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Curr Opin Infect Dis. Author manuscript; available in PMC 2015 June 14.

Published in final edited form as:

Curr Opin Infect Dis. 2012 October ; 25(5): 555–563. doi:10.1097/QCO.0b013e328357e569.

Burden of disease from Cryptosporidiosis

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Abstract

Purpose of review—The global significance of cryptosporidiosis is widespread and far-reaching. In this review, we present recent data about strain diversity and the burden of disease, along with developments in therapeutic and preventative strategies.

Recent findings—*Cryptosporidium* is an emerging pathogen that disproportionately affects children in developing countries and immunocompromised individuals. Without a diagnostic tool amenable for use in developing countries the burden of infection and its relationship to growth faltering, malnutrition, and diarrheal mortality remain underappreciated. Disease incidence is also increasing in industrialized countries largely as a result of outbreaks in recreational water facilities. Advances in molecular methods, including subtyping analysis, have yielded new insights into the epidemiology of cryptosporidiosis. However, without practical point-of-care diagnostics, an effective treatment for immunocompromised patients, and a promising vaccine candidate, the ability to reduce the burden of disease in the near future is limited. This is compounded by inadequate coverage with antiretroviral therapy in developing countries, the only current means of managing HIV-infected patients with cryptosporidiosis.

Summary—Cryptosporidiosis is one of the most important diarrheal pathogens affecting people worldwide. Effective methods to control and treat cryptosporidiosis among high risk groups present an ongoing problem in need of attention.

Keywords

cryptosporidiosis; review; malnutrition; HIV; diarrhea

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Introduction

Cryptosporidium is an Apicomplexan oocyst-forming protozoan, first recognized as a causative agent of gastroenteritis in 1976 (1). It is one of the most common human enteropathogens worldwide, with young children living in developing countries and persons with HIV/AIDS experiencing more frequent and more severe illness sometimes complicated by malnutrition and long term impairment of physical fitness. Reported cases in industrialized countries are also rising due to the leading role that *Cryptosporidium* plays as a cause of waterborne outbreaks. However, the true global burden of cryptosporidiosis is not known, owing at least in part to the lack of simple, inexpensive diagnostic tools, underappreciation of the frequency and severity of disease in immunocompetent patients, and difficulties quantifying the impact of an infection that causes an acute illness with long term sequelae.

This report reviews recent literature that expands our knowledge of the burden of cryptosporidiosis as a global pathogen, and the new insights provided by an expanding armamentarium of molecular diagnostics. Areas that might be addressed in the future to decrease the morbidity and mortality associated with this infection are discussed.

The Organism

During the last decade, the development of molecular typing techniques such as PCR-RFLP analysis of the small subunit rRNA-gene has distinguished ~20 species of *Cryptosporidium* and shown that *C. hominis* (found mainly in humans) and *C. parvum* (found commonly in humans and bovines) are the major species infecting humans. Occasionally, other species infect people, including *C. meleagridis, C. felis, C. canis, C. andersoni, C. suis,* C. *baylei,* and *C. muris* (2, 3). *C. hominis* and *C. parvum* can be subtyped by sequencing the 60 kDA glycoprotein (gp60, also called gp40/15), a surface antigen involved in parasite attachment and invasion (4). Sequence differences in the non-repeat regions are used to distinguish subtype families (designated Ia, Ib, etc. for *C. hominis* and IIa, IIb, etc. for *C. parvum*). Within each family, subtypes are based on the number of trinucleotide tandem repeats at the 5’ (gp40) end of the gene. Subtypes Ib, IIa, IIc, and IId are among those most commonly observed in humans (5). Greater genetic diversity is seen in developing countries, particularly in rural settings (6), and distinct populations can arise because of geographic segregation (7–11). Subtyping provides useful information regarding source of transmission (e.g., zoonotic versus anthroponotic); however, the correlation between subtype and clinical manifestations and the existence of homotypic and heterotypic subtype immunity are among the issues that require further exploration (4).

