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A Survey of U.S. Obstetrician-Gynecologists' Clinical and Epidemiological Knowledge of Cryptosporidiosis in Pregnancy sampled from the American College of Obstetricians and Gynecologists, 2010

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An abstract of

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Abstract

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Background: Although still largely unexplored, studies suggest that pregnancy increases the likelihood and severity of *Cryptosporidium* infection. Although cryptosporidiosis is common in the U.S., there has been very little assessment of obstetrician-gynecologist knowledge about this disease. A divergence between perceived risk and knowledge and estimated annual case load in pregnant patients impacts not only clinical management and preventative strategies but also can illuminate weaknesses of public health surveillance networks.

Goal: The goal of this joint CDC and American College of Obstetricians and Gynecologists *Cryptosporidium* spp. survey analysis is to pinpoint weaknesses of American obstetrician and gynecologists' knowledge of risk factors, diagnosis, treatment, and prevention of cryptosporidiosis in pregnant women.

Methods: In 2010, the American College of Obstetrics and Gynecology (ACOG) and Centers of Disease Control distributed a questionnaire about the diagnosis and treatment of the parasitic disease cryptosporidiosis with 3 mailings to a national sample of 1000 obstetrician-gynecologists and received 431 surveys that met inclusion criteria (43.1% response rate). The questionnaire was developed at ACOG and CDC and pilot tested by ACOG obstetrician-gynecologists. Data were analyzed through multivariate regression models.

Results: Clinically oriented questions had a higher rate of correct responses than epidemiologically oriented questions, though no survey question had higher than a 50% correct response rate and overall provider knowledge about cryptosporidiosis was low. Only 44.4% of providers correctly identified that prolonged, intermittent diarrhea would lead them to consider cryptosporidiosis in a differential diagnosis. Routine ova and parasites (O&P) testing was incorrectly chosen by 30.4% respondents to identify cryptosporidiosis in stool. As for prevention-related knowledge, only 14.1% of respondents identified alcohol-based hand sanitizers as an ineffective tool to inactivate *Cryptosporidium* spp., and less than 10% of physicians knew that cryptosporidiosis is a reportable disease in their state of practice. Mutivariate analysis found that greater than 19 years in practice, correlating to higher physician experience, was positively associated with knowledge of O&P diagnostic testing, while rural practice location, compared to suburban practice location, was significantly associated with knowledge of FDA guidelines for the drug nitazoxanide, as well as knowledge of the correct FDA pharmaceutical pregnancy category for nitazoxanide.

Discussion and Conclusion: The low overall clinical and epidemiological knowledge level of obstetrician-gynecologists about cryptosporidiosis in pregnancy indicates a lack of communication and congruency between current clinical education curricula and the public health system. This analysis found an overwhelming need to educate physicians about all aspects of cryptosporidiosis, particularly treatment guidelines and prevention strategies with short, tailored education tools that pinpoint current weaknesses in diagnosis, treatment, prevention, and reporting to optimize patient care and strengthen national reportable disease surveillance for cryptosporidiosis in pregnancy.

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Review of the Literature

Introduction

Caused by the intestinal protozoan parasite *Cryptosporidium*, cryptosporidiosis is one of largest sources of waterborne diarrhea that occurs each year, both globally and domestically (CDC). Although cryptosporidiosis is well-understood as geographically dispersed and generally problematic, the global burden of *Cryptosporidium* infection remains unascertained, most notably due to the indigenous nature of animal reservoirs, widespread clinical case mismanagement and misdiagnosis, and inadequate, fledgling national and global surveillance systems (CDC, reviewed in Putignani *et al.*, 2010). In developing countries, prevalence estimates range from 3 to 20%, while in developed countries prevalence is estimated at 0.5 to 2.5% in immunocompetent adults and remains undetermined in pregnancy (Arrowood *et al.*, 2008). Chronic under-reporting is exemplified in the United States, with only approximately 7,000 to 11,000 of over 836,000 total estimated cases of cryptosporidiosis reported each year (reviewed in Yoder and Beach, 2010). Due to the high volume of asymptomatic and self-limited disease, the true burden in the United States is unknown (reviewed in Yoder and Beach, 2010).

Although a majority of these infections occur in immune-competent individuals and are asymptomatic or self-limited, *Cryptosporidium* is one of the most highly infectious enteric pathogens identified and can quickly become problematic for high risk patients, such as children aged 1-4 (the patient ages in which cases are most frequently reported) and pregnant women. Although still largely unexplored, it is suggested, and

generally accepted, that pregnancy increases the likelihood and severity of infection (Hoveyda *et al.* 2002). However, a majority of aspects of cryptosporidiosis in pregnancy are poorly understood by American physicians. This influences not only diagnosis and treatment choices but also disease reporting practices and the reliability of public health surveillance networks. This divergence between perceived risk and knowledge and estimated annual case load in patients impacts not only clinical management and preventative medicine but also illuminates weaknesses of public health surveillance networks, particularly for rarely-studied high risk groups such as pregnant women. Therefore, there is a need to assess American obstetricians and gynecologists for their knowledge of *Cryptosporidium* and identify specific knowledge gaps to maximize the ability of physicians to educate patients correctly, minimize misdiagnosis, and manage domestic infections effectively, as well as to identify gaps in surveillance and more effectively understand the magnitude of disease in the U.S.

Brief History

First recognized by Clarke and Tyzzer in 1907, cryptosporidiosis was understood as a solely zoonotic organism that presented clinically primarily as prolonged diarrhea in animals (reviewed in Guerrant, 1997). The first two sporadic human cases were reported in 1976, and only seven more cases were described until 1982, five of which occurred in immunosuppressed patients (reviewed in Guerrant, 1997). In the early 1980s, with the rise of the AIDS epidemic, cryptosporidiosis became recognized as a severely debilitating, widespread pathogen causing cholera-like diarrheal symptoms in immune-compromised AIDS patients (reviewed in Dillingham *et al.*, 2002). In 1994, the

Counsel of State and Territorial Epidemiologists (CSTE) recommended that cryptosporidiosis become a nationally notifiable disease (reviewed in Dietz *et al.*, 2000). In 1995, the first states began to report cases of *Cryptosporidium* infection to the CDC (reviewed in Dietz *et al.*, 2000). In 1996, *Cryptosporidium* was classified as an emerging pathogen by the Centers for Disease Control and Prevention, due to its recognition as an increasing and widespread threat in immune-competent patients in the U.S. (reviewed in Bushen *et al.*, 2006). By the year 2000, forty-seven states had made cryptosporidiosis a reportable disease according to the CSTE recommendations (reviewed in Dietz *et al.*, 2000). Currently, all 50 states require physicians, healthcare providers, and laboratories to report all cases of *Cryptosporidium* infection to the state health department within seven days of diagnosis, who voluntarily report cases of cryptosporidiosis to the CDC through the National Notifiable Diseases Surveillance System (NNDSS) (Yoder and Beach, 2010).

Ecology and Organism

Cryptosporidium is a coccidian, food- and water-borne protozoan parasite whose complete life cycle occurs within a single host (Bushen *et al.*, 2006). Thirteen distinct species of the parasite exist ubiquitously today in the environment, of which five species of the smaller, intestinal *Cryptosporidium* spp. have been shown to infect humans (Bushen *et al.*, 2006). The most common animal reservoirs include reptiles, fish, poultry and other birds, small mammals such as dogs and rodents, and large mammals such as pre-weaned calves, sheep, and goats (Bushen *et al.*, 2006). *Cryptosporidium hominis*, which primarily infects humans, and *Cryptosporidium parvum*, which infects humans

and pre-weaned calves, are transmitted through the fecal-oral route (reviewed in Chen *et al.*, 2002). These two species are the primary epidemiological focus of human illness (reviewed in Bushen *et al.*, 2006). When ingested by the human or animal host, stomach acid activates *C. parvum* and *C. hominis* thick-walled oocycsts to excyst and release infective sporozoites that migrate to the lumen of the small intestine (Chakrabarti and Chakrabarti, 2009). This results in the formation of intracellular, extra-cytoplasmic vacuoles in the surface of microvilli epithelial cells (Chakrabarti and Chakrabarti, 2009). Here, the parasites complete type 1 and type 2 asexual reproduction and infect neighboring epithelial cells in the gastrointestinal tract, causing persistent or severe infection in immune-compromised, first-time, or at-risk hosts (Bushen *et al.*, 2006). Following asexual reproduction, sexual reproduction produces zygotes that form thin-walled auto-infectious oocysts or thick-walled oocysts that are shed in stool (Bushen *et al.*, 2006). These thick-walled oocysts are highly infectious to other hosts in the environment immediately upon excretion (Bushen *et al.*, 2006).

Cryptosporidium oocysts have five unique characteristics that place it among the most problematic emerging enteric pathogens today. First, *Cryptosporidium* oocysts are highly infectious, with mathematical models hypothesizing an infectious dose of as few as 1 to 10 oocysts and outbreak case studies demonstrating a median ingestion of 132 oocysts causing illness (reviewed in Bushen *et al.*, 2006). Additionally, infected immunocompetent patients can excrete 10^8-10^9 oocysts per bowel movement for up to 60 days after diarrheal symptoms cease (reviewed in Yoder and Beach, 2010). Immunocompromised individuals, such as AIDS patients, and children have the potential

to excrete oocysts for even longer time periods (reviewed in Yoder and Beach, 2010). Secondly, the small size and environmental hardiness make cryptosporidial oocysts highly resistant to a majority of conventional water treatment methods (reviewed in Bushen *et al.*, 2006). This includes most filters used in public water purification systems, as demonstrated by the 1993 Milwaukee, Wisconsin municipal water source outbreak that sickened over 403,000 people (reviewed in Jones *et al.*, 2005). Third, *Cryptosporidium* oocysts are highly chlorine tolerant, and can only be inactivated by ozone, freezing, or heating above 38 degrees C (reviewed in Bushen *et al.*, 2006). Fourth, since *Cryptosporidium* oocyst development is completed in a single host, the organism is infectious immediately upon excretion and has high propensity for rapid person-to-person transmission (reviewed in Bushen *et al.*, 2006). Lastly, except for *C. hominis*, most genotypes of *Cryptosporidium* are widely zoonotic and can easily be passed not only within a species but from animals to humans, hindering effective environmental infection control and prevention strategies (reviewed in Bushen *et al.*, 2006).

In the United States, multiple high-risk activities can lead to *Cryptosporidium* infection, though infection occurs relatively sporadically. Most published reports describe cryptosporidiosis as a phenomenon seen in high-risk groups such as travelers, immunocompromised patients, and in waterborne outbreak settings (reviewed in Bushen *et al.*, 2006). Because of the highly publicized waterborne outbreaks of *Cryptosporidium*, the majority of risk is thought to be associated with water-borne sources, such as drinking untreated lake water or swimming in a pool or recreational

water source (Bushen *et al.*, 2006)). Additionally, contact with the most important environmental reservoirs of human disease, particularly pre-weaned calves and sheep, has been identified as a risk behavior (Chen *et al.*, 2002). Risk factors such as consuming unpasteurized apple cider or milk appear to be more context-specific and lead to smaller outbreaks, therefore being less widely recognized in literature. Clinically, close contacts of infected patients have been identified at increased risk for cryptosporidial infection, including household and family contacts, sexual partners, health care workers, and day-care personnel (reviewed in Chen *et al.*, 2002). Most notably, very few publications explicitly state pregnant women as at risk for severe disease (Chen *et al.*, 2002). Due to the endemic natural of disease in the United States, most information about risk behaviors and outcomes is obtained through individual case reports or outbreak summaries (Fayer *et al.*, 2000). Problematically, population-based outcome studies from U.S. water-borne outbreaks have largely focused on morbidity and mortality only in HIV/AIDS individuals, neglecting to study other risk groups such as pregnant women (Hoxie *et al.*, 1997). This indicates a general lack of knowledge about increased susceptibility and effects of cryptosporidiosis in pregnancy and provides further support for needed research in this risk group (Hoxie *et al.*, 1997).

