Molecular Epidemiology of Human Cryptosporidiosis

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Abstract

Cryptosporidium is a parasite that causes diarrheal disease, Cryptosporidiosis, affecting humans and animals. It belongs to the Apicomplexan protozoan family and has a complex life cycle. There are around 25 species and several genotypes, with *Cryptosporidium hominis* and *Cryptosporidium parvum* being the most common species causing human infections. Cryptosporidiosis spreads primarily through the faecal-oral route, consuming viable oocysts, which are excreted with feces that contaminate food or water. Waterborne transmission is also common, making drinking water and recreational water the most likely sources of infection. The infection is more common in developing countries, causing 10-15% of severe diarrheal illness cases. In industrialized countries, the prevalence is lower, but it remains a significant public health concern. *Cryptosporidium* infection is a significant health concern worldwide, causing diarrhoea in both immune-compromised and immune-competent individuals. Molecular methods are being increasingly used in research to enhance epidemiological data and improve risk assessments for managing *Cryptosporidium*.

Keywords: *Cryptosporidium*, molecular epidemiology.

Introduction

Among the parasites that cause about 1 million deaths every year, Cryptosporidiosis resulted in over 50,000 deaths (Gerace, Presti, and Biondo 2019). Although the number of worldwide reported cases of cryptosporidiosis in the last years is increased with a number of 3 cases per 100,000 population, numerous indicators (i.e., clinical symptoms) indicate that the frequency of infection is likely to be 100-fold higher than the number of reported cases (Shrivastava et al. 2017).

The prevalence of *Cryptosporidium* infection is significantly lower in developed countries compared to developing countries since, in the latter, many people still lack a basic level of drinking water and sanitation (Bouzid, Kintz, and Hunter 2018; Shoultz, de Hostos, and Choy 2016).

Differences in Epidemiological Features of Cryptosporidiosis Between Developing and Developed Countries:

the epidemiological features of human cryptosporidiosis in developing countries differ greatly from those in developed countries due to higher endemicity, lower hygiene levels, and less intensive animal farming (Nichols, Chalmers, and Hadfield 2014).

1- Major risk factors: Poor hygiene, contact with animals (especially calves), overcrowding, poor drinking water, young age, and household diarrhea are major risk factors for cryptosporidiosis(Adamu et al. 2014; Bouzid et al. 2018; Conan et al. 2017; Huang, Chen, and LaRusso 2004; Krumkamp et al. 2020; Shalaby and Shalaby 2015). While animal contact is a common risk factor, studies have shown that contact with *Cryptosporidium*-positive household members or neighbouring children is a higher risk factor than contact with positive animals (Bauhofer et al. 2020). Interestingly, one study found that contact with animals provided a protective effect against *Cryptosporidium* infection in children in Mozambique(Krumkamp et al. 2020).
2- Susceptible population: Pediatric cryptosporidiosis is prevalent in children under 2 years old in developing countries due to contamination and poor hygiene. It is also prevalent in immunocompromised individuals, especially those with HIV. In developed countries, it occurs later, typically after the age of 2. Human cryptosporidiosis can occur at any age and in individuals with varying immune statuses due to improved hygiene practices and water treatment (Chalmers, Davies, and Tyler 2019; Gerace et al. 2019; Khan, Shaik, and Grigg 2018; Painter et al. 2016; Xiao and Cama 2018).
3- Major clinical symptoms: Cryptosporidiosis in children in developing countries often causes diarrhoea, nausea, vomiting, abdominal cramps, low-grade fever, headache, and fatigue(Chalmers et al. 2019; Squire and Ryan 2017). Diarrhea usually resolves within 1 to 2 weeks without treatment(Kattula et al. 2017). In developed countries, both children and adults often experience diarrhoea, possibly due to prior exposure, colostrum, or host genetics (Chalmers et al. 2019; Xiao and Cama 2018).
4- Outbreaks: Although cryptosporidiosis is highly endemic in developing countries, it rarely causes outbreaks there. This is probably due to the high level of population immunity. In developed countries, human cryptosporidiosis is best known for foodborne, waterborne, and animal contact-associated outbreaks (Bouzid et al. 2018; Cacciò and Chalmers 2016; Gharpure et al. 2019).

