Cryptosporidium in Tap Water
Comparison of Predicted Risks with Observed Levels of Disease

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Waterborne transmission of Cryptosporidium parvum is well-established as a source in outbreaks of cryptosporidiosis; however, the role of tap water in endemic disease is unclear. The authors applied a risk assessment approach incorporating uncertainty analysis to examine the potential role of tap water in the transmission of endemic C. parvum infection. The model had two components: exposure-infection, to relate low-dose exposure to infection; and infection-outcome, to include the probabilities of clinical outcomes leading to case detection and reporting. The population was divided into four subgroups: adults and children with and without acquired immunodeficiency syndrome (AIDS). Because of the high degree of uncertainty associated with available measures, a plausible baseline concentration of oocysts, 1 per 1,000 liters, was assumed for input to the model. In the non-AIDS subgroups, the predicted median annual risk of infection was approximately 1 in 1,000 (non-AIDS adults: 0.0009 infection/person/year, 95% confidence interval (CI) 0.0003–0.0028), while in the AIDS subgroups the predicted risk was 2 in 1,000 (AIDS adults: 0.0019 infection/person/year, 95% CI 0.0003–0.0130). When the risks were applied to the 1995 New York City population, more than 6,000 infections were estimated, with 99% occurring in the non-AIDS categories. Estimates of the overall probabilities that an infection would result in a reported case predicted that three reported illnesses would occur out of every 10,000 infections in non-AIDS adults (95% CI 5 x 10^{-5} to 2 x 10^{-3}), with a 10-fold higher probability in the non-AIDS pediatric subgroup. In contrast, the majority of infections occurring in the AIDS subgroup were predicted to result in reported cases (AIDS adults: probability = 0.61, 95% CI 0.39–0.80). When the model was applied to the New York City population, the calculated number of tap-water-related cases per year in the non-AIDS subgroups was six (95% CI 1–29), and in the AIDS subgroups it was 34 (95% CI 6–240).


acquired immunodeficiency syndrome; cryptosporidiosis; Cryptosporidium parvum; diarrhea; risk assessment; water; water microbiology

The role of tap water in the transmission of microbial illness exclusive of outbreaks is unclear. Substantial concern persists that low levels of pathogen occurrence may be responsible for the transmission of background (endemic) levels of enteric disease (1, 2). Cryptosporidium is a prime candidate for worrisome levels of endemic transmission, because it is ubiquitous in surface waters and is extremely resistant to various environmental pressures, including chemical disinfection; few, if any, barriers to its passage exist in water supplies, and none of the barriers, including filtration, can be considered fail-safe (3, 4). Epidemiologic evaluations of the contribution of tap water to cryptosporidiosis in the endemic setting are not yet available. Therefore, a risk assessment approach (5)—i.e., an approach predicting endemic disease rates as a function of the concentration of Cryptosporidium in drinking water supplies—may contribute to our understanding of the significance of the water route and to the formulation of strategies for public-health protection.

Cryptosporidium is an intracellular parasite that infects intestinal epithelial cells (6). Transmission occurs when infectious Cryptosporidium oocysts shed in the feces of an infected host are ingested by a new host (6). Every oocyst contains four sporozoites, each of which can invade a host cell and initiate an infection (6). Among the recognized species of Cryptosporidium, only one, C. parvum, infects humans (6). Surveys of limited US population samples have found
Not all infections with *C. parvum* produce symptoms (9). Symptomatic infections are marked by diarrhea that is often watery and profuse but self-limiting in immunocompetent persons, while in persons with acquired immunodeficiency syndrome (AIDS), cryptosporidial diarrhea is often severe, persistent, and profoundly debilitating (10). There is currently no effective drug treatment for cryptosporidiosis, and infection may be life-threatening in persons with AIDS (10–12).

Transmission of *C. parvum* occurs by various permutations of the fecal-oral route and has been shown to involve drinking water, recreational water, and foodborne, person-to-person, and animal-to-person exposures or contacts (4, 13). Some studies have suggested that the contribution of sexual practices may be important among persons with human immunodeficiency virus (HIV) infection, but the majority of cases are left unexplained (14, 15). Although reactivation of latent infections due to declining CD4+ T lymphocyte (CD4) counts might play a role in the appearance of cryptosporidiosis (10), waterborne outbreaks have indicated the significance of recent exposures in the acquisition and expression of cryptosporidiosis in persons with AIDS (11, 16).

It is clear that transmission of *C. parvum* from water supplies may frequently go unrecognized (10, 11, 17). Besides large-scale outbreaks of the type that occurred in Milwaukee, Wisconsin, in 1993 (18), more limited waterborne outbreaks have been documented; the distinction between epidemic and endemic transmission is obscured by the limited capacity to recognize an outbreak (17). For example, the 1994 Clark County, Nevada (Las Vegas) outbreak could easily have escaped detection had a sizable AIDS population and active surveillance system for cryptosporidiosis both not been present (11). A case-control study strongly implicated the water supply in this outbreak, despite its high quality and state-of-the-art treatment. It is also notable that the limited monitoring of the water supply did not detect any *Cryptosporidium* oocysts (11, 19). Similarly, a case-control investigation of a small cryptosporidiosis outbreak in 1991 in South London demonstrated a significant association with tap water ingestion, including a dose-response effect (20). Detection of this outbreak was attributed to the affected population’s having been served by a regional public health laboratory which had the unusual practice of screening all stool samples for *Cryptosporidium*.

