings where various surfaces with which they come into contact may be continuously contaminated (Addiss et al., 1991).

A prospective randomized trial comparing three strategies for control of *Giardia* in infant-toddler day care centers found that more strict intervention (exclusion and treatment of both symptomatic and asymptomatic infected children) did not result in complete control of infections; an initial *Giardia* prevalence of 18-22% in the three intervention groups was reduced to 7-8% in each group at 6 months intervention (Bartlett et al., 1991).

Water. *Giardia* cysts are distributed worldwide in surface waters, even those of excellent quality and have been found in surface waters from the Arctic to the tropics (U.S. EPA, 1998). Cysts occur in surface waters throughout all months of the year. Waterborne outbreaks have been reported, and some have resulted in a large number of cases of illness (U.S. EPA, 1998). In 26 waterborne outbreaks associated with drinking water in the United States, levels of *Giardia* cysts ranging from <1/100L to 580,000/100L were detected from either treated or source water (U.S. EPA, 1998). Children, as well as adults, have been affected by outbreaks associated with drinking water systems and recreational waters (U.S. EPA, 1998). Endemic waterborne giardiasis in adults and children has also been associated with drinking unfiltered surface water or shallow wells and swimming (U.S. EPA, 1998).

Giardia has been the most commonly identified pathogen in waterborne outbreaks reported in the United States since 1971. During 1965 to 1996, 133 waterborne outbreaks and almost 28,000 cases of giardiasis were reported in the United States, primarily in unfiltered surface water systems (U.S. EPA, 1998). Ten (8%) of these outbreaks were associated with the use of individual drinking water systems or non-potable water sources, and 108 (81%) outbreaks were associated with public water systems; 14 (11%) outbreaks were associated with accidental ingestion of water during recreation. Unfiltered surface water systems were responsible for 56% of

the reported waterborne giardiasis outbreaks in the United States. Communities with unfiltered surface water systems experienced a waterborne outbreak rate that was eight times greater than communities where surface water is both filtered and disinfected (U.S. EPA, 1998). Children were included among the reported cases in these outbreaks, but limited information is available on the number of cases or attack rates for children. In a waterborne outbreak in Berlin, New Hampshire, 38% of children under 10 years of age were infected; an infection rate of 60% was found in children 10-19 years (Lopez et al, 1980). The infection rate among adults also ranged from 38 to 62%.

Studies in Colorado (Wright et al., 1977), Minnesota (Weiss et al., 1977), Washington (Harter et al., 1982; Frost et al., 1983), New Hampshire (Chute et al., 1987; Dennis et al. 1993), Utah (Laxer, 1985), and Vermont (Birkhead and Vogt, 1989) have suggested that consumption of untreated drinking water may be an important cause of endemic infection and illness in the United States. A survey of 518 children, one to three years of age, in two Washington counties found no risk of *Giardia* infection for source (surface or well) of drinking water, but a higher risk was associated with use of unfiltered surface water (Harter et al., 1983). Ten of 175 (7%) children residing in homes using unfiltered surface water were found to be infected with *Giardia* compared with only one of 37 (3%) children residing in a home using filtered surface water. An increased prevalence of infection was also found in children who had a history of drinking untreated surface water from streams or lakes during recreational activities. Dennis et al. (1993) conducted a case-control study of 273 cases of giardiasis from New Hampshire's disease registry and 375 controls: 89 (33%) cases were under the age of 11. An increased risk of giardiasis was associated with shallow well as a residential water source (OR=2.4; 95% CI=1.3-47.0), a recent history of drinking untreated surface water (OR=3.4; 95% CI=2.1-5.5).

In the other studies, the risks among children were not specifically analyzed, but children were included among the cases studied. A 1973 survey (Wright et al., 1977) of 256 Colorado residents having *Giardia*-positive stools, when compared to 256 controls matched by age, gender, race, and place of residence, showed a higher proportion of cases among those who visited Colorado mountains (69% vs. 47%), camped overnight (38% vs. 18%), and drank untreated mountain water (50% vs. 17%). Birkhead and Vogt (1989) studied risk factors among 1211 cases of laboratory-confirmed giardiasis that were not associated with outbreaks in Vermont and found increased risks of giardiasis for persons using municipal surface water systems without filtration, well water, and persons using private water systems. The average annual incidence rate of giardiasis in populations using municipal surface water systems with filtration (15.1/100,000) was about half the rate of giardiasis in

populations using municipal surface water systems without filtration (28.6/100,000), populations using municipal well water (26.8/100,000), or persons using private water systems (32.8/100,000). In a case-control study of 171 cases seen at the Dartmouth-Hitchcock Clinic and 684 controls, Chute et al. (1987) found that households with shallow well or surface water sources had a higher risk of giardiasis than those with a drilled well or municipal water (OR=2.1; 95% CI=1.3-3.2).

In Dunedin, New Zealand, Fraser and Cooke (1991) found that the risk of giardiasis in an area of the city where water was treated by coagulation/flocculation and direct dual media filtration (anthracite and sand) was one-third that in an area without such water treatment.

Because of its low infectious dose, *Giardia* can be transmitted via the accidental ingestion of relatively small volumes of contaminated water while swimming. Although relatively few recreational water outbreaks of giardiasis have been described in the literature, they have involved children. In an infant and toddler swim class in Washington State, 71 participants were found to have *Giardia*- positive stools (Harter et al., 1984). Most children were diaper age; 58.5% of the infants and toddlers were infected. Fecal accidents were often reported at the swim pools during the class. Nine cases of giardiasis were identified in people who had been swimming at an indoor pool in New Jersey during one day in September 1985 when an infected handicapped child had a fecal accident (Porter et al., 1988). Two of nine cases of giardiasis were in children. In Manitoba, Canada, an outbreak that primarily affected children 5 to 10 years of age was associated with the use of a water slide; four children were hospitalized (Greensmith et al., 1988). A potential source of fecal contamination of the slide water occurred when an adjacent toddler's wading pool was emptied into the slide pool. In an epidemiological study where 33% of giardiasis cases were under the age of 11, Dennis et al. (1993) found an increased risk of giardiasis in New Hampshire associated with swimming in a lake or pond (OR=4.6; 95% CI=2.4-86.0).

Travel. Children traveling to endemic areas are also at risk of infection. A suspected waterborne outbreak of giardiasis affected a 70% of 125 school children aged 10 to 12 years and 11 teachers from Walsall and Wolverhampton England who had gone on a cruise in the Western Mediterranean (Thompson et al., 1974). Novotny et al. (1990) found that the only risk factor for *Giardia* infection of children not attending day-care centers in Denver was travel to the Colorado mountains.

Secondary person-to-person transmission. As noted previously, not only is the spread of *Giardia* likely among children in day-care centers, but secondary transmission of infection may occur among family members

and other persons who have opportunities for contact with infected children, especially activities that involve contact with feces through diaper changing and poor personal hygiene. Dennis et al. (1993) found that an increased risk of giardiasis in New Hampshire was associated with recent contact with a child in day care. Infections were reported to have been spread to as many as 23% of the children's household contacts (ICAIR, 1984). In an outbreak of giardiasis in a day-care center in Washington, D.C., Polis et al. (1986) reported that infection was spread to at least one household contact of 47% of the infected children. In a prospective study of diarrheal illness in children up to 36 months of age in day care centers in Arizona, Bartlett et al. (1991) found *Giardia* in 19% of asymptomatic child contacts of symptomatic infected children. In one study in the United States, 25% of the family members of 58 *Giardia*-positive children were found infected, whereas, none of the family members of *Giardia*-negative children were infected; in Canada diarrhea was reported in 12% of 181 family contacts of 89 day care children with diarrhea due to *Giardia* (Pickering et al., 1986). Overall secondary attack rates for gastroenteritis in family contacts for outbreaks of giardiasis in day care centers was 17% (Pickering et al., 1986).

Secondary transmission was also found to be important within families having *Giardia*-positive children between 1- and 3-years-old (ICAIR, 1984). An important risk factor identified by Harter et al. (1982) in a study in Washington State was having two or more siblings between the ages of 3- and 10-years-old. Esrey et al. (1989) found an important risk of infection for preschool children in rural Lesotho, South Africa, was the presence of a child older than 24 months in the household.

Secondary transmission of infection can also occur when the primary or index case has been infected from waterborne exposures, travel, or other exposures. Quantitative information is severely limited about secondary transmission from children to other children, family members, and other adults or from adults to children.

Pets. Pets have been thought to present a risk for children, but there has been little epidemiological evidence that they pose a significant risk even though dogs and cats are often found infected. *Giardia* infection was found in 153 (77%) of 200 dogs and 9 (3%) of 300 cats tested in Minnesota (Bemrick 1961). Similar prevalences were reported in Spain (Lopez-Brea, 1982) and Japan (Miyamoto and Kutsume, 1978; Asano et al., 1991; Arashima et al., 1990). Kirkpatrick (1986) reported the prevalence of *Giardia* infection in cats to range from 1 to 11 percent in the United States. Franco and Cordeiro (1996 abstract) studied possible transmission of

Giardia from pets in a study in Campinas, Brazil, but fecal examinations of the domestic animals were negative for both *Giardia* and *Cryptosporidium*. Chute et al. (1987) found no elevated risk of giardiasis associated with household cats or dogs in a study conducted in New Hampshire. De Sa Cardoso et al. (1995 abstract) found no association between *Giardia* infection in children under 5 years of age and domestic animals in a study in Aracaju, Brazil.