The Centers for Disease Control, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America outlined Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents guidelines to avoid each of the commonly recognized modes of transmission of cryptosporidiosis, as described above (2009). At-risk patients, outlined

here as immunocompromised individuals, are advised to prevent direct contact with infected adults, diaper-aged children, and diarrhea from any infected animals, especially cats and dogs less than six months of age, as well as contaminated water sources during recreational swimming, drinking contaminated water, and eating contaminated food (CDC, 2009). Behaviors to lower risk include hand washing after several activities that increase risk as listed above, plus gardening or having contact with soil, before preparing food and eating, and before and after sex (CDC, 2009). The guidelines warn at-risk individuals that lakes, rivers, salt-water beaches, swimming pools, and recreational water parks could be contaminated with human or animal waste that contains Cryptosporidium (CDC, 2009). Additionally, over the past two decades, outbreaks of cryptosporidiosis have been associated with drinking water, so at-risk individuals are advised to boil all water for a minimum of 3 minutes, as well as using submicron personal-use water filters or bottled water to reduce risk during outbreaks, though some filters are not fine enough to remove oocysts and should be used with caution (CDC, 2009). Insufficient data exists for non-outbreak recommendations, and more data from non-outbreak settings is necessary to understand the general population's risks of infection (Juranek *et al.*, 1995). At-risk populations must pasteurize all fruit juices and dairy products (CDC, 2009). Finally, sources of infection such as farm animals, including pre-weaned calves and sheep and people experiencing diarrhea should be avoided. Alcohol-based hand sanitizers are ineffective in inactivating *Cryptosporidium* oocysts (CDC, 2009). The guidelines briefly note that nitazoxanide is not teratogenic in animal models and may be used in pregnancy after the first trimester in severely symptomatic

patients, but also indicate that no human data of use in pregnancy is available and that treatment should focus on rehydration (CDC, 2009).

Clinical Features of Cryptosporidiosis in Pregnancy

Most infections, particularly in immune-competent individuals, are asymptomatic. When symptomatic, clinical cryptosporidiosis is characterized by self-limited but often acute and persistent and prolonged watery, frequent, voluminous and occasionally explosive diarrhea without the presence of red blood cells or leukocytes (Bushen *et al.*, 2006). Several non-specific signs and symptoms such as abdominal pain and cramping, malaise, and anorexia were are present in more than 80% of patients in recent outbreaks, particularly in the 1993 Milwaukee outbreak, described above, and more than 50% of patients experienced nausea, vomiting, weight loss, chills, sweats, generalized myalgias, headache, and low-grade fever (reviewed Bushen *et al.*, 2006). Some immunosuppressed patients, particularly in the late stages of AIDS, present with right upper quadrant pain, indicative of direct luminal spread of organisms from the duodenum, causing acalculous cholecystitis, schlerosing cholangitis, or pulmonary or pancreatic infection (Chen *et al.*, 2002). However, this non-specific pain may also be indicative of infection from other water-borne protozoan parasites such as *Cyclospora* or *Isospora*, complicating diagnosis (Bushen *et al.*, 2006). The incubation period from ingestion of oocysts to disease manifestation ranges from 2 to 14 days and onset is acute, but also highly dependent on the immune status of the patient (Bushen *et al.*, 2006). In immune-competent patients, symptoms tend to last two to three weeks, but

in immunosuppressed individuals, the clinical course of illness may be prolonged and fulminant, leading to death (Arrowood *et al.*, 2008).

Little literature exists to support whether signs and symptoms are particularly severe in pregnant patients, or if pregnant patients should be categorized similarly to immune suppressed patients with regards to cryptosporidiosis (Hoveyda *et al.* 2002). At least one publication on the occurrence of food- and water-borne disease in vulnerable people recognizes that immune systems of pregnant women are physiologically impaired and require specific infection studies (Lund and O'Brien, 2011). One potential explanation for compromised immunity is the decreased cellular response by the host to certain pathogens caused by hormone changes during pregnancy (Roberts *et al.*, 2001). Though hypothetical at best, mouse models indicate that pregnancy appears to increase susceptibility of mice to protozoan infections that require a Th1 cell response by the host, such as *Cryptosporidium* infection (reviewed in Riggs *et al.*, 2002). Evidence for this hypothesis is strengthened by similar loss of cell-mediated immune response and deficient cytokine IFN-gamma commonly observed in AIDS patients infected with *Cryptosporidium* (reviewed in Bushen *et al.*, 2006). Additionally, Riggs pinpointed the well-established importance of interferon-gamma produced by *C. parvum* antigen-specific CD4+ T cells as a function of cell-mediated immune response and recovery from infection in immunocompetent hosts (reviewed in Riggs, 2002). Both risk groups tend to demonstrate higher disease incidence and severity, though additional research on cryptosporidiosis and pregnancy is necessary to understand the clinical consequences of infection in pregnancy.

Despite the maintenance of a many normal immune functions in pregnancy, the possibly increased risk of severe cryptosporidiosis infection during pregnancy corresponds with documented incidences of increased severity of illness and complications in pregnant patients compared with immunocompetent, non-pregnant patients (Hoveyda *et al.* 2002). Though it is difficult to draw substantiated conclusions from individual case studies, the few published case reports of cryptosporidiosis in pregnancy do suggest that illness can be sufficiently severe to require hospitalization, generally due to dehydration and malabsorption (Hoveyda *et al.* 2002, Jones *et al.*, 2005). Though diarrhea presentation typically occurs without blood in stool, one cryptosporidiosis case report noted a hospitalized pregnant woman presented with a substantial drop in hemoglobin and bloody stools (Hoveyda *et al.* 2002). Similarly, in a recent outbreak of cryptosporidiosis in adults in the UK, one report stated that 12% of patients complained of bloody diarrhea (reviewed in Hoveyda *et al.* 2002). Additionally, adverse effects of prolonged and severe maternal diarrhea on child development may exist, both *in utero* and after birth (Lahdevirta *et al.*, 1987). Severe diarrhea may be a risk factor for premature labor, which can have multiple developmental or immunological consequences for the developing fetus. Also, a case study of a late-gestation pregnant woman presenting with prolonged diarrhea demonstrated a fetal and subsequent neonatal failure to thrive because *Cryptosporidium* oocysts were inadvertently transmitted to a neonate through delivery or later contact between the mother and child (Lahdevirta *et al.*, 1987).

Diagnosis and Treatment of Cryptosporidiosis in Pregnancy

Clinical diagnosis of cryptosporidiosis can be difficult. No obvious environmental exposure is necessary, and no distinct physical examination or laboratory results are generally found (Bushen *et al.*, 2006). When cryptosporidiosis is suspected, conventional detection of cryptosporidiosis requires concentration and differential staining of fecal smears from multiple bowel movements, which is highly time consuming and may lack sensitivity and specificity (reviewed in Fayer *et al.*, 2000). However, microscopical detection of the parasite in fecal smears is considered a definitive diagnosis (Chen *et al.*, 2002). Immunological detection methods are now commonly used in clinical diagnostic laboratories and including polyclonal fluorescent antibody tests, latex agglutination, immunofluorescence with monoclonal antibodies, enzyme-linked immunosorbent assays (ELISA), reverse passive hemagluttination (RPH) tests, and solid-phase qualitative immune-chromatographic assays (reviewed in Fayer *et al.*, 2000). These techniques have sensitivity and specificity that approach 100% for *Cryptosporidium*, particularly in clinical diagnosis. Direct fluorescence antibody assay (DFA) is highly sensitive and specific and considered the “gold standard” by many laboratories (reviewed in Yoder and Beach, 2010). Epidemiologically, cross-reactivity to other microorganisms found in soil and water poses a major problem with this diagnostic test (reviewed in Fayer *et al.*, 2000). Molecular techniques, such as polymerase chain reaction tests, though rapid, highly sensitive, and accurate, have limitations such as high susceptibility to interference from detection of naked nucleic acids, non-viable microorganisms, or lab contamination (reviewed in Fayer *et al.*, 2000). Molecular tests are the only test technique that will provide genotype and subtype

Cryptosporidium results, necessary for molecular surveillance, but these are not routinely used in the United States for *Cryptosporidium* identification (reviewed in Yoder and Beach, 2010). Due to the prevalence of *Cryptosporidium* antibodies in the American population, serological tests are not useful diagnostic tools (Chen *et al.*, 2002). Routine ova and parasite tests do not include *Cryptosporidium* species identification methods without an explicit request for *Cryptosporidium* testing (Chen *et al.*, 2002). This is often not understood by clinicians who attempt to order diagnostic tests for cryptosporidiosis and contributes significantly to the under-diagnosis and under-reporting of *Cryptosporidium* infection in the U.S. (Chen *et al.*, 2002).

To date, no vaccine exists to prevent *Cryptosporidium* infection, and a number of therapeutic agents have been unsuccessfully evaluated for anti-cryptosporidial efficacy (reviewed in Collinet-Adler and Ward, 2010). Nitazoxanide, produced commercially under the trade name Alinia by Romark Laboratories, is a broad-spectrum anti-parasitic that is the only FDA-approved drug available for clinical treatment of *Cryptosporidium* infection (Anderson and Curran, 2007). First approved as an oral suspension by the U.S. Food and Drug Administration in December of 2002 for treatment of diarrhea caused by *Cryptosporidium* species in pediatric patients aged 1-11 years, it has since also been approved to treat cryptosporidiosis in patients over age 12 (Fox and Saravolatz, 2005). Nitazoxanide is a nitrothiazolyl-salicylamide derivative and functions through non-competitive inhibition of pyruvate:ferredoxin/flavodoxin oxidoreductases in amitochondriate intestinal protozoans such as Giardia and likely targets a parallel anaerobic pathway in *Cryptosporidium* (Chakrabarti and Chakrabarti, 2009).

Based on a double-blind, controlled clinical trial in Egypt showing consistent results with other controlled clinical trials, nitazoxanide has high clinical cure rates in immunocompetent adults and children (up to 72% and 88%, respectively, Abdel-Maboud *et al.*, 2000). Drug efficacy is largely unknown in pregnancy, due to specific exclusion of pregnant women from controlled clinical trials (reviewed in Anderson and Curran, 2007). Nitazoxanide is classified as a Category B pregnancy drug, based on non-teratogenic properties observed in rabbit and rat models, and is not expected to have adverse fetal effects when administered during pregnancy (reviewed in Jones *et al.*, 2005). Despite this understanding, a majority of cryptosporidiosis treatment in pregnancy focuses solely on supportive care, such as rehydration and proper maternal nutrition (Bushen *et al.*, 2006). Additionally, published reports from *Cryptosporidium* infection in pregnancy dated prior to 2002 had limited drug options or information on safety of available drugs, so only effectiveness of supportive care in pregnancy has been studied to date (Hoveyda *et al.* 2002).