The spectrum of clinical responses associated with *C. parvum* infection poses considerable difficulties in the study of this pathogen. We were struck by an observation made by MacKenzie et al. in their investigation of the 1993 Milwaukee outbreak: "[Our] findings suggest that people with diarrhea seek health care infrequently, do so only when the illness is severe or prolonged, and are unlikely to be tested for Cryptosporidium infection" (18, p. 166). We have quantified the probabilities embedded in this statement, in order to relate risk assessment estimates of endemic waterborne *C. parvum* infection to the case counts available from surveillance efforts.

In this paper, we apply a risk assessment approach to examine the potential role of tap water in the transmission of endemic *C. parvum* infection. We evaluate the plausibility of such a role and consider whether the risk assessment results are consistent with available information, assuming a low occurrence of *C. parvum* in drinking water and using population and surveillance data from New York City for 1995.

**MATERIALS AND METHODS**

**Overview of the risk assessment approach**

Figure 1 outlines the framework utilized in this paper to address the following question: What numbers of infections and detected cases are expected to occur in a population exposed to a low concentration of infective *Cryptosporidium* oocysts via its tap water? Given a long-term average concentration, the estimated numbers of infections due to ingestion of tap water will depend on parameters which characterize host–microbe interactions in the exposed population. In this paper, the total population is divided into four main subgroups, as described below. For each subgroup, the annual intake of tap water governs the total exposure occurring via this route. Because we are evaluating low-level exposure, we utilize estimates of the probability that exposure to a single oocyst will lead to a clinical infection (i.e., a dosage of 1 is considered potentially infective). Combining the exposure and dose-response data provides an estimate of the likelihood and number of infections for each subgroup. The probability of enteric illness with symptoms of diarrhea may in turn be estimated. Risk assessments usually stop at or before this point, because it is difficult to go further on the basis of the dose-response data. However, we proceed to derive estimates of additional outcomes leading to the detection and reporting of a case.

The mathematical model derived from the framework has two major endpoints: numbers of infections and numbers of reported cases for each subgroup. The
model presented here is basically multiplicative in nature, except that the total numbers of infections and cases were obtained by summing across the subgroups. The percentages of infections and cases occurring in the subgroups were calculated and were compared with an observed distribution.

Uncertainties in the model were assessed by incorporating ranges and distributions for the input parameters, followed by determination of the uncertainties in the model outputs. Appropriate inputs for each parameter are central tendency estimates for the subgroup in question, along with 95 percent confidence intervals encompassing both uncertainty in the estimate and variability in the measure. A hybrid method, chosen for its relative transparency, was used: direct calculations for the multiplicative components with Monte Carlo analysis—i.e., an analysis of the distribution of predicted results based on the uncertainties of the input parameters—for the overall results (21, 22).

**Exposure–infection model**

The model for relating low-dose exposure to infection is:

\[ I_j = C \times \text{Pop}_j \times Q_j \times r_j, \]

where \( I \) = calculated number of infections per year, \( C \) = relevant \( C. \ parvum \) concentration (number of organisms/liter), \( \text{Pop} \) = population of the exposed subgroup (number of persons), \( j \) = subgroup, \( Q \) = annual tap water intake (liters/year), and \( r \) = single organism infectivity (infection/organism/person).

**Concentration assessment.** For the purposes of this risk assessment, an estimate of the long-term (e.g., annual) average occurrence in tap water of viable \( C. \ parvum \) oocysts which were both infective and pathogenic to humans was required—in other words, the true concentration that is relevant to public health. This concentration has not been reliably measured to date, because of shortcomings in the testing method in general use (fluorescent antibody staining and microscopic analysis of a portion of large-volume filtered water samples (3)). The present analysis evaluated a plausible baseline, or unit, concentration of 1 oocyst per 1,000 liters, because of the large degree of uncertainty associated with this parameter. Measurements reported for drinking water from surface supplies in the United States (23–26) suggest average concentrations of approximately 1 \( C. \) oocyst per 100 or 1,000 liters. A number of problems are associated with relating measured concentrations to a central tendency estimate of the true \( C. \ parvum \) concentration in a given water supply; these problems include: 1) recovery efficiencies which are low (<5–10 percent) and highly variable, 2) a lack of information concerning viability, 3) imperfect specificity of the antibody for \( C. \ parvum \), and 4) detection limits of >1 oocyst per 100 liters (3). Taken together, these factors contribute substantial uncertainty to the central tendency estimate, and are characterized by a >100-fold range in the 95 percent confidence interval (see Appendix). Note that uncertainty in the central tendency estimate...
might be even greater if the stochastic distribution of oocysts in the environment and the timing, number, and size of the samples were fully considered.

**Populations at risk of infection.** A rationale for subdividing the exposed population is suggested from consideration of the Las Vegas outbreak (11). In that waterborne outbreak, most of the detected cases of cryptosporidiosis were identified in persons with AIDS, with the remainder occurring primarily in immunocompetent children. This pattern seemed to reflect: 1) the strong tendency of persons with AIDS to experience severe outcomes following infection, as well as awareness of and testing for the disease among their doctors (11), and, presumably, 2) among persons without AIDS, a tendency for children to be more severely affected and/or more likely to be seen by a doctor than adults. Combining the two classifications results in four subgroups: adult AIDS, pediatric AIDS, adult non-AIDS, and pediatric non-AIDS. Our pediatric groups consisted of children under 13 years of age, which is consistent with the AIDS surveillance definition (27).