Food. Rabbani and Islam (1994) indicated that eating raw or undercooked food because of taste considerations or to conserve heat-sensitive nutrients might increase the risk of spreading *Giardia* through food. As noted earlier, eating vegetables was identified as the only risk factor for giardiasis among children attending a day nursery used by high socioeconomic families in Brazil (de Sa Cardoso et al., 1995 abstract). There is a lack of quantitative data on the occurrence of *Giardia* cysts in foods (U.S. EPA, 1998). Although foodborne outbreaks of giardiasis have involved fish, sandwiches, vegetables, fruit and noodle salad, the source of cyst contamination of the food has generally been epidemiologically associated with infected food handlers (U.S. EPA, 1998). In one instance, the food had been prepared in the home of women who had a diapered child and a pet rabbit, both positive for *G. lamblia*.

Soil and air. No published reports on the occurrence of *Giardia* in soil or air were found (U.S. EPA, 1998). There is no evidence that *Giardia* can be transmitted by aerosols (Hall, 1994).

6. Risk Assessment

Information available about the health effects and epidemiology of giardiasis in children was used to assess the importance of waterborne, day-care center, and secondary transmission of *Giardia* in the United States.

Giardia is the most frequently identified etiologic agent causing waterborne outbreaks in public water systems in the United States. Epidemiological studies of endemic giardiasis and reported waterborne outbreaks have identified higher risks among persons using unfiltered surface water. An estimated 155 million people in the United States continue to use unfiltered surface water from municipal water systems (U.S. EPA, 1998). Public water systems that use surface water sources without filtration and that do not meet provisions of the SWTR (U.S. EPA, 1989) are considered at very high risk for waterborne transmission of giardiasis. Of an estimated 270,933,000 persons of all ages in the United States in 1998, 77,750,000 are under the age of 20

(Table 7) (U.S. Census Bureau, 1998). Based on the population distribution of children in the United States, it is estimated that 44.6 million children are exposed to public water systems that use unfiltered surface water (Table 7).

Persons using shallow surface water are also at a higher risk of giardiasis. It is not known how many persons in the United States use shallow well water, and an estimate of children exposed to shallow surface water is not available. Outbreak investigations and epidemiological studies show that *Giardia* is also transmitted during swimming and other water recreational activities and the ingestion of contaminated water while attending picnics, camping, and hiking. Accidental ingestion of contaminated water while swimming and water play is also an important waterborne risk for young children. It is not known how many children may be exposed to potentially contaminated swimming pools, wading pool, lakes, and streams.

Table 7. Estimated exposures of children to unfiltered public surface water systems in the United States

Age	Estimated population (U.S. Census Bureau, 1998)	Percent of total population	Estimated population exposed to unfiltered surface water
<5 years	18,974,000	7.0%	10,900,000
5-9 years	19,931,000	7.4%	11,500,000
10-14 years	19,291,000	7.1%	11,000,000
15-19 years	19,554,000	7.2%	11,200,000
All ages	270,933,000		155,000,000

Water is only one of several modes of transmission of *Giardia*. Children attending day-care centers also have much higher risks of *Giardia* infection. In 1994, it was estimated that 2,218,000 children attended day-care facilities in the United States (U.S. Census Bureau, 1999). Foodborne outbreaks of giardiasis have been much less frequently reported than waterborne outbreaks and are not considered an important risk for children. Epidemiological studies have not found an increased risk of infection associated with pets. Other important transmission routes and risk factors for children include person-to-person transmission and travel to endemic areas.

Since the major risk factors for infection in children in the United States are likely to be use of day-care centers and waterborne transmission, the hazards of these exposures were assessed. Although the information is limited, prevalence and other epidemiological data were used characterize the hazards associated with the waterborne and day-care transmission of *Giardia*.

6.1 Hazard Characterization, United States

Prevalence of infection. The prevalence of *Giardia* in children 1 to 3 years of age was estimated to be 7% in two counties of Washington State (Harter et al, 1982), and Bartlett et al. (1991) found that 11% of infants and toddlers tested for admission to day care centers were already infected. If these limited data can be applied to children under 5 years of age, 1.3 to 2.1 million children under 5 years of age may be infected in the United States. Most will be asymptomatic. Even if the prevalence of infection among these young children is as low as 4%, the lowest prevalence for all age groups found by Kappus et al (1994), over 750,000 children under 5 years of age may be infected in the United States. If the 4% prevalence rate can be applied to all children under 19 years of age, 3.1 million children and young adults in the United States may be infected.

Incidence of giardiasis. Information about the incidence of *Giardia* in children for Vermont (Birkhead and Vogt, 1989) suggests that 34,000 new cases of symptomatic and asymptomatic laboratory-confirmed giardiasis may occur each year in children under age 19 in the United States. Based on the incidence reported by Wright et al. (1977) for children under 15 years of age in Colorado, 2400 cases of symptomatic giradiasis may occur in children under age 19 each year in the United States. In Vermont, an active laboratory surveillance program was used to estimate incidence, whereas in Colorado incidence was based on passive surveillance, which will detect fewer cases.

Incidence of hospitalized cases of giardiasis. Based on the incidence of 4.6 hospitalizations for giardiasis per 100,000 per year found for children under 5 years of age (Lengerich et al., 1994), it is estimated that as many as 900 hospitalized cases of giardiasis in children under 5 years of age occur annually in the United States. Mortality associated with *Giardia* infection in the United States is rare (ICAIR, 1984; Bennett et al., 1987).

Waterborne transmission. Bennett et al. (1987) estimated that 120,000 cases of waterborne giardiasis may occur each year in the United States. In preparing this estimate, Bennett et al. (1987) considered that 60%

of cases of giardiasis were waterborne and queried personnel from the Centers for Disease Control regarding the number of cases of giardiasis may go unreported each year. Because this estimate is based on professional judgement rather than epidemiological studies, the estimated 120,000 cases is considered speculative and probably an over estimate. Using this estimated number of cases of waterborne giardiasis (Bennett et al., 1987) and assuming these waterborne cases occur in a similar proportion as the current estimated age-specific population distributions (i.e., children under 5 years of age are 7% of the total population and 7% of the 120,000 estimated cases of waterborne giardiasis), 34,500 cases of waterborne giardiasis would be expected to occur each year in children (Table 8). Lengerich et al. (1994) felt that the hospitalized cases of giardiasis in the United States reflected the general distribution of less severe giardiasis. If 60% of hospitalized giardiasis cases are waterborne, 540 hospitalizations of children under 5 years of age with giardiasis each year may be due to waterborne transmission (Table 8).

Table 8. Estimated waterborne giardiasis in children in the United States

Age	Estimated cases based on incidence reported by Birkhead and Vogt (1989)	Estimated cases based on information from Bennett et al. (1987)	Estimated cases based on incidence reported by Wright et al. (1977)	Estimated hospitalized cases based on information reported by Lengerich et al. (1994)
<5 years	16,000	8400	--	540
5-9 years	4,800	8900	--	--
10-14 years	1,900	8500	--	--
15-19 years	2,300	8700	--	--
0-19 years	25,000	34,500	1400	--

An estimate that considers limited epidemiological data on the incidence of laboratory-confirmed cases during active surveillance of giardiasis from 1983 to 1986 in Vermont (Birkhead and Vogt, 1989) is similar to that of Bennett et al. (1987) if it is presumed that 60% of giardiasis is waterborne. The average annual incidence rate for giardiasis in all ages was 45.9 cases per 100,000 persons per year, higher than reported in other states (Birkhead and Vogt, 1989). If this incidence is applicable to the U.S. population, approximately 124,380 cases would be expected to occur each year with 42,000 cases occurring in persons under 20 years of

age. If 60% of these cases are waterborne as Bennett et al. suggest, then about 75,000 cases of waterborne giardiasis are expected to occur each year with 25,000 of these cases in children.

Another estimate that considers data from passive surveillance during 1972 to 1973 in Colorado (Wright et al., 1977) is much lower and may be partially due to the under reporting of giardiasis in that study. Using the rate of giardiasis reported by Wright et al. (11.59 and 3.05 cases per 100,000 persons of all ages and persons under the age of 15 years, respectively), 31,500 cases of waterborne giardiasis would be expected each year with 1400 cases expected in children.

Day-care transmission. Epidemiological studies in various areas of the United States have found that 7% to 54% of children attending day-care centers are infected with *Giardia*, and this would suggest that 155,000 to 1,198,000 children attending day-care centers in the United States may be infected with *Giardia*.

Secondary transmission. Secondary transmission of *Giardia* from children in day-care centers is estimated to be 5% to 20% for household contacts and 9% to 35% for staff. This means an additional 15,000 to 480,000 *Giardia* infections may occur in adults from contact with children in day care settings. Secondary transmission from children who were infected from waterborne exposures could not be estimated.