Epidemiology

Cryptosporidium is associated with diarrheal disease in all regions of the world with the exception of Antartica, but is most common in less developed countries (12). The distribution of *C. hominis* and *C. parvum* in humans varies by geographic region. *C. hominis* tends to predominate in most parts of the world, especially in developing countries, while *C. parvum* is more frequent in the Middle East and both species are common in the Europe (4).

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Cryptosporidium is transmitted primarily by the fecal-oral route either by direct contact with an infected human or animal or indirectly via contaminated food or water. Contamination of crops, other agricultural products, and surface water with feces from cattle and other livestock is another important mechanism of zoonotic transmission. Several intrinsic properties of this parasite help to explain its epidemiologic behavior. For one, oocysts are infectious immediately upon being excreted in feces, are shed in high numbers (up to 109 per stool), and can be passed for as long as 2 months after cessation of diarrhea (13, 14). Secondly, the infectious dose is low, with as few as 9–10 oocysts of certain *C. parvum* and *C. hominis* strains producing symptoms in healthy volunteers (15–17). Third, oocysts can remain infectious in the environment for at least 6 months if kept moist, resist disinfection (including chlorination (18)), and survive in properly chlorinated recreational water venues for >10 days (19). Fourth, the protracted incubation period (average 7 days, range 1–30 days) allows transmission to continue for days before an outbreak is recognized by public health authorities (14). Finally, age-related decreases in disease incidence suggest that immunity induced by prior exposure is protective (20); thus, those lacking protective immunity (e.g., children in endemic settings and immunocompromised persons) are most at risk. With this in mind, one can appreciate how *Cryptosporidium* spreads proficiently in settings without adequate sanitation and hygiene in both developed and developing countries (21). A good example of its remarkable transmissibility is a statewide outbreak in the United States during May to December 2007 which involved 5,697 cases and ~450 contaminated recreational water venues. As the outbreak propagated, secondary transmission from ill contacts became increasingly important, eventually outweighing recreational water exposure as a risk factor (19).

In the United States, cryptosporidiosis is widespread geographically, occurs more commonly during the warm, rainy months, and has a bimodal age distribution, with the greatest number of reported cases occurring among children 1–9 year and among adults aged 25–39 years (18). Risk factors associated with sporadic infection include contact with ill persons and cattle, travel abroad (18), and anal intercourse among homosexuals (22). Outbreaks in child care centers are also common, and can result in spread to the community (23).

In developing countries, incidence of disease peaks in young children, who are often infected by the age of two years (12, 24, 25). Exclusive breastfeeding during the first 3 months of life, and partial breast feeding (compared to no breastfeeding) thereafter, appears to afford some protection (26). Peaks usually occur during warm rainy months (27).

Clinical manifestations

A wide spectrum of disease severity is seen, influenced by the age, nutritional, and immune status of the host and possibly by the infecting species and subtype (28). Many infections are asymptomatic or mild and self-limited and often go unrecognized. The cardinal symptom is diarrhea, which is typically watery, and accompanied by abdominal cramps, fatigue, nausea, and anorexia. Fever and vomiting may occur. Diarrhea tends to persist longer (median of 5 to 10 days) than that seen with other etiologies and may relapse. In industrialized countries, most cases are immunocompetent adults who experience a self-limited illness. Among children in developing countries, the diarrhea often lasts for 14 days or longer (29), making

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Cryptosporidium one of the most important causes of persistent diarrhea in this population. Several prospective studies have examined the complex bidirectional relationship between malnutrition and both symptomatic and asymptomatic *Cryptosporidium* infection in infants and children (30–34). Malnutrition is a risk factor for both diarrhea and prolonged diarrhea caused by *Cryptosporidium*, with significantly higher rates of infection in malnourished children controlling for HIV status (34–37). Moreover, cohort studies have demonstrated that a single episode during infancy, even if asymptomatic, can lead to growth faltering that persists for months (32, 33). Long term follow-up also suggests an association with poor physical fitness, as children who had cryptosporidiosis during the first 2 years of life had Harvard Step Test fitness scores that were 10% lower than children who did not, when measured 4–7 years later (38). Given the magnitude of this effect, even in a small study, these results warrant further exploration. Cryptosporidiosis is also an independent risk factor of childhood mortality (33, 35, 39, 40).