Population data for the non-AIDS segments were taken from the 1990 US Census (as cited by the New York City Department of Health (28)), while the 1995 adult and pediatric AIDS populations were estimated from surveillance data collected by the New York City Department of Health (28), with adjustments to account for lags in reporting of diagnoses and incomplete reporting of AIDS deaths. Values used in the model are listed in table 1.

**Tap water intake rates.** Available data on US tap water intakes (29) were adjusted to account for the fraction used in the preparation of hot foods and beverages (30). Because there is evidence that persons with AIDS may exhibit significant avoidance of tap water (11), consistent with published advice from AIDS advocacy organizations, their average intake was estimated to be further reduced relative to that of the non-AIDS population (table 1).

**Dose-response assessment and risk of infection.** Dupont et al. (9) conducted an infectivity experiment with healthy adult volunteers who did not have serologic evidence of prior exposure to C. parvum. Subjects were administered doses ranging from 30 oocysts to one million oocysts. Infection was defined as the detection of oocysts in a subject's feces more than 36 hours postchallenge, and it occurred in 18 of 29 subjects, including one of five at the lowest dose level (9). These dose-response data were used to evaluate the probability that a single oocyst may initiate a detectable infection, referred to here as the infectivity parameter (31). This probability was derived by applying an exponential ("single hit") model, which contains the assumption that each oocyst has an equal and independent probability of initiating infection. The estimate of the single organism infectivity among the subjects was reported as 1:239 (0.0042), with a 95 percent confidence interval of 1:132 to 1:465 (31).

In a population-based risk assessment, three factors influence the appropriateness of utilizing the derived infectivity estimate for different segments of the general population (9, 31). First, data were derived from a single strain of C. parvum. In the absence of information on the infectivity of other C. parvum strains, the tested strain was assumed to be typical with regard to

**TABLE 1. Inputs to the exposure-infection component of a model examining the potential role of tap water in the transmission of endemic Cryptosporidium parvum infection**

<table>
<thead>
<tr>
<th>Parameter* (units)</th>
<th>Adult non-AIDS</th>
<th>Pediatric non-AIDS</th>
<th>Adult AIDS</th>
<th>Pediatric AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tap water intake (liters/year)</td>
<td>214</td>
<td>107-427</td>
<td>2</td>
<td>181</td>
</tr>
<tr>
<td>Infectivity (infection/oocyst/person)</td>
<td>0.0042</td>
<td>0.0017-0.0105</td>
<td>2.5</td>
<td>0.0042</td>
</tr>
<tr>
<td>Tap water intake (liters/year)</td>
<td>6,080</td>
<td>5,530-6,680</td>
<td>1.1</td>
<td>1,240</td>
</tr>
<tr>
<td>Tap water avoidance</td>
<td>0.3</td>
<td>0.1-0.9</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>Adjusted tap water intake (liters/year)</td>
<td>150</td>
<td>41-549</td>
<td>2.5</td>
<td>126</td>
</tr>
<tr>
<td>Infectivity multiplier</td>
<td>3</td>
<td>1-9</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Adjusted infectivity (infection/oocyst/person)</td>
<td>0.0126</td>
<td>0.0030-0.0526</td>
<td>4.2</td>
<td>0.0126</td>
</tr>
</tbody>
</table>

* A lognormal data distribution is assumed for each parameter.
† For a lognormally distributed variable X (21), the standard deviation, σ, is related to the dispersion factor, k, by the expression σ = ln(k)/1.96; k indicates deviation about the median, M, as Prob[M/k < X < kM] = 0.95; the range of the 95% confidence interval can be characterized by the ratio of its upper and lower limits, or k2; and for Y = X1X2...Xn, generally, kY = exp{ln[M(k1)] + ln[M(k2)] + ln[M(kn)] + ...}.
‡ AIDS, acquired Immunodeficiency syndrome.
the reported central tendency estimate, although a somewhat wider confidence interval was assigned. The two remaining factors are host-related: Study subjects were healthy adults, and study candidates who were seropositive for Cryptosporidium were excluded. For the non-AIDS population, it was assumed that persons who might be more susceptible than the volunteers were balanced by persons who might be less susceptible for reasons such as partial immunity from prior exposure. For the pediatric group, we assumed that the infectivity was the same as that in the adult group. While susceptibility might be higher in children than in adults, age-specific attack rates during the Milwaukee outbreak were actually lower in the youngest age classes (18); this could reflect similar susceptibility to infection but lower tap water consumption.

Because the detection of an infection in the volunteer study depended on stool analysis, which requires relatively high densities of the parasite (approximately 5,000 oocysts per gram of feces (32)), it is likely that not all colonizations were detected in the healthy adults. Since persons with AIDS tend not to clear the parasite while severe immunosuppression is present, colonization may be more likely to be followed by infection and illness (33). Support for a ≤10-fold greater infectivity among persons with AIDS comes from calculations based on the Las Vegas outbreak utilizing approximate values for the detection limit of water monitoring, the duration of the outbreak, and disease rates among persons with and without AIDS (11, 19) (calculations not shown). Cryptosporidiosis in persons with HIV infection is manifested chiefly as a late-stage infection, mainly evident in advanced AIDS (i.e., CD4 cell counts less than 100 cells/μl) (11, 12, 34). Since the infectivity is likely to increase as the CD4 count of the host declines, from perhaps the general population risk at CD4 counts above 200 to a five- or 10-fold higher infectivity at counts below 100 or 50, we used an approximate central tendency value of threefold higher infectivity (0.0126) for persons with AIDS. Values are summarized in table 1.