The distribution of *Cryptosporidium* species in humans in Developing and Developed Countries:

Over 20 *Cryptosporidium* species and genotypes have been reported in humans. Among them, *C. parvum* and *C. hominis* are two major species, being responsible for over 90% of human cryptosporidiosis cases in most areas. Other less commonly detected species include *C. meleagridis, C. canis, C. felis, C. ubiquitum, C. cuniculus, C. viatorum, Cryptosporidium chipmunk* genotype I, and *C. muris* in the order of numbers of reported cases. The remaining ones have each been occasionally detected in several cases. (Feng, Ryan, and Xiao 2018; Ryan, Hijjawi, and Xiao 2018)

Molecular epidemiological studies of human cryptosporidiosis have recognized *C. hominis* as the dominant species in both children and HIV-positive patients in developing countries (Xiao and Cama 2018). In contrast, *C. hominis* and *C. parvum* infections appear to be equally common in both immunocompromised and immunocompetent persons in European and Middle East countries as well as New Zealand (Cacciò and Chalmers 2016; Costa et al. 2020; Garcia-R et al. 2020; Nazemalhosseini-Mojarad, Feng, and Xiao 2012; Xiao and Cama 2018). In some developed countries, such as the United States, Canada, Australia, and Japan, although

most human cryptosporidiosis cases are caused by *C. hominis*, there is a high occurrence of *C. parvum* in rural areas (Abal-Fabeiro et al. 2015; Deshpande et al. 2015; Loeck et al. 2015; Morris et al. 2019).

The distribution of other human-pathogenic *Cryptosporidium* species is also different between developing countries and developed countries. Most human infections with *C. meleagridis, C. felis, C. canis, C. viatorum, and C. muris* have been reported in studies conducted in developing countries or in persons who have travelled to these areas (Adamu et al. 2014; Elwin et al. 2012; Insulander et al. 2013; Steiner et al. 2018; Xiao and Cama 2018). In contrast, most human infections with *C. ubiquitum, C. cuniculus, and chipmunk* genotype I are from developed countries (Chalmers et al. 2011; Deshpande et al. 2015; Feltus et al. 2006; Garcia-R et al. 2020).

Molecular epidemiological of *C. hominis* in human

Molecular epidemiological studies have shown that *Cryptosporidium* infections in children in developing countries are dominated by *C. hominis*, which accounts for over 65% of cases on average. This dominance could be due to environmental contamination and direct person-to-person transmission, as observed in a case-control study of *Cryptosporidium* transmission in Bangladeshi households. This study revealed a high rate of secondary infection and infection with the same subtype within families. *C. hominis* is also a major species in HIV-positive patients in developing countries.

Based on sequence analysis of the 60-kDa glycoprotein (gp60) gene, *C. hominis* is divided into five major subtype families with very divergent sequences: Ia, Ib, Id, Ie, and If. Molecular analyses of *C. hominis* have revealed a much higher number of subtype families in humans in developing countries than in developed countries, where subtype family Ib contributes to over 90% of *C. hominis* infections. The high heterogeneity of *C. hominis* in developing countries is considered an indication of the high intensity of cryptosporidiosis transmission in areas of endemicity.

The distribution of common *C. hominis* subtype families varies among geographic areas. In Asia, Ia is a major subtype family, followed by Id, Ie, Ib, and If. In Africa, the frequencies of Ia, Ib, Id, and Ie are about the same and significantly higher than that of If. In the Middle East, Id is most common, followed by Ia and Ib, with only limited occurrence of Ie and If. In the Americas, Ib is the most common subtype family of *C. hominis*, followed by Ia, Id, and Ie, with an absence of If. These differences possibly reflect variations in the transmission of *C. hominis* in humans among areas.

Geographical segregation is seen in the distribution of subtypes within some of the common subtype families. For instance, two major subtypes are seen within the subtype family Ib: IbA9G3 and IbA10G2. The former is common in Jordan, Tanzania, Uganda, Kenya, Bangladesh, and India, while the latter is common in Peru, Jamaica, Colombia, Argentina, Brazil, and South Africa. Other subtypes, such as IbA13G3, IbA10G1, IbA11G2, and IbA12G3, were reported only in limited regions. This geographic segregation in *C. hominis* subtypes has been confirmed by multilocus sequence type (MLST) analysis of specimens from several countries.

Molecular epidemiological of *C. parvum* in human

Cryptosporidium parvum is responsible for about 20% of cases of human cryptosporidiosis in developing countries. At the gp60 locus, there are multiple subtype families within *C. parvum*. The distribution of common *C. parvum* subtype families

varies greatly among different geographic regions and socioeconomic conditions. This variation is likely due to differences in infection sources and transmission routes (Nichols et al., 2014).

In developing countries, IIc contributes to over half of the disease burden due to *C.* parvum, followed by IIa, while the contribution of IId is limited. In Middle Eastern countries, which are highly industrialized, the disease burdens of IId and IIa are significantly higher than that of II*C.* In contrast, IIa is responsible for over 80% of *C. parvum* infections in developed countries, whereas IId subtypes are seen mostly in New Zealand and Europe, and IIc infections are associated with travel to developing countries (Costa et al., 2020; Garcia-R et al., 2020).