6.2 Quantitative Risk Assessment, United States

Rose et al. (1991b) used an exponential model to evaluate risks of *Giardia* infection from estimated exposures to *Giardia* in drinking water in the United States. Drinking water exposures were obtained from survey data describing the occurrence of *Giardia* in polluted and pristine water sources and considering average removals and inactivation of cysts with various types of water treatment. The same approach was used in the development of the SWTR where performance-based standards for the control of *Giardia* were used to meet the EPA's recommended public health goal of no more than one *Giardia* infection per 10,000 persons from drinking water exposures (U.S. EPA, 1989). The EPA felt that this goal could be maintained by achieving 99.9% reductions of *Giardia* cysts through filtration and disinfection in all water systems.

Annual risks of *Giardia* infection from drinking water, including asymptomatic infections, averaged approximately 20×10^{-4} (20 infections per 10,000 people annually) and were as high as 250×10^{-4} (250

infections per 10,000 people annually). These annual risk estimates are presented as point estimates without confidence limits and do not account for *Giardia* speciation and viability or analytical sensitivity and specificity. Although the estimates have many limitations, they do suggest that the annual risk of infection due to current levels of *Giardia* in treated drinking water may be greater than the recommended annual risk of *Giardia* infection that the EPA feels drinking water systems should attempt to maintain. Point estimates of computed risk are 10 to 100 times the recommended risk level of no more than one *Giardia* infection per 10,000 persons from drinking water exposures.

If the quantitative risk assessment of Rose et al. (1991) can be applied to children, 155,500 to 1,944,000 waterborne infections are expected annually among children under 19 years of age. For children under the age of five, 38,000 to 474,000 cases of waterborne giardiasis may occur. These estimates assume that the dose-response curves for children and adults are similar.

Teunis et al. (1997) recently completed a comprehensive risk assessment of both *Cryptosporidium* and *Giardia* using Monte Carlo analysis and the distributions rather than single estimates for the following parameters: levels of oocysts and cysts (average <1/1000 L), analytical method recovery effectiveness (<2%), viability of the recovered cysts (15%), removal of protozoa during water treatment based on *Clostridium* spores (2.8 $\log_{10}$), the daily consumption of tap water (0.15 L/day), and dose-response *r* values (*Giardia* = 0.01982). The cumulative estimate for an annual risk of waterborne infection ranged from 10^{-5} to 10^{-4} for *Giardia* and from 10^{-4} to 10^{-3} from exposure to both organisms. The data used to develop the parameters utilized by Teunis et al. (1997) were specific to the Netherlands with exception of the viability and the dose-response models, and using a similar approach in other geographical areas should result in different annual risks worldwide based the occurrence of protozoa in water, water treatment practices, and water consumption in the area evaluated. For example, in the United States a higher estimate for the annual risk of waterborne *Giardia* infection is expected because of the higher occurrence and exposure to these protozoa in drinking water. A comparison of the estimated risks of waterborne *Giardia* infection from the Netherlands and the United States computed using the different mathematical models shows that risks in the United States are higher (e.g., 200 to 2500 times greater). This may be due to both higher drinking water exposures and limitations of the model used to compute the risk estimates (e.g., lack of consideration of analytical recoveries and viability in the model).

7. Summary and Research Recommendations

7.1 Summary

Giardiasis is the most commonly reported intestinal protozoan infection worldwide, and in North America, commonly occurs among children under five years of age. Giardiasis in infants and children can present as (1) asymptomatic infection; (2) acute diarrhea; (3) chronic diarrhea. *Giardia* infection is often asymptomatic for children. It is not clear whether the initial infection is always acquired without producing symptoms, as infection may result in a transient, mild, diarrheal illness that passes without notice.

The parasite is transmitted via the fecal-oral route of exposure, and both endemic and epidemic giardiasis can occur. Ingestion of contaminated water is only one source of infection, and the relative importance of waterborne transmission among other risk factors will vary from place to place depending on general sanitation practices.

Occurrence of infection and disease. The prevalence of infection among children world-wide has been found to range from 1% to 36% and as high as 72% depending on the age group and country. In many developing countries, *Giardia* infections are acquired in early childhood and by the age of 5 most children have been infected at least once. This may be related to frequent opportunities for exposure. In the United States, the highest incidence and prevalence of infection is found among children under 5 years of age, especially for those attending day-care centers. In two counties of Washington State, a prevalence of 7.1% was found in children aged 1 to 3 years. Bartlett et al. (1991) found that 11% of infants and toddlers tested for admission to day care centers in Arizona were already infected. In an epidemiological study of endemic laboratory-confirmed cases of giardiasis reported in Vermont, Birkhead and Vogt (1989) found that children aged one to four years had the highest incidence rate for *Giardia* symptomatic infection of any age group. In nine outpatient clinics in the United States, *Giardia* was detected in 15% of children (age 2-11 years) with acute diarrhea. In British Columbia, the majority of *Giardia*-positive patients were in the 1-5 year age group.

A high prevalence of infection has been reported in settings where infants and young children in diapers are collectively cared for. In developed countries, the prevalence of infection can be as high as 54% among children attending child care centers with attack rates of 50% or more occurring in outbreaks (Adam, 1991; Hall, 1994; Ortega and Adam, 1997; Steketee et al., 1989). The ranges of reported prevalence rates for children in day care centers seem to fall into two groups: low prevalence (7% to 16 %) and high prevalence (29% to

54%). The most susceptible children were 1 to 3 years old. About half of the infected children had symptoms that included diarrhea. Secondary transmission of the infection is important for both asymptomatic and symptomatic children in day care settings; as many as 23% of the infected child's household contacts may become infected.

An epidemiological study of endemic cases of giardiasis in Vermont found that child-care attendees had an incidence rate 50% greater than non-attendees (Birkhead and Vogt, 1989). In Denver, Novotny et al. (1990) found that toddlers attending day-care centers had almost twice as many infections as toddlers who were not attending day-care center.

In a single study, *Giardia* was detected in 8.4% of HIV-positive pediatric patients (mean age of 6.3 years, mean CD4 count of 504.7/$mm^{3)}$ in Madrid, Spain (Del Aguila et al., 1997).

Health effects. The wide clinical spectrum of giardiasis ranges from asymptomatic infection to acute self-limiting diarrhea to more persistent chronic diarrhea, which sometimes fails to respond to chemotherapeutic agents. The mechanisms by which *Giardia* produces diarrhea and malabsorption and the key immunologic determinants for clearance of acute infection and development of protective immunity are not well understood.

Data on the nature of human immune response to giardiasis are somewhat limited, but there are indications that both humoral and cellular responses are present. Most subjects infected with *Giardia* produce detectable levels of anti-parasite antibodies. However, the role of specific antibody to *Giardia* in determining the host's clinical response to infection has not been delineated. Two cohort studies of infants and young children provide evidence that protective immunity develops slowly in children.

There is no evidence that *Giardia* is transmitted from mother to fetus, but infants can acquire infections at an early age suggesting that mothers can infect their children very soon after childbirth. Breast milk has been found to contain secretory antibodies which could theoretically afford protection against *Giardia* infection. Although studies in developing countries have provided supportive evidence that breast-fed infants have a lower risk of *Giardia* infection, several have reported similar risks of infection or diarrhea in breast-fed infants. Breast milk may protect some infants from *Giardia* infection. This may be due to secretory antibodies in breast milk (Hall, 1994; Miotti et al., 1985) or enzymes in breast milk that have been found *in vitro* to release substances

that kill *Giardia* trophozoites (Reiner et al., 1986). The use of breast milk also offers fewer opportunities for the infant to become infected from other foods and water.

Giardia infection is often asymptomatic, especially among young children. However, asymptomatic *Giardia* infection for children may be epidemiologically significant because infections may last for months or years and infected children may transmit the infection to other children, care givers, and family members.

Infection can lead to illness, which may be severe and require hospitalization. In both the United States and Scotland, hospitalized cases of giardiasis were primarily observed for children under the age of five. In Michigan, 66% of the children under 5 years of age hospitalized with a diagnosis of giardiasis were one year of age or younger. The high hospitalization rate for young children with giardiasis may reflect greater concern by the physician over a possible adverse outcome than severe illness. Young children have fewer reserves and are more susceptible to fluid and nutritional losses from infection. Robertson (1996) felt that infants and young children may have increased susceptibility to giardiasis because of immunological factors and behavior that increases the likelihood of exposure.

In some cases, symptoms may persist for years resulting in steatorrhea and significant weight loss. Burke (1975) considered it second to cystic fibrosis as a cause of childhood steatorrhea in Kentucky. Intestinal malabsorption of fats and vitamins such as vitamin A and B_{12} has also been reported in children. In selected populations, chronic giardiasis may be as common as the acute illness, but the incidence and host determinants of chronic giardiasis are not well known.

Prolonged malabsorption of fat and its excretion in stools can lead to a significant loss of potential dietary energy. This will be of greater consequence for young children since they have greater requirements for energy than adults and have small stomachs. Chronic malabsorption has been described in children infected with *Giardia*. In severe infection, increased protein loss with associated hypoalbuminemia has been reported, but a study in The Gambia suggests this is not a common phenomenon even in severely malnourished infants and children. Using fecal alpha 1-antitrypsin measurements as an index of protein-losing enteropathy, Sullivan et al. (1992 abstract) examined children with and without parasitic infection of the gut. Only a minority (2 of 17) of children infected with *G. lamblia* had raised fecal alpha 1-antitrypsin excretion and this was not associated with hypoalbuminemia. Evidence of protein-losing enteropathy was found to be associated with hypoalbuminemia in children infected with *Strongyloides stercoralis*.