The infection–outcome model

Since definite diagnosis of C. parvum infection requires stool testing, only those infections resulting in illness and physician contact can come to the attention of the appropriate health agency. Testing for Cryptosporidium is done primarily at the request of physicians (35), with the result that most requests come from physicians who are treating patients with AIDS (11, 36). Diagnostic evaluation of patients with acute enteric illness is not always indicated, because most cases resolve spontaneously, requiring, at most, supportive therapy (37). Ova and parasite testing is recommended when warranted by clinical suspicion and/or when the illness is prolonged, unresponsive, or medically important (e.g., an immunocompromised host or a case with severe volume depletion, bleeding, high fever, etc.) (37, 38).

The sequence of events leading from infection to case reporting has been described elsewhere (17). We modified and refined this sequence for Cryptosporidium infection and cast these events as a series of conditional probabilities, in such a way that intermediate outcomes of interest could also be examined. The model that was used to relate the estimated infections to the estimated number of reported cases is:

\[ R_j = I_j \times p(R|I_j) = I_j \times pD_j \times pM_j \times pV_j \times pO_j \times pC_j \times pR_j, \]

where \( R = \) calculated number of reported cases per year, \( I = \) calculated number of infections per year, \( j = \) subgroup, \( p(R|I) = p(\text{case detection and reporting}|\text{infection}), \) \( pD = p(D|I) = p(\text{diarrheal illness}|\text{infection}), \) \( pM = p(M|D) = p(\text{moderate-severe illness}|D), \) \( pV = p(V|M) = p(\text{physician visit}|M), \) \( pO = p(O|V) = p(\text{ova and parasite examination}|V), \) \( pC = p(C|O) = p(\text{Cryptosporidium test}|O), \) and \( pR = p(R|C) = p(\text{case detection and reporting}|C). \)

Explanations of each of the component probabilities are presented below, along with quantitative estimates and 95 percent confidence intervals (21, 39) (summarized in table 2).

\( p(\text{diarrhea}|\text{infection}), \) \( pD. \) Infection with Cryptosporidium may frequently be asymptomatic (6, 40). The volunteer study provided an estimate which may be applicable to the general adult population. Although it had a small sample size, this was the only study performed in an experimental setting. Of the 18 experimentally infected subjects, seven (39 percent) were completely asymptomatic, four (22 percent) had enteric symptoms without diarrhea, and seven (39 percent) had diarrhea with or without other symptoms (9, 41); the development of symptoms was not correlated with dosage (31). A probability of 0.7 (95 percent confidence interval (CI) 0.35–1.00) was estimated for the non-AIDS pediatric-population, midway between the value of 0.4 (95 percent CI 0.20–0.80) applied to adults and the probability of 1.0 that might be expected for a first infection occurring in an infant. Reports of asymptomatic infections in persons with AIDS have been published, but it is not clear that those cases never experienced attributable diarrhea (42). For the AIDS population, both pediatric and adult, a probability of 0.95 (95 percent CI 0.80–1.00) was applied.

\( p(\text{moderate-severe illness}|\text{diarrhea}), \) \( pM. \) Morbidity in the moderate-severe range is defined as diarrheal
illness (with or without other symptoms) that has resulted in severe impairment (e.g., debilitation and/or dehydration) or moderate-severe impairment which is not improving after about 1 week. In the volunteer study, of the seven diarrheal subjects, three shed oocysts for 7 or more days, but the maximum duration of clinical diarrhea was only 4 days, and none of the illnesses were characterized as severe (9, 41). A community survey performed during the Milwaukee outbreak showed that the duration of watery diarrhea ranged from 1 day to 38 days, with a median of 3 days among adults who experienced this symptom (18). An estimate of $p_M$ of 0.15 (95 percent CI 0.08–0.30) was made on the basis of this information. For the pediatric population, it was assumed that the likelihood of moderate-severe morbidity will be about one third higher than that in adults, or 0.2 (95 percent CI 0.10–0.30). This is supported by findings which have shown a greater susceptibility to more severe illness among neonatal and very young subjects (6, 43). For the adult and pediatric AIDS populations, we considered observations that *Cryptosporidium* infections occurring in persons with CD4 counts below 180 cells/µl are generally not self-limiting (44). A value of 0.95 (95 percent CI 0.80–1.00) was selected for $p_M$ in this population, which is consistent with observations that most *Cryptosporidium* infections in persons with AIDS are severe and/or chronic.

$p(\text{physician visit}|\text{moderate-severe illness}), p_V$. Given the presence of moderate-severe gastrointestinal symptoms, we are interested here in the probability that the condition will receive medical attention from a physician. Other physician contacts may occur, since people with less severe cases may seek care and telephone contacts may occur as well, but these other instances are unlikely to result in an ova and parasite examination. Physician contact for diarrhea is likely to be influenced by factors reflecting illness severity, access to care, and other personal factors such as tendencies or biases toward seeking physician care.