Physician Knowledge of Infections in Pregnancy

Obstetricians and gynecologists are a crucial source of preventative information and treatment about various infectious diseases to pregnant women. Despite the importance of physician as educators, widespread gastrointestinal infectious diseases associated with diarrhea are not generally presented in most well-known maternal-fetal medicine handbooks, and very few studies exist to determine the knowledge level of physicians about maternal infection in pregnancy, particularly waterborne protozoan parasites that cause diarrhea like *Cryptosporidium* (reviewed in Acs et al., 2010). Some

major limitations of all of the surveys discussed below are generally low response rates, lack of multivariable data to identify demographic differences among responses, and that respondents who were more knowledgeable about subject matter may have been more likely to complete the survey, leading to an overestimation of knowledge.

A survey conducted of a cross-section of American College of Obstetricians and Gynecologists to determine the knowledge of obstetrician/gynecologists of common anti-parasitic therapies in pregnancy indicated that less than half of respondents knew that a specific request for *Cryptosporidium* spp. testing was necessary in most laboratories (rather than a general stool ova and parasite test) (Jones *et al.*, 2005). Additionally, 61.4% of respondents incorrectly identified cryptosporidiosis treatments in pregnant women, citing trimethoprim-sulfamethoxazole and metronidazole as recommended treatment in pregnancy, when neither of those medications is effective against cryptosporidiosis (Jones *et al.*, 2005). Lastly, almost a quarter of respondents incorrectly identified raspberries as associated with large cryptosporidiosis outbreaks and only 28.2% identified drinking contaminated water as a risky behavior for *Cryptosporidium* infection, demonstrating several missing pieces of basic knowledge regarding the diagnosis, correct treatment, and epidemiology of *Cryptosporidium* infection (Jones *et al.*, 2005).

Published literature on physician knowledge of cryptosporidiosis is sparse, so relevant surveys on physician knowledge of gastrointestinal, protozoan parasites and additional infections in pregnancy were considered. In one example, Krueger *et al.* analyzed a survey of physician knowledge on giardiasis in pregnancy, using a sample of

obstetricians and gynecologists from the American College of Obstetricians and Gynecologists Collaborative Ambulatory Research Network and general cohort to identify major diagnosis and treatment knowledge gaps (2007). Generally, a majority of physicians correctly pinpointed diagnostic methods, transmission mechanisms, disease outcomes, and prevention strategies, but lacked confidence in knowledge about treatment of giardiasis, particularly in drug efficacy and safety during the first trimester of pregnancy (Krueger *et al.*, 2007). Currently, the most effective treatment for *Giardia* is the nitroimidazole drug group, including metronidazole and tinidazole, both of which have shown efficacies of over 90% (Krueger *et al.*, 2007). Additionally, nitazoxanide was approved for treatment of *Giardia* in the U.S. in 2003 (Krueger *et al.*, 2007). The authors hypothesized that potential reasons for physician lack of confidence in current drug treatment was due first to a lack of definitive research on drug effects during the first trimester, and secondly due to lack of physician education. While 75% of participants believed metronidazole to be the safest medication to administer during the first trimester, it rapidly enters the fetal circulation after maternal absorption and is not considered safe for use in early pregnancy (Krueger *et al.*, 2007). General physician knowledge of use of metronidazole stem from studies that have shown it to be safe and effective during the second and third trimester (Krueger *et al.*, 2007). However, due to lack of clinical trial data, it is not recommended during the first trimester. This example of physician knowledge of treatment of parasite infection in pregnancy indicates that physicians may be unable to stay abreast of new developments from ongoing drug

research studies. Additionally there is clearly a need for additional and periodic provider education on new treatments for parasitic infections in pregnancy.

Laboratory testing surveys have provided increasingly useful information on physician testing practices for *Cryptosporidium*. Physician use of parasite tests in the United States, surveyed from 1997 to 2006, included a regional focus on testing data obtained from the *Cryptosporidium* outbreak in Utah in 1997 (Polage *et al.*, 2010). The study found that many physicians are uncertain about when to order the correct tests (reviewed in Polage *et al.*, 2010). Microscopic ova and parasite testing (O&P) is traditionally ordered for fecal parasite diagnosis by physicians, but has been found to be insensitive for parasites such as *Giardia* or *Cryptosporidium* spp., a little-known fact among American physicians (reviewed in Polage *et al.*, 2010). Over 75% of physicians surveyed in Connecticut, regardless of specialty, rarely or never ordered the testing necessary to detect *Cryptosporidium*, despite suspecting infection in patients presenting with symptoms consistent with cryptosporidiosis (Morin et al, 2007 and reviewed in Polage *et al.*, 2010). In the same Connecticut survey, only 5% of all stool samples submitted for O&P testing to surveyed labs over a 9-month study period were tested for *C. parvum* (Roberts *et al.*, 1996). A FoodNet laboratory survey performed to determine clinical laboratory practices for several parasites found that acid-fast staining was the most popular *C. parvum* testing method used, which could contribute to the low positivity found in the Connecticut survey (Jones *et al.*, 2000). Results of these two surveys were hypothesized to occur due to general unawareness of cryptosporidiosis symptoms and testing procedures among both physicians and laboratories (Morin *et al.*,

1997). Similarly, a survey performed of physicians in three California counties found that 89% of respondents did not specifically request a cryptosporidiosis test when requesting an O&P exam (Berger and Weintraub, 2005). Surprisingly, Krueger *et al.* found that 89.2% of respondents indicated EIA as the correct diagnostic test, though standard O&P alone was not a survey answer choice (Krueger *et al.*, 2007). Additionally, 91.1% of respondents indicated that classic microscopy diagnostic methods may miss *Giardia*, leading to false negative test results (Krueger *et al.*, 2007). Despite this understanding, as demonstrated by common laboratory practices across the U.S., there is a continued discrepancy between knowledge of test capabilities and tests used for detection of protozoan parasites in high-risk groups (Krueger *et al.*, 2007). Contrasting survey results may be the result of several biases, including small sample sizes and low response rates. Additionally, the overestimation of physician knowledge may have occurred due to "responder bias", i.e. the higher likelihood of those physicians with more cryptosporidiosis knowledge to answer the survey, as opposed to those with less knowledge. Also, the lack of fixed denominators between different questions could additionally bias survey results (Krueger *et al.*, 2007). Even with numerous publications illustrating the increased sensitivity of immunoassays, and some physician knowledge of tests such as EIA for detection of protozoan parasites, a majority of laboratories do not routinely utilize these assays without a physician order (Polage *et al.*, 2010).

Another survey of physician diagnostic practices for patients with acute diarrhea found that a majority of physicians assumed testing for cryptosporidiosis was included in standard O&P testing (Hennessy *et al.*, 2004). Even under outbreak conditions, data

from Utah indicated that greater than 68% of cryptosporidiosis cases were tested using only O&P until the outbreak etiology was identified by the Utah Department of Health and recommendations were issued for physicians to specifically request *Cryptosporidium* EIA (Polage *et al.*, 2010). Most notably, zero cases were detected by O&P testing alone during the initial weeks of the outbreak (Polage *et al.*, 2010). Both studies indicated that in general, parasite testing was conducted without adequate provider knowledge regarding frequency of infection, expected parasites, or test performance, indicating a critical need for additional practice guidelines and education tools for physicians regarding parasite diagnostic methods (Polage *et al.*, 2010, Hennessy *et al.*, 2010). In Connecticut, one laboratory even identified a lack of physician knowledge of testing methods as a specific testing barrier (Roberts *et al.*, 1996). A survey of California physicians identified physician misperceptions of cryptosporidiosis as always self-limited, rarely occurring, and with low transmission risk as specific barriers to testing (Berger and Weintraub, 2005). In addition, lack of knowledge of treatment options also kept physicians from collecting stool samples for cryptosporidiosis testing from patients suffering from acute diarrheal illness (Berger and Weintraub, 2005). Most problematically, underutilization of *Cryptosporidium* testing, despite lessons learned during the 1993 Milwaukee outbreak, likely contributed to delayed recognition of etiology of the Utah outbreak and a stalled public health response.

Surveys discussing parasitic and other infections occurring in pregnancy also provided useful information on physician training and comfort with aspects of infectious

diseases in pregnancy. One obstetrician survey assessed knowledge of roundworm, tapeworm, and fluke parasite risks associated with eating raw or undercooked fish during pregnancy (Jones *et al.*, 2011). Results indicated that although a high percentage understood this risky behavior, few physicians identified freezing fish to kill parasites as a prevention strategy (82% versus 19%, respectively, Jones *et al.*, 2011). Additionally, a majority of respondents understood that parasite treatment during pregnancy could be more difficult (Jones et al., 2011). Generally, the survey results found that additional education, particularly epidemiological risk factors and prevention strategies, would benefit obstetricians and increase safety of pregnant patients (Jones *et al.*, 2011).

A multi-specialty physician survey was performed to determine the knowledge, attitudes, and practices of obstetrician/gynecologists regarding prevention of infections in pregnancy, and focused on infections for which reduction of behavioral risks could protect the mother and fetus from infection (Ross *et al.*, 2009). Included in this survey were common pregnancy-associated infections: *Toxoplasma gondii*, influenza, Hepatitis B virus, Varicella-zoster virus, *Listeria Monocytogenes*, Parvovirus B19, cytomegalovirus, *Bordetella pertussis*, and lymphocytic choriomeningitis virus (Ross *et al.*, 2009). Seventy-nine to eighty-eight percent reported counseling pregnant women to prevent infection from *Toxoplasma gondii*, hepatitis B, and influenza, while 50%-68% counseled patients about varicella-zoster virus, *Listeria monocytogenes*, and Parvovirus, while less than 50% discussed *Bordetella pertussis* and cytomegalovirus with patients (Ross *et al.*, 2009). Differences in knowledge, risk perception, and limited appointment time contributed highly to which infections were discussed with patients, focusing heavily on

hepatitis B and influenza testing and diagnoses (Ross *et al.*, 2009). Risk perception played a larger role with *T. gondii*, since only 7% of physicians reported testing all patients for the pathogen but 70% reported testing once the patient requested a test (Ross *et al.*, 2009). Additionally, patients were highly counseled about *T. gondii* infection, despite less than 20% of physicians having diagnosed toxoplasmosis in patients since 2003, indicating a high level of knowledge about the dangers of toxoplasmosis in pregnancy (Ross *et al.*, 2009). Physicians reported a high percentage of knowledge about certain risk behaviors and prevention recommendations outlined by CDC and ACOG, as well as clinical and epidemiological aspects of the various surveyed infections in pregnancy (Ross *et al.*, 2009). Two recommended behaviors that were well known by physicians were hand washing after diaper changing (89.7%) and avoiding wild or pet rodents (88.5%), which cause infections in pregnant women and potentially harm a fetus (Ross *et al.*, 2009). Interestingly, perceived risk, assessed through patient counseling about these risk behaviors, was much lower, as fewer physicians reported counseling patients on these risk behaviors (Ross *et al.*, 2009). A FoodNet practices and perceptions survey analysis of physicians as food safety educators found similar results (Wong *et al.*, 2004). Forty-three percent of the survey sample was comprised of obstetrician-gynecologists, and the level of perceived risk of patients was a significant indicator of whether physicians counseled their patients on food-borne infections and prevention (Wong *et al.*, 2004). This demonstrated a knowledge and perception gap evident in various national sample cohorts of obstetricians and gynecologists, and emphasizes an ongoing need to educate and integrate physicians into public health

infection prevention strategies through more consistent information dissemination to a high-risk group. In addition, the exclusion of protozoan parasites from physician surveys, particularly *Giardia* and *Cryptosporidium* spp., emphasizes the need to expand research in this area.