Nutritional insufficiency associated with giardiasis may have profound effects on growth and development. Since first described in 1921, impaired weight and height gain have been reported by a number of investigators in children who have severe manifestations of infection. During the hospitalizations of the children younger than 5 years in the United States, volume depletion occurred in 22% and "failure to thrive" was diagnosed in 19%. In Scotland, dehydration did not occur as frequently with giardiasis (rehydration treatments are more widely self-administered in Scotland), and 11% of the children were found lacking in expected normal physiological development.

The importance of *Giardia* as a cause of growth retardation continues to be debated. However, evidence supportive of an association has been reported. Farthing et al. (1986) observed differences in weight gain during the second year of life among *Giardia*-infected children in Guatemala. Reduction in weight gain was associated with the duration and severity of giardiasis; greater reduction in weight gain occurred when infection was prolonged and accompanied by diarrhea (Farthing, 1996). In another study of Guatemalan children, Gupta et al. (1982) found treatment of *Giardia* infection with metronidazole produced a modest increase in age-adjusted weight and height gain with effects being most striking in children 2 to 4 years of age (Farthing, 1996). Although limited, this evidence suggests that *Giardia* infection is at least one factor involved in the failure of children to grow normally. "Failure to thrive" may be related to both infection and other interacting factors, and the importance of the consequences will likely differ among children in specific populations (e.g., whether persons are asymptomatic or severely ill and malnourished). A case report from Switzerland suggests that catch-up growth and completion of pubertal development are possible even after the age of 20 years if nutritional supply is sufficient. Additional research is needed to better identify children at risk of growth retardation and the role of transient or permanent immune defects in increasing the risk of growth retardation from *Giardia* infection.

Malabsorption of iron was reported in a one study of children with symptomatic giardiasis, but in another study, asymptomatic giardiasis did not affect the intestinal absorption of iron and the hemoglobin response to oral iron therapy in iron-deficient anemic children.

Inflamation of the synovial membranes of major joints has been seen in children with giardiasis, but following anti-giardia chemotherapy, both intestinal and synovial symptoms were abated. Although uncommon, giardiasis can cause severe synovitis, and *Giardia* synovitis has been described in children.

Although evidence for an association between cystic fibrosis and *Giardia* infection is very limited, the clinical implications of *Giardia* infection (i.e., malabsorption of fat and fat-soluble vitamins) in cystic fibrosis patients, especially children should be recognized.

"Salt and pepper" retinal changes diagnosed in 20% of the children with giardiasis (mean age was 4.7 years) in a study in Italy suggest that asymptomatic, non-progressive retinal lesions may be common in young children with giardiasis. It was felt that the lesions likely do not cause functional changes in the retina, but this finding should be confirmed in longer term follow-up. Risk did not seem to be related to the severity of infection, its duration, or use of metronidazole but may reflect a genetic predisposition.

Risk factors. *Giardia* is frequently spread directly from person to person, especially among young children attending day-care centers, nurseries, institutions, or living in areas with poor sanitation and hygiene. Children traveling to endemic areas are at risk of infection. Siblings are also an important risk factor for infection. For preschool children, the presence of a child older than 24 months in the household is important for risk of infection. There is little epidemiological evidence that pets pose a significant risk even though dogs and cats are often found infected. Several small foodborne outbreaks of giardiasis have been associated with the contamination of ice and foods by infected food service workers, but restaurant-associated transmission of *Giardia* does not appear to be a significant public health problem for children.

Epidemiological studies in various areas of the United States have found that 7% to 54% of children attending day-care centers are infected with *Giardia*, suggesting that 155,000 to 1,198,000 children attending day-care centers in the United States may be infected with *Giardia*. Infected children in day-care centers are frequently asymptomatic. Infected infants and children, both symptomatic and asymptomatic, may infect other children and adults, especially family members or other care-givers. Secondary transmission of *Giardia* from children in day-care centers has been reported to range from 5% to 20% for household contacts and 9% to 35% for staff. This suggests an additional 15,000 to 480,000 *Giardia* infections may occur in adults from contact with children in day care settings. Secondary transmission from children who are infected from waterborne exposures may occur but could not be estimated.

In the United States, *Giardia* is the most frequently identified etiologic agent causing waterborne outbreaks, especially in unfiltered surface water systems. Higher risks found in populations using unfiltered surface water systems may be due to inadequate disinfection commonly employed before the EPA's SWTR

(U.S. EPA, 1989) became effective. It is estimated that 44.6 million children are exposed to public water systems that use unfiltered surface water. Children have been among the cases reported in waterborne outbreaks, but limited information is available on attack rates in these outbreaks. In one waterborne outbreak in Berlin, New Hampshire, 38% and 60% of children under 10 years of age and children 10-19 years, respectively, were found infected. Children are also at an increased risk of endemic waterborne infection from shallow wells and water recreational activities. Poorly maintained wading and swimming pools and heavily used swimming areas at lakes and ponds pose a risk for children, especially if the swimming areas are used by diaper-age toddlers or other children prone to fecal accidents.

Risk assessment models have estimated the risk of waterborne *Giardia* infection in the United States. Based on levels of *Giardia* cysts found in treated drinking water in the United States, the annual risks of *Giardia* infection are estimated to be 20×10^{-4} (20 waterborne *Giardia* infections per 10,000 persons annually) and may be as high as 250×10^{-4} (250 waterborne *Giardia* infections per 10,000 persons annually). If this quantitative risk assessment can be applied to children, 155,500 to 1,944,000 waterborne infections are expected annually among children under 19 years of age. For children under the age of five, 38,000 to 474,000 cases of waterborne giardiasis may occur. These estimates assume that the dose-response curves for children and adults are similar. It is also difficult to ascertain the level of accuracy that these risk estimates represent, since no comparable risk estimates are available from epidemiological studies. In addition, the interpretation of these risks depends on occurrence data for *Giardia* cysts in the environment. Methods used to date generally provide little or no information on viability, infectivity, or species identification when *Giardia* cysts are detected in environmental samples, and quantitative data may not be reliable due to low efficiency and precision of methods. Other estimates suggest that 1400 to 34,500 cases of waterborne giardiasis would be expected to occur each year in children and that 540 hospitalizations of children under 5 years of age with giardiasis each year may be due to waterborne transmission.

Giardiasis is very common in populations living in poverty and with poor sanitation, and a high level of fecal contamination of the environment, and the relative importance of waterborne transmission among other risk factors for giardiasis will vary among populations depending on general sanitation practices. For example, providing piped, high quality drinking water to some populations in developing countries may not significantly reduce the incidence of giardiasis. Although contaminated drinking water is a likely source of exposure, the variety of other exposures including personal hygiene, food hygiene, and environmental factors may overwhelm the beneficial effect of clean drinking water. Farthing (1994) felt that despite the public health importance of

waterborne giardiasis, especially in developed countries, waterborne transmission may represent a relatively small proportion of all infections worldwide.

7.2 Research Recommendations

Most prevalence studies have been conducted in developing countries, and additional data are needed to better assess the current prevalence of *Giardia* infection among children in the United States. This will assist in evaluating formal risk assessments for waterborne giardiasis.

The immunologic determinants for clearance of acute infection and development of protective immunity are not well defined and require additional research.

Breast milk has been found to contain secretory antibodies which could theoretically afford protection against *Giardia* infection. Although studies in developing countries have provided supportive evidence that breast-fed infants have a lower risk of *Giardia* infection, several have reported risks of infection or diarrhea in breast-fed infants. Breast milk may protect some infants from *Giardia* infection because of protective immunity of secretory antibodies in breast milk or because of breast milk enzymes that have been found *in vitro* to release substances which kill *Giardia* trophozoites. The use of breast milk also offers fewer opportunities for the infant to become infected from other foods and water. Further study is required to better define the significance of these factors in protecting breast-fed infants from infection.

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Additional research is needed to help clarify the association between giardiasis and growth impairment and other important factors so that children at greatest risk of growth retardation can be identified. The role of transient or permanent immune defects in increasing the risk of growth retardation from *Giardia* infection should also be investigated.

Differences in results of studies of growth retardation may be explained by the design of the study. It is possible that cross-sectional studies correlating *Giardia* infection with growth retardation in children may not detect an effect if only children with permanent or transient immune deficiencies are at risk of growth retardation from *Giardia* infection. This was suggested in studies which found an association. If a cohort of children with immune deficiencies can be identified, studies should focus on the effect of infection on growth in this group of children. The role of hypogammaglobulinemia as a risk factor for chronic giardiasis and possible

failure to thrive requires additional research. It is possible that many children may suffer from transient hypogammaglobulinemia which can predispose them to chronic diarrhea or other adverse effects from chronic *Giardia* infections. The prevalence of transient hypogammaglobulinemia in children is unknown.