For example, it has been shown that among populations meeting clinical definitions of chronic irritable bowel syndrome, less than half reported ever having seen a physician for the condition (45). An additional consideration which may decrease the tendency to seek and receive in-person care, even among those with moderate-severe *Cryptosporidium* infection, are the frequent absences of systemic illness, fever, and abdominal pain (18, 46). For the adult non-AIDS population, $p_V$ was estimated to be one third (probability = 0.33, 95 percent CI 0.17–0.66). It was estimated that children are approximately 50 percent more likely than adults to visit a physician as a result of moderate-severe enteric infection; this provides a 0.5 probability (95 percent CI 0.25–0.75). For the adult and pediatric AIDS subgroups, respectively, probabilities of 0.9 (95 percent CI 0.80–1.00) and 0.95 (95 percent CI 0.70–1.00) were selected, because AIDS patients are generally under a regular and frequent schedule of care and the diarrheal symptoms are likely to be prolonged and therefore present when a visit occurs.

Given that a diarrheal illness has occurred, the combined probabilities of moderate-severe illness ($p_M$) and physician visits ($p_V$) provide the following summary probabilities for visits to a physician in the non-AIDS subgroups: 5 percent for adults and 10 percent for children. These figures are in accord with other available estimates. In Milwaukee, 6.5 percent of adults in the general population who had experienced watery diarrhea reported visiting a physician (18). A study of diarrheal illness in children under 5 years of age estimated that approximately 9 percent of episodes resulted in physician contact (47). Lastly, it has been estimated that physician contacts are sought in 8 percent of acute cases of infectious intestinal disease in the United States (48).

$p(\text{ova and parasite examination}|\text{physician visit}), p_O$. The next event in the sequence is the ordering and submission of a stool sample for an ova and parasite examination.
examination, which may or may not include testing for Cryptosporidium, as described below. The probability of this occurring (\(p_O\)), given that a patient with moderate-severe diarrheal illness is seen by a physician, might be expected to be somewhat high, since the preceding series of events was constructed in such a way that it might be reasonable for a physician to request ova and parasite testing. Decreasing the likelihood that an ova and parasite test will be ordered are the possibilities that: 1) a supportive approach might be taken, with subsequent improvement; 2) other testing would be done first, with subsequent improvement; 3) there would be no unusual circumstances (e.g., foreign travel, camping, etc.) which might arouse clinical suspicion of parasitic infection; and 4) there might be questions regarding the cost-effectiveness and value of stool testing (49). In addition, even if a physician orders an ova and parasite test, ambulatory patients may not submit the requested samples or may do so in an inappropriate or untimely manner.

For the non-AIDS adult group, we estimated that one fourth (0.25, 95 percent CI 0.10–0.63) would have ova and parasite examinations performed. A probability of 0.50 (95 percent CI 0.20–0.75) was selected for the non-AIDS pediatric group, because children may receive a more aggressive diagnostic approach (50), and also because suspicion of parasitic infection may be aroused coincidentally in young patients receiving day care, this being a widely recognized setting for parasite transmission (40, 50). In persons with HIV infection, aggressive testing for an etiologic agent of chronic diarrhea has been described and recommended (37, 51, 52); probabilities of 0.9 (95 percent CI 0.80–1.00) and 0.95 (95 percent CI 0.70–1.00) were selected for the adult and pediatric AIDS subgroups, respectively.

\(p(Cryptosporidium \text{ test(ova and parasite examination)}, p_C)\). Testing for Cryptosporidium as part of the ova and parasite examination may be expected to depend primarily on physician and patient characteristics, diagnostic laboratory policies, and state/local requirements. The primary benefit of diagnosis from the clinical perspective may be the exclusion of other causes, since no drug therapies for Cryptosporidium have proven effective (35). Awareness among physicians of the symptoms of cryptosporidiosis is not universal, and many physicians may mistakenly assume that Cryptosporidium testing is a routine component of the ova and parasite examination (36). Evidence strongly suggests that it is likely that in the majority of ova and parasite examinations conducted for patients who are not HIV-positive, Cryptosporidium testing will not be requested.

In the United States, only 5 percent of laboratories performing ova and parasite examinations routinely screen for Cryptosporidium (35). An additional 7 percent of surveyed laboratories cited liquid stool specimens as an indication for their performing Cryptosporidium screening (35). There have also been general recommendations that children be targeted for Cryptosporidium screening (6, 20). Probabilities of 0.1 (95 percent CI 0.05–0.20) and 0.15 (95 percent CI 0.08–0.30) were selected for the non-AIDS adult and pediatric cases, respectively. In persons with AIDS, a probability of 0.95 (95 percent CI 0.80–1.00) was selected for Cryptosporidium testing, because most physicians treating AIDS patients are aware of cryptosporidiosis as an opportunistic disease affecting the medical management of these patients.

\(p(\text{case detection and reporting}|\text{Cryptosporidium test}), p_R\). The likelihood that a cryptosporidiosis case will be diagnosed and reported to the appropriate health authority subsequent to a stool examination for Cryptosporidium depends on the sensitivity of the testing and the effectiveness of the reporting system. The overall sensitivity of testing will be affected by the number of examinations performed, the intermittence, duration, and intensity of oocyst shedding, and the laboratory's diagnostic sensitivity and proficiency. The volunteer study demonstrated that for the seven infected subjects with diarrheal illness, the median percentage of positive stools found during illness was 62.5 percent (41). In comparison with this research setting, most clinical laboratories use a less sensitive detection technique (35), and they may also be more time-constrained or less proficient. This could be offset by instances in which multiple samples are submitted (as per the general recommendation that up to three tests be performed if parasites are strongly suspected). The presence of an active surveillance system that is essentially 100 percent effective in soliciting case reports was assumed. Therefore, a value of 0.6 (95 percent CI 0.40–0.80) was assigned to \(p_R\) for the non-AIDS populations. For persons with AIDS, there is an increased likelihood that repeat samples will be submitted and that oocyst shedding will be heavy and persistent; a study showed that nearly 100 percent of AIDS-related infections were detected with one or two samples (53). For both AIDS groups, we ascribed probabilities of 0.95 (95 percent CI 0.80–1.00) to \(p_R\).