Compared to developed countries, developing countries have substantially higher subtype diversity of *C. parvum* in humans. Asia has the highest subtype diversity of *C.* parvum, followed by Africa, the Middle East, Europe, Oceania, South America, and North America. Up to eight subtype groups, namely IIa to IIe, IIm, IIn, and IIo, have been identified in Asia. The IIa and IIc subtype families are the most prevalent among them.

Africa has as many as nine subtype groups recognized, including IIa to IIe, IIg, IIh, IIi, and IIm. The most common subtype family among them is II*C.* However, the IIa subtype family appears to be frequent in AIDS patients in Ethiopia (Adamu et al., 2014).

In the Middle East, the genetic diversity of *C. parvum* in humans is much lower. Although four subtype families are recognized, two of them have very low frequency. Among them, IId contributes to over half of the *C. parvum* infections. The importance of IId in human infections in Middle Eastern countries may be related to the importance of small ruminants, which are commonly infected with *C. parvum* IId subtypes. This is followed by IIa, which accounts for almost all the remaining *C. parvum* infections there (Santin, 2020). In South America, only IIc and IIa have been reported in humans (Higuera et al., 2020).

The dominance of the IIc subtype family in humans in developing countries suggests that anthroponotic transmission plays a major role in cryptosporidiosis in this area (Nichols et al., 2014).

Epidemiological Features of Cryptosporidiosis in Egypt

- Various studies suggest that *Cryptosporidium* is more commonly found in children under the age of 5 years (Elsawey et al. 2020; Helmy et al. 2013; Mohammad et al. 2021; Naguib et al. 2018). This may be due to the fact that children in this age group often eat without washing their hands, lack knowledge about hygiene, and have an immature gut mucosa (El-Helaly, Aly, and Attia 2012).
- On the other hand, adults aged between 21-40 years old have a higher prevalence of *Cryptosporidium*. This may be due to sociodemographic differences, contact with contaminated resources, and/or occupational risks (Factors et al. 2022; Gawad et al. 2018; Mohamed and Masoud 2023).
- Studies show that males above 45 years have a higher rate of infections, which might be due to outdoor hand-working activities (Ibrahim et al. 2022).
- The main detected symptoms of cryptosporidiosis are diarrhoea, abdominal pain, vomiting, and fever. However, diarrhoea is often associated with

cryptosporidiosis (Elsawey et al. 2020; Factors et al. 2022; Helmy et al. 2013; Ibrahim et al. 2022; Mohamed and Masoud 2023; Naguib et al. 2018).

- Animal contact, especially in rural areas, is an important risk factor in *Cryptosporidium* infection (Factors et al., 2022; Gawad et al., 2018; Mohamed and Masoud, 2023).

Prevalence of Human Cryptosporidiosis in Egypt

In the Ismailia governorate in 2013, a study investigated the prevalence of *Cryptosporidium* in children suffering from diarrhoea was 49.1% using PCR. Genotypic characterization of PCR-positive specimens showed that *C. hominis* and *C. parvum* were the only species detected; *C. hominis* was 1.6 times more prevalent than *C. parvum* (Helmy et al. 2013).

In Cairo governorate in 2016, a study investigated the prevalence of *Cryptosporidium* in children with diarrhoea was 9.3 %using MZN stain, and 23.4 % using PCR (Ghallab et al. 2016).

In El-Dakahlia, El-Gharbia, and Damietta governorates in 2018, a study investigated the prevalence of *Cryptosporidium* in children was 1.4% using PCR; the low occurrence of *Cryptosporidium* spp. in this study might be due to the older age of children enrolled in this study. Genotypic characterization of PCR-positive specimens identified *C. hominis* and *C.* parvum, each with three subtype families. The *C. hominis* subtypes were IbA6G3, IdA17, IdA24 and IfA14G1R5, while *C. parvum* subtypes were IIdA20G1, IIaA15G2R1, and IIcA5G3a (Naguib et al. 2018).

In the Beni-Suef Governorate 2018, a study investigated the prevalence of *Cryptosporidium* in diarrheic patients was 9.5% using MZN stain and 21% using PCR (Gawad et al. 2018).

In Qena Governorate 2018, a study investigated the prevalence of *Cryptosporidium* in patients suffering from Chronic Kidney Disease and treated with hemodialysis was 40% using MZN stain (El-kady et al. 2018).

In Cairo governorate in 2019, a study investigated the prevalence of *Cryptosporidium* in children was 5.7% using MZN stain, out of positive cases 37.5% were positive using PCR. Genotypic characterization of PCR-positive specimens showed that *C. hominis* was the only species recognized (El-Missiry et al. 2019).

In Mansoura governorate 2020, a study investigated the prevalence of *Cryptosporidium* in children with GIT manifestations was 34% using MZN stain, and 59% using PCR. Genotypic characterization of PCR-positive specimens identified four *Cryptosporidium* species: *C. hominis* (52.5%), *C. parvum* (33.9%), C. meleagridis (8.5%) and *C. felis* (5.1%) (Elsawey et al. 2020).

In Sharqiya Governorate 2021, a study investigated the prevalence of *Cryptosporidium* in children suffering from diarrhoea was 27.8% using MZN stain, and 25.5% using PCR. Genotypic characterization of PCR-positive specimens showed that 62.2% had *C. hominis*, 29.7% had *C. parvum,* and 8.1% had mixed infections of both genotypes (Mohammad et al. 2021).

In Alexandria governorate in 2022, a study investigated the prevalence of *Cryptosporidium* in HIV patients was 15% using MZN stain, and 11% using PCR. Genotypic characterization of PCR-positive specimens revealed the presence of three different species of *Cryptosporidium* in HIV patients, with the anthroponotic species, *C. hominis* being the most common (45.4%) followed by *C. parvum* (27.3 %) and *C.*

meleagridis (18.2%). A mixed infection (*C. hominis* and *C. meleagridis*) was detected in one patient (Mohamed et al. 2022).

In Kafr El-Sheikh Governorate 2022, a study investigated the prevalence of *Cryptosporidium* in diarrheic patients (immunocompetent & immunocompromised) with diabetic, renal, hepatic failure, and/ or on immunosuppressive drugs was 5.5% in immunocompetent and 9% in immunocompromised using AF stain, 7.5%in immunocompetent and 11.5%in immunocompromised using PCR. Genotypic characterization of PCR-positive specimens revealed that human strain was predominating in immunocompetent and immunocompromised: 60% with C. *hominis*, 40% *C. parvum* in immunocompetent and 82.6% with *C. hominis* , 17.4% *C. parvum* in immunocompromised (Factors et al. 2022).

In the Beni-Suef Governorate 2022, a study investigated the prevalence of *Cryptosporidium* in patients with chronic renal disease undergoing hemodialysis was 13.3% using MZN stain. (Ibrahim et al. 2022)

In the Sohag Governorate in 2020, a study investigated the prevalence of *Cryptosporidium* in out-patients (immunocompetent & immunocompromised) was 45% using MZN stain and immunochromatographic test. (Mohamed, El-Hady, and Ahmed 2020) while in 2022, a study investigated the prevalence of *Cryptosporidium* in chronic kidney disease (CKD) patients was 35% using MZN stain. (Abd El-Mawgood et al. 2022)

In Fayoum Governorate 2023, a study investigated the prevalence of *Cryptosporidium* in adult suffering from diarrhoea was 17.1% using MZN stain. Genotypic characterization of PCR-positive specimens showed that zoonotic *C. parvum* 72.7% and *C. hominis* 27.2%. This indicated that zoonotic transmission is more prevalent, especially in farming areas (Mohamed and Masoud 2023).

the predominance of the anthroponotic genotype (*C. hominis)* over the zoonotic genotype (*C.* parvum) clarifies that anthroponotic transmission plays a major role in cryptosporidiosis in many areas in Egypt.

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الملخص العربي

الوبائية الجزيئية ل داء خفيات الأبواغ البشرية

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ملخص البحث:

خفية الأبواغ هو نوع من الطفيليات يسبب مرض الإسهال المعوي المعروف باسم داء خفيات الأبواغ، ويمكن أن يؤثر على الإنسان والحيوانات. ينتمي هذا الطفيلي إلى عائلة الطفيليات وحيدة الخلية البوغية وله دورة حياة معقدة تشمل مراحل جنسية ولاجنسية. هناك حوالي 25 نوعًا وعدة أنماط جينية من خفية الأبواغ، وبعضها معروف بالإصابة بالإنسان. وأكثر الأنواع الشائعة التي تسبب الإصابة بالإنسان هي خفية الأبواغ البشرية وخفية الأبواغ الصغيرة.

تشكل الإصابة ب خفية الأبواغ مشكلة صحية مهمة في جميع أنحاء العالم، حيث تسبب الإسهال في كل من الأفراد الذين يعانون من ضعف المناعة والأفراد الذين يتمتعون بصحة جيدة. ويعد الإسهال هو السبب الرئيسي للوفاة للأطفال دون سن الخامسة في البلدان النامية. ويتم استخدام الأساليب الجزيئية بشكل متزايد في الأبحاث لتحسين البيانات الوبائية. ومن خلال استخدام التقنيات الجزيئية لمراقبة خفية الأبواغ في المياه والحيوانات والبشر، يمكننا الحصول على فهم أفضل لأنماط الإصابة والنقل، مما يمكن أن يساعد في إدارة خفية الأبواغ من خلال تحسين تقييم المخاطر.

الكلمات الافتتاحية: خفية الأبواغ، الوبائية الجزيئية