Conclusions

In summary, targeting physician understanding and practices about cryptosporidiosis in pregnancy allows the critical examination of the strengths and weaknesses of the domestic public health surveillance system of parasitic threats to vulnerable populations, particularly pregnant women. Physicians are an integral aspect not only of infectious disease diagnosis and treatment, but also of disease surveillance, control, and prevention. Lack of physician knowledge regarding widespread waterborne parasites, particularly in high risk groups such as pregnant women, has multiple public health implications, most visibly under-diagnosis and under-reporting of cryptosporidiosis in the U.S. The nature of passive disease surveillance in the U.S. results in only a fraction of cases of food- and waterborne diseases being reported each year, despite a large estimated domestic burden of disease (Hennessy *et al.*, 2004). In order for a case of cryptosporidiosis to be reported to the CDC, the patient must seek medical care, a stool specimen must be collected and sent to a laboratory with the correct diagnostic tests requested, the laboratory must test for the organism in question in the differential diagnosis, a positive result must be obtained, the laboratory and physician must report it to the state health department via the correct electronic reporting systems, and then the state health department must report it to the CDC,

unless it is automatically reported from the local level (Hennessy *et al.*, 2004). With increased knowledge and action, physicians can influence more than one step of this system in order to better estimate true disease incidence in pregnancy but also gain knowledge about case management in vulnerable populations. Physicians are in a unique position to be able to directly influence disease control and prevention at the individual level, through education of patients about high risk behaviors, and on the population level, by expediting organism detection, case treatment, and reporting illness.

Goal

The goal of this joint CDC and American College of Obstetricians and Gynecologists *Cryptosporidium* knowledge survey analysis is to expand our understanding of American obstetrician and gynecologists' knowledge of cryptosporidiosis in pregnancy by isolating specific clinical and epidemiological knowledge gaps.

Aims

- To analyze the general demographics and trends of respondent knowledge, based on frequencies of correct answers given to each question
- To analyze specific relationships between respondent demographics, including gender, number of years in practice, practice type, location, and region and likelihood of correctly answering each question
- To provide data-driven knowledge gaps in both univariable and multivariable analyses
- To present major knowledge gaps of physicians n a manuscript that provides a platform for creation of easily accessed and usable physician education materials

on basic diagnosis, laboratory testing, treatment, and prevention of cryptosporidiosis in pregnancy

Significance

Since cryptosporidiosis is endemic in the U.S., it will be encountered by obstetrician-gynecologists, and it is essential that they understand the heightened risks of infection in pregnancy. This allows physicians to facilitate increased diagnosis, optimal treatment, more consistent illness reporting, and prevention of illness. Physicians serve as an immediate defense against wide-spread infection, particularly in vulnerable populations such as pregnant women. However, lack of knowledge and general unawareness of patient susceptibility to infection pose major barriers to effective intervention. Analysis of this survey will assess specific aspects of obstetrician-gynecologists' current clinical knowledge of cryptosporidiosis in pregnancy in order to measure the capacity of U.S. health care providers to detect and manage cases of illness. From a public health perspective, assessing physician understanding of disease epidemiology with specific questions on cryptosporidiosis risk factors, prevention measures, and reporting status will illuminate major knowledge barriers to notifiable disease prevention and reporting. Pinpointing specific clinical and epidemiological obstetrician-gynecologist training gaps allows education materials to be created that target these weaknesses effectively, with particular focus on evolving drug developments and adverse fetal outcomes of infection based specifically on how comfortable physicians are with these survey questions. Since most physicians can dedicate very little time to continued education, tailored programs promote higher use

and retention of information. In turn, this results in optimal patient care and increased discourse between clinical medicine and public health surveillance for parasitic infections in pregnancy.

Author's Contribution

ACOG developed the obstetrician-gynecologist survey instrument, performed a pilot test in 2009, modified and administered the survey in 2010, and collected and cleaned the data. Jeff Jones oversaw survey data cleaning, analysis, and professional manuscript drafting. Juan Leon oversaw data analysis, manuscript drafting, and thesis compilation. Jay Schulkin and Britta Anderson provided additional data and oversight of manuscript editing. Michele Hlavsa assisted in manuscript editing.

Introduction

Caused by the intestinal protozoan parasite *Cryptosporidium*, cryptosporidiosis is one of largest causes of waterborne diarrhea that occurs each year, both globally and domestically (CDC). Although cryptosporidiosis is well-understood as geographically dispersed and problematic, the global burden of *Cryptosporidium* infection remains unascertained. This is mostly due to the indigenous nature of animal reservoirs, widespread clinical case mismanagement and misdiagnosis, and inadequate national and global surveillance systems (CDC, reviewed in Putignani *et al*.). In developing countries, prevalence estimates range from 3 to 20%, while in developed countries prevalence is estimated at 0.5 to 2.5% in immunocompetent adults and remains undetermined in pregnancy (Arrowood *et al.*, 2008). Chronic under-reporting is extensive in the United States, with only approximately 9,000 to 10,000 of over 836,000 total estimated cases of cryptosporidiosis reported each year (reviewed in Yoder and Beach, 2010). Due to high volume of asymptomatic or mild cases, many patients do not seek medical care or do not have stool samples tested for *Cryptosporidium* (reviewed in Yoder and Beach, 2010). This indicates that true burden in the United States is unknown (Yoder and Beach, 2010).

In the United States, several high-risk groups for Cryptosporidium infection have been identified, including immunocompromised AIDS patients, travelers, and young children, and immunocompetent caretakers and close contacts of infected individuals (reviewed in Bushen *et al.*, 2006). Notably, though recently recognized as a potential high-risk group, very little literature also addresses risks of infection in pregnancy

(Bushen *et al.*, 2006). The literature focuses almost exclusively on waterborne outbreaks, so activities that can lead to *Cryptosporidium* infection are usually associated with swimming or swallowing unfiltered, untreated recreational water (reviewed in Bushen *et al.*, 2006). However, day care center outbreaks have garnered increased attention (reviewed in Bushen *et al.*, 2006).

Clinical diagnosis and treatment of cryptosporidiosis can be problematic. Clinical diagnosis of cryptosporidiosis can be difficult and insensitive, though multiple testing options exist. Direct fluorescence antibody assay (DFA) is highly sensitive and specific and considered the "gold standard" by many laboratories (reviewed in Yoder and Beach, 2010). Routine ova and parasite tests do not include *Cryptosporidium* species identification methods, though this is often not understood by clinicians who attempt to order diagnostic tests for suspected cryptosporidiosis patients (Chen *et al.*, 2002). To date, no vaccine exists to prevent *Cryptosporidium* infection, and a number of therapeutic agents have been unsuccessfully evaluated for anti-cryptosporidial efficacy (reviewed in Collinet-Adler and Ward, 2010). Nitazoxanide, produced commercially under the trade name Alinia by Romark Laboratories, is a broad-spectrum anti-parasitic that is the only FDA-approved drug available for clinical treatment of *Cryptosporidium* infection in all individuals over 12 months of age (reviewed in Anderson and Curran, 2007).

Although a majority of these infections occur in immune-competent individuals and are asymptomatic or self-limited, *Cryptosporidium* is one of the most highly infectious enteric pathogens identified and can quickly become problematic for high risk

patients, especially pregnant women. Although still largely unexplored, it is suggested, and generally accepted, that pregnancy increases the likelihood and severity of infection (reviewed in Riggs, 2002). The most likely explanation of this increased susceptibility of the host to *Cryptosporidium* spp. may due to a lowered Th1 cell-mediated immune response, demonstrated in mouse models (reviewed in Riggs, 2002). Despite the general understanding of the increased vulnerability of patients to infections such as cryptosporidiosis by the medical and scientific communities, aspects of cryptosporidiosis are poorly understood by American physicians, primarily due to the lack of training in this area. Widespread gastrointestinal infectious diseases associated with diarrhea are not generally presented in most well-known maternal-fetal medicine handbooks, and very few studies exist to determine the knowledge level of physicians about maternal infections in pregnancy (reviewed in Acs *et al.*, 2010). This influences not only diagnosis and treatment choices but also disease reporting practices and the reliability of public health surveillance networks. This divergence between perceived risk and knowledge and estimated annual case load in patients impacts not only clinical management and preventative medicine but also illuminates weaknesses of public health surveillance networks, particularly for rarely-studied high risk groups such as pregnant women. Therefore, there is a need to assess American obstetricians and gynecologists for their knowledge of cryptosporidiosis and identify specific knowledge gaps to maximize the ability of physicians to educate patients correctly, minimize misdiagnosis, and manage domestic infections effectively, as well as to identify gaps in surveillance and more effectively understand the magnitude of disease in the U.S.

To address these needs, a survey was conducted in 2010 by the American College of Obstetricians and Gynecologists (ACOG) in collaboration with Centers for Disease Control and Prevention (CDC) on physician knowledge of cryptosporidiosis in pregnancy. The goal of this joint survey analysis was to identify American obstetrician-gynecologists' specific clinical or epidemiological knowledge gaps of cryptosporidiosis in pregnancy by analyzing surveys designed to gauge basic Cryptosporidium knowledge. By identifying cryptosporidiosis knowledge gaps of obstetrician-gynecologists, we will be able to design tailored intervention strategies and create specific, user-friendly education tools to increase physician knowledge of cryptosporidiosis. This educational supplementation will improve recognition, diagnosis, treatment, and reporting of cryptosporidiosis and in turn, improve the consistency and reliability of disease surveillance in pregnant women, a vulnerable and high-risk group.

Methods

Study Population

The American College of Obstetrics and Gynecology (ACOG), in conjunction with CDC medical and epidemiological staff, developed and distributed a questionnaire about the diagnosis and treatment of the parasitic disease cryptosporidiosis to a national sample of obstetrician-gynecologists to determine the knowledge of U.S. obstetrician-gynecologists about risk factors, diagnosis, and treatment of cryptosporidiosis in pregnant women. The survey was pilot tested by five ACOG physicians in 2009. The study obtained CDC and ACOG IRB exemption status and was classified as public health non-research.

Sample size

To maximize response rate, a total of 1000 surveys were mailed from the ACOG facility in Washington, D.C. to 200 CARN and 200 non-CARN physicians over three initial cycles, dated January 18, March 14, and April 9, 2010. CARN physicians were sampled from ACOG's Collaborative Ambulatory Research Network, comprised of practicing physicians volunteering for periodic knowledge and practice surveys. Non-CARN physicians were randomly selected from the national ACOG membership, comprised of 29,661 physicians, in 2010. To increase the number of respondents, a fourth mailing was sent to 600 CARN obstetricians-gynecologists over the summer in 2010. Due to sample size, the data were not stratified by CARN or non-CARN status for data analysis.

Data Cleaning and Inclusion Criteria

Data obtained from returned surveys were assembled and cleaned by ACOG staff using Microsoft Excel. Data were analyzed using SAS 9.3 and OpenEpi Version 2.3 (Cary, NC).

From the 470 returned surveys, individual responses failing to meet specific survey criteria were removed, including not completing the survey or being unreachable (N=27), post-retirement (N=7), suspended practice (N=1), Canadian residency (N=3), and using Epocrates software (mobile health software application providing reference information) to answer survey questions (N=1). A total of 431 responses remained for analysis. Answer choices for each survey question were dichotomized to correct and incorrect, when necessary. Due to the small sample size of some subsets, some low frequency survey answer choices for the demographic variables region, practice type, and practice location were combined in an "other" category for each question. For analysis, the continuous variable "years in practice" was dichotomized at the median value, allowing comparison of less than 19 years in practice and greater than or equal to 19 years in practice. This was done in order to simplify analysis of greater versus less experienced physicians.