Other observed associations with *Giardia* infection also require additional study including cystic fibrosis, synovitis, pancreatic or hepatic disease, and ocular changes. Asymptomatic, non-progressive retinal lesions may be common in young children with giardiasis; the risk does not seem to be related to the severity of infection, its duration, or use of metronidazole but may reflect a genetic predisposition. "Salt and pepper" retinal changes found in a study in Italy were not felt to cause functional changes in the retina, and this finding should be confirmed in longer term follow-up studies.

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8. References

Abdel Fattah, S.M., Maklad, K.A., Gadallah, M.S. 1991. Age-related seropositivity of antibody to *Giardia* in Different age groups in Cairo. J. of the Egyptian Society of Parasitology. 21(3):707-713.

Adam RD. 1991. The biology of *Giardia* spp. Microbiological Reviews 55(9):706-732.

Addiss, D.G., Stewart, J.M., Finton, R.J., Wahlquist, S.P., Williams, R.M., Dickerson, J.W., Spencer, H.C., and Juranek, D.D. 1991. *Giardia lamblia* and *Cryptosporidium* infections in child day-care centers in Fulton County, Georgia. Pediatr. Infect. Dis. J., 10:907-1011.

Ahmed, M.M. 1991. Haematological values and parasitic infections in school children in Riyadh [Abstract], Saudi Arabia. J. Egyptian Soc. Parasitology, 21(3):831-8.

Arancon Viguera, A., Segura Torres, J.C., Galan Labaca, I., Trapero Carrascosa, J.L., Maqueda Blasco, J. 1990. A study of family carriers in 132 cases of *Giardia lamblia* infestation [Abstract]. [Spanish] Atencion Primaria, 7(6):416-8.

Arashima, Y., Iguchi, K., Kubo, N., Kumasaka, K., Okuyama, K., Kawano, K., Harado, M., Shimabukuro, H., Saitoh, T., Isa, H. 1990. Studies on the giardiasis as the zoonosis. Kansenshogaku-Zasshi, 64:295-298.

Asano, R., Hokari, S., Murasugi, E., Arashima, Y., Kubo, N., Kawano, K. 1991. II. Giardiasis in dogs and cats. Kansenshogaku-Zasshi, 65: 157-161.

Bai, J.C. 1998. Malabsorption syndromes. Digestion 59(5):530-46.

Bartlett, A.V., Englender, S.J., Jarvis, B.A., Ludwig, L., Carlson, J.F., and Topping, J.P. 1991. Controlled trial of *Giardia lamblia*: control strategies in day care centers. Am. J. Public Health, 81(6):1001-1006.

Bemrick W.J. 1961. A note on the incidence of three species of *Giardia* in Minnesota. J. Parasitol., 47:87-89.

Benenson A.S. 1995. Giardiasis. Control of Communicable Disease in Man. Sixteenth Edition, American Public Health Association, Washington, DC.

Bennett, J.V., Holmberg, S. D., Rogers, M.F., Solomon, S.L. 1987. In: Closing the Gap: The Burden of Unnecessary Illness, Amler, R.W. and Dull, H.B., eds., Oxford Univ. Press, New York, 102-114.

Birkhead, G. and Vogt, R.L. 1989 Epidemiological surveillance for endemic *Giardia lamblia* infection in Vermont. Amer. J. Epidemiol., 129:762.

Brannan, D.K., Greenfield, R.A., Owen, W.L., Welch, D.F., Kuhls, T.L. 1996. Protozoal colonization of the intestinal tract in institutionalized Romanian children. Clinical Infectious Diseases, 22(3):456-61.

Buchrieser, C., Sixl, W., Buchrieser, V., Miorini, T., Stunzner, D., Brosch, R. 1988. Investigation of human stool samples from the Cape Verde Islands (district Santa Cruz/Santiago) [Abstract]. Geographia Medica - Supplement, 1:61-4.

Bulut, B.U., Gulnar, S.B., and Aysev, D. 1996. Alternative treatment protocols in giardiasis: a pilot study. Scand J Infect Dis 28:493-495.

Burke, J.A. 1975. Giardiasis in childhood. Am J Dis Child, 129:1304-1310.

Caeiro, J.P., Mathewson, J.J., Smith, M.A., Jiang, Z.D., Kaplan, M.A., Dupont, H.L. 1999. Etiology of outpatient pediatric nondysenteric diarrhea: a multicenter study in the United States. Pediatr. Infect. Dis.J., 18:94-97.

Carroccio, A., Montalto, G., Iacono, G., Ippolito, S., Soresi, M., Notarbartolo, A. 1997. Secondary impairment of pancreatic function as a cause of severe malabsorption in intestinal giardiasis: a case report. Am J. Trop. Med. Hyg., 56(6): 599-602.

Carswell, F.,Gibson, A.A.M., McAllister, T.A. 1973. Giardiasis and coellac disease. Arch Dis Child, 48:414-18.

Casterline, J.E., Allen, L.H., Ruel, M.T. 1997. Vitamin B-12 deficiency is very prevalent in lactating Guatemalan women and their infants at three months postpartum. The Journal of Nutrition, 127:1966-72.

Char, S., Cevallos, A.M., Yamson, P., Sullivan, P.B., Neale, G., Farthing, M.J. 1993. Impaired IgA response to *Giardia* heat shock antigen in children with persistent diarrhea and giardiasis. Gut, 34(1):38-40.

Chavez, B., Gonzalez-Mariscal, L., Cedillo-Rivera, R., Martinez-Palomo, A. 1995. *Giardia lamblia*: in vitro cytopathic effect of human isolates [Abstract]. Experimental Parasitology, 80(1):133-8.

Chute, C.G., Smith, R.P., and Baron, J.A. , 1987. Risk factors for endemic giardiasis, Am. J. Public Health, 77 (5): 585-87.

Cody, M. M., Sottnek, H. M., and O'Leary, V. S. 1994. Recovery of *Giardia lamblia* cysts from chairs and tables in child day-care centers. Pediatrics, 94(6 Pt 2):1006-1008.

Cole, T.J. and Parkin J.M. 1977. Infection and its effect on growth of young children: a comparison of The Gambia and Uganda. Trans R Soc Trop Med Hyg, 71:196-98.

Corsi, A., Nucci, C., Knafelz, D., Bulgarini, D., Di Iorio, L., et al. 1998. Ocular changes associated with *Giardia lamblia* infection in children. British J. Ophthalmology, 82:59-62.

Curtale, F., Nabil, M., el Wakeel, A., Shamy, M.Y. 1998. Anaemia and intestinal parasitic infections among school age children in Behera Governorate, Egypt. Behera Survey Team. Journal of Tropical Pediatrics, 44(6):323-8.

Danciger M. and Lopez M. 1975. Number of *Giardia* in the feces of infected children. American Journal of Tropical Medicine and Hygiene, 24(2): 237-242.

Dennis, D.T., Smith, R.P., Welch, J.J., Chute, C.G., Anderson, B., Herndon, J.L., von Reyn, C.F. 1993. Endemic giardiasis in New Hampshire: a case-control study of environmental risks. J. Infect. Dis., 167(6):1391-5.

Derylo, A., Sodowska, H., Grygierczyk, D. 1994. Application of immunoassay for the detection of giardiasis in children and adults[abstract]. [Polish] Przeglad Epidemiologiczny, 48(1-2):35-7.

Di Prisco, M.C., Hagel, I., Lynch, N.R., Barrios, R.M., Alvarez, N., Lopez, R. 1993. Possible relationship between allergic disease and infection by *Giardia lamblia* [Abstract]. Annals of Allergy, 70(3):210-3.

Di Prisco, M.C., Hagel, I., Lynch, N.R., Jimenez, J.C., Rojas, R., Gil, M., Mata, E. 1998. Association between giardiasis and allergy. Annals of Allergy, Asthma, & Immunology, 81(3):261-5.

De Morais, M.B., Suzuki, H.U., Corral, J.N., Machado, N.L., Neto, U.F. 1996. Asymptomatic giardiasis does not affect iron absorption in children with iron deficiency anemia [see comments]. Journal of the American College of Nutrition, 15(5):434-8.

De Morais, M.B. and Suzuki, H.U. 1997. Weight gain in children with asymptomatic giardiasis and iron-deficiency anaemia during oral iron therapy [letter]. Journal of Tropical Pediatrics, 43(2):121-2.

de Sa Cardoso, G., de Santana, A.D., de Aguir, C.P. 1995. Prevalence and epidemiolgic aspects of giardiasis in day care centers in the Municipality of Aracaju, SE, Brazil [Abstract]. [Portuguese] Revista Da Sociedade Brasileira de Medicina Tropical, 28(1):25-31

Del Aguila, C., Navajas, R., Gurbindo, D., Ramos, J.T., Mellado, M.J., Fenoy, S., Munoz Fernandez, M.A., Subirats, M., Ruiz, J., Pieniazek, N.J. 1997. Microsporidiosis in HIV-positive children in Madrid (Spain). Journal of Eukaryotic Microbiology, 44(6):84S-85S.

Dos Santos, J.I. and Vituri C. de L. 1996. Some hematimetric findings in human *Giardia lamblia* infection [Abstract]. Revista do Instituto de Medicina Tropical de Sao Paulo, 38(2):91-5.