In persons with HIV/AIDS, it is not until the CD4 count falls below ~100 cells/ mm3 that the risk increases for severe, unrelenting disease accompanied by malabsorption, weight loss, and high case fatality (5, 41), although asymptomatic or mild infection can occur even in this group (42). Symptoms can be ameliorated and mortality rates diminished with immune reconstitution following antiretroviral therapy (43). In developing countries where most HIV-infected people lack access to antiretroviral therapy, the burden of severe cryptosporididosis remains high (8, 18, 44, 45).

Extra-intestinal manifestations of *Cryptosporidium* infection are seen. Biliary tract disease, including acalculous cholecystitis, pancreatitis, cholangitis, and stricture formation, is a well-documented complication in severely immunocompromised patients and carries a poor prognosis (46). Respiratory cryptosporidiosis has been described, most often in children (47). Infection is often asymptomatic, but may manifest as pulmonary infiltrates and respiratory distress.

Several studies suggest that *C. hominis* produces more severe disease than *C. parvum* (48, 49). Evidence for a possible correlation between subtype and clinical manifestations is accumulating. In a birth cohort of children from Lima, Peru *C. hominis* subtype family Ib was associated with nausea, vomiting and malaise, whereas *C. hominis* subtype family Ia, Id and Ie and the other species were not (28). Risk factors such as hygiene practices, presence of animals and economic variables were not associated with specific genotypes and subtypes. In a case series of nine HIV-infected patients from Italy, the four patients with the most severe disease, all who had a CD4+ T lymphocyte count <50 cells/mm^3, harbored *C. parvum* subtypes within the family IIc (50). Larger studies are needed to validate these observations.

Diagnosis

The diagnosis of cryptosporidiosis is usually made by detection of oocysts, oocyst antigens, or oocyst DNA in stool specimens (Table 1)(51–54), although histologic examination of intestinal biopsies is also possible (12). Recent advances have produced high performing diagnostic tools; however, the expense and requirement for technical expertise have limited

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their use in resource-poor settings. The most commonly used method continues to be microscopic examination of stool (preferably preserved with formalin and concentrated) to detect this small (4–6 μm) coccidion parasite; however, microscopy requires a skilled operator. Identification is enhanced using modified acid fast staining, but the detection limit is only 50,000 to 500,000 cysts per gram of stool (55). Sensitivity of microscopy is further improved by with the use of fluorescent or immunofluorescent stains.

Many clinicians are not aware that superior methods for diagnosing cryptosporidiosis are available (56), such as enzyme immunoassays (EIA). EIA is relatively simple to perform while achieving high levels of sensitivity and specificity (51, 52, 57). Antigen tests that simultaneously detect multiple parasitic enteropathogens with high accuracy have been validated internationally, are moderately simple to perform, and can be tested in batches (58). However, a confirmatory test to distinguish the offending agent may be required. Immunochromatography, which can be performed in minutes, has high specificity, but only moderate sensitivity (52). Extremely sensitive PCR methods are available in reference laboratories and may prove useful for the diagnosis of *Cryptosporidium* infection in the future (59, 60).

Burden of disease in developing countries

The greatest burden of cryptosporidiosis occurs among children living in developing countries. However, the burden is difficult to quantify as estimates vary widely, even among studies from the same geographic region, as a result of differences in study design, sample size, age range, HIV status, severity of disease and sensitivity of diagnostic methods used (5). For example, *Cryptosporidium* was detected by modified acid fast staining of fecal smears in only 2% of children less than five years with diarrhea attending health centers in Accra, Ghana (61), compared with 8.7% of a similar population from Accra using real time PCR of fecal DNA (62). The impact of study design on disease burden estimates was demonstrated in a recent review of studies from sub-Saharan Africa that used health care-seeking behavior as a proxy for more severe illness, and found higher rates of cryptosporidiosis among children recruited in hospital-based studies (14.6–22.2%) compared to community-based studies (7.5–12.5%) (39). Studies of diarrheal disease do not reflect the rate of infection in asymptomatic children, which can be high (27, 63), and negatively impact a child's growth. Figure 1a (6, 40, 62, 64–69) shows the results of recent studies demonstrating the wide, but consistently high prevalence rates of cryptosporidiosis in young children in developing countries seeking hospital care.