Statistical Analyses

Frequencies and confidence intervals were obtained using binomial proportions in OpenEpi Version 2.3 software to describe the multiple answer choices of each survey question. A two-sample t-test was used to compare mean ages of survey respondents with 2010 ACOG membership data, while a chi-squared test was used to compare gender distribution between the two groups to assess if significant demographic differences were present between the sampled physicians and the ACOG membership (OpenEpi Version 2.3, 2009). Crude odds ratios and confidence intervals, as well as corresponding p-values were obtained from bivariate associations between selected

demographic groups and correct survey questions using the chi-square or logistic regression in SAS 9.3 (Cary, NC). A multivariable logistic regression model, adjusting for potential confounding among variables gender, years in practice, region, practice type, and location of practice was performed for each relevant survey question. No multi-collinearity was found between the variables. Effect modification was not assessed due to small sample size, absence of only one main effect, and lack of published data indicating the potential presence of effect modification between demographic variables of physician surveys. $P < 0.05$ was considered significant.

Results

Of the 1000 surveys mailed to ACOG fellows, 470 (47%) surveys were returned and 431 (43.1%) surveys met eligibility criteria for analysis. Slightly more respondents were female than male (54.8%, Table 1). The average age of survey participants was 50 years (Table 1). Median years in practice was 19 years, and the mean year of residency completion was 1991 (Table 1). A majority of respondents practiced in the south (37.9%) while 22.8% practiced in the Midwest, 20.6% in the northeast, and 18.7% in the west (Table 1). Most participants were general obstetrician-gynecologists in a partnership or group (76.0% and 45.0%, respectively, Table 1). Practice locations indicated were suburban (35.5%), urban, non-inner city (32.0%), rural (19.1%, and urban, inner-city (13.4%) (Table 1).

Demographic data was compared between survey respondents and total ACOG membership in 2010. A two-sample t-test comparing mean ages found that survey respondents were statistically significantly different (mean 50.0 years) from ACOG members (mean 50.58 years) ($p<0.01$). However, this does not appear to be a clinically significant difference. A chi-square analysis showed a significant difference in gender distribution between survey respondents and ACOG members, with 54.8% versus 46.5% of individuals being female, respectively (uncorrected chi-square=18.21, $p < 0.01$, OpenEpi Version 2). No additional ACOG membership demographic data from 2010 were available for comparison to the analysis subgroup.

The distributions of answers for each survey question are presented in Table 2. Notably, no survey question had higher than a 50% correct response rate. Generally, clinical

questions had a higher correct response rate than epidemiological or public health focused questions; however, FDA age guidelines for the anti-parasitic nitazoxanide for treatment of immunocompetent patients had a correct response rate of only 5.6% and was the most missed question of the survey. In addition, only 9.0% of respondents correctly classified nitazoxanide as an FDA pharmaceutical pregnancy Category B drug (Table 2).

Clinical Knowledge

While both clinical and epidemiological questions revealed a high level of uncertainty in provider knowledge, survey respondents demonstrated slightly higher comfort with clinical information about cryptosporidiosis in pregnancy. For example, 44.4% of providers correctly identified that prolonged, intermittent diarrhea would lead them to consider cryptosporidiosis in a differential diagnosis (Table 2). However, almost as many physicians did not know the symptoms of cryptosporidiosis (38.6%, Table 2). Knowledge of diagnostic testing was also low. Routine ova and parasites (O&P) testing was incorrectly chosen by 30.4% respondents to identify cryptosporidiosis in stool and 42.8% of respondents did not know which parasites are identifiable by O&P testing (Table 2). As mentioned above, both questions gauging respondent knowledge of FDA guidelines for drug treatment of Cryptosporidium infection in immunocompetent and pregnant patients were highly missed (Table 2). Few physicians surveyed had experience diagnosing cryptosporidiosis among their patient populations. When asked about incidence of cryptosporidiosis among their patients since 2003, 62.6% of physicians indicated that they had not diagnosed cryptosporidiosis in any of their

patients to date, while 31.6% indicated that they did not know how the incidence of cryptosporidiosis has changed in their patients (Table 2). In a related question, when asked how the availability of nitazoxanide has affected the frequency of diagnostic test ordering for suspected cases of cryptosporidiosis, 93.8% of survey respondents indicated that they have not ordered any cryptosporidiosis diagnostic testing for any patients to date (Table 2). Lastly, more than half of the respondents did not know the complications caused by cryptosporidiosis during pregnancy (60.1%, Table 2).

In multivariable analysis, few significant associations were found between demographics and correct answer choice selection in either clinical or epidemiological survey questions. For clinical questions, though insignificant in bivariate crude analysis, when controlling for additional variables, female gender was significantly, negatively associated with correct identification of symptoms for a differential diagnosis, compared to male gender ($p=0.05$, Table 3). In both bivariate and adjusted analyses, greater than 19 years in practice, correlating to a higher level of practitioner experience, was significantly, positively associated with correctly knowing the uses of O&P testing ($p<0.01$ and $p=0.03$, Table 3). Interestingly, female gender was significantly, positively associated with correct identification of uses of O&P testing in bivariate analysis but insignificantly associated with correct answer choice in adjusted analysis, compared with male gender ($p=0.03$ and $p=0.37$, respectively, Table 3). In both bivariate and adjusted analyses, solo practice type was significantly, positively associated with correctly identifying the parasite species included in a routine O&P stool test, compared to partnership or group practice type ($p=0.02$, Table 3). In both bivariate and adjusted

analyses, urban, non-inner city and rural practice locations were both significantly and positively associated with knowing the correct FDA guidelines for nitazoxanide use in immunocompetent patients, as compared to suburban practice location (p=0.04 and p=0.02, respectively, Table 3). In both crude and adjusted analysis, rural practice location was significantly, positively associated with knowledge of the correct FDA pharmaceutical pregnancy category for nitazoxanide, as compared to suburban practice location (p=0.02, Table 3). In adjusted analysis only, greater than 19 years in practice, compared to less than 19 years of practice, was significantly, negatively associated with correctly knowing the complications of severe cryptosporidiosis infection in pregnancy (p=0.01, Table 3). In both bivariate and adjusted analyses, practice location in the northeast was significantly associated with knowing consequences of severe infection, compared to the practice location in the south (p=0.004, Table 3). In crude bivariate analysis, urban non-inner city practice location was significantly and positively associated with knowing consequences of severe infection of *Cryptosporidium* in pregnancy, compared to suburban practice location (p=0.04, Table 3). Interestingly, this association became insignificantly in the adjusted analysis (Table 3).

Epidemiological Knowledge

Comparatively, respondents demonstrated even less familiarity with public health-based knowledge about cryptosporidiosis. Almost 40% of physicians could not identify any risky activities that lead to *Cryptosporidium* infection, although a quarter of respondents were able to identify all correct risk activities listed (Table 2). Prevention knowledge was overwhelmingly poor. Only 14.1% of respondents identifying alcohol-

based hand sanitizers as an ineffective tool to inactivate *Cryptosporidium* spp., and an overwhelming majority (72.7%) responded that they did not know (Table 2). While 20.2% of physicians did answer correctly, most admitted not knowing the correct CDC and AAP swimming recommendations for recently diagnosed patients (74.7%, Table 2). Finally, and most worrisome from a public health perspective, less than 10% of physicians knew if cryptosporidiosis is a reportable disease in their state (9.6%, Table 2).

In multivariable analyses, for epidemiological questions, in both bivariate and adjusted analyses, practice location in the west was significantly and positively associated with correctly identifying risky activities for *Cryptosporidium* infection, compared to practice location in the south (p=0.007, Table 4). Practice location in the northeast compared to in the south and practicing in a multi-specialty practice type compared to partnership or group were both significantly associated with correctly knowing that alcohol-based hand sanitizers do not effectively inactivate *Cryptosporidium* spp., though region of practice demonstrated a negative association while practice type was positively associated with correct answer choice (p=0.02 and p=0.05, respectively, Table 4). While female gender was insignificantly, negatively associated with knowledge of reporting in crude bivariate analysis, female gender compared to male gender was significantly, positively associated with correctly identifying cryptosporidiosis as a reportable disease in the respondent's state, or territory in multivariate analysis (p=0.04, Table 4). Overall, although some subgroups demonstrated a higher level of clinical or public health related cryptosporidiosis

knowledge, the survey indicated that general obstetrician-gynecologist knowledge about cryptosporidiosis was low.

Discussion

This survey was designed to assess basic clinical and epidemiological knowledge of cryptosporidiosis in pregnancy of a sample of obstetrician-gynecologists. Overall, the survey indicated that a majority of physicians sampled demonstrated a poor foundation of knowledge of cryptosporidiosis in pregnancy, likely due to lack of training and misperceptions about patient risks and implications of illness in this high-risk group. Obstetrician-gynecologists could benefit from increased education in multiple aspects of this pathogen, including risk factors and transmission, diagnosis, illness control, prevention, and reporting.

Clinical Concepts

Though physicians demonstrated more knowledge of clinical aspects than cryptosporidiosis epidemiology, diagnostic competency among sampled physicians was lacking. For questions focusing on diagnosis, only 44.4% of respondents correctly indicated that a patient presenting with intermittent diarrhea lasting longer than 3 days would lead to a consideration of cryptosporidiosis in the differential diagnosis (Table 2). However, 37.1% mistakenly indicated that some presentation of bloody diarrhea would lead to a differential diagnosis of cryptosporidiosis. Though this symptom can present in complicated cryptosporidiosis, it is uncommon (Bushen *et al.*, 2006). Physician confusion may arise due to the high number of infections that can occur in pregnancy, and association of bloody stools with potentially more commonly recognized food-borne infections such as *Campylobacter jejuni*, *Shigella*, and severe *E. coli* infections, which have the same seasonal summer-time peaks as *Cryptosporidium* infections (CDC).

Additionally, only one third of respondents were able to identify that severe and prolonged cryptosporidiosis in pregnancy leads to dehydration. One reason may be that other pathogens with different symptoms and complications, such as *T. gondii*, are much more publicized in pregnant patients, and physicians have learned to associate only particular symptoms with parasitic infections in pregnancy (Jones *et al.*, 2005). Finally, a survey of clinical laboratories in FoodNet showed that 99% of laboratories routinely culture for *Campylobacter jejuni*, *Shigella*, and *E. coli* in stool samples, while rarely testing for *Cryptosporidium* unless explicitly ordered (Hennessy *et al.*, 2004). Along with the reasons given above, this is likely to indicate that both laboratories and physicians have more familiarity with diagnosis of these pathogens than with *Cryptosporidium*.