Enekwechi, L.C. and Azubike, C.N. 1994. Survey of the prevalence of intestinal parasites in children of primary school age [Abstract]. West African Journal of Medicine, 13(4):227-30.

Esrey, S.A., Collett, J., Miliotis, M.M., Koornhof, J., Makhale, P. 1989. The risk of infection from *Giardia lamblia* due to drinking water supply, use of water, and latrines among preschool children in rural Lesotho. Int. J. Epidemiol., 18(1):248-253.

Franco, R.M. and Cordeiro, N. da S. 1996. Giardiasis and cryptosporidiosis in day-care centers in the municipality Campinas SP [Abstract]. [Portuguese] Revista Da Sociedade Brasileira de Medicina Tropical, 29(6):585-91.

Farthing, M.J.G., Mata, L., Urrutia, J.J., et al. 1986. Natural history of *Giardia* infection of infants and children in rural Guatemala, and its impact on physical growth. Am J Clin Nutr, 43:393-403.

Farthing, M.J.G. 1994. Giardiasis as a disease. In: *Giardia*: From Molecules to Disease, R.C.A. Thompson, J.A. Reynoldson, and A.J. Lymbery, eds., CAB INTERNATIONAL, Wallingford, U.K., pp. 15-37.

Farthing, M.J.G. 1996. Giardiasis. Gastroenterology Clinics of North America, 25(3):493-515.

Ferguson, A., Gillon, J., Munro, G. 1990. Pathology and pathogenesis of the intestinal mucosal damage in giardiasis. In Giardiasis, E.A. Meyer ed., Elesiver Science Publishers, Amsterdam, pp. 155-174.

Filer, L.J., Jr. 1996. Iron deficiency, giardiasis, and HIV disease. J Amer. College Nutrition, 15(5):421.

Fraser, D. 1994. Epidemiology of *Giardia lamblia* and *Cryptosporidium* infections in childhood. Israel Journal of Medical Sciences, 30(5-6):356-61.

Fraser, D., Dagan, R., Naggan, L., Greene, V., El-On, .J, Abu-Rbiah, Y., Deckelbaum, R.J. 1997. Natural history of *Giardia lamblia* and *Cryptosporidium* infections in a cohort of Israeli Bedouin infants: a study of a population in transition. American Journal of Tropical Medicine & Hygiene, 57(5):544-9.

Fraser, G.G. and Cooke, K.R. 1991. Endemic *Giardia*sis and municipal water supply. Am. J. Public Health, 81: 760.

Freeman, C.D., Klutman, N.E., and Lamp, K.C. 1997. Metronidazole. Drugs, 54(5):679-708.

Frost, F., Hartner, L., Plan, B., Fukutaki, K., Holman, B. 1983. Giardiasis in Washington State. Project Summary. U.S. Environmental Protection Agency (EPA-600/S1-82-016), Research Triangle Park, NC.

Gamboa, M.I., Basualdo, J.A., Kozubsky, L., Costas, E., Cueto Rua, E., Lahitte, H.B. 1998. Prevalence of intestinal parasitosis within three population groups in La Plata, Argentina. European Journal of Epidemiology, 14(1):55-61.

Garcia, J.L., Marquez, S., Alvarez-Dardet, C., Perea, E.J. 1989. Healthy carriers of enteropathogenic micro-organisms among the child population of Seville [Abstract]. [Spanish] Enfemedades Infecciosas y Microbiologia Clinica, 7(9):478-81.

Gendrel, D., Richard-Lenoble, D., Kombila, M., Dupont, C., Moreno, J.L., Gendrel, C., Nardou, M., Chaussain, M. 1992. Influence of intestinal parasitism on lactose absorption in well-nourished African children [Abstract]. American Journal of Tropical Medicine & Hygiene, 46(2):137-40.

Gillin, F.D., Das, S., Reiner, D.S. 1990. Nonspecific defenses against human *Giardia*. In: Human Parasitic Diseases, Vol. 3, Giardiasis, E.A. Meyer, ed., Elsevier Science Publishers, Amsterdam, pp. 199-213.

Gilman RH, Marquis GS, Miranda E, Vestegui M, Martinez H, Rapid reinfection by *Giardia lamblia* after treatment in a hyperendemic Third World community. Lancet 1988 Feb 13;1(8581):343-5.

Goldin, A,J., Apt, W., Aguilera, X., Zulantay, I., Warhurst, D.C., Miles, M.A. 1990. Efficient diagnosis of giardiasis among nursery and primary school children in Santiago, Chile by capture ELISA for the detection of fecal *Giardia* antigens. American Journal of Tropical Medicine & Hygiene, 42(6):538-45.

Golinska, Z., Lach, J., Bany, J., Chas, J. 1997. Intestinal parasites in four Warsaw kindergarten children in 1994-1996 [Abstract]. [Polish] Przeglad Epidemiologiczny 1997;51(4):411-6.

Granot, E., Spira, D.T., Fraser, D., Deckelbaum, R.J. 1998. Immunologic response to infection with *Giardia lamblia* in children: effect of different clinical settings. Journal of Tropical Pediatrics, 44(4):241-6.

Gray, S.F. and Rouse, A.R. 1992. Giardiasis--a cause of travellers' diarrhoea [Abstract]. Communicable Disease Report. CDR Review. 2(4):R45-7.

Greensmith, C.T., Stanwick, R.S., Elliot, B.E., Fast, M.V. 1988. Giardiasis associated with the use of a water slide. Pediatric Infectious Dis. J., 7(2):91-91.

Guimaraes S, Sogayar MI, Occurrence of *Giardia lamblia* in children of municipal day-care centers from Botucatu, Sao Paulo State, Brazil [Abstract]. Revista do Instituto de Medicina Tropical de Sao Paulo 1995 Nov-Dec;37(6):501-6.

Gupta, MC, Urrutia JJ, Effect of periodic anti-Ascaris and anti-*Giardia* treatment on nutritional status of pre-school children. Am J Clin Nutr 36:79-86, 1982.

Hall, A. 1994. *Giardia* infections: epidemiology and nutritional consequences. In: *Giardia*: From Molecules to Disease, R.C.A. Thompson, J.A. Reynoldson, and A.J. Lymbery, eds., CAB INTERNATIONAL, Wallingford, U.K., pp. 251-279.

Harter, L., Frost, P., Jakubowski, W. 1982. *Giardia* prevalence among 1-to-3-year-old children in two Washington State counties. Am. J. Public Health, 72(4):386-388.

Harter, L., Frost, F., Gruenenfelder, G., et al. 1984. Giardiasis in an infant and toddler swim class. Am. J. Public Health, 74:155-156.

Herzog, D., Hammer, B., Neuweiler, J., Werder, E. 1998. Chronic giardiasis with intestinal dwarfism and delayed puberty in immunoglobulin deficiency syndrome: complete catch-up growth after therapy [Abstract]. [German] Schweizerische Medizinische Wochenschrift. Journal Suisse de Medecine, 128(16):623-8.

Heyworth, M.F., Carlson, J.R., Ermak, T.H. 1987. Clearance of giardia muris infection requires helper/inducer T lymphocytes. J. Exp. Med. 165, 1743-1748.

Hopkins, R.S. and Juranek, D.D. 1991. Acute giardiasis: an improved clinical case definition for epidemiologic studies. Am. J. Epidemiol., 133:402-407.

ICAIR, Life Systems, Inc., 1984, Criteria Document on *Giardia*, U.S. EPA, Washington, DC.

Isaac-Renton, J.L. and Philion, J.J. 1992. Factors associated with acquiring giardiasis in British Columbia residents. Can. J. Public Health, 83(2):155-158.

Jokipii, L., Miettinen, A., Jokipii, A.M.M. 1988. Antibodies to cysts of Giardia lamblia in giardiasis and in the absence of giardiasis. J Clin Microbiology, 26(1):121-125.

Islam, A., Stoll, B.J., Ljungstrom, I. Biswas, J., Nazrul, H., Huldt, G. 1983. *Giardia lamblia* infections in a cohort of Bangladeshi mothers and infants followed for one year. J. Paediatrics, 103: 996-1000.

Janoff, E.N., Mead, P.S., Mead, J.R., Echeverria, P., Bodhidatta, L., Bhaibulaya, M., Sterling, C.R., Taylor, D.N. 1990a. Endemic *Cryptosporidium* and *Giardia lamblia* infections in a Thai orphanage. American Journal of Tropical Medicine & Hygiene, 43(3):248-56.

Janoff, E.N., Taylor, D.N., Echeverria, P., Glode, M.P., Blaser, M.J. 1990b. Serum antibodies to *Giardia lamblia* by age in populations in Colorado and Thailand. Western Journal of Medicine 152(3):253-6.

Jarabo, M.T., Garcia-Moran, N.P., Garcia-Moran ,J.I. 1995. Prevalence of intestinal parasites in a student population [Abstract]. [Spanish] Enfermedades Infecciosas y Microbiologia Clinica, 13(8):464-8.

Kang, G., Mathew, M.S., Rajan, D.P., Daniel, J.D., Mathan, M.M., Mathan, V.I., Muliyil, J.P. 1998. Prevalence of intestinal parasites in rural Southern Indians. Tropical Medicine & International Health, 3(1):70-5.