Seroprevalence studies have been useful in providing evidence that infection is more widespread than appreciated (70). Seropositive rates of 17–54% were found in the United States, reaching 70% among children living near the Mexican border. Rates were somewhat higher in Southern and Eastern Europe (33–88%) and in some developing countries (64–94%) (71–74). An increased frequency and severity of cryptosporidiosis in AIDS-associated diarrhea among adults and children in developing countries is well-documented (75), although, prevalence estimates vary considerably from study-to-study as with HIV-uninfected populations (76, 77). The burgeoning HIV epidemic in sub-Saharan Africa has

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undoubtedly enhanced the burden. Figure 1b (77–86) depicts recent prevalence estimates of cryptosporidiosis among HIV populations in developing countries.

Valuable information is forthcoming from the Global Enteric Multi-Center Study (GEMS) regarding the attributable burden of a comprehensive panel of enteric pathogens in children under 5 years of age living in developing countries in South Asia and sub-Saharan Africa with moderate to severe diarrhea. Preliminary results using a standard EIA at all sites indicate that *Cryptosporidium* is one of the most important pathogens.

Cryptosporidiosis in Industrialized countries

Although *Cryptosporidium* is an uncommon cause of acute sporadic diarrhea in industrialized countries, it is a leading cause of waterborne outbreaks (87, 88). The 1993 outbreak of cryptosporidiosis in Milwaukee, Wisconsin which affected over 400,000 people using the municipal water supply during a 2 month period is probably the best known example. The cost of outbreak-associated illness was estimated to be over 96 million US dollars (89).

In the United States cryptosporidiosis is a notifiable disease and was implicated in 60 (44.8%) of the 134 recreational water-associated outbreaks reported for 2007–2008, making it the most commonly identified pathogen in this setting (90). About 10,500 cases were reported in 2008, part of an overall increasing trend (18). Similarly, review of all published protozoan outbreaks that occurred worldwide between 2004–2010 showed that *Cryptosporidium* accounted for the majority (60%) of outbreaks, with most reports coming from Australia, North America and Europe (91). Many outbreaks undoubtedly go unrecognized, even in countries with established surveillance, and many sporadic cases actually may be part of an unrecognized outbreak.

With the wide spread availability of antiretroviral therapy in the United States, the incidence of cryptosporidiosis has decreased among people living with HIV/AIDS (44). The increasing number of transplant recipients and those receiving immunosuppressive drugs may contribute significantly to the burden in the future (92, 93).

Treatment

The thiazole compound, nitazoxanide is the only drug FDA approved for the treatment of cryptosporidiosis. Nitazoxanide has been shown to improve both clinical and microbiological cure rates and decrease the duration and severity of symptoms in immunocompetent patients. Diarrhea was resolved in 80% of adults and children within 7 days of being randomized to receive a 3 day course of nitazoxanide compared to only 41% of those randomized to placebo. Elimination of oocysts shedding occurred in 75% of nitazoxanide recipients compared to 20% of those receiving placebo (94). Several other thiazoles have been shown to have *in vitro* activity against *C. parvum* and may serve as candidates for future drug development (95). Conversely, nitazoxanide is ineffective in HIV-infected patients (96), even when high doses and prolonged treatment are used (96). Paromomycin, a nonabsorbable aminoglycoside with some activity against *Cryptosporidium* in immunocompetent people, is also not curative in HIV/ AIDS patients (41). Resolution of

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symptoms relies on restoration of immune status using combination antiretroviral therapy. Combination anti-parasitic and antiretroviral therapy, especially with a protease inhibitor based therapy which seems to have some additional anti-parasitic activity, seems to benefit patients with cryptosporidiosis (41).

Nitazoxanide is used uncommonly in developing countries. In Peru, children receiving empiric nitazoxanide had a shorter duration of diarrhea associated with multiple etiologies compared with those receiving placebo (97). This benefit was also seen in the large group of patients with no identified enteropathogen. No cases of cryptosporidiosis were detected, but diagnosis relied upon stool microscopy, which may have lacked sufficient sensitivity to detect the organism.