**Observed disease levels**

At this time, the only data on the incidence of endemic C. parvum infection in the United States come from states where cryptosporidiosis is a reportable disease or from AIDS surveillance programs. Surveillance generally relies on reporting from laboratories that perform stool examinations and/or from
health care providers (17). New York City was one of the first public health authorities in the United States to mandate reporting of cryptosporidiosis (54, 55). Under the auspices of the New York City Department of Health, active laboratory-based surveillance for cryptosporidiosis has occurred since November 1994. Basic demographic data are ascertained from laboratory and physician records, and are supplemented by case-patient interviews. While no outbreaks have been recognized, approximately 35–40 new cases were identified monthly during the first 2 years of the program (54, 55), mostly in persons with HIV infection (56). Among persons with AIDS, rates of cryptosporidiosis in New York City have generally been similar to national rates (28).

Chronic cryptosporidiosis of greater than 1 month’s duration is an AIDS-defining condition (27). The current surveillance definition of AIDS includes HIV infection plus a CD4 count lower than 200 cells/μl or the diagnosis of a specific opportunistic infection (27). Therefore, it is likely that most HIV-positive persons diagnosed with cryptosporidiosis meet the surveillance definition for an AIDS case. A partial summary of data for 1995 is presented in table 3.

TABLE 3. Approximated results of cryptosporidiosis surveillance, by AIDS* status and age group, New York City, 1995†

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Non-AIDS-related</th>
<th>AIDS-related</th>
<th>All data combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td>No. of cases</td>
<td>%</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Adult</td>
<td>40</td>
<td>9</td>
<td>390</td>
</tr>
<tr>
<td>Pediatric</td>
<td>30</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>All ages</td>
<td>70</td>
<td>15</td>
<td>400</td>
</tr>
</tbody>
</table>

* AIDS, acquired immunodeficiency syndrome.
† These data were estimated from 1) the reported proportions of cases occurring in persons with human immunodeficiency virus infection in the age classes <20 and ≥20 years (25% and ≥91%, respectively) (56), with the assumption that most cases with human immunodeficiency virus infection meet the AIDS case definition, cryptosporidiosis being an AIDS-defining condition (27); and 2) the reported proportions of cases occurring in the age groups 0–9 years and 10–19 years, linearly apportioned to ages 10–12 years (54, 55).

TABLE 4. Predicted annual risks and numbers of Cryptosporidium infections from consumption of tap water with a unit concentration of oocysts (0.001 oocysts/liter) in non-AIDS* and AIDS subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Central tendency</th>
<th>95% confidence interval</th>
<th>Dispersion factor (k)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult non-AIDS</td>
<td>0.0009</td>
<td>0.0003–0.0028</td>
<td>3.2</td>
</tr>
<tr>
<td>Pediatric non-AIDS</td>
<td>0.0008</td>
<td>0.0002–0.0024</td>
<td>3.2</td>
</tr>
<tr>
<td>Adult AIDS</td>
<td>0.0019</td>
<td>0.0003–0.0130</td>
<td>6.9</td>
</tr>
<tr>
<td>Pediatric AIDS</td>
<td>0.0016</td>
<td>0.0002–0.0110</td>
<td>6.9</td>
</tr>
</tbody>
</table>

* AIDS, acquired immunodeficiency syndrome.
† New York City, 1995.

RESULTS

Table 4 summarizes the output from the exposure-infection component of the model. Estimates of the annual risk of infection to individuals from exposure to C. parvum via tap water are presented for each of the four subgroups in the upper part of table 4. In the non-AIDS subgroup, the median annual risk of infection is close to 1 in 1,000 at the unit concentration; risks associated with other concentrations can be calculated by multiplying by the ratio of the concentration of interest and the unit concentration. Infection risks for the AIDS subgroups are approximately double those in the respective non-AIDS subgroups, reflecting the assumptions regarding relative tap water avoidance and increased susceptibility to infection. Wider confidence intervals in the estimates for the AIDS subgroups follow from the increased uncertainties associated with these assumptions. At the lower end of the confidence intervals, risks are similar across the subgroups. At the upper end, the AIDS estimates are equivalent to approximately a 1 percent annual risk, a level which approaches available estimates of the incidence of cryptosporidiosis in this group (10, 15). The fact that low risks affecting large populations can result in moderate impacts is also illustrated (lower part of table 4); more than 6,000 infections are estimated if the risks associated with the unit concentration are applied to the New York City population, with approximately 99 percent occurring in the non-AIDS categories.

Estimates of the overall probabilities that an infection will result in a reported case demonstrate the expected divergence between the non-AIDS and AIDS subgroups (table 5). Only about three reported ill-
nesses out of 10,000 infections occurring in non-AIDS adults are predicted (95 percent CI 5.4 X 10⁻⁵ to 1.6 X 10⁻³). In comparison, for the pediatric non-AIDS subgroup, the overall effect of the moderately higher estimates of the component probabilities is an approximately 10-fold higher estimate of the probability of a case report. Uncertainties in these estimates for the non-AIDS subgroups are substantial, as reflected in the ranges of the confidence intervals (two orders of magnitude). However, the estimates appear reasonable when compared with information from outbreak situations.