Kappus, K.D., Lundgren, R.G., Juranek, D.D., Roberts, J.M., and Spencer, H.C. 1994. Intestinal parasitism in the United States: update on a continuing problem. Am. J. Trop. Med. Hyg., 50(6):705-713.

Keating, J., Giardiasis. 1992. Textbook of Pediatric Infectious Diseases, third edition, Volume II, Feign, R.D. and Cherry, J.D. eds., W.B. Saunders Company, Philadelphia, pp. 2032-2035.

Kirkpatrick, C.E. l986. Feline giardiasis: a review. J. Small Anim. Pract., 27: 69-80.

Kopecky, K., Giboda, M., Aldova, E., Dobahi, S.S., Radkovsky, J. 1992. Pilot studies on the occurrence of some infectious diseases in two different areas in south Yemen (Aden). Part I. Parasitology [Abstract]. Journal of Hygiene, Epidemiology, Microbiology & Immunology, 36(3):253-61.

Kumkum, Khanna, R., Nain, C.K., Mehta, S., Vinayak, V.K. 1988. Depressed humoral immune responses to surface antigens of *Giardia lamblia* in persistent giardiasis. Pediatr Infect Dis J. 7(7):492-498.

Lanata, C.F., Black, R.E., Maurtua, D., Gil, A., Gabilondo, A., Yi ,A., Miranda, E., Gilman, R.H., Leon-Barua, R., Sack, R.B. 1992. Etiologic agents in acute vs persistent diarrhea in children under three years of age in peri-urban Lima, Peru. Acta Paediatrica. Supplement, Sep;381:32-8.

Laxer, M.A. 1985. Potential exposure of Utah army national guard personnel to giardiasis during field training exercise: a preliminary survey. Military Medicine, 150:23-26.

Lengerich, E.J., Addiss, D.G., and Juranek, D.D. 1994. Severe giardiasis in the United States. Clinical Infectious Diseases, l8:760-763.

Letts, M., Davidson, D., Lalonde, F. 1998. Synovitis secondary to giardiasis in children. American Journal of Orthopedics, 27(6):451-4.

Lindo, J.F., Levy, V.A., Baum, M.K., Palmer, C.J. 1998. Epidemiology of giardiasis and cryptosporidiosis in Jamaica. American Journal of Tropical Medicine & Hygiene, 59(5):717-21.

Lopez, C.E., Dykes, A.C., Juranek, D.D., et al. 1980. Waterborne giardiasis: a communitywide outbreak of disease and a high rate of asymptomatic infection. Amer. J. Epidemiol. 112(4):495-507.

Lopez-Brea, M. 1982. *Giardia lamblia*: incidence in man and dogs. Trans. Roy. Soc. Trop. Med. Hyg., 76: 565.

Magambo, J.K., Zeyhle, E., Wachira, T.M. 1998. Prevalence of intestinal parasites among children in southern Sudan [Abstract]. East African Medical Journal, 75(5):288-90.

Mahmud, M.A., Chappell, C., Hossain, M.M., Habib, M., Dupont, H.L. 1995. Risk factors for development of first symptomatic *Giardia* infection among infants of a birth cohort in rural Egypt. American Journal of Tropical Medicine & Hygiene, 53(1):84-8.

Makhlouf, S.A., Sarwat, M.A., Mahmoud, D.M., Mohamad, A.A. 1994. Parasitic infection among children living in two orphanages in Cairo [Abstract]. Journal of the Egyptian Society of Parasitology, 24(1):137-45.

Mason, P.R. and Patterson, B.A. 1987. Epidemiology of Giardia lamblia infection in children: cross-sectional and longitudinal studies in urban and rural communities in Zimbabwe. American Journal of Tropical Medicine & Hygiene, 37(2):277-82.

Millar, A.J., Bass, D.H., van der Merwe, P. 1989. Parasitic infestation in Cape Town children. A random study of 101 patients [Abstract]. South African Medical Journal, 76(5):197-8.

Miotti, P.G., Gilman, R.H., Pickering, L.K., Ruiz-Palacios, G., Park, H.S., and Yolken, R.H. 1985. Prevalence of serum and milk antibodies to *Giardia lamblia* in different populations of lactating women. J. Infect. Dis., 152:1026-1031.

Miotti, P.G., Gilman, R.H., Santosham, M., Ryder, R.W., and Yolken, R.H. 1986. Age-related rate of seropositivity of antibody to *Giardia lamblia* in four diverse populations. Journal of Clinical Microbiology, 24(6):972-975.

Miyamoto, K. and Kutsume, H. 1978. Studies on zoonoses in Hokkaido, Japan. 1. An epidemiological survey of protozoan and helminthic infections of stray dogs in Kamikawa district. Japanese J. Parasitol., 27: 369-374.

Nahnias, J., Greenburg, Z., Djerrasi, L., Gildai, L. 1991. Mass treatment of intestinal parasites among Ethiopian immigrants. Israel J. Med. Sciences, 27:278-283.

Nash, T.E., Herrington, D.A., Losonsky, G.A., Levine, M.M. 1987. Experimental human infections with *Giardia lamblia*. J. Infect. Dis., 156:974-984.

Nakano, I., Miyahara, T., Ito, T., Migita. Y., Nawata, H. 1995. Giardiasis in pancreas. Lancet, 345 (February 25):524-5.

Nayak, N., Ganguly, N.K., Walia, B.N.S., Wahi, V., Kanwar, S.S., and Mahajan, R.C. 1987. Specific secretory IgA in the milk of *Giardia lamblia*-infected and uninfected women. J. Infect. Dis., 155(4):724-727.

Ngan, P.K., Khanh, N.G., Tuong, C.V., Quy, P.P., Anh, D.N., Thuy, H.T. 1992. Persistent diarrhea in Vietnamese children: a preliminary report. Acta Paediatrica. Supplement, 381:124-6.

Nikolic, A., Djurkovic-Djakovic, O., Bobic, B. 1998. Intestinal parasitic infections in Serbia [Abstract]. [Serbo-Croatian (Cyrillic)] Srpski Arhiv Za Celokupno Lekarstvo, 126(1-2):1-5.

Novotny, T.E., Hopkins, R.S., Shillam, P., Janoff, E.N. 1990. Prevalence of *Giardia lamblia* and risk factors for infection among children attending day-care facilities in Denver. Public Health Reports, 105(1):72-5.

Olszok, I. and Kucharz, E.J. 1996. Giardiasis [Abstract]. [Polish] Przeglad Lekarski, 53(7):579-81.

Omar, M.S., Mahfouz, A.A., Abdel Moneim, M. 1995. The relationship of water sources and other determinants toprevalence of intestinal protozoal infections in a rural community of Saudi Arabia. Journal of Community Health, 20(5):433-40.

Ortega, Y.R. and Adam, R.D. 1997. *Giardia*: overview and update. Clinical Infectious Diseases, 25:545-50.

Pedraza Duenas, A., Ripoll Lozano, M.A., Sahagun Salcedo, B. 1994 Infestation by *Giardia lamblia* of children in the basic health area of East Rural Avila [Abstract]. [Spanish] Revista de Sanidad e Higiene Publica, 68(3):399-404.

Perez Armengol, C., Ariza Astolfi, C., Ubeda Ontiveros, J.M., Guevara Benitez, D.C., de Rojas Alvarez, M., Lozano Serrano, C. 1997. Epidemiology of children's intestinal parasitism in the Guadalquivir Valley, Spain [Abstract]. [Spanish], Revista Espanola De Salud Publica, 71(6):547-52.

Perlmutter, D.H., Leichtner, A.M., Goldman, H., Winter, H.S. 1985. Chronic diarrhea associated with hypogammaglobulinemia and enteropathy in infants and children. Dig. Dis. Sci., 30:1149-1155.

Pesce, F., Barabino, A., Dufour, C., Caffarena, P.E., Callea, F., Gatti, R. 1992. Hypertrophic gastropathy with transient sessile polyps. Journal of Pediatric Gastroenterology & Nutrition, 14(3):323-6.

Pickering, L.K., Woodward, W.E., DuPont, H.L., Sullivan, P. 1984. Occurrence of *Giardia lamblia* in children in day care centers. J. Pediatrics, 104(4):522-26.

Pickering, L.K., Bartlett, A.V., Woodward, W.E. 1986. Acute infectious diarrhea among children in day care: epidemiology and control. Reviews of Infectious Diseases, 8(4):539-47.

Polis MA., Tuazon CU., Alling DW., Talmanis E. 1986. Transmission of *Giardia lamblia* from a day care center to the community. American Journal of Public Health, 76(9):1142-4.

Porter, J.D., Ragazzani, H.P., Buchanon, J.D., Waskin, H.A., Juranek, D.D., and Parkin, W.E. 1988. *Giardia* transmission in a swimming pool. Am. J. Public Health, 78(6):659-662.

Rabbani, G.H. and Islam,A. 1994. Giardiasis in humans: Populations most at risk and prospects for control. In: *Giardia*: From Molecules to Disease, R.C.A. Thompson, J.A. Reynoldson, and A.J. Lymbery, eds., CAB INTERNATIONAL, Wallingford, U.K., pp. 83-97.