Uncertainty of diagnostic testing of cryptosporidiosis was worrisome. A third of respondents incorrectly identified routine O&P testing of stool samples for *Cryptosporidium* diagnosis; direct fluorescence antibody assays (DFA) are highly sensitive and specific and considered the "gold standard" by many laboratories for *C. parvum* detection (Yoder and Beach, 2010). Problematically a laboratory survey indicated that a majority of laboratories do not routinely utilize assays such as DFAs without a direct physician order (Yoder and Beach, 2010, Polage *et al.*, 2010). In agreement with our findings, over 75% of physicians surveyed in Connecticut, regardless of specialty, rarely or never ordered the testing necessary to detect cryptosporidiosis, despite suspecting infection in patients presenting with symptoms consistent with cryptosporidiosis (Morin *et al.*, 2007,Polage *et al.*, 2010). In a survey of *Cryptosporidium*

testing practices in Connecticut, one laboratory identified a lack of physician knowledge of testing methods as a specific testing barrier (Roberts *et al.*, 1996). Similarly, a survey performed of physicians in three California counties found that 89% of respondents did not specifically request a cryptosporidiosis test when requesting an O&P exam (Berger and Weintraub, 2005). Our survey found that only 5.6% of respondents correctly identified the three pathogens identified by O&P testing (i.e. Giardia, *E. histolytica*, and ascaris), though some physicians were able to individually identify *Entamoeba histolytica* or *Giardia* as pathogens included in standard O&P testing (43.6% and 46%, respectively, Table 2). Several studies on physician use of diagnostic testing or practices regarding cryptosporidiosis indicated that a majority of physicians assume testing for *C. parvum* is included in O&P testing, when in fact, tests must be specifically requested by physicians (Dietz *et al.*, 2000. Our survey, along with supporting research, indicates a need to re-educate physicians on correct uses of O&P testing, since very few physicians know which pathogens can be identified by stool examination (Hennessy *et al.*, 2004). Since the opportunity to diagnose a reportable infection in a high-risk population is currently being frequently missed at several levels of care, providers need to be made aware of which tests are done in a routine O&P examination. Physicians should be trained to order specific tests for any suspect organisms that could be causing illness, particularly if they are made aware of increased risks in their patient population and geographic areas.

Treatment questions were the most missed questions of the survey. Only 5.6% of respondents could identify that nitazoxanide is currently FDA-approved in

immunocompetent patients aged one year or older, and only 9.0% of respondents knew that nitazoxanide is a FDA pharmaceutical pregnancy category B drug, meaning it is not expected to have teratogenic effects on fetal development when used in pregnancy (Table 2). Though nitazoxanide efficacy is unknown in pregnancy due to specific exclusion of pregnant patients from clinical trials, mouse and rabbit models have shown a non-teratogenic effect in pregnancy (Jones *et al.*, 2005). Despite the availability of this safe and effective drug, a majority of cryptosporidiosis treatment in pregnancy focuses solely on supportive care, such as rehydration and proper maternal nutrition (Bushen *et al.*, 2006). Additionally, published reports of *Cryptosporidium* infection in pregnancy dated prior to 2002 had limited drug options or information on the safety of available drugs (Hoyveda *et al.*, 2002). Therefore, only the effectiveness of supportive care, not drug efficacy, has been studied in pregnant cryptosporidiosis patients (Hoyveda *et al.*, 2002). This lack of clinical trials in pregnant patients is the most likely reason for the low knowledge of drug availability or safety in pregnancy among obstetrician-gynecologists in our sample cohort. This lack of research is the same reason that even when educated about the availability of a safe treatment, obstetrician-gynecologists are often warned to use nitazoxanide with caution in pregnancy (Jones *et al.*, 2005). Because nitazoxanide holds a FDA pregnancy category B classification and is generally expected to be safe to use after the first trimester, physicians should be informed of indications for nitazoxanide use in severely symptomatic cases of cryptosporidiosis in pregnancy (Jones *et al.*, 2005).

Our survey evaluated demographic factors that might account for differences of physician knowledge about cryptosporidiosis in pregnancy across a sample of obstetrician-gynecologists. Although it was expected that greater years in practice would affect correct answer choice, variations were tested across gender, region of practice, practice type, and practice location. As expected, higher level of physician experience, extrapolated from greater than 19 years in practice, compared to less than 19 years in practice, was significantly, negatively associated with identification of complications of cryptosporidiosis in pregnancy and positively associated with correctly identifying uses of O&P testing (Table 3). An ACOG survey on physician knowledge of Chagas disease found that having completed residency more than 20 years ago was associated with higher knowledge of disease in pregnancy (Verani *et al.*, 2010). The authors proposed that having completed medical training over 20 years prior to the survey may indicate changes in medical school or residency curricula over time (Verani *et al.*, 2010). It also may be an indication of increased experience and exposure to cryptosporidiosis and other various types of gastrointestinal illness in pregnancy. Furthermore, since 2003, 62.6% of sampled physicians indicated that they did not diagnose any patients with cryptosporidiosis to date, and 93.8% of physicians had not ordered *C. parvum* testing for any patients to date, additionally indicating that an overall lack of exposure may account for clinical knowledge gaps of cryptosporidiosis (Table 2).

Female gender, compared to male gender, was significantly, negatively associated with the correct identification of prolonged, non-bloody diarrhea leading to differential diagnosis of cryptosporidiosis (Table 3). Similar to a survey conducted by

ACOG in a cohort of obstetrician-gynecologists to investigate provider knowledge about Chagas disease, gender was included to adjust for the increased proportion of female physicians to investigate the role of practice type, experience, practice location, and region of practice on question outcomes (Verani *et al.*, 2010). As hypothesized in the Chagas disease study, the association found between gender and correctly identifying prolonged diarrhea as the correct answer is likely the result of unmeasured confounders.

Northeast region location of practice, compared to location in the south, was associated with correct identification of severe cryptosporidiosis leading to dehydration (Table 3). Through examining national cryptosporidiosis surveillance from 1995-1998, Dietz *et al.* discovered that the northeast region had the highest mean rates for cryptosporidiosis reporting to the CDC, alluding to higher levels of diagnosis and subsequent reporting from physicians in this region. However, MMWR notifiable disease surveillance reports indicate that the highest number of cases reported in 2008 were from the Midwest (CDC, 2011). Similarly, both urban, non-inner city and rural practice locations were positively associated with correctly identifying FDA indications for use in immunocompetent patients, while rural practice location was also positively associated with identification of nitazoxanide as an FDA pharmaceutical pregnancy category B drug, compared to suburban practice location (Table 3). One reason for geographical variability of knowledge could be related to locations of publicized outbreaks in both urban and rural areas, as well as localized in the northeast, as

exemplified by the 1993 Milwaukee, Wisconsin outbreak, 1995 New York City outbreak, and 2006 Wyoming outbreak (CDC, 1997, 2007).

Epidemiological Concepts

Respondents struggled more with epidemiological, than clinical, questions, which is not surprising as physicians have varying levels of education and context of public health. Only approximately a quarter of respondents identified all high-risk activities associated with *Cryptosporidium* infection, though 79.4% of physicians identified the most publicized and widely known factor of ingesting unfiltered, untreated water, either from an environmental or recreational water source such as swimming pool (Table 2). This is not surprising, since *Cryptosporidium* infection is often associated with wide-spread and well-publicized water-borne outbreaks in the United States, such as the 1993 Milwaukee, Wisconsin municipal water source outbreak that sickened over 403,000 individuals (Chen *et al.*, 2002). In the U.S., *Cryptosporidium* oocysts are most likely to contaminate swimming pools and recreational water sources (Hoxie *et al.*, 1997). Most epidemiological research has been based on outbreak data, since over 80% of infections are asymptomatic or sporadic and rarely result in medical attention (Bushen *et al.*, 2006). Approximately a quarter of respondents were able to identify additional, more commonly known activities like traveling outside of the U.S. and having contact with persons ill with diarrhea, particularly children, as leading to *Cryptosporidium* infection (Table 2). Unfortunately, pertinent research on transmission routes from environmental reservoirs is often not published in clinical medical journals. This includes studies that indicate risks of cryptosporidiosis in farm animals, such as the

increased susceptibility of pre-weaned cattle to infection and subsequently serve as a cause of environmental dissemination of oocysts and transmission of disease to humans through food- or water-borne routes (Bushen *et al.*, 2006. Therefore, these are not typically presented to physicians in this context, which could account for many physicians failing to understand the risk of these behaviors when considering differential diagnoses of diarrheal illness.

Very few physicians knew that alcohol-based hand sanitizers do not effectively inactivate *Cryptosporidium* oocysts, which has public health and epidemiological implications, particularly prevention of illness (Bushen *et al.*, 2006)(Table 2). In opportunistic infection prevention and treatment guidelines published by the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America, hand washing is recommended after potential contact with human feces, including diapering small children, handling pets or animals, gardening, preparing food, eating, and before and after sex (2009). Additionally, wearing gloves and paying attention to hygiene are also highly recommended (CDC, 2009). Although updated frequently, this document may have limited usability by some physicians such as obstetrician-gynecologists seeking quick and easy answers to patient care questions. Problematically, despite stating the importance of hand hygiene at several points, providers may interpret this to include alcohol hand sanitizers, since this document does not explicitly state that hand sanitizers will not deactivate *Cryptosporidium* oocysts. This potential misinterpretation of confusing published material on cryptosporidiosis indicates a need for specific, easy to use education materials created for physician use.

From a public health perspective, the most concerning survey result revealed that less than 10% of all respondents knew that cryptosporidiosis was a reportable disease in their state of practice. Though this holds many public health surveillance indications, one reason for this lack of knowledge could be the low level of training that physicians receive on the importance of public health and epidemiology during their medical school or residency. Based on a physician attitudes and practices survey regarding prevention of infection in pregnancy, cryptosporidiosis is considered rare and non-threatening, which limits the risk perception of providers (Ross *et al.*, 2009). Other parasitic infections, particularly toxoplasmosis, have substantial research that delineates dangers of infection in pregnancy (Jones *et al.*, 2005). Additionally, supplementary education materials for risk factors and the reporting status of toxoplasmosis in pregnancy are accessible by obstetricians, while intermittent, single case studies and unproven drug efficacy of cryptosporidiosis in pregnancy give less visibility to the reporting status of this illness (Jones *et al.*, 2005).

A few associations between demographic data and correct answer choice selection were found from epidemiological questions. Practice location in the west, compared to in the south, was significantly, positively associated with correctly knowing all risk factors of *Cryptosporidium* infection, which is a finding that correlates with physicians in California being more likely to request a stool culture for patients with acute diarrhea, as found by a physician practices survey in 2004 (Hennessy *et al.*, 2004). Though this presents a geographic difference in physicians' abilities to identify risk factors of cryptosporidiosis, as suggested in a study with similar findings, these

variations are likely actually due to differences in individual practice style or habit, particularly since analysis controlled for relevant factors such as practice type and years in practice (Hennessy *et al.*, 2004). Therefore, these findings do not necessarily reflect differences in geographic distribution in illness that would cause variations in physician exposure and knowledge, since *Cryptosporidium* is environmentally ubiquitous. Interestingly, practicing in a multi-specialty practice type, compared to partnership or group, was positively associated with identifying that alcohol-based hand sanitizers were ineffective in inactivating *Cryptosporidium* oocysts (Table 4). A related study found that physicians were more likely to order stool cultures for diarrheal illness if they had a patient referred or worked in a referral service, or if they had higher contact with AIDS or other immunocompromised patients (Hennessy *et al.*, 2004). This could lead to the inference that multi-specialty practices may have more exposure to a wider range of patients and physician expertise and experience, which would explain this finding.