Prevention

No effective vaccine is available to prevent cryptosporidiosis. Evidence that vaccination might be an effective preventive strategy comes from observations of age-related declines in infection among children from developing countries (which presumably reflects acquisition of immunity), and human challenge studies showing protection associated with previous exposure (20). Efforts to develop vaccine are limited by insufficient understanding of the immune responses mediating protection. The surface-associated immunodominant antigens (gp15, gp40, p27) present on the invasive stage of the organism is one target of interest (98, 99). Antibody to the p23 antigen is observed in children with cryptosporidiosis compared to those with non-cryptosporidial diarrhea and the *p23* sequence appeared to be relatively conserved among infection species and subtype families, making it another promising vaccine antigen (100). Antigens associated with the intracellular and sexual stages are also of interest and incorporation of multiple antigens into a vaccine may eventually be required (101). A recently developed reproducible model of cryptosporidiosis in weaned mice may provide a useful tool for vaccine development (102). Passive and other novel immunotherapies are also being explored [98,99].

Conclusion

Cryptosporidiosis is one of the most significant enteropathogens worldwide. Advances in molecular epidemiology have improved our knowledge about strain diversity. However, prevention is difficult, given the organism’s high infectivity, robustness, and resistance to disinfection, highlighting the need for improved therapeutics particularly for immunocompromised individuals, and a safe and effective vaccine.

Acknowledgments

Disclosures:

Debbie-Ann Shirley receives research support through the NIH grant 2 T32 AI07524-15.

Karen Kotloff receives research support in part from the Bill and Melinda Gates Foundation and the National Institutes of Health.

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Recommended reading

• of special interest

•• of outstanding interest

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Key points

- *Cryptosporidium* spp. is one of the most common and virulent enteropathogens in humans
- Malnourished children and those living with HIV/ AIDS in developing countries bear the brunt of the burden associated with this disease
- Advances in molecular epidemiology will expand our understanding of the epidemiology of this infection
- Anti-parasitic therapies are ineffective in HIV/ AIDS patients
- Prevention is difficult, given the organism's high infectivity, robustness, and resistance to disinfection highlighting the need for a safe and effective vaccine

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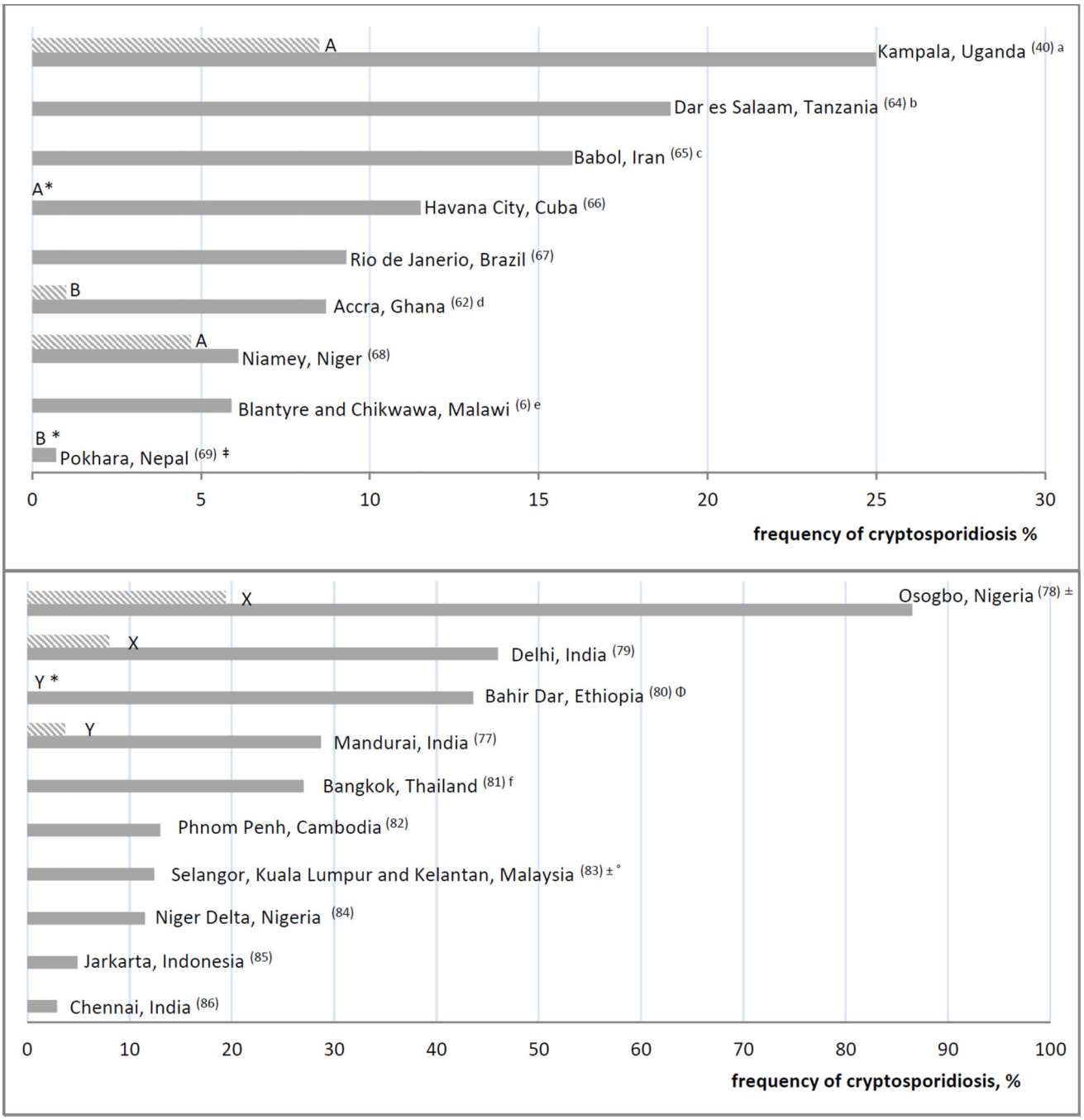