Rajeshwari, K., Jaggi, N., Aggarwal, V., Kalra, K.K., Mittal, S.K., Baveja, U. 1996. Determinants of symptomatic giardiasis in childhood [Abstract]. Tropical Gastroenterology, 17(2):70-6.

Reiner, D.S., Wang, C-S, Gillin, F.D. 1986. Human milk kills *Giardia lamblia* by generating toxic lipolytic products. J. Infect. Dis., 154:825-832.

Roberts, D.M., Craft, J.C., Mather, F.J., Davis, S.H., Wright, J.A. Jr. 1988. Prevalence of giardiasis in patients with cystic fibrosis. Journal of Pediatrics, 112(4):555-9.

Roberts-Thompson, I.C., Stevens, D.P., Mahmoud, A.A.F., Warren, K.S. 1976. Giardiasis in the mouse: An animal model. Gastroenterol, 71:57-61.

Robertson, L.J. 1996. Severe giardiasis and cryptosporidiosis in Scotland, UK. Epidemiol. Infect., 117:551-561.

Rodriguez-Hernandez, J., Canut-Blasco, A., Martin-Sanchez, A.M. 1996. Seasonal prevalences of *Cryptosporidium* and *Giardia* infections in children attending day care centers in Salamanca (Spain) studied for a period of 15 months [Abstract]. European J. Epidemiol., 12:291-295.

Rojas, L., Torres, D.R., Mediola, B.J., Finlay, C.M. 1989. Detection of specific anti-Giardia serum antibody by an immunofluorescence test in children with clinical giardiasis. Am. J. Trop. Med. Hyg., 40(5):477-479.

Rosales-Borjas, D.M., Diaz-Rivadeneyra, J., Dona-Leyva, A., Zambrano-Villa, S.A., Mascaro, C., Osuna, A., Ortiz-Ortiz, L. 1998. Secretory immune response to membrane antigens during *Giardia lamblia* infection in humans. Infection & Immunity, 66(2):756-9.

Rose, J.B., Haas, C.N., Regli, S. 1991. Risk assessment and control of waterborne giardiasis. Am. J. Public Health, 81(6): 709-13.

Salem, G., van de Velden, L., Laloe, F., Maire, B., Ponton, A., Traissac, P., Prost, A. 1994. Intestinal parasitic diseases and environment in Sahelo-Sudanese towns: the case of Pikine (Senegal) [Abstract]. [French] Revue d Epidemiologie et de Sante Publique, 42(4):322-33.

Savidge, T.C., Shmakov, A.N., Walker-Smith ,J.A., Phillips, A.D. 1996. Epithelial cell proliferation in childhood enteropathies. Gut, 39(2):185-93.

Shetty, N., Narasimha, M., Elliott, E. Raj, I.S., Macaden, R. 1992. Age-specific sero-prevalence of amoebiasis and giardiasis in southern Indian infants and children. Journal of Tropical Pediatrics, 38(2):57-63.

Shukry, S., Zaki, A.M., DuPont, H.L., Shoukry, I., el Tagi ,M., Hamed, Z. 1986. Detection of enteropathogens in fatal and potentially fatal diarrhea in Cairo, Egypt. Journal of Clinical Microbiology, 24(6):959-62.

Skorochodzki, J. Oldak, E., Taraszkiewicz, F., Kurzatkowska, B., Sulik, A., Zagorska, W., Rozkiewicz, D. 1998. Frequency of giardiasis in children with chronic abdominal pain coming from North-East Poland [Abstract]. [Polish] Przeglad Epidemiologiczny, 52(3):309-15.

Snider, D.P., Skea, D. Underdown, B.J. 1988. Chronic giardiasis in B-cell-deficient mice expressing the xid gene. Infection and Immunity, 56:2838-2842.

Soliman, M.M., Taghi-Kilani, R., Abou-Shady, A.F., El-Mageid, S.A., Handousa, A.A., Hegazi, M.M., Belosevic, M. 1998. Comparison of serum antibody responses to *Giardia lamblia* of symptomatic and asymptomatic patients. American Journal of Tropical Medicine Hygiene, 58(2):232-9.

Steketee, R.W., Reid, S., Cheng, T., Stoebig, J.S., Harrington, R.G., and Davis, J.P. 1989. Recurrent outbreaks of giardiasis in a child day care, Wisconsin. Am. J. Public Health, 79(40):485-490.

Stazzone, A.M., Slaats, S., Mortagy, A., Kleinosky, M., Diab, A., Mourad, A., Hebert, A., Merrell, B.R., Watson, R.R., and Murphy, J.R. 1996. Frequency of *Giardia* and *Cryptosporidium* infections in Egyptian children as determined by conventional and immunofluorescence methods. Pediatr. Infect. Dis. J., 15(11):1044-1046.

Sullivan, P.B., Lunn, P.G., Northrop-Clewes, C.A., Farthing, M.J. 1992. Parasitic infection of the gut and protein-losing enteropathy [Abstract]. Journal of Pediatric Gastroenterology & Nutrition, 15(4):404-7.

Swarbrick, A., Lim, R.L., Upcroft, J.A., Stewart, T.S. 1997. Nucleotide variation in the cytidine triphosphate synthetase gene of *Giardia duodenalis*. Journal of Eukaryotic Microbiology, 44(6):531-4.

Teunis, P.F.M., Medema, G.J., Kruidenier, L., Havelaar, A.H. 1997. Assessment of the risk of infection by *Cryptosporidium* and *Giardia* in drinking water from a surface water source. Water Research, 31(6):1333-1346.

Thompson, R.G., Karandikar, D.S., Leek, J. 1974. Giardiasis an unusal cause of epidemic diarrhea. Lancet Apr 6: 615-6.

Thompson, S.C. 1994. *Giardia lamblia* in children and the child care setting: a review of the literature. J. Pediar. Child Health, 30:202-209.

Turner, J.A. 1985. Giardiasis and infections with *Dientamoeba fragilis*. Pediatric Clinics of North America, 32(4):865-79.

U.S. Census Bureau. 1998. Resident population of the United States, by age and sex, internet release December 28.

U.S. Census Bureau. 1999. Who's minding our preschoolers? Fall 1994 (Update), internet release April 1.

U.S. EPA. 1989. Guidance Manual for Compliance with Filtration and Disinfection Requirements for Public Water Systems using Surface Water Sources. United States Environmental Protection Agency, (EPA Report No. 570/9-89-018), Washington, D.C.

U.S. EPA. 1998. Drinking Water Criteria Document on *Giardia*. Environmental Protection Agency, Washington, DC.

Upcroft, J.A., Boreham, P.F., Campbell, R.W., Shepherd, R.W., Upcroft, P. 1995. Biological and genetic analysis of a longitudinal collection of *Giardia* samples derived from humans. Acta Tropica, 60(1):35-46.

Valencia, M.E., McNeill, G., Haggarty, P., Moya, S.Y., Pinelli, A., Quihui, L., Davalos, R. 1995. Energetic consequences of mild *Giardia intestinalis* infestation in Mexican children. American Journal of Clinical Nutrition, 61(4):860-5.

Varga, L. and Delage, G. 1990. *Giardia lamblia* infestation at child day care centers. Nutritional impact in infested children[Abstract]. [French] Archives Francaises de Pediatrie, 47(1):5-8.

Vinayak, V.K., Kumkum, Khanna, R. 1989. Serum antibodies to giardia surface antigens: lower titres in persistent than in non-persistent giardiasis. J. Med. Microbiology, 30(3):207-212.

Wasilewska, E.R., Trippner, M., Hofman, J., Kaczmarski, M., Stasiak-Barmuta, A. 1995. Allergic constitution and immunological condition of children infected with *Giardia lamblia* [Abstract]. Roczniki Akademii Medycznej W Bialymstoku, 40(3):649-54.

Walia, B.N., Ganguly, N.K., Mahajan, R.C., Kimar, D., Madan, I.J., Gambhir, S.K., Kanwar, S.S. 1986. Morbidity in preschool *Giardia* cyst excretors. Trop Geograp. Med., 38(4):367-70.

Weiss, H.B., Winegar, D.A., Levy, B.S., Washburn, J.W. 1977. Giardiasis in Minnesota, 1971-1975. Minn. Med., 60:815-820.

White, K.E., Hedberg, C.W., Edmonson, L.M., Jones, D.B.W., Osterholm, M.T., MacDonald, K.L. 1989. Journal Infectious Disease, 160(2):298-304.

Wolfe, M.S. 1992. Giardiasis. Clinical Microbiology Reviews, 5(1):93-100.

Wright, R.A., Spenser, H.C., Brodsky, R.E., Vernon, T.M. 1977. Giardiasis in Colorado: an epidemiological study. Am. J. Epidemiol., 105:330-336.

Zaki, A.M., DuPont, H.L., el Alamy, M.A., Arafat, R.R., Amin, K., Awad, M.M., Bassiouni, L., Imam, I.Z., el Malih, G.S., el Marsafie, A., et al. 1986. The detection of enteropathogens in acute diarrhea in a family cohort population in rural Egypt. American Journal of Tropical Medicine & Hygiene, 35(5):1013-22.