Strengths, Limitations and Future Research

Particular strengths of our survey include utilizing a cross-section of a national cohort of physicians and performing logistic regression multivariable analysis to examine the relationships between the demographics and knowledge levels of survey respondents while controlling for potential confounding that may be present. There are also several limitations to this survey. First, several sources of bias present in this study may have systemically overestimated the knowledge level of this sample of obstetrician-gynecologists. A majority of respondents are ACOG Collaborative Ambulatory Research Network members, who explicitly volunteer for periodic knowledge and practice surveys

and may be more interested in infections in pregnancy than non-respondents. Also, since no data was collected on where physicians attended medical school, regional difference analysis may be compromised. Also, respondents may be more comfortable with the information that is being assessed than non-respondents. Additionally, the response rate was relatively low (43.1%), although consistent with what is often seen in physician surveys. Comparisons between ACOG membership and the survey sample demonstrated some significant differences in gender distribution between the two groups, indicating that the survey sample may not be fully representative of a national cohort of obstetrician-gynecologists.

Further investigation is necessary to continue to investigate ongoing treatment developments and consequences of infection of cryptosporidiosis in pregnancy. One specific suggestion is that subsequent cryptosporidiosis surveys be performed in various medical specialty groups, such as pediatricians and general practitioners, to pinpoint knowledge differences between specialties, as well as general knowledge gaps across clinical medicine as a whole. Programmatically, supplemental physical education tools should be created and piloted by physicians with a variety of specialties and backgrounds based on specific knowledge deficiencies from this survey to determine the effectiveness of the tools to augment basic physician cryptosporidiosis knowledge.

Acknowledgements

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Public Health Implications

The survey's findings have several important public health implications. The low overall obstetrician-gynecologist knowledge level of cryptosporidiosis in pregnancy indicates a lack of communication and congruency between current clinical education curricula and the public health system. There is an overwhelming need to educate physicians about all aspects of cryptosporidiosis, because there are several intervention opportunities present within the public health reporting pyramid. Each level of the current reporting structure holds potential for decreasing chronic under-reporting biases, which is able to be influenced directly by increased physician action at each step. the reveals how the specific clinical and epidemiological knowledge gaps of cryptosporidiosis in pregnancy correlate directly to incomplete public health surveillance. This charts the greatest needs and opportunities to educate physicians and enhance, as outlined below:

Clinically:

- Low recognition of cryptosporidiosis symptoms in pregnancy leads to missed case detection
- Failing to order correct tests for case detection even in the even that stool samples are collected and sent for testing, resulting in false-negative Cryptosporidium results and underestimation of national case occurrence
- Failing to understand safe and effective treatments for appropriate age groups could increase risk of severity of illness in pregnancy, potentially leading to adverse fetal outcomes

Indicated Supplemental Material Focus:

- Major cryptosporidiosis symptoms in pregnancy
- Signs of complications of infections
- Correct available diagnostic tests
- Protocol for test ordering
- Current drug availability, efficacy, and FDA recommendations in pregnancy, plus resources for continual drug development

Epidemiologically:

- Low familiarity with risk factors and epidemiology of cryptosporidiosis indicates likelihood of missed cases
- Low knowledge of prevention strategies indicates incomplete ability to educate at-risk patients correctly
- Extremely low reporting knowledge directly impacts the completeness and effectiveness of domestic cryptosporidiosis surveillance and indicates low information dissemination about domestic risk of infection

Indicated Supplemental Materials Focus:

- Risk factors and high-risk behaviors, with emphasis on ingesting unpasteurized products, swimming in various recreational water sources, and contact with children in diapers during pregnancy
- High-risk groups for cryptosporidiosis infection and complications, with emphasis on pregnant women
- Prevention strategies for patients, particularly hand-washing and food and water safety
- The status of cryptosporidiosis as a reportable disease to the state health department in each state within 7 days of diagnosis by all physicians, health care providers, and laboratories, as required by law
- Tutorial for physicians in reporting procedures and forms required by the state of current practice

Appendix

Table 1: Demographics for a survey sample of 431 CARN and non-CARN physician members of the American College of Obstetricians and Gynecologists, 2010

Characteristic		Number	Percent
Gender (N=419)	Female	230	54.8
Age (Mean, SD) (N=425)		50 (10.1)	
Years in Practice (Median) (N=424)	<19	212	50.0
Year Completed Residency (Mean, SD) (N=420)		1991 (10)	
Region of Current Practice* (N=422)	Region I	87	20.6
	Region II	96	22.8
	Region III	160	37.9
	Region IV	79	18.7
Primary medical specialty (N = 421)	General OB/GYN	320	76.0
	Gynecology only	54	12.8
	Maternal-Fetal Medicine	26	6.2
	Other†	21	5.0
Secondary medical specialty (N=78)	General OB/GYN	29	37.2
	Gynecology only	11	14.1
	Urogynecology	12	15.4
	Other†	26	33.3
Practice type (N = 418)	Solo Practice	72	17.2
	OB/GYN partnership or group	188	45.0
	Multi-specialty group	74	17.7
	University full-time faculty/practice	62	14.8
	Other†	22	5.26
Practice location (N = 425)	Urban, inner city	57	13.4
	Urban, non-inner city	136	32.0
	Suburban	151	35.5
	Rural (<50,000)	81	19.1

*U.S. states and Puerto Rico divided into four Census Bureau standardized regions: Region I (Northeast): Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, Puerto Rico, Pennsylvania; Region II (Midwest): Illinois, Indiana, Michigan, Minnesota, Ohio, Wisconsin, Iowa, Kansas, Missouri, Nebraska, North Dakota, South Dakota; Region III (South): Delaware, District of Columbia, Maryland, Virginia, West Virginia, Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, Tennessee, Arkansas, Louisiana, Oklahoma, Texas; Region IV (West): New Mexico, Colorado, Montana, Utah, Wyoming, Arizona, California, Hawaii, Nevada, Alaska, Idaho, Oregon, Washington

†Primary Medical Specialty: Reproductive Endocrinology and Infertility, Urogynecology, Obstetrics only, and other; Secondary Medical Specialty: Maternal-fetal Medicine, Reproductive Endocrinology and Infertility, Obstetrics only, and other; Practice type: HMO (staff model) and other

Table 2: Frequencies and confidence intervals of correct response about cryptosporidiosis in pregnancy from a survey sample of 431 CARN and non-CARN physician members of the American College of Obstetricians and Gynecologists, 2010

Questions	Answer Choices	Number	%	95% CI
Clinical				
Symptoms that would lead you to consider cryptosporidiosis in the differential diagnosis:	*Prolonged (diarrhea lasting >3 days) intermittent diarrhea	190 (N=428)	44.4	39.7 – 49.1
	Bloody diarrhea	90 (N=429)	21.0	17.3 – 25.0
	Reactive arthritis	8 (N=429)	1.9	0.9 – 3.5
	All of the above	69 (N=429)	16.1	12.8 – 19.8
	None of the above	7 (N=429)	1.6	0.7 – 3.2
	Don't know	165 (N=428)	38.6	34.0 – 43.2
Routine ova and parasites (O & P) testing of stool specimens includes identifying:	*Giardia	198 (N=428)	46.3	41.6 – 51.0
	*Entamoeba histolytica (amebiasis)	186 (N=427)	43.6	38.9 – 48.3
	Cryptosporidium	130 (N=428)	30.4	26.2 – 34.9
	*Ascaris	127 (N=426)	29.8	25.6 – 34.3
	Trichinella	43 (N=428)	10.1	7.5 – 13.2
	Cyclospora	34 (N=428)	7.9	5.7 – 10.8
	Toxoplasma	33 (N=427)	7.7	5.5 – 10.6
	All of the above	45 (N=428)	10.5	7.9 – 13.7
	None of the above	3 (N=428)	0.7	0.2 – 1.9
	Don't know	183 (N=428)	42.8	38.1 – 47.5
	*Ascaris, E. histolytica, Giardia (correct combination)	24 (N=431)	5.6	3.7 – 8.0
Nitazoxanide is currently FDA approved in immunocompetent patients aged: **(N = 430)**	*Greater than or equal to 1 year of age	24	5.6	3.7 – 8.1
	Greater than or equal to 12 years of age only	22	5.1	3.3 – 7.5
	1-11 years of age only	8	1.9	0.9 – 3.5
	Don't know	376	87.3	84.1 – 90.3
Nitazoxanide falls under which FDA pharmaceutical pregnancy category? **(N = 424)**	Category A	0	0.0	N/A
	*Category B	38	9.0	6.5 – 12.0
	Category C	17	4.0	2.4 – 6.2
	Category D	1	0.2	0.0 – 1.2
	Category P	0	0.0	N/A
	Category X	1	0.2	0.0 – 1.2
	Don't know	367	86.6	83.1 – 89.6
Since 2003, incidence of cryptosporidiosis among your patients has: **(N = 430)**	Increased	16	3.7	2.2 – 5.9
	Decreased	3	0.7	0.2 – 2.0
	Remained relatively stable	6	1.4	0.6 – 2.9
	I have not diagnosed any of my patients with cryptosporidiosis to date	269	62.6	57.9 – 67.0
	Don't know	136	31.6	27.4 – 36.1
How has the availability of nitazoxanide impacted the frequency with which you order diagnostic testing for suspected cryptosporidiosis? (N = 425)	Order testing more frequently	0	0.0	N/A
	Order testing less frequently	0	0.0	N/A
	No change in frequency of ordered testing	26	6.1	4.1 – 8.7
	I have not ordered *Cryptosporidium* testing for any of my patients to date	399	93.8	91.3 – 95.9
Severe cryptosporidiosis in pregnancy most likely leads to: **(N = 423)**	*Dehydration	138	32.6	28.3 – 37.2
	Anemia	16	3.8	2.6 – 5.9
	Premature rupture of membranes	9	2.1	1.0 – 3.9
	Placental abruption	2	0.5	0.1 – 1.6
	None of the above	4	1.0	0.3 – 2.3
	Don't know	254	60.1	55.3 – 64.6
Epidemiological				
Activities that can lead to	Ingesting unfiltered, untreated water from a	188 (N=430)	43.7	39.1 - 48.4

***Cryptosporidium* infection:**	lake, river, or stream			
	Swallowing water while swimming/playing in a pool, water park, interactive fountain, river, lake, ocean	153 (N=429)	35.7	31.2 – 40.3
	Having contact with persons ill with diarrhea, particularly those in diapers	123 (N=430)	28.6	24.5 – 33.0
	Traveling outside the U.S.	109 (N=430)	25.4	21.4 – 29.6
	Having contact with animals, particularly cows and calves	84 (N=430)	19.5	16.0 - 23.5
	Consuming unpasteurized or improperly pasteurized milk	75 (N=430)	17.4	14.1 – 21.3
	Consuming unpasteurized apple juice/cider	56 (N=430)	13.0	10.1 – 16.5
	*All of the above	114 (N=430)	26.5	22.5 – 30.8
	None of the above	3 (N=430)	0.7	0.2 – 1.9
	Don't know	164 (N=429)	38.2	33.7 – 42.9
Alcohol-based hand gels and sanitizers effectively inactivate *Cryptosporidium*. (N = 425)	*False	60	14.1	11.1 – 17.7
	True	56	13.2	10.2 – 16.7
	Don't know	309	72.7	68.3 – 76.8
CDC and AAP recommend patients diagnosed with cryptosporidiosis abstain from swimming until: (N=426)	*Two weeks after diarrhea has resolved	86	20.2	16.6 – 24.2
	Diarrhea has resolved	13	3.1	1.7 – 5.0
	Complete 3-day nitazoxanide treatment course	4	0.9	0.3 – 2.2
	None of the above	5	1.2	0.4 – 2.6
	Don't know	318	74.7	70.4 – 78.6
Cryptosporidiosis is a reportable disease in your state, locality, territory, or freely associated state? (N = 427)	*Yes (for 50 states and DC)	41	9.6	7.1 – 12.7
	No	17	4.0	2.4 – 6.2
	Don't know	369	86.4	82.9 – 89.4

*Correct answer

Table 3: Characteristics associated with correct response about cryptosporidiosis in pregnancy from a survey sample of 431 CARN and non-CARN physician members of the American College of Obstetricians and Gynecologists, 2010: Clinical Questions

Survey Question	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Prolonged diarrhea is a symptom that would lead consideration of cryptosporidiosis in differential diagnosis		
Gender (female versus male)	1.25 (0.84, 1.84)	0.64 (0.41, 0.99)*
Years in Practice (≥ 19 years versus < 19 years)	0.76 (0.52, 1.11)	0.65 (0.41, 1.01)
Region		
South	-	-
Northeast	1.35 (0.80, 2.28)	1.45 (0.82, 2.53)
Midwest	1.28 (0.77, 2.13)	1.27 (0.73, 2.21)
West	1.27 (0.73, 2.20)	1.21 (0.65, 2.23)
Practice Type		
Partnership or group	-	-
Solo Practice	0.74 (0.42, 1.29)	0.90 (0.49, 1.66)
Multi-specialty group	1.08 (0.63, 1.85)	1.29 (0.71, 2.36)
University full-time faculty	0.89 (0.50, 1.60)	0.86 (0.45, 1.66)
Other†	0.69 (0.28, 1.71)	0.82 (0.31, 2.17)
Location		
Suburban	-	-
Urban, Inner-city	0.84 (0.45, 1.56)	0.81 (0.39, 1.67)
Urban, Non-inner city	1.28 (0.80, 2.04)	1.31 (0.78, 2.18)
Rural (<50,000)	0.69 (0.40, 1.21)	0.74 (0.41, 1.35)
Routine Ova and Parasites (O&P) stool testing identifies ascaris, E. histolytica, and giardia		
Gender (female versus male)	2.55 (1.07, 6.10)*	0.64 (0.25, 1.68)
Years in Practice (≥ 19 years versus < 19 years)	5.36 (1.80, 15,97)*	3.69 (1.16, 11.77)*
Region		
South	-	-
Northeast	0.91 (0.33, 2.53)	1.17 (0.39, 3.53)
Midwest	0.13 (0.02, 1.02)	0.15 (0.02, 1.21)
West	0.83 (0.28, 2.45)	0.87 (0.27, 2.86)
Practice Type		
Partnership or group	-	-
Solo Practice	4.17 (1.52, 11.43)*	3.53 (1.20, 10.43)*
Multi-specialty group	1.48 (0.42, 5.20)	2.07 (0.54, 7.97)
University full-time faculty	0.42 (0.05, 3.52)	0.45 (0.05, 4.01)
Other†	1.23 (0.14, 10.50)	1.48 (0.16, 13.82)
Location		
Suburban	-	-
Urban, Inner-city	0.88 (0.23, 3.36)	0.56 (0.11, 2.99)
Urban, Non-inner city	0.86 (0.31, 2.37)	0.93 (0.31, 2.80)
Rural (<50,000)	1.04 (0.34, 3.21)	0.58 (0.17, 1.93)
Nitazoxanide is currently FDA-approved for all immunocompetent patients aged 1 or older		

Gender (female versus male)	1.34 (0.58, 3.10)	0.85 (0.34, 2.15)
Years in Practice (≥ 19 years versus < 19 years)	1.71 (0.73, 4.00)	1.71 (0.67, 4.40)
Region		
South	-	-
Northeast	1.05 (0.30, 3.68)	0.95 (0.26, 3.45)
Midwest	1.97 (0.69, 5.63)	1.83 (0.58, 5.74)
West	1.47 (0.45, 4.78)	1.66 (0.46, 5.93)
Practice Type		
Partnership or group	-	-
Solo Practice	0.38 (0.08, 1.74)	0.27 (0.06, 1.30)
Multi-specialty group	0.97 (0.33, 2.82)	0.52 (0.15, 1.80)
University full-time faculty	0.68 (0.19, 2.47)	0.54 (0.14, 2.10)
Other†	0.64 (0.08, 5.12)	0.56 (0.06, 4.98)
Location		
Suburban	-	-
Urban, Inner-city	2.74 (0.54, 13.99)	3.51 (0.64, 19.17)
Urban, Non-inner city	4.34 (1.19, 15.91)*	4.07 (1.06, 15.64)*
Rural (<50,000)	4.73 (1.19, 18.83)*	5.47 (1.31, 22.72)*
Nitazoxanide is a Category B FDA pharmaceutical pregnancy category drug		
Gender (female versus male)	1.68 (0.84, 3.39)	0.78 (0.36, 1.67)
Years in Practice (≥ 19 years versus < 19 years)	2.37 (1.16, 4.84)*	1.95 (0.88, 4.31)
Region		
South	-	-
Northeast	0.87 (0.34, 2.22)	0.90 (0.34, 2.44)
Midwest	1.14 (0.49, 2.64)	1.41 (0.56, 3.58)
West	0.78 (0.29, 2.10)	0.95 (0.31, 2.97)
Practice Type		
Partnership or group	-	-
Solo Practice	0.84 (0.32, 2.19)	0.39 (0.12, 1.27)
Multi-specialty group	0.93 (0.37, 2.32)	0.72 (0.27, 1.95)
University full-time faculty	0.62 (0.20, 1.89)	0.73 (0.22, 2.42)
Other†	0.42 (0.05, 3.29)	0.54 (0.06, 4.54)
Location		
Suburban	-	-
Urban, Inner-city	1.18 (0.35, 4.00)	1.04 (0.26, 4.28)
Urban, Non-inner city	1.22 (0.48, 3.09)	1.24 (0.47, 3.28)
Rural (<50,000)	3.30 (1.36, 8.03)*	3.05 (1.18, 7.87)*
Severe cryptosporidiosis in pregnancy most likely leads to dehydration		
Gender (female versus male)	1.08 (0.71, 1.64)	0.66 (0.40, 1.06)
Years in Practice (≥ 19 years versus < 19 years)	0.67 (0.45, 1.03)	0.53 (0.33, 0.86)*
Region		
South	-	-
Northeast	0.41 (0.22, 0.77)*	0.37 (0.19, 0.73)*
Midwest	0.87 (0.51, 1.48)	0.81 (0.45, 1.46)
West	0.79 (0.45, 1.39)	0.70 (0.37, 1.33)
Practice Type		
Partnership or group	-	-
Solo Practice	0.94 (0.52, 1.70)	0.95 (0.49, 1.84)
Multi-specialty group	1.03 (0.58, 1.83)	1.00 (0.52, 1.94)
University full-time faculty	0.81 (0.43, 1.54)	0.73 (0.36, 1.48)
Other†	1.17 (0.47, 2.94)	1.22 (0.45, 3.30)

Location		
Suburban	-	-
Urban, Inner-city	1.31 (0.68, 2.53)	1.23 (0.57, 2.65)
Urban, Non-inner city	1.69 (1.03, 2.78)*	1.57 (0.91, 2.72)
Rural (<50,000)	0.86 (0.47, 1.61)	0.78 (0.40, 1.54)

*association significant at $p<0.05$

†Practice type: HMO (staff model) and other

Table 3: Characteristics associated with correct response about cryptosporidiosis in pregnancy for a survey sample of 431 CARN and non-CARN physician members of the American College of Obstetricians and Gynecologists, 2010: Epidemiology Questions

Survey Question	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Identification of all activities that lead to *Cryptosporidium* infection		
Gender (female versus male)	0.92 (0.59, 1.42)	1.08 (0.66, 1.77)
Years in Practice (≥ 19 years versus < 19 years)	0.99 (0.65, 1.53)	0.99 (0.60, 1.61)
Region		
South	-	-
Northeast	1.04 (0.55, 1.95)	1.15 (0.59, 2.24)
Midwest	1.60 (0.90, 2.86)	1.53 (0.81, 2.87)
West	2.19 (1.21, 3.98)*	2.47 (1.27, 4.78)*
Practice Type		
Partnership or group	-	-
Solo Practice	1.27 (0.68, 2.38)	1.13 (0.57, 2.25)
Multi-specialty group	1.88 (1.05, 3.39)	1.83 (0.96, 3.49)
University full-time faculty	1.31 (0.68, 2.53)	1.52 (0.72, 3.19)
Other†	1.99 (0.78, 5.06)	1.91 (0.69, 5.26)
Location		
Suburban	-	-
Urban, Inner-city	0.71 (0.34, 1.47)	0.47 (0.20, 1.11)
Urban, Non-inner city	0.82 (0.48, 1.40)	0.61 (0.34, 1.09)
Rural (<50,000)	1.33 (0.74, 2.39)	1.09 (0.57, 2.06)
Alcohol-based hand gels and sanitizers do not effectively inactivate *Cryptosporidium*		
Gender (female versus male)	0.73 (0.41, 1.31)	1.09 (0.58, 2.06)
Years in Practice (≥ 19 years versus < 19 years)	0.77 (0.44, 1.33)	0.64 (0.34, 1.22)
Region		
South	-	-
Northeast	0.31 (0.11, 0.83)*	0.30 (0.11, 0.85)*
Midwest	1.06 (0.54, 2.06)	0.68 (0.32, 1.45)
West	0.79 (0.37, 1.68)	0.71 (0.31, 1.65)
Practice Type		
Partnership or group	-	-
Solo Practice	0.96 (0.41, 2.27)	0.92 (0.36, 2.37)
Multi-specialty group	2.09 (1.03, 4.26)*	2.23 (1.01, 4.93)*
University full-time faculty	1.46 (0.65, 3.29)	1.61 (0.65, 3.96)
Other†	1.18 (0.32, 4.30)	0.77 (0.16, 3.74)
Location		
Suburban	-	-
Urban, Inner-city	0.62 (0.22, 1.74)	0.70 (0.23, 2.11)
Urban, Non-inner city	1.20 (0.62, 2.33)	1.00 (0.48, 2.07)
Rural (<50,000)	1.16 (0.53, 2.51)	0.94 (0.40, 2.21)
Cryptosporidiosis is a reportable disease		
Gender (female versus male)	0.62 (0.31, 1.22)	2.22 (1.03, 4.78)*
Years in Practice (≥ 19 years versus < 19 years)	1.55 (0.80, 3.01)	1.95 (0.93, 4.10)
Region		
South	-	-
Northeast	0.61 (0.23, 1.62)	0.75 (0.27, 2.09)

Midwest	1.09 (0.49, 2.43)	1.01 (0.41, 2.49)
West	0.82 (0.32, 2.06)	0.91 (0.33, 2.51)
Practice Type		
Partnership or group	-	-
Solo Practice	0.95 (0.33, 2.74)	0.97 (0.32, 2.96)
Multi-specialty group	2.16 (0.93, 5.00)	2.46 (0.98, 6.20)
University full-time faculty	2.10 (0.86, 5.12)	2.41 (0.87, 6.66)
Other†	0.62 (0.08, 4.95)	0.63 (0.07, 5.34)
Location		
Suburban	-	-
Urban, Inner-city	0.55 (0.18, 1.70)	0.37 (0.09, 1.45)
Urban, Non-inner city	0.78 (0.37, 1.65)	0.59 (0.26, 1.38)
Rural (<50,000)	0.59 (0.22, 1.55)	0.55 (0.20, 1.54)

*association significant at $p<0.05$

†Practice type: HMO (staff model) and other

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