In contrast to the results for the non-AIDS subgroups, the analysis predicts that the majority of infections occurring in persons with AIDS are likely to result in case reports, with the confidence intervals encompassing a plausible range of estimates (e.g., for adults with AIDS, the 95 percent CI is 0.39–0.80).

The overall results combining the exposure–infection and infection–outcome components are presented in tables 6 and 7, which summarize the numbers and proportions of tap water-related cases per year, by age class and AIDS status, that are estimated to occur in the sample (New York City) population following exposure at the unit concentration.

In comparing the model output (tables 6 and 7) with surveillance data for cryptosporidiosis in the sample population (table 3), we must recognize that we do not know what the actual amount of infective C. parvum in tap water was, nor do we know the fraction of endemic cases which are actually due to tap water consumption. In terms of magnitude, the central tendency estimates corresponding to the unit concentration for the overall population and its components are approximately 5–10 percent of the surveillance figures; the confidence interval for the total number of predicted cases represents ~2 percent–50 percent of the total number of cases detected by cryptosporidiosis surveillance in 1995. A comparison of the predicted proportions of cases by age and AIDS status (table 7) shows that the model estimates are quite similar to the surveillance data. These patterns are dominated by the high proportion of cases occurring in adults with AIDS, which was close to 85 percent for both the model and the surveillance data. This prediction depends on the actual population of persons in this category, and in the model this figure is most sensitive to the assumption regarding the relative susceptibility of persons with AIDS to infection.

Reviewing the uncertainties in the model, as indicated by the dispersion factors (k) in tables 4–7, it is apparent that much of the uncertainty in the AIDS subgroups is contributed by the exposure–infection component (table 4), while for the non-AIDS subgroups more uncertainty is contributed by the infection–outcome component (table 5). However, the overall uncertainties (tables 6 and 7) are similar for the different subgroups, with approximate 50- to 60-fold ranges in the confidence intervals (obtained from k²) for all four subgroups. At present, these uncertainties are overshadowed by the large degree of uncertainty associated with the concentration parameter, which was described above as taking at least a 100-fold range over its 95 percent confidence interval.

**DISCUSSION**

In this paper, we used a risk assessment model to examine the potential role of tap water in the transmission of endemic C. parvum infection. The present study differed from previous approaches in two fundamental ways: 1) the exposed population was divided according to AIDS status and age, and 2) the probabilities of numerous outcomes along the entire spectrum from infection to case reporting were quantified. The model output was generally reconcilable with available data. Previous risk assessments of Cryptosporidium in drinking water reported mixed results when attempting to compare predicted risks with observed disease rates, reflecting, in part, difficulties associated with interpreting infection as an endpoint.

**TABLE 6. Numbers of tap-water-related cases of cryptosporidiosis per year, by AIDS* status and age group, in New York City in 1995†, as calculated by the model at the unit concentration (0.001 oocysts/liter)**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Non-AIDS</th>
<th>AIDS</th>
<th>All data combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Central tendency</td>
<td>95% confidence interval</td>
<td>Dispersion factor (k)</td>
</tr>
<tr>
<td>Adult</td>
<td>2</td>
<td>0–13</td>
<td>7.9</td>
</tr>
<tr>
<td>Pediatric</td>
<td>3</td>
<td>0–23</td>
<td>7.9</td>
</tr>
<tr>
<td>All ages</td>
<td>6</td>
<td>1–29</td>
<td></td>
</tr>
</tbody>
</table>

* AIDS, acquired immunodeficiency syndrome.
† Numbers of cases for all categories were obtained from the distribution of results of Monte Carlo simulations (n ≥ 6,000); numbers for all ages and/or combined AIDS status groups are not equivalent to marginal totals.
TABLE 7. Calculated proportions of tap-water-related cases of cryptosporidiosis per year in the overall model, by AIDS* status and age group, New York City, 1995†

<table>
<thead>
<tr>
<th>Age group</th>
<th>Non-AIDS</th>
<th></th>
<th></th>
<th>AIDS</th>
<th></th>
<th></th>
<th>All data combined</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proportion (%)</td>
<td>95% confidence interval</td>
<td>Proportion (%)</td>
<td>95% confidence interval</td>
<td>Proportion (%)</td>
<td>95% confidence interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>4</td>
<td>0–35</td>
<td></td>
<td>85</td>
<td>29–98</td>
<td></td>
<td>90</td>
<td>40–99</td>
<td></td>
</tr>
<tr>
<td>Pediatric</td>
<td>8</td>
<td>0–53</td>
<td></td>
<td>2</td>
<td>0–20</td>
<td></td>
<td>10</td>
<td>1–60</td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>12</td>
<td>1–66</td>
<td></td>
<td>88</td>
<td>34–99</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* AIDS, acquired immunodeficiency syndrome.
† Numbers of cases were calculated at the unit concentration (0.001 oocysts/liter). Proportions were based on average numbers of cases occurring in each category, with confidence intervals based on the distribution of results.

(57, 58). The approach taken in this paper, particularly the characterization of host susceptibility and the consideration of the spectrum of clinical manifestations, represents changes in the traditional chemical risk assessment paradigm which are desirable in the assessment of risks from pathogens (5).