Figure 1.

a: Hospital based cryptosporidiosis prevalence rates among children under 6 years with diarrhea in developing countries**

** HIV status was unknown or unreported in these studies; unless otherwise noted, primary detection of cryptosporidiosis was by microscopy with acid fast staining

[a] Detection by PCR

b: Urban Hospital and HIV clinic based cryptosporidiosis frequency rates among HIV-infected adult patients with diarrhea in developing countries***

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*** Unless otherwise noted, primary detection of cryptosporidiosis was by microscopy with acid fast staining, ± = pediatric patients included, Φ = only 80% of HIV-infected patients in this study had diarrhea, [X] = HIV-infected controls without diarrhea, [Y] = HIV-negative controls, frequency of cryptosporidiosis was 0, [Z] = HIV-negative controls with diarrhea, • Studies above line included controls, IF = immunofluorescent staining, frequency 18.4% with acid fast staining

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Table 1

Sensitivity and specificity of Cryptosporidium assays*

Method	Sensitivity (%)	Specificity (%)	Comments	Ref
Microscopic visualization of oocysts				
AF	37–84	99–100	Least expensive, reagents widely available but insensitive, time consuming.	(51) (52) (53) (54)
FS	92	100	More sensitive and less time consuming than AF, requires fluorescent microscope	(52)
DFA	97	100	More sensitive than EIA and FS but more laborious than EIA, requires fluorescent microscope	(52)
Antigen detection				
EIA	91–94	92–100	Relatively simple to perform, no need for skilled microscopist; some kits also detect *Entamoeba* and/ or *Giardia* so confirmatory tests may be required	(51) (52)
IC	83–85	100	Simple to perform with quick turnaround time but less sensitive than EIA	(52) (54)
Molecular tests				
PCR	100	100	Best performance, can differentiate species, most costly and time consuming	(51) (52) (53) (54)

*Based on studies that either used PCR as the gold standard, or that included PCR as part of the gold standard if the sensitivity and specificity of PCR was 100%

AF = modified acid fast stain, FS = fluorescence stain (auromine phenol), DFA = direct immunofluorescence stain, EIA = enzyme immunoassay, IC = immunochoromatography, PCR = polymerase chain reaction.