The analysis was consistent with and lends support to the premise that low-level transmission via tap water can represent an important exposure route for endemic *Cryptosporidium* infection, even at very low levels of the pathogen in drinking water. Secondary transmission was not incorporated into our model, since it has not been shown to play a large role in outbreaks, but it could increase the importance of low-level endemic transmission. There is a clear need for improved epidemiologic investigations of the role of tap water relative to other exposures, especially for persons with AIDS (3).

Although the uncertainties inherent in our risk assessment are substantial, it was shown that the uncertainty contributed by the concentration parameter remains dominant; this finding was consistent with other risk assessments for waterborne pathogens (22, 58, 59). The model was evaluated at a unit concentration, the magnitude of which is consistent with but not equivalent to data derived from *Cryptosporidium* monitoring performed to date in the United States. The application of new monitoring technologies is likely to provide improved characterizations of the relevant concentration, reducing the uncertainty inherent in a risk assessment of this type.

The analysis presented here offers a further demonstration of the manner in which the disciplines of risk assessment and epidemiology may inform one another (22). The model presented in this paper made extensive use of descriptive epidemiologic data. Risk assessment cannot by itself demonstrate cause and effect, but it may provide support to epidemiologic efforts in evaluating plausibility and helping to formulate relevant questions, as well as assisting in the design of epidemiologic investigations. For example, the model demonstrated how surveillance for detected cases of a reportable illness may substantially underestimate rates of infection and morbidity. As has been noted, investigations of the incidence of *Cryptosporidium* infection (or other enteric infections with a wide spectrum of clinical manifestations) may usefully focus on serologic evidence of exposure and infection (3).

Since there are no treatments for cryptosporidiosis, reduction of exposure is crucial for those persons most susceptible to severe outcomes following infection. The analysis presented here supports recommendations for clear general advisories to immunocompromised persons regarding the avoidance of unboiled tap water (4).

The relative susceptibility of persons with AIDS to infection (or to chronic outcomes following infection) may change over time, and we may be witnessing this currently. The number of reported cases of cryptosporidiosis in New York City and throughout the United States generally has dropped since the end of 1996 (60–62). This reduction coincides with significant declines in the rate of death from AIDS (63), which has been attributed to improved combination drug therapies used against HIV (press release ACTG 320, National Institute of Allergy and Infectious Diseases, February 24, 1997). It is possible that there has been a decline in the number of *Cryptosporidium* infections in the AIDS population and/or that outcomes are less severe (e.g., asymptomatic, mild, or self-limiting) in hosts whose immune status is no longer characterized by an inexorable decline. These welcome developments may indicate that some of the assumptions used in our model—such as the use of a community’s AIDS population as a surrogate for the number of persons at risk for severe illness resulting from *Cryptosporidium* infection—would require revision for applicability to the current situation.
Perhaps the most interesting finding of this analysis was the indication that the observed patterns of disease could result from an exposure common to the entire population. This holds true irrespective of whether tap water is a major source. In other words, the higher levels of cryptosporidiosis that have been observed in persons with AIDS do not necessarily require a unique or unusual exposure route. In more general terms, the record of a disproportionate occurrence of a condition in a particular subgroup of the population does not automatically implicate a specific or exclusive exposure.

ACKNOWLEDGMENTS

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REFERENCES


APPENDIX

An evaluation of the uncertainty associated with a central tendency estimate of the true concentration of infective Cryptosporidium parvum derived from monitoring data can be made as follows. Consider the following example, typical of data from published reports for finished surface water that is ready for distribution (23–25): 15 percent of samples had positive findings for Cryptosporidium; the mean concentration for positive samples was 0.033 oocysts/liter; and typical analyzed volumes were approximately 50 liters (i.e., a 0.02 oocysts/liter detection limit).

A nominal mean concentration can be estimated from the pooled results:

\[ C_{\text{nominal}} = 0.15 \times 0.033 = 0.005 \text{ oocysts/liter} \]

The true concentration may be approximated from \( C_{\text{nominal}} \) by taking into account the recovery efficiency of the assay, the fraction of \( C. \text{parvum} \) that is viable, and the fraction of detected organisms which are actually pathogenic:

\[ C_{\text{true}} = C_{\text{nominal}} \times (1/\text{recovery}) \times \text{viability} \times \text{pathsppp} \]

Estimates of these modifying parameters, with lognormal distributions, can be made by considering available information (3, 23–25):
APPENDIX TABLE. Estimates of the modifying parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Central tendency</th>
<th>95% CI*</th>
<th>Dispersion factor†</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECOVERY</td>
<td>0.10</td>
<td>0.02-0.50</td>
<td>5</td>
</tr>
<tr>
<td>VIABILITY</td>
<td>0.10</td>
<td>0.02-0.60</td>
<td>6</td>
</tr>
<tr>
<td>PATHSPP</td>
<td>0.50</td>
<td>0.25-1.00</td>
<td>2</td>
</tr>
</tbody>
</table>

* CI, confidence interval.
† The dispersion factor describes the 95% confidence interval (see table 1 footnotes for details).

$0.10 \times 0.50 = 0.003$ oocysts/liter, with a 95 percent confidence interval of 0.0002–0.03, representing a 150-fold range. Note that the uncertainty in this value was estimated by calculating the overall dispersion factor:

$$k_T = \exp\left[\sqrt{(\ln^2 5 + \ln^2 6 + \ln^2 2)}\right] = 12.3$$

$C_{\text{TRUE}}$ can then be calculated as $0.005 \times (1/0.10) \times (95$ percent confidence interval $\{C_{\text{TRUE}}/k_T$ to $C_{\text{TRUE}} \times k_T\